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Radiation Dosimetry for Studying the Late Effects of Radiotherapy

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Abstract

Evidence that radiation-related cardiovascular disease and second primary cancers can occur in cancer survivors following radiation therapy (RT) has emerged from several independent sources. Cardiotoxicity and second cancers are of particular concern for patients with good prognosis, such as those with Hodgkin lymphoma (HL). HL patients are among the youngest to receive RT, which means that those who are cured of their cancer have decades-long natural life-expectancies during which treatment-related long-term toxicities may cause years of excess morbidity or premature mortality. A considerable amount of research has been conducted to investigate the risk of radiation-related cardiotoxicity and second cancers. However, there are still substantial gaps in knowledge. It is therefore important to improve our understanding regarding these risks and develop treatment approaches and survivorship care to minimise their impact on patients' quality of life. In this thesis, I have investigated the risk of congestive heart failure (CHF) in a cohort of 2619 HL survivors and presented, for the first time, dose-response relationships for risk of CHF versus cardiac radiation doses. I also validated the radiation dosimetry method used to estimate the cardiac doses in this study as well as for other reconstruction methods, versus a gold standard based on the patients' own computed tomography scans. Additionally, I investigated what effect the dose reconstruction errors had on the dose-response relationships. I then focused on modern RT methods and specifically on proton RT. Based on published dose-response relationships (including that developed in this thesis) I predicted cardiovascular and second cancer risks for patients treated with advanced RT. This thesis has provided new knowledge in the study of late effects in HL patients who were treated decades ago as well as for patients treated more recently with advanced RT methods. The results here can be used to facilitate progress towards personalised RT in terms of choosing the appropriate RT method by integrating individualised risk prediction in advanced RT treatment planning. The research here provides the basis for further work towards evidence-based case selection for HL patients for the first NHS proton therapy centres in the UK, opening in 2018-2021.

Guide for Readers

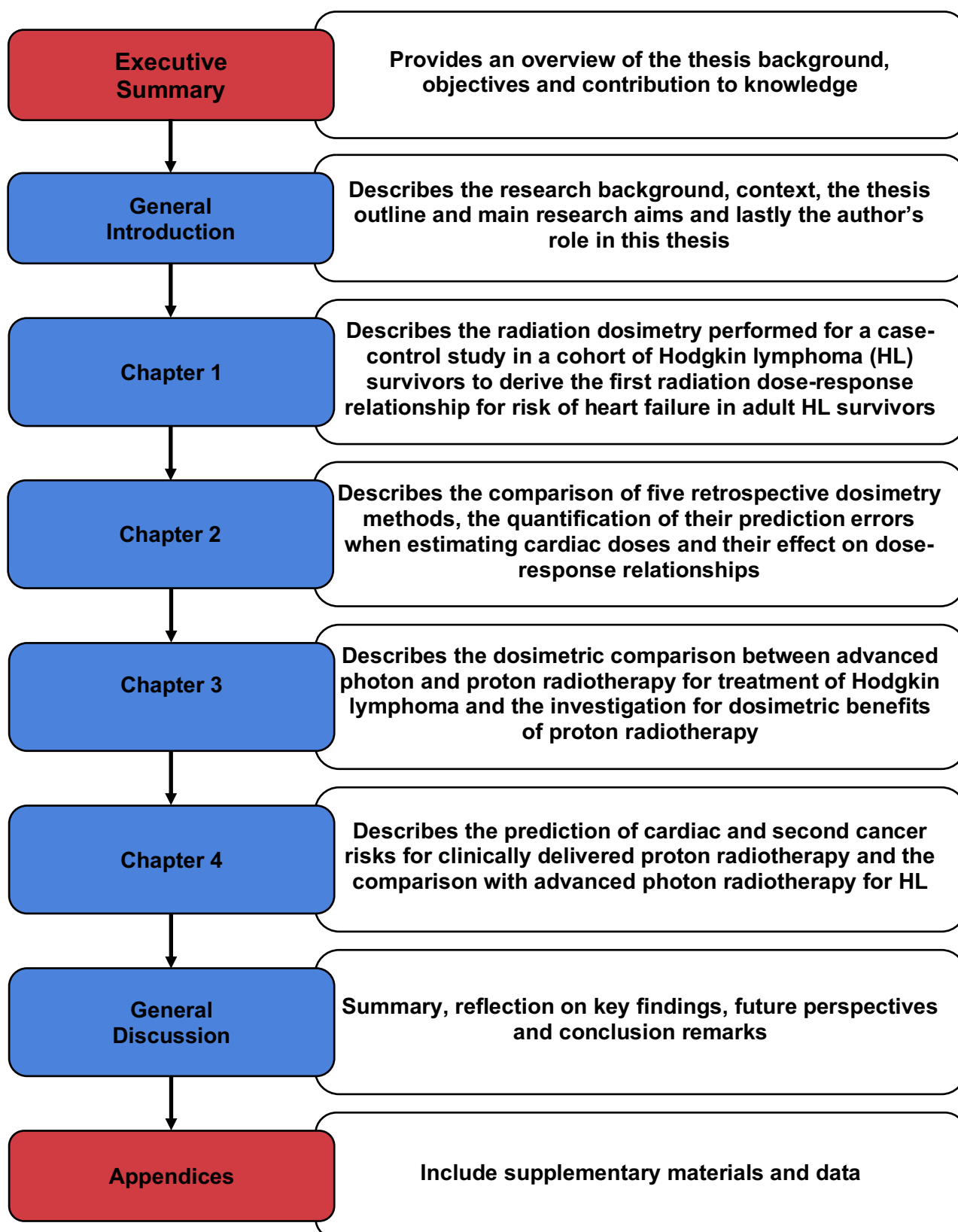


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List of Abbreviations

AAA: anisotropic analytic algorithm
AGE_TX: age at treatment
CCA: common carotid artery
CCSS: Childhood Cancer Survivor Study
CHD: coronary heart disease
CHF: congestive heart failure
CHEMO: chemotherapy
CI: confidence intervals
Clx: conformity index
CT: computed tomography
CTV: clinical target volume
CVD: cardiovascular disease
DICOM: digital imaging and communications in medicine
DVHs: dose volume histograms
GY: Gray
EQD2: equivalent dose in 2 Gy fractions
EOR: excess odds ratio
ERR: excess relative risk
EUR: Europe
HL: Hodgkin lymphoma
HR: hazard ratio
IHD: ischemic heart disease
IMRT: intensity modulated radiotherapy
LAD: left anterior descending
LQ: linear quadratic model
MBD: mean breast dose
MeV: mega electro-voltage
MHD: mean heart dose
MLD: mean lung dose
MLVD: mean left ventricular dose
MOD: mean oesophageal dose
MUs: monitor units
MV: megavoltage
OAR: organs at risk
PartArc: partial arc
PBS: pencil beam scanning
PTV: planning target volume
RR: relative risk
RT: radiotherapy
SD: standard deviation
SOBP: spread-out Bragg peak

SIR: standardised incidence ratio
SSD: source to skin distance
USA: United States of America
VHD: valvular heart disease
VMAT: volumetric-modulated arc therapy
Y: years
3D-CRT: three-dimensional conformal radiotherapy

Context of research

Radiotherapy (RT) is a powerful treatment against cancer and functions by using ionising radiation to kill or damage malignant cells within the body. It has been used for decades either as definitive or as an adjuvant therapy and it has dramatically improved the cure or local control rates for various types of cancer. However, like other cancer treatments such as chemotherapy, it can cause acute and late side effects. Evidence that radiation-related cardiovascular disease (CVD) can occur in cancer survivors following radiation therapy has emerged from several independent sources.^{1–4} It has also been established that where organs such as lungs, breast and oesophagus receive incidental radiation exposure during RT, patients can be at increased risk of radiation-related second primary cancers.^{5–7}

Cardiotoxicity and second cancers are of particular concern for patients with good prognosis, such as those with Hodgkin lymphoma (HL). HL patients are among the youngest to receive combined treatment of chemotherapy followed by RT. This means that those who are cured of their cancer have decades-long natural life-expectancies during which treatment-related long-term toxicities may cause years of excess morbidity or premature death.⁸ Due to concerns about these late toxicities, researchers have investigated the potential of omitting RT for subgroups of HL patients and treating them only with chemotherapy.⁹ However, the final results of the most recently reported randomised trial in early stage [European Organisation of Research and Treatment of Cancer, Lymphoma Study Association, and Fondazione Italiana Linfomi (EORTC/LYSA/FIL) H-10] have concluded that omitting RT may increase the risk of relapse.¹⁰

Radiotherapy has evolved to reduce long-term risks

In response to the concern over late radiation toxicity, RT techniques have evolved and substantial reductions in the dose and volume of irradiated tissue have been achieved. Modern techniques have incorporated several technological advances that allow reduction of radiation exposure to the heart and other organs at risk (OAR) for HL patients. One of the most advanced RT methods and efficient approaches to achieving reduction in incidental radiation and thus risks is proton RT, where steep dose gradients allow further reductions in incidental radiation.¹¹

The importance of accurately estimating risks

Since the risks of late toxicities mentioned above were observed in patients treated with older RT methods using larger radiation treatment fields, it is important to estimate the risks for patients treated with modern RT and reduced fields. In order to minimise the long-term RT risks to patients by, for example, tailoring the treatment regimen, referring them for specialised therapies such as proton RT or by suggesting lifestyle changes that reduce those risks, it is essential that high risk patients can be accurately identified. In order to identify these patients, their risks of radiation-related diseases need to be estimated. This will enable oncologists to reassure patients for whom there is little risk and to identify those at high risk and potentially refer them for advanced treatment such as proton RT.

Development of dose-response relationships

In many cases, estimating radiation-induced late effects in patients treated with RT requires observational studies for patients treated in the past in order to develop models that predict the risks for current and future patients. Case-control or cohort studies provide a powerful tool to investigate the risks of disease associated with a specified exposure. If the exposure (e.g. radiation dose) is known and the patient

follow-up is long enough for late effects to manifest, those studies can determine radiation dose-response relationships for the late effect of interest.

Retrospective dosimetry

However, when information about radiation doses to normal tissues and organs is not available, which is the case in most observational studies, retrospective estimation of these radiation doses must be made. The estimated radiation doses are then used to derive radiation dose-response relationships. Retrospective dosimetry is the only way to produce organ-specific radiation dose-response relationships when organ specific dose information is not available, although this poses various challenges. Inaccuracies in the estimation of dose to normal tissues are inevitable and it is important that a substantial effort is made to optimise the retrospective dosimetry methods and account for any inaccuracies.

Risk prediction

Once reliable dose-response models have been developed, they can be used to predict risks for patients who have already received or who are going to receive RT. This provides oncologists and patients with more accurate data regarding the potential risks of treatment so that these can be balanced against the benefits. Scientists and clinicians can use this information for the assessment of risks/benefits in choosing the most appropriate cancer treatment option.

Structure of the thesis and research objectives

In this thesis, I perform radiation dosimetry for the study of late effects following treatment for HL. In the **General introduction** chapter, I provide an overview of the relevant background theory and a detailed description of the aims and objectives of the thesis. In **Chapter 1**, I provide the retrospective dosimetry and medical physics input for a case-control study in a cohort of 2,617 HL survivors. The main aim of this

study was to estimate the cardiac doses for 369 cases and controls in order to derive the first ever dose-response relationship for risk of congestive heart failure (CHF) in adult survivors of HL. In **Chapter 2**, I validate my retrospective dosimetry method against a “gold standard” by considering a group of HL patients for whom computed tomography (CT) scans were available. This enabled my reconstructed doses to be compared with “true doses” based on CT scans. I evaluate other dose reconstruction methods that have been used in literature to reconstruct cardiac doses in previous epidemiological studies. I then compare the accuracy of dose reconstruction for all methods and evaluate the effect of their reconstruction errors in dose-response relationships which have been derived using those reconstruction methods. Lastly, I propose a methodology to correct dose-response models for errors in the dose reconstruction.

In **Chapter 3**, I investigate modern RT methods for the treatment of HL such as pencil beam scanning (PBS) proton RT and advanced photon RT. Firstly, I compare all RT methods in order to identify which method achieves the largest reductions in incidental radiation in OAR, using a group of 21 HL patient who were treated with PBS proton RT between 2014 and 2016. I also identify those HL patients for whom PBS proton RT provided substantial dosimetric benefits from those where photon RT would have delivered equal dosimetric results. In **Chapter 4**, I develop a risk prediction model based on the epidemiological data from this thesis and from other published observational studies and use it to predict cardiovascular and second cancer risks for the patient group described in Chapter 3. Apart from radiation-related risks, the risks associated with chemotherapy were also investigated, as well as the effect that the background population risks have on the predicted treatment-related risks. In the final **General Discussion** chapter, I discuss the main findings,

strengths and limitations of this thesis and provide recommendations for future research.

Contribution to knowledge of this thesis

- This thesis presents, for the first time, a radiation dose-response relationship for the risk of CHF in adult HL survivors. It also demonstrates an increased risk of CHF following chemotherapy. These results, when combined with other recently published dose-response relationships for the risk of different cardiac diseases, will further improve our understanding of radiation-related heart disease overall, and will enable more accurate prediction of cardiac risks for HL patients based on their individual cardiac doses.
- To the best of my knowledge, this is the first study to evaluate the accuracy and feasibility of several radiation dose reconstruction methods for use in retrospective cardiac dosimetry. It is also the first study to quantify the effect that the dose reconstruction errors had on published dose-response relationships and to provide a methodology for researchers to include those uncertainties in the dose-response models.
- Additionally, to my knowledge, this is the largest group of HL patients treated with PBS proton RT for which a comprehensive dosimetric analysis has been reported. It is also the first attempt to identify HL patients based on specific disease characteristics for whom PBS proton RT can provide additional dosimetric benefits compared to the rest of HL patients.
- Lastly, this is the first study to estimate cardiovascular and second cancer risks for a group of HL patients who were treated with PBS proton RT. Furthermore, all the recently derived cardiac disease-specific radiation dose-response relationships have been combined in order to produce overall

cardiac mortality risks based on long follow-up epidemiological studies. This is to my knowledge, the first time that regional background mortality rates have been taken into account in predicting risks for patients that have been treated with proton RT.

In Summary, this thesis contributes new knowledge in our current understanding of treatment-related late effects in HL patients, in retrospective cardiac-radiation dose reconstruction and in the use of PBS proton RT in the treatment of HL.

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General Introduction

Radiotherapy is a powerful treatment against cancer and functions by using ionising radiation to kill or damage malignant cells within the body. RT has been used for decades either as definitive or as an adjuvant therapy and it is one of the factors that has led to the substantial increase in survival over the last few decades for many types of cancer. In the UK, cancer survival has doubled during the last 40 years in the UK and now half of cancer patients will survive at least 10 years after diagnosis.¹

Part of this improvement in cancer survival is due to technological and scientific advancements in RT. However, like other treatments, RT can cause acute or late side effects. Hence, a proportion of cancer survivors go on to develop radiation-related diseases such as CVD or second malignancies which affect the quality of life or lead to death. Survivors of HL provide an appropriate cohort for studying late effects. The 5-year survival rate in the UK is 85%, whilst more than 80% of HL patients will survive at least 10 years.¹ The high survival rates combined with the relatively young age of diagnosis provide the opportunity for long-term follow up studies which enable characterisation of late effects such as cardiac disease or second cancers. Studying the late effects of RT, understanding the risks involved, identifying patients at high risk and finally developing novel treatment techniques to minimise those risks is, therefore, a crucial research field.

Studying late effects

One way of investigating radiation-related late effects in patients treated with RT, is via population-based observational studies of patients treated in the past. A prolonged follow-up is essential as it can take decades for late effects to manifest

following irradiation. Case-control or cohort studies provide a powerful tool to investigate the risks of disease associated with a specified exposure. If the exposure (i.e. radiation dose) is known and the patient follow-up is long enough, such studies can lead to radiation dose-response relationships for late effects such as cancer and CVD. However, sufficient information about radiation doses to the relevant normal tissues is not usually available. Therefore, retrospective radiation dosimetry is required to reconstruct the regimens used and obtain the relevant organ-specific doses. The reconstructed doses can then be used to derive dose-response relationships which describe ways in which disease risk is related to the radiation dose received by the relevant organ.

The reconstructed doses to each organ are, however, subject to errors due to various sources of uncertainty and this can affect the accuracy of the dose-response relationships. Hence, it is important to identify and quantify these errors and where possible, correct for their effect. Once this is done, reliable dose-response relationships to describe the risks of late effects can be developed. These dose-response relationships can then be used to estimate risks for patients who have been treated in the past and, where relevant, to suggest appropriate follow-up and frequent monitoring. They can also be used to identify current patients who are likely to be at high risk of developing late effects and enable adaptation of their treatment in order to minimise them by, for example, tailoring their treatment regimen, suggesting lifestyle changes that could reduce the risks, or referring the patient for specialised treatments.

In addition to empirical studies of the type described above, various radiobiological models have also been developed to predict radiation-related late effects.² However, their accuracy has been questioned due to the assumption that

all radiation-mutated cells would be sterilised and that the risk does not depend on factors other than the radiation exposure.² Epidemiological studies, however, suggest that the risks increase as the organ doses increase.⁴ Recently developed radiobiological models are starting to take such factors into account and correct for these uncertainties.⁵ This thesis, however, focusses on population-based risk models derived from epidemiological studies.

Basic epidemiological concepts and terminology

In this section some basic epidemiological concepts are introduced to set the foundation and define the epidemiological terminology in this thesis. One important measure is the "incidence rate", which is the rate at which new cases of a disease occur in a population, and another is the "mortality rate", or "death rate", which is the rate at which deaths from the disease occur. The rates used in epidemiology are hazard rates. Mathematically, a hazard rate is the limiting ratio of the changes in two quantities - here number of events (cases or deaths) and time - as the denominator (i.e. time) tends to zero. In epidemiology it is usually adequate to estimate a rate by considering the number of events in a time interval, such as a year, divided by the average of the number of people at risk of experiencing the event during that time interval. Two further important concepts in epidemiology are "risk" which is the probability of an event (either a new case of a disease or a death from it) and "cumulative risk" which is the probability that an individual suffers an event over a defined interval (e.g. 10 years, 20 years, etc).

The rate ratio (RR) is the rate of disease among a group exposed to a risk factor (e.g. radiation) divided by the rate among a group not exposed to the factor and is often converted into an "excess rate ratio" (ERR), defined as $ERR = RR - 1$. The term hazard ratio (HR) is sometimes used synonymously with rate ratio. Rather

confusingly, the abbreviation RR is also commonly used to refer to "relative risk", which is the ratio of the risk of disease in a group exposed to a risk factor to the risk in an unexposed group, and the abbreviation ERR is also commonly used to refer to excess relative risk.

The term "background" (or "baseline") is often used to indicate rates and risks in people who are not exposed to a factor of interest, such as radiation or chemotherapy. When a quantitative measure of exposure to a risk factor is available, rather than just exposed or unexposed, the relationship between a disease rate and exposure is referred to as a dose-response relationship, especially when the relationship is thought to be a causal one. All the above quantities may well vary with the attained age of an individual, age at exposure, time since exposure, dose received and sex.

The term standardised incidence ratio (SIR) is used to refer to the ratio of the incidence rate in a particular population to the rate in a population with similar age and sex structure observed over the same period of calendar time, but with incidence rates equal to that of a "reference" population, such as that of a state or country. The SIR can be calculated simply by taking the observed number of incident cases of a disease in the population of interest and dividing it by the number of cases that would be expected if the population had the same incidence rates as the reference population. The term standardised mortality ratio (SMR) is defined in a similar way.

Cardiovascular disease in HL survivors

Evidence that radiation-related CVD can occur in HL survivors following radiation therapy (RT) and anthracycline containing chemotherapy has emerged from several observational studies.⁶⁻¹¹ A variety of CVD have been reported such as coronary

heart disease (CHD), myocardial infarction, valvular heart disease (VHD), pericarditis, CHF and stroke.^{12–14} The mechanisms of radiation damage to the heart are not fully understood yet. However, there is some evidence that radiation- and anthracycline-related cardiovascular damage can be of different pathogenesis compared to heart disease occurring to the general public.¹⁴ Radiation leads to accelerated atherosclerosis and increased risk of vascular stenosis which might be caused by damage to the endothelium of blood vessels. Anthracyclines are typically associated with loss of myocardial mass, which can cause cardiac dysfunction and eventually failure.¹⁴

Large epidemiological studies have reported a 2- to 7-fold increase in risk of cardiac death in HL survivors.^{6,15,16} Van Nimwegen et al.¹⁷ reported 4 to 6-fold increased standardised incidence ratio (SIR) of CHD and CHF compared to the general public in a long term follow-up study on HL patients up to 35 years after treatment. The risk of developing CHD, VHD and CHF as first cardiovascular events was increased by 2.7-fold, 6.6-fold and 2.7-fold respectively. Anthracycline-containing chemotherapy increased the risks of VHD by 1.5-fold and of CHF by 3-fold. Mediastinal RT increased the risk of CVD incidence if the patients were treated at younger age. Another large study reported CVD risk in 9 trials conducted by the European Organization for Research and Treatment of Cancer between 1964 to 2004.¹⁸ The hazard ratio for CVD following RT was 1.015 per Gray (Gy) increase in mean heart dose (MHD) and for chemotherapy 1.077 per 50mg/m² cumulative dose of anthracyclines.

In order to be able to predict CVD risks for future patients more accurately, taking into account anthracycline dose and organ-specific radiation dose, more dose-response models need to be developed through long term observational

studies for the full range of cardiac diseases. During recent years, evidence for dose-response relationships for specific cardiac diseases has emerged from case-control studies.^{10,11,19,20} These recent risk models have provided valuable information for the relationship between radiation dose to the whole heart or cardiac substructures and the risk of specific cardiac diseases in adult HL patients and childhood cancer survivors. In a case-control study in a cohort of 2617 HL survivors by van Nimwegen et al.¹⁰ (325 cases and 1204 matched controls) the risk of CHD increased linearly by 7.4% per Gy of MHD. In another case-control study by Cutter et al.¹¹ (89 cases and 200 controls), within the same patient cohort, a non-linear dose-response relationship was reported for risk of VHD based on mean dose to the affected valves. For doses of ≤ 30 , 31–35, 36–40, and ≥ 40 Gy, VHD rates increased by factors of 1.4, 3.1, 5.4, and 11.8, respectively. In two studies within the Childhood Cancer Survivor Study (CCSS), Chow et al.^{19,20} reported increasing CHF risk by factors of 1.6, 3.1 and 10.5 following MHDs of 5-14, 15-34 and ≥ 35 Gy respectively, and increased incidence of CHD by factors of 1.2, 2.7, 2.9 and 6.1 for MHDs of < 5 , 5-14, 15-34, and ≥ 35 Gy respectively, compared with patients who did not have any cardiac radiation exposure. Increased risk of stroke has also been reported in HL survivors. De Bruin et al.¹² reported a standardised incidence ratio (SIR) of 2.2 (95%CI, 1.7 to 2.8) in adult HL survivors and that radiation to the neck was an independent risk factor. Bowers et al.²¹ reported a RR of stroke among paediatric HL survivors of 4.32 (95%CI, 2.01 to 9.29). Chow et al.²⁰ showed increased risk of stroke compared to non-irradiated individuals by a factor of 1.8, 4.5 and 7.5 following cranial radiation doses of 20-29, 30-49 and ≥ 35 Gy respectively. However, no dose-response relationship was reported by any of these studies. Maraldo et al.²² estimated linear dose-response curves and reported

excess risks of stroke by using the epidemiological data described above by De Bruin and Bowers. The estimated excess risks for 20, 25 and 30 years were 0.6%, 0.86%, and 1.3% for 3D-conformal radiotherapy (3D-CRT); 0.67%, 0.96%, and 1.47% for volumetric-modulated arc therapy (VMAT), 0.61%, 0.96%, and 1.33% for proton RT; and 1.3%, 1.72%, and 2.61% for mantle field RT respectively.

These studies provided new, crucial knowledge for accurately estimating CVD risks. However, more epidemiological studies are needed to establish dose-response models for further cardiac diseases and in cohorts of patients treated with modern RT methods. Also, a larger range of radiation doses and particularly lower doses would increase the accuracy of risk prediction following modern RT methods. Lastly, the potential multiplicative effect between chemotherapy and RT needs to be investigated further as well as the dependence of treatment-related risk on other CVD risk factors such as smoking, obesity and diabetes mellitus.

Second cancers in HL survivors

Multiple studies have demonstrated that HL survivors are at increased risk of second cancers following RT and chemotherapy.^{4,16,23–27} When compared to the general population, HL survivors have high relative risks of sarcoma, thyroid cancer, non-Hodgkin lymphoma and leukaemia (6- to 15-fold) and moderate relative risks of other solid cancers such as lung, breast, oesophageal and stomach cancer (2- to 6-fold).¹⁴ In the most recent study of second cancer risks amongst 3905 HL survivors by Schaapveld et al.⁴ cumulative incidence up to 40 years after treatment was reported. This study found that the cumulative incidence of a second cancer was 33.2% at 30 years and 48.5% at 40 years, as compared with the background cumulative risks of cancer in the general population of 9.6% and 19.0%, respectively.⁴ In an earlier study amongst 18,862 5-year HL survivors, Hodgson et

al.²⁸ reported 30-year cumulative risks of second solid cancers of 18.0% and 26.0% for men and women respectively, compared with 7.0% and 9.0% in the general population.

Although chemotherapy containing alkylating agents has been associated with increased risks of lung, stomach and pancreatic cancers²³, increased risk of second solid cancers has been largely attributed to RT.^{2,4,14} The risk of second solid cancers (lung, breast, stomach, pancreatic and oesophageal) has been shown to increase linearly with RT doses ^{23,24,26,27,29,30} (Table 1).

Table 1 Summary of the dose-response relationships for risk of second cancers in Hodgkin lymphoma survivors

<i>Travis et al.</i> ²⁹ (2003)	International population-based 105 cases and 266 controls Median age_tx:22 y Treated 1965-1994	Breast cancer	ERR/Gy = 0.15
<i>Travis et al.</i> ²³ (2002) & <i>Gilbert et al.</i> ³¹ (2003)	International population-based 227 cases and 455 controls Median age_tx:50 y Treated 1965-1994	Lung cancer	RT:ERR/Gy = 0.15 Chemo: RR = 4.3
<i>Morton et al.</i> ²⁷ (2014)	International population registry 36 cases and 71 controls Median age_tx:34 y Treated 1943-1992	Oesophageal cancer	ERR/Gy=0.38
<i>Dores et al.</i> ³² (2014)	International population registry 36 cases and 70 controls Median age_tx:47 y Treated 1953-2003	Pancreatic cancer	EOR/Gy=0.098
<i>Morton et al.</i> ²⁶ (2013)	International population registry 89 cases and 190 controls Median age_tx:30 y Treated 1953-2003	Stomach cancer	EOR/Gy=0.09

Abbreviations: y: years, age_tx: age at treatment, RR: relative risk, ERR: excess relative risk, EOR: excess odds ratio, Gy: Gray, Chemo: chemotherapy containing alkylating agents

These risks have been derived by HL patient cohorts treated decades ago, and their relevance for patients treated with modern RT techniques involving reduced radiation fields as well as chemotherapy with lower doses of alkylating agents has been questioned.² However, a recent study by Schaapveld et al.⁴ showed that, although radiation treatment fields and alkylating agent-containing chemotherapy had been reduced in a most recent treatment era (1989-2000), the risks persisted for solid cancers. This conclusion was surprising considering that most evidence suggests that the risks of late effects are decreased when radiation doses are decreased. The authors hypothesized that it could be attributed to the fact that modern RT treatments had not yet been fully adopted in the treating institutions. Additionally, the absence of a decrease in breast cancer incidence in the most recent era was attributed to better screening and earlier detection. Other studies⁶⁹ have investigated the risk of second cancers in more recently treated patients (1988-2009) and shown that the risks were reduced in the group treated between 2000-2009. Another hypothesis, however, is that even with smaller radiation fields and doses, the risk of second cancers indeed remain high.³³

The above findings underline the need for more observational studies with longer follow-up of patients treated in the modern era are needed to confirm these findings. Additionally, the importance of improving the dosimetric methods to derive more accurate dose-response relationships based on organ specific doses.

Hodgkin lymphoma and treatment

In the early 1960s, the introduction of linear accelerators for RT for HL and combination chemotherapy (vincristine, procarbazine, mustard and prednisone; MOPP), were pivotal in the successful breakthrough against HL.³⁴ However, the success was followed by a price in terms of late effects. In the early 1980s, there

was recognition that several HL survivors developed late side effects such as second cancers, cardiac disease and sterility. As the majority of HL survivors were diagnosed in their early 20s and 30s, a significant effort was made to improve their survivorship and to improve treatment for the future HL patients. More effective and less toxic chemotherapeutic regimens such as (doxorubicin, bleomycin, vinblastine, and dacarbazine) known as “ABVD” and a seven-drug chemotherapy program, known as “BEACOPP,” were developed in an effort to reduce chemotherapy-related side effects.

RT also evolved and smaller treatment fields combined with technological advancements that provided more conformity and dose homogeneity contributed to the reduction of radiation-related late effects.³⁵ Radiation fields were reduced incrementally along with the technological advancement in medical imaging and treatment planning which enabled more accurate delineation of the tumour volumes and OAR. The fields were reduced from total lymph node irradiation (i.e. all lymph nodes irradiated on both sides of diaphragm), to extended-field RT (i.e. involved and non-involved lymph nodes irradiated), followed by involved-field RT (i.e. only the involved nodes irradiated in predefined anatomical regions) and to the more recent concepts of involved-site RT and involved-node RT in which the radiation fields are tailored to include only the lymph node sites initially involved (Figure 1).

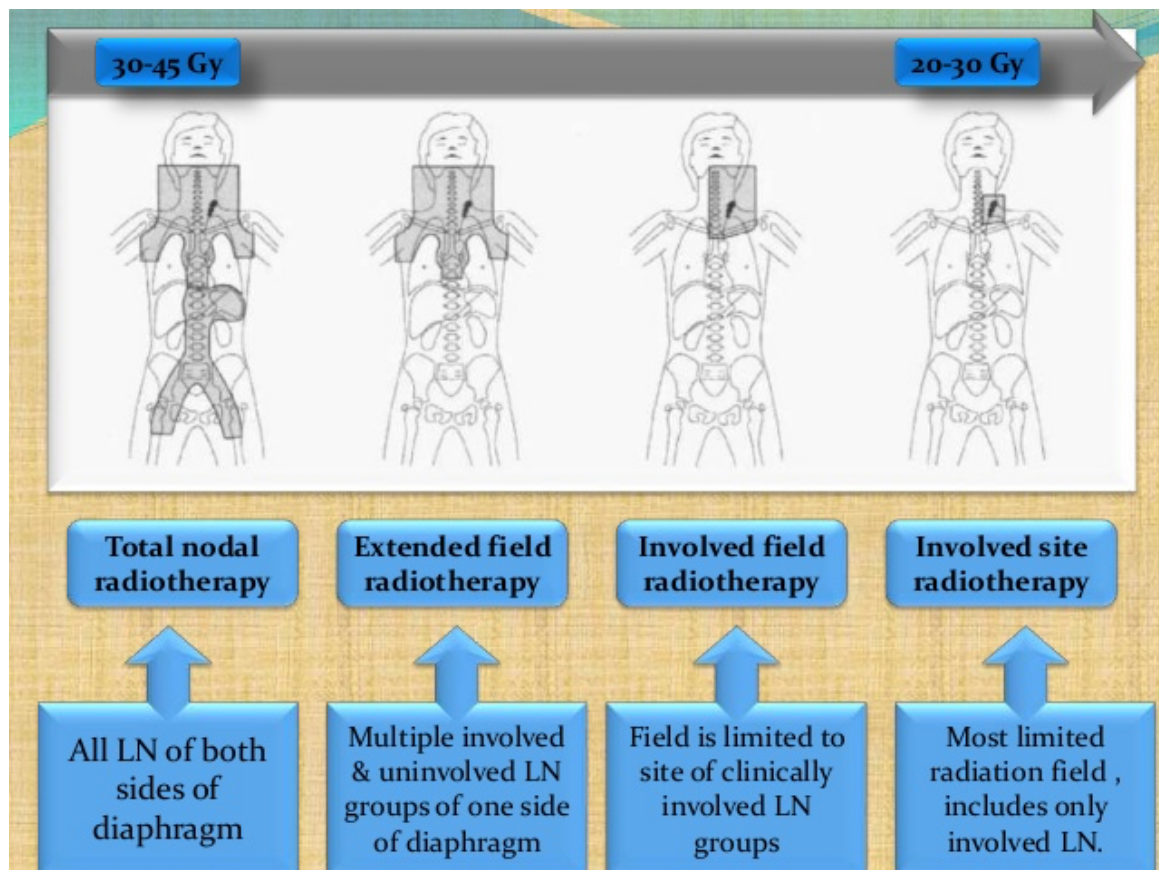


Figure 1 The evolution of RT in the management of HL.

Source: <http://www.slideshare.net/dharmendrasingh3910/hodgkins-lymphoma-early-stage-management> (last visited 02/2017)

Mantle field photon radiotherapy

In the early 1960s, Henry Kaplan from Stanford University introduced the use of linear accelerators (Linacs) in the treatment of HL and established the guidelines and techniques that became the standard of care for the next two decades.³⁶ This technique included extended “mantle” RT fields used to irradiate the lymph nodes in the supra-diaphragmatic and “Inverted Y” RT fields used to treat the sub-diaphragmatic areas. For mediastinal RT, two fields were usually used, one anterior and one posterior (AP-PA). Lead blocks were used to provide shielding to the normal tissue such as lungs, larynx, humeral heads and the spinal cord. Localisation radiographic films (also known as simulation films) were used to verify the patient’s treatment position and simulate the treatment in order to design patient specific lead blocks shielding.

The treatment configuration can be seen in Figure 2. The prescribed dose varied between 36 Gy and 44 Gy and the dose was delivered usually in fractions varying in size from 0.75 Gy to 2.75 Gy, depending on the RT centre. One field was delivered per day (in contrast to more modern techniques where both anterior and posterior fields are delivered on the same day) and the total treatment lasted for approximately 4 weeks.^{36–38}

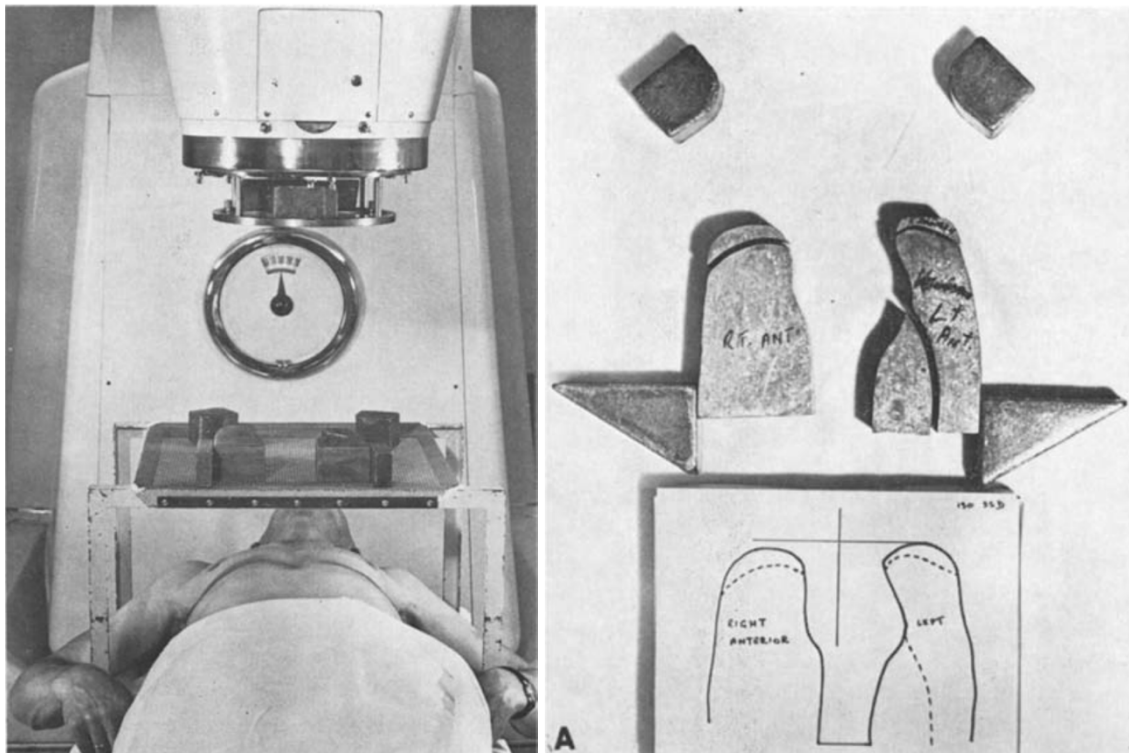


Figure 2 Mantle field configuration for RT in HL. Patient in supine position ready to receive irradiation from an anterior field using a linac. The lead blocks can be seen placed on a tray above the patient (left image) and arranged during the treatment planning process (right image) to provide with the required shielding for the lungs and humeral heads.³⁷

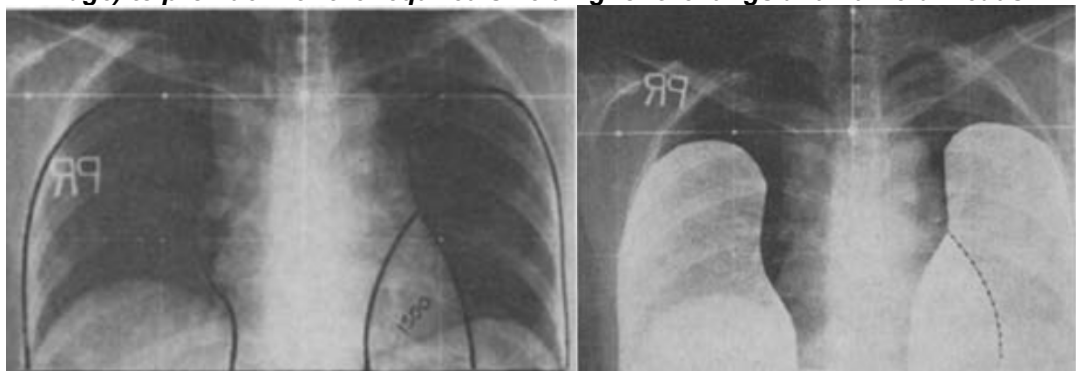


Figure 3 An example of an original simulation film with lung block borders marked in black (left) and with the actual lead blocks placed on the treatment tray. (right) The white shadow from the lead blocks seen on the film was due to beam attenuation by the lead blocks.³⁷

One of the main challenges with mantle field HL radiotherapy, was to provide accurate and reproducible lung shielding as well as delivering a precise and homogeneous dose distribution within the target volumes. Due to the limited computing and imaging infrastructure of that period, the delivered dose to the prescription point (usually the midplane) varied within $\pm 10\%$ of the prescribed dose. In some cases, when additional shielding was added or the mediastinal field was narrower than usual (width up to 4.5 cm) the delivered dose to the midplane could be up to 20% lower than the prescribed dose.³⁷ The doses in OAR such as the lungs or the heart could not be calculated due to the lack of 3D imaging. However, retrospective dosimetry studies on patients who received similar mantle RT, have estimated that the average mean dose to the heart varied between 20.9 Gy and 27.5 Gy^{39–41}, 14.7 Gy for lungs and 9.0 Gy for breast³⁹, all of which are substantially higher than in modern RT.

Three-dimensional photon radiotherapy

Following two decades of routine use of mantle field RT, late effects in the form of second breast and lung cancer as well as cardiac disease started to be reported. Consequently, more sophisticated treatment techniques started to be developed in the early 1990s in an attempt to improve tumour control and at the same time reduce late toxicities.

Parallel opposed fields (AP-PA) radiotherapy

The first revolution in HL radiotherapy came through treatment planning based on 3D medical imaging such as CT.⁴² Delineation of target volumes was improved dramatically, which enabled more accurate target coverage. The tumour was drawn onto each cross-sectional images of the CT creating a reconstructed 3D volume.

The location of the OAR was defined more accurately, and their exposure was reduced, resulting in a reduced frequency of radiation-related complications. The use of computerised treatment planning facilitated superior dose calculation accuracy compared to the manual dose calculations performed until then and allowed visualisation of the dose distribution within the patient (Figure 4). It also improved the dose homogeneity within the target volumes and enabled the introduction of dose volume histograms in the assessment of treatment plan quality⁴³ (Figure 5). The AP-PA field arrangement also used in mantle field RT was maintained for most cases but the technique was later evolved into 3D-CRT.

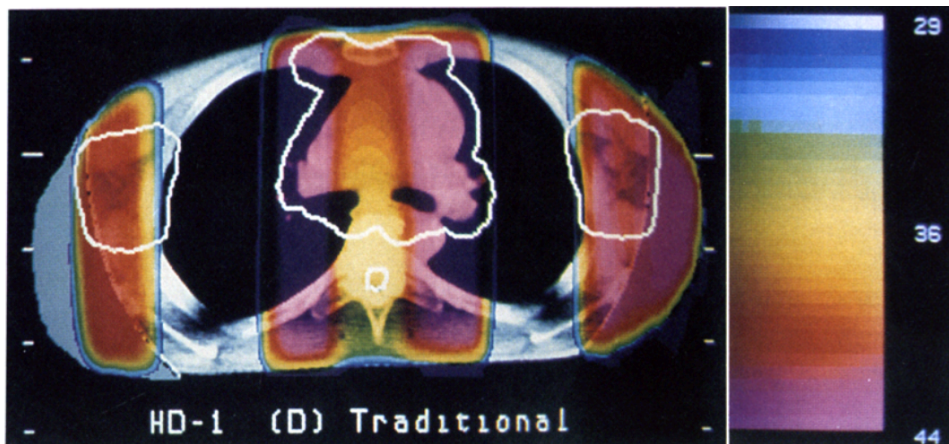


Figure 4 One of the first applications of 3D-imaging based treatment planning for AP-PA treatment of HL. Dose distribution shown in colour wash on transverse thoracic image. (left) Scale of colour corresponding to dose. (right) Any remaining tissue receiving < 29.0 Gy is shown in grey.⁴²

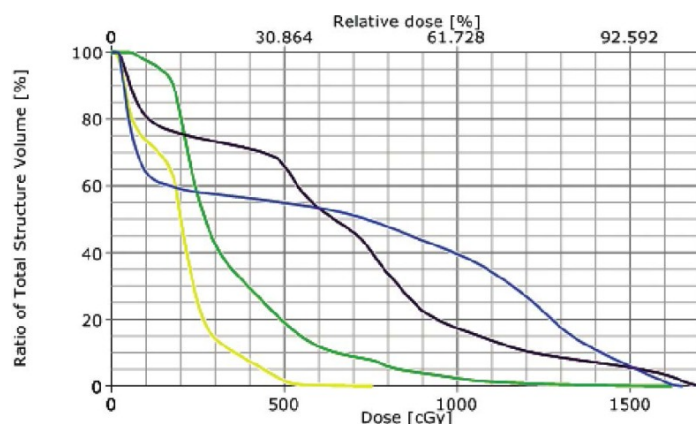


Figure 5 Dose volume histograms (DVHs) used in the assessment of treatment plans. The different lines represent different organs: Yellow-both lungs, green-right lung, blue-left lung, black-heart. These cumulative DVHs shows the % volume of each organ (y-axis) that received the specified radiation dose in cGy (0.01Gy) (x-axis).⁴⁴

Conformal radiotherapy techniques

With the introduction of modern Linacs and the improvement in computer technology and medical imaging, more conformal RT techniques were developed such as 3D-CRT, intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT).

3D-CRT was the first method to be introduced in the mid 1990s. A more sophisticated field arrangement approach than opposing AP-PA was introduced in many cases and the field shape and size were defined by collimators within the Linac head. Lead blocks and later Multi-leaf collimators (MLCs) were used to conform the radiation field around the target volumes and to shield the normal tissue from excessive exposure (Figure 6). Dose distribution homogeneity and normal tissue sparing were improved dramatically and treatment preparation and delivery times were reduced (Figure 7). 3D-CRT still plays a significant role in HL treatment in many countries until today and it has been the gold standard technique for the last two decades.

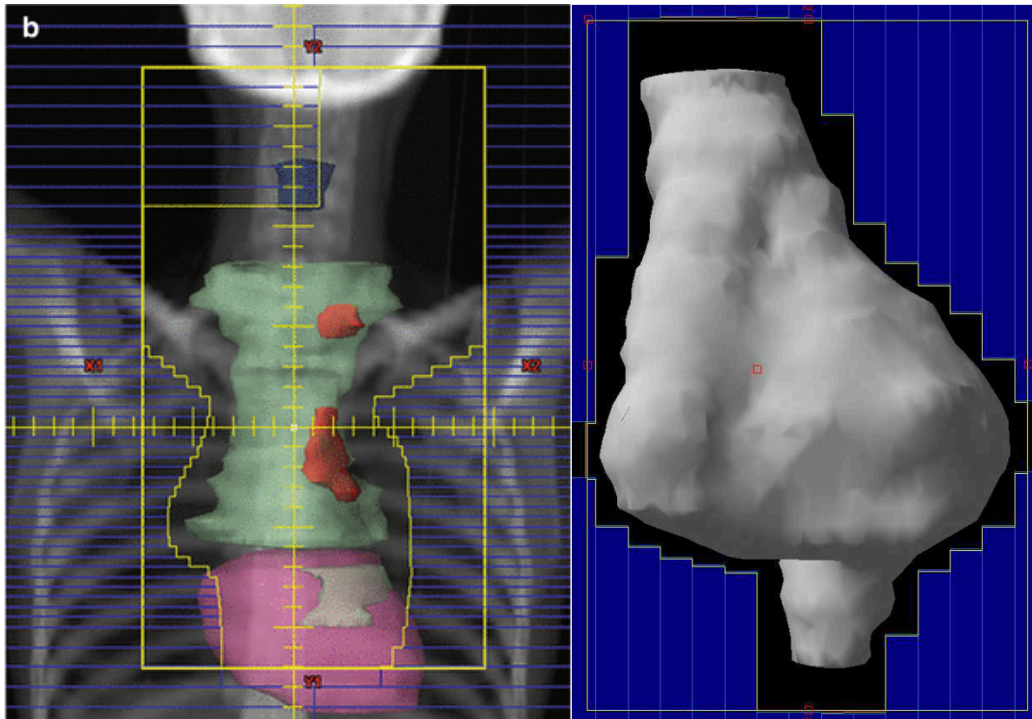


Figure 6 Beams eye view of a 3D-CRT fields. On the left, mediastinal HL case, the MLCs in blue outline are used to shape the field around the target volume (green contour) and to shield part of the heart (in pink) and thyroid (in dark blue). On the right, tumour contoured in grey and the field is shaped with MLCs.^{45,46}

In the early 2000s; IMRT, an advanced form of 3D-CRT, was initially introduced for treatment of prostate and head and neck cancer.^{47,48} IMRT produces highly conformal plans and sharp dose gradients. The radiation intensity varies across the beams, in contrast to the uniform intensity used in 3D-CRT. Each beam is divided into hundreds of beamlets of different energy which enables the construction of a highly conformal and intentionally inhomogeneous dose distribution. The tumour tissue can receive a highly-escalated dose but at the same time normal organs can be spared from high dose even if they extend within the tumour volume, something not possible with uniform-intensity beams.⁴⁵ IMRT was first introduced in HL treatment by Goodman et al.⁴⁹ who demonstrated improved target volume coverage and reduction in normal tissue dose.

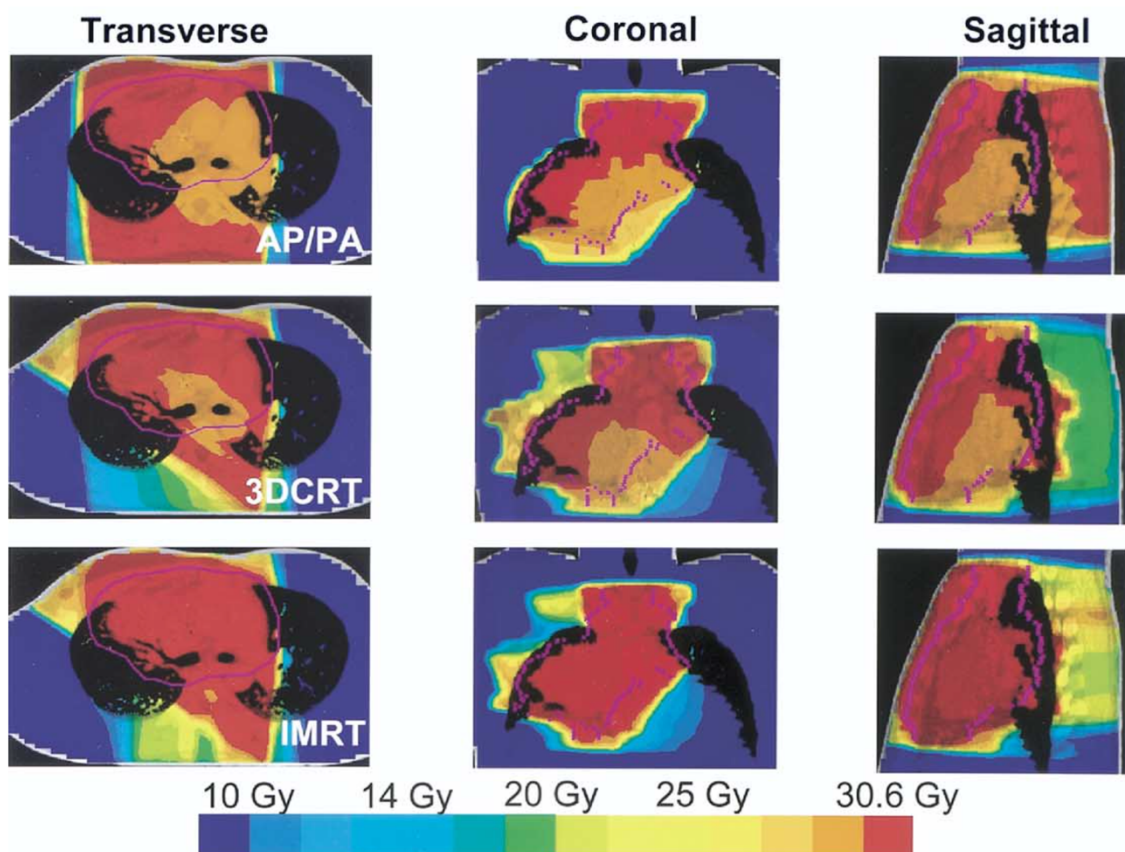


Figure 7 Comparison of dose distributions for (AP–PA) vs. 3D-CRT vs. IMRT treatment plans for a large mediastinal target volume (contoured in pink). It can be seen that IMRT performs superiorly in terms of dose homogeneity within the target volume.⁴⁹

The improvements in treatment quality and dosimetry that IMRT introduced came with the cost of increased overall treatment time. VMAT⁵⁰ was presented as an alternative solution that would maintain the treatment benefits of IMRT but at the same time deliver the treatment more efficiently by using a single dynamically modulated arc instead of the static fields used in IMRT. In VMAT, the prescribed dose is delivered continuously during one or more gantry rotations of 360° allowing for reduced dose delivery times and additional flexibility in dose conformality. The beam intensity and dose rate are modulated throughout the rotation and the MLCs also move continuously, reducing the overall treatment time.

Despite all the improvements in treatment introduced by advanced RT techniques, there is still scepticism regarding their use for the treatment of HL. One of the challenges that both IMRT and VMAT face is the increased amount of normal tissue volume exposed to low-dose radiation (known as a “low dose bath”) compared to 3D-CRT. The increased number of beams used in IMRT and especially in VMAT, as well as the longer ‘beam on’ time result in an increase in lower radiation doses to a larger volume of normal tissue. Although the long-term effects of a low dose bath are not yet fully understood, second malignancies have been linked with low radiation doses in the atomic bomb survivors and in other large studies of populations of RT survivors.⁵¹

In HL, the organs at highest risk of second malignancies are the lungs and female breasts. The main argument against using IMRT or VMAT for the treatment of HL is that the tumours are extremely radiosensitive and do not require high prescribed doses and thus high conformity. For example, in prostate cancer the prescribed doses can reach over 70 Gy and normal organs can potentially receive extremely high doses, far beyond their maximum tolerance. In contrast, the maximum prescription doses for HL are currently 40 Gy and usually do not exceed 30 Gy, which results in lower normal tissue doses. Therefore, the benefits of a highly conformal technique can be limited in that group of patients. However, studies have shown that for a sub-group of HL patients, namely adolescents and young adults with bulky disease, the dose in OAR can be reduced significantly and the overall survival can be improved when using IMRT or VMAT.^{52–54} Further retrospective studies in HL survivors treated with modern RT techniques will be required to determine whether the reduced treatment fields and doses in OAR result in better overall survival and reduced late effects.

Proton radiotherapy

An additional approach to achieving reductions in risks in HL patients is proton RT where steep dose gradients allow more dose conformity around the tumour as well as further reductions in incidental radiation to OAR, i.e. without the 'low dose bath'.⁵⁵ The dose distribution along a single line for proton versus other types of radiation can be seen in Figure 8, where the physical principles of lower ionisation along the beam path and behind the superiority of proton RT in terms of dose deposition and OAR sparing can be clearly seen. The pristine Bragg peak in red (i.e. the maximum dose near the end of range) and the rapid fall of deposited energy demonstrates how proton RT can achieve high dose deposition in the tumour whilst at the same time spare neighbouring OAR. A sum of distinct beams of different energies provides a sum of Bragg peaks which can then be integrated to achieve the so-called spread-out Bragg peak (SOBP) which is used to deposit the dose in the tumour.^{56–58}

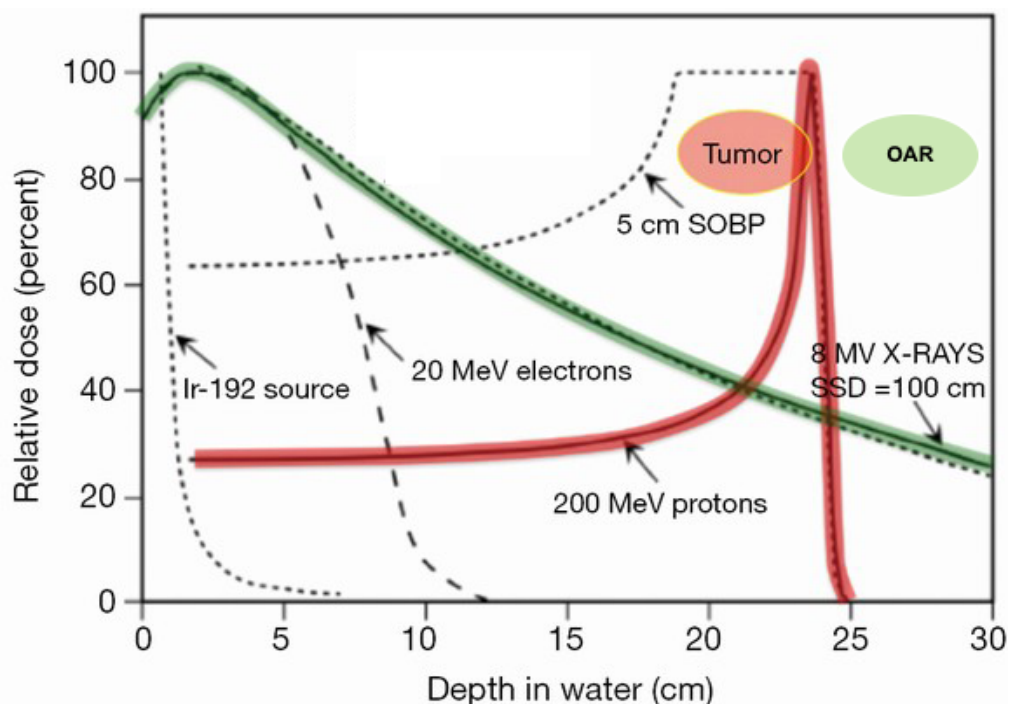


Figure 8 Schematic of percentage depth dose curves for proton beam therapy (red and SOBP) versus other types of radiation. Ir: Iridium, MeV: Mega-electrovolts, MV: Megavoltage, OAR: Organs at risk, SOBP: spread-out Bragg peak; SSD, source-to-skin distance. (Slightly modified figure taken by Giap et al.⁵⁶)

Proton RT is also different from photon RT in terms of cell killing power. The relative biological effectiveness (RBE) for proton RT is estimated at, on average, 1.1 times that for photons. In other terms, it has a 10% higher cancer cell killing capability for each delivered Gy than photon RT.⁵⁸ The use of a fixed RBE of 1.1 for proton RT has been questioned and the discussion is continuing as to whether a variable RBE should be used instead, taking into account uncertainties due to tissue properties, total dose and fractionation.⁵⁸ It is essential to recognise the range uncertainties regarding where the proximal and distal edges of the Bragg peak will be in the patient and to perform treatment planning optimisation and robustness analysis prior to treating with proton RT. However, this topic is beyond the scope of this thesis and, as in current clinical practice, an RBE of 1.1 will be used in the following work. Proton RT can be delivered with two different techniques: passive scattering proton therapy or PBS. In passive scattering, the tumour is irradiated as a whole, using collimators and compensators for dose conformality, a similar principle to that in photon 3D-CRT. With PBS on the other hand, the tumour is scanned spot-by-spot with a narrow proton beam, enabling intensity-modulated proton therapy.^{56–59} There is a substantial amount of evidence for the dosimetric benefits of both proton RT methods in the treatment of HL patients⁵⁵ and the use of PBS in particular is examined later in this thesis.

Further technological advancements

Another technique that has been proven to reduce radiation doses in OAR and specifically in the heart and lungs, is a gating method called deep inspiration breath-hold (DIBH). During RT, patients are asked to take a deep breath for a short period of time (usually between 20 and 30 second) whilst the tumour is getting irradiated. This results in OAR being pushed out of the RT field and therefore receiving lower

doses. Many studies have shown that the use of DIBH during RT, and especially when combined with advanced RT methods such as IMRT and proton RT, resulted in reduced doses on the heart and lungs and consequently a reduction in radiation-related late effects such as CVD and second malignancies.^{60–62} This method can be well tolerated generally in a young and relatively healthy patient group such as HL patients.

Structure of the thesis and research objectives

In this Thesis I investigate the late effects caused by radiation treatment for HL. Firstly, I provide the retrospective dosimetry and medical physics input for a case-control study carried out within a cohort of 2,617 HL survivors. The main aim of this study was to derive the first ever dose-response relationship for risk of CHF in adult survivors of HL. Additionally, I refine and validate this retrospective dosimetry method in order to evaluate its accuracy and the effect of the reconstruction errors in the dose-response relationship. I then propose a methodology to correct already published or future dose-response models for errors in the dose reconstruction.

I then investigate modern RT methods for the treatment of HL to identify which method achieves the highest reductions in incidental radiation in OAR and consequently risks of CVD or second malignancies. In order to conduct the latter, I develop a risk prediction model for cardiovascular and second cancer risks based on epidemiological data from this thesis and from other published studies. A more detailed description of the aims and objectives of each chapter is presented below.

Aims of Chapter 1

To provide the retrospective radiation dosimetry for an international case-control study for the development of the first dose-response relationship for risk of CHF in a cohort of 2,617 HL survivors.

Objectives

- To further develop and optimise the retrospective radiation dosimetry method for use in this and future studies.
- To estimate patient specific cardiac radiation doses for 369 patients (n=91) CHF cases and (n=278) matched controls.
- To perform radiobiological corrections on the doses and validation testing on the dosimetry method.

Justification

Previous research undertaken by researchers from our group in collaboration with researchers from the Netherlands, has pioneered the study of cardiovascular risk following HL radiotherapy. They developed the first dose-response relationships for the risk of CHD and VHD in adult HL survivors.^{10,11} However, HL survivors treated with RT and/or chemotherapy are also known to have increased risks of CHF, but a radiation dose-response relationship has not previously been derived. This study derives a dose-response relationship for the risk of CHF. This will enable estimation of CHF risk for patients before treatment, during RT planning, and during follow-up. It will improve our understanding of radiation-related heart disease overall. It will enable more accurate prediction of cardiac risks for HL patients based on their individual cardiac doses. It will improve HL patient care by enabling treatment regimens to be adapted for future patients and by defining appropriate follow-up care for HL survivors who have received high cardiac doses in the past.

Author's contribution

I performed the radiation dosimetry for this study and estimated the cardiac doses for more than 350 patients. I optimised the representative dosimetry method used in previous studies and performed some physics validation testing. Our collaborators from the Netherlands performed the statistical analysis and used the doses to derive the dose-response relationship. I then prepared a journal article as first co-author with van Nimwegen (shown in Appendix A).

Aims of Chapter 2

To identify the current dose reconstruction methods used in epidemiological studies in order to estimate cardiac doses and evaluate their accuracy and feasibility. To quantify the effect that the cardiac dose reconstruction errors have on the derived dose-response relationships and to provide a methodology for researchers to account for those errors when deriving new dose-response relationships or adjusting the already published. Based on these findings, to evaluate the trade-off between accuracy and complexity for each method as well as their efficiency and feasibility for use in large epidemiological studies.

Objectives

- To use five reconstruction methods to estimate cardiac doses in a group of recently treated HL patients and compare the reconstructed doses versus the 'true doses' derived from the patients' own CT scans.
- To use regression analysis to derive regression models for each reconstruction method. These models will be used to quantify the effect of the dose reconstruction systematic errors on the dose-response relationships.

- To use regression calibration in order to quantify the effect of the dose reconstruction random errors on the dose-response relationships.

Justification

Several dose reconstruction methods for HL patients have been described^{11,63–68} and although their dose prediction accuracy has at times been questioned, it has not previously been investigated. It is important to understand how dosimetry uncertainties might affect the results of dose–response analyses and how they should be accounted for.

Author’s contribution

I performed the dose reconstruction using the three out of five methods investigated in this chapter. The reconstructed doses using the two remaining methods were provided by our collaborators* since access to their methods was not possible. I then performed all the statistical and regression analysis presented in this chapter.

**Doses were kindly provided by Prof Rebecca Howell, Associate Professor of Radiation Physics, The University of Texas (MD Anderson Cancer Centre) and by Prof David Hodgson, University of Toronto, Department of Radiation Oncology, Princess Margaret Hospital.*

Aims of Chapter 3

To perform a dosimetric comparison for 21 HL patients who were treated with PBS proton therapy. To evaluate the dosimetric differences between their clinical PBS treatment plans and planned PartArc and 3D-CRT, all delivered in DIBH. To identify sub-groups of HL patients based on their pre-chemotherapy extent of disease who should be considered for proton RT.

Objectives

- To perform a detailed dosimetric comparison between clinically delivered PBS proton RT versus planned PartArc and 3D-CRT, all in DIBH and evaluate the potential dosimetric benefits or disadvantages of PBS.

- To investigate whether specific characteristics of the irradiated target volume such as thoracic extent of the clinical target volume (CTV), axillary involvement and planning target volume (PTV) can be used to predict which patients would benefit substantially by PBS.

Justification

Proton RT and particularly PBS has been suggested as an option to further reduce radiation doses in OAR in HL patients.⁵⁵ Due to its physical properties, proton beam therapy can have an advantage over conventional photon RT. However, access to it is currently limited and it demands a considerable increase in costs compared to conventional RT. Hence, patient referral to proton RT must be prioritised with the aim of reducing the number of patients going through a detailed treatment planning assessment thus making the selection process more straightforward in a busy healthcare environment with scarce resources. This is the first study to evaluate the dosimetric benefits of clinical PBS delivered in DIBH versus PartArc and to identify HL patients who would benefit particularly by PBS based on their pre-chemotherapy extent of disease.

Author's contribution

I created treatment plans for the patient group in this study using PartArc and 3D-CRT. The patients' CT scans and the PBS treatment plans were provided by our collaborators from Prague where the patients have been previously treated using PBS proton RT. I performed all the analysis described in this chapter.

Aims of Chapter 4

To predict cardiovascular and second cancer mortality risks for 21 HL patients who were treated with PBS proton therapy and chemotherapy. To investigate the potential risk reduction when using PBS compared to photon RT and to investigate how variation in patients' background mortality risk affects the predicted risks from RT and chemotherapy.

Objectives

- To predict background mortality risk for CVD and second cancers for each patient and repeat the calculations using mortality rates from 4 geographical regions (USA, Western Europe, Eastern Europe and Japan).
- To predict RT and chemotherapy-related 30-year cumulative mortality risk for CVD and second cancers for each patient treated with PBS.
- In order to investigate the potential risk reduction from using PBS instead of photon RT, to estimate 30-year cumulative cardiac mortality for each patient as if they had received 3D-CRT and PartArc.

Justification

In order to minimise the long-term RT risks in HL patients by, for example, tailoring their treatment regimens, referring them for specialised therapies such as PBS proton RT or by suggesting lifestyle changes that reduce those risks, it is essential that high risk patients can be identified. The development of a risk prediction model for CVD and second cancer risks which is based on population survival studies, is crucial so that these patients can be accurately identified.

Author's contribution

I performed the whole analysis presented in this chapter.

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Chapter 1 Risk of congestive heart failure in survivors of Hodgkin lymphoma, effects of cardiac exposure to radiation & anthracyclines

1.1 Introduction

With 10-year survival rates of over 80%, HL is a model of a curable malignancy.¹ The efficacy and safety of combined-modality treatment continues to improve, but late effects, including CVD, have caused substantial treatment-related morbidity and mortality in HL survivors treated in the past. Since the early 1990's, when several publications revealed the long term toxicities associated with extended field RT for HL, its use has declined ², but modern RT remains an important component of HL treatment today.

In many cases, understanding of radiation-induced late effects in patients treated with RT requires observational studies. Case-control or cohort studies provide a powerful tool to investigate the risks of disease associated with a specified exposure. If the exposure (e.g. radiation dose) is known and the patient follow-up is long enough for late effects to manifest, those studies can determine radiation dose-response relationships for the late effect of interest. However, when information about radiation doses to normal tissues and organs is not available, retrospective estimation of the radiation doses received must be made. The estimated radiation doses are then used to derive radiation dose-response relationships. Retrospective dosimetry is the only way to produce organ-specific radiation dose-response relationships when dose information is not available.

Retrospective dosimetry poses various challenges. Treatments usually occurred a few decades earlier and crucial patient data such as treatment records and imaging datasets are often not available. Inaccuracies in the estimation of dose to normal tissues are inevitable and it is important that a substantial effort is made

to optimise the methods and account for any inaccuracies. Once reliable dose-response models have been developed, they can be used to provide oncologists and patients with more accurate data regarding the potential risks of treatment so that these can be balanced against the benefits. Scientists and clinicians can use this information for the assessment of risks/benefits in choosing the most appropriate cancer treatment option.

It has been shown that mediastinal RT and/or anthracycline-containing chemotherapy increase the risk of CHD, VHD and CHF in HL survivors.^{1,3–8} A linear dose-response relationship for the risk of radiation-related CHD was previously found in HL survivors, with the excess rate increasing by 7.4% per Gy,³ and a non-linear dose-response relationship was found for VHD, with 1.4, 3.1, 5.4, and 11.8-fold increased VHD rates for doses of ≤ 30 Gy, 31–35 Gy, 36–40 Gy and >40 Gy, respectively.⁴ Mediastinal RT has also been associated with CHF in survivors of both HL and childhood cancer.^{6,9} However, the shape of the radiation dose-response relationship has not previously been described, either for patients who received RT alone, or for patients who received RT in combination with anthracyclines.

This collaborative study determined the shape of the first radiation dose-response relationship for risk of CHF, described the risk of CHF after RT and anthracyclines in long-term adult HL survivors, assessed the contribution of other possible determinants of CHF risk and has already been published (Appendix A - main article).¹⁰ The radiation dosimetry for that study is presented below. The findings of the overall case-control study are also summarised, and future perspectives are discussed.

1.2 Epidemiological context of the dosimetry

This collaborative study took the format of a nested case-control study conducted within an existing multicentre hospital-based cohort (N=2,617) of HL survivors treated in the Netherlands between 1965 and 1995 before the age of 51 years, and who had survived ≥ 5 years after HL diagnosis. The epidemiological data collection was performed by the collaborators at the Netherlands Cancer Institute, Amsterdam. A detailed description of patient selection, data collection and treatments has been published previously^{1,6,11} as well as the assessment of cardiovascular events during follow-up⁶. Briefly, Patients were eligible for this study if: a) they survived at least 5 years after HL diagnosis; b) they were diagnosed with HL before the age of 51 years; c) HL was their first primary malignancy (except for non-melanoma skin cancer, or carcinoma in situ of the cervix uteri or the breast); and d) RT for HL was the only radiotherapy given to the neck or trunk prior to the cut-off date. The cut-off date was defined as date of CHF for the cases, while for each control it was defined as date of HL diagnosis plus a time interval equal to the interval from date of HL diagnosis to date of CHF diagnosis of the corresponding case. A total of (n=91) CHF cases and (n=278) matched controls were selected for this study. The data provided by the Dutch group included RT charts, medical records and RT treatment positioning x-rays. This data was used for the dosimetric work presented below.

1.3 Retrospective radiation dosimetry methods

In the 1960s HL patients were treated with orthovoltage or cobalt-60 therapy and from the 1970s onwards, linear accelerators were used. Patients usually received 40 Gy in fractions varying between 1.0-2.0 Gy when they were treated with RT only and 30-36 Gy in fractions varying between 0.6-2.0 Gy when they received

chemotherapy as well. Mantle field RT including mediastinal, axillary and neck nodes, para-aortic and “inverted-Y” fields (Figure 1-1) were the most commonly applied irradiation from the early 1970s to the late 1980s. Individual blocks were used to shield normal tissues as much as possible. Since the late 1980s, a growing number of patients received more limited radiation fields.

1.3.1 Treatment reconstruction

In order to reconstruct the RT regimens retrospectively, the Eclipse treatment planning system (TPS) (Version 13.0.28, Varian Medical Systems, Palo Alto, CA) was used to develop the dose reconstruction method based on representative CT scans (RepCT). Two substitute CT data sets (1 male and 1 female) were chosen from a library of 50 patients (25 male and 25 female) to be representative regarding anatomy (in terms of mediastinal separation and heart volume) and typical estimated MHD from a standardized 8 mega-voltage (MV) mantle field. The heart and sub-structures of the heart were outlined by a clinical oncologist as per published guidelines.¹² Treatment planning variables such as prescribed dose, fractionation regime, beam arrangement, energy, field size and field shielding were extracted from the patients’ original RT prescription cards (Figure 1-2).

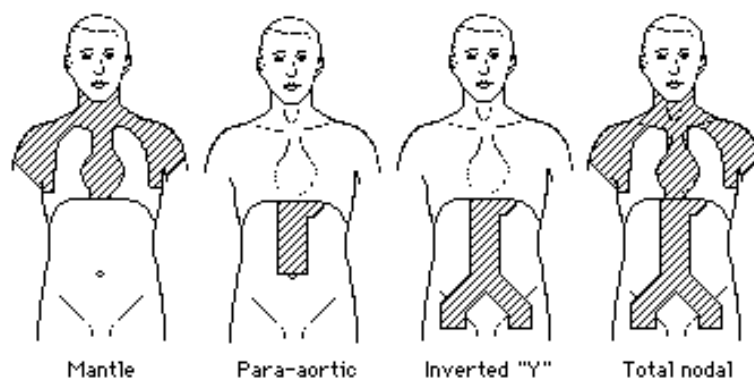
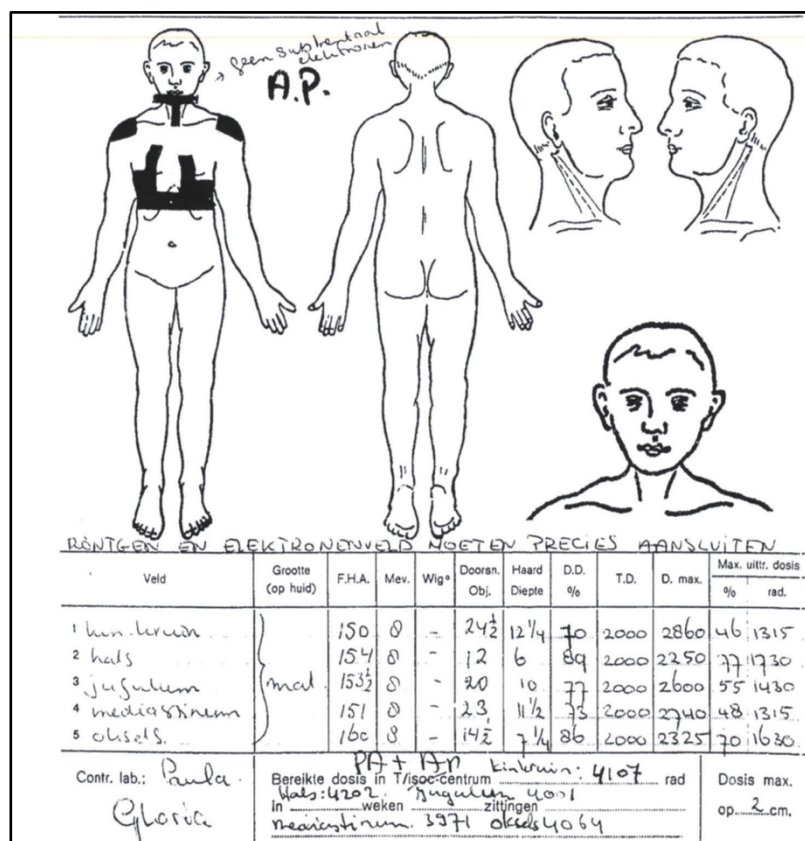


Figure 1-1 Commonly used radiation fields for HL treatment (Source: www.med-ed.virginia.edu/courses/path/innes/wcd/hodgclinic.cfm - visited December 2015)



VELD	1 Kin. kluin	2 Hals	3 Jugulum	4 Mediastinum
F.H.A./Veldgrootte	150 / mal	154 / mal	153 1/2 / mal	151 / mal
Sec/ME per 100-MPD	101.20 x 100 = 31.8	61.89 x 100 = 38.4	101.77 x 100 = 33.5	101.73 x 100 = 32.8
Bloed of Folio				
Datum				
Aantal bestr. dagen				
Nr. bestr.				
Sec/ME				
TD. per bestr.				
TD. totaal				
Sec/ME				
TD. per bestr.				
TD. totaal				
21000-400000-9-74	1 1	200 64 64	200 77 77	200 67 67
12-9-74	2	400 127 191	400 154 231	400 134 201
16-800-350-000-3-9-74	3 3	677 215 406	677 260 491	677 227 428
16-9-74	4 4	677 215 406	677 260 491	677 227 428
17-9-74	5 5	677 215 406	677 260 491	677 227 428
18-9-74	6 6	677 215 406	677 260 491	677 227 428
19-9-74	7 7	677 215 406	677 260 491	677 227 428
20-9-74	8 8	677 215 406	677 260 491	677 227 428
21-9-74	9 9	677 215 406	677 260 491	677 227 428
22-9-74	10 10	677 215 406	677 260 491	677 227 428
23-9-74	11 11	677 215 406	677 260 491	677 227 428
24-9-74	12 12	677 215 406	677 260 491	677 227 428
25-9-74	13 13	677 215 406	677 260 491	677 227 428
26-9-74	14 14	677 215 406	677 260 491	677 227 428
27-9-74	15 15	677 215 406	677 260 491	677 227 428
28-9-74	16 16	677 215 406	677 260 491	677 227 428
29-9-74	17 17	677 215 406	677 260 491	677 227 428
30-9-74	18 18	677 215 406	677 260 491	677 227 428
31-9-74	19 19	677 215 406	677 260 491	677 227 428
1-10-74	20 20	677 215 406	677 260 491	677 227 428
2-10-74	21 21	677 215 406	677 260 491	677 227 428
3-10-74	22 22	677 215 406	677 260 491	677 227 428
4-10-74	23 23	677 215 406	677 260 491	677 227 428
5-10-74	24 24	677 215 406	677 260 491	677 227 428
6-10-74	25 25	677 215 406	677 260 491	677 227 428
7-10-74	26 26	677 215 406	677 260 491	677 227 428
8-10-74	27 27	677 215 406	677 260 491	677 227 428
9-10-74	28 28	677 215 406	677 260 491	677 227 428
10-10-74	29 29	677 215 406	677 260 491	677 227 428
11-10-74	30 30	677 215 406	677 260 491	677 227 428
12-10-74	31 31	677 215 406	677 260 491	677 227 428
13-10-74	32 32	677 215 406	677 260 491	677 227 428
14-10-74	33 33	677 215 406	677 260 491	677 227 428
15-10-74	34 34	677 215 406	677 260 491	677 227 428
16-10-74	35 35	677 215 406	677 260 491	677 227 428
17-10-74	36 36	677 215 406	677 260 491	677 227 428
18-10-74	37 37	677 215 406	677 260 491	677 227 428
19-10-74	38 38	677 215 406	677 260 491	677 227 428
20-10-74	39 39	677 215 406	677 260 491	677 227 428
21-10-74	40 40	677 215 406	677 260 491	677 227 428
22-10-74	41 41	677 215 406	677 260 491	677 227 428
23-10-74	42 42	677 215 406	677 260 491	677 227 428
24-10-74	43 43	677 215 406	677 260 491	677 227 428
25-10-74	44 44	677 215 406	677 260 491	677 227 428
26-10-74	45 45	677 215 406	677 260 491	677 227 428
27-10-74	46 46	677 215 406	677 260 491	677 227 428
28-10-74	47 47	677 215 406	677 260 491	677 227 428
29-10-74	48 48	677 215 406	677 260 491	677 227 428
30-10-74	49 49	677 215 406	677 260 491	677 227 428
31-10-74	50 50	677 215 406	677 260 491	677 227 428
1-11-74	51 51	677 215 406	677 260 491	677 227 428
2-11-74	52 52	677 215 406	677 260 491	677 227 428
3-11-74	53 53	677 215 406	677 260 491	677 227 428
4-11-74	54 54	677 215 406	677 260 491	677 227 428
5-11-74	55 55	677 215 406	677 260 491	677 227 428
6-11-74	56 56	677 215 406	677 260 491	677 227 428
7-11-74	57 57	677 215 406	677 260 491	677 227 428
8-11-74	58 58	677 215 406	677 260 491	677 227 428
9-11-74	59 59	677 215 406	677 260 491	677 227 428
10-11-74	60 60	677 215 406	677 260 491	677 227 428
11-11-74	61 61	677 215 406	677 260 491	677 227 428
12-11-74	62 62	677 215 406	677 260 491	677 227 428
13-11-74	63 63	677 215 406	677 260 491	677 227 428
14-11-74	64 64	677 215 406	677 260 491	677 227 428
15-11-74	65 65	677 215 406	677 260 491	677 227 428
16-11-74	66 66	677 215 406	677 260 491	677 227 428
17-11-74	67 67	677 215 406	677 260 491	677 227 428
18-11-74	68 68	677 215 406	677 260 491	677 227 428
19-11-74	69 69	677 215 406	677 260 491	677 227 428
20-11-74	70 70	677 215 406	677 260 491	677 227 428
21-11-74	71 71	677 215 406	677 260 491	677 227 428
22-11-74	72 72	677 215 406	677 260 491	677 227 428
23-11-74	73 73	677 215 406	677 260 491	677 227 428
24-11-74	74 74	677 215 406	677 260 491	677 227 428
25-11-74	75 75	677 215 406	677 260 491	677 227 428
26-11-74	76 76	677 215 406	677 260 491	677 227 428
27-11-74	77 77	677 215 406	677 260 491	677 227 428
28-11-74	78 78	677 215 406	677 260 491	677 227 428
29-11-74	79 79	677 215 406	677 260 491	677 227 428
30-11-74	80 80	677 215 406	677 260 491	677 227 428
1-12-74	81 81	677 215 406	677 260 491	677 227 428
2-12-74	82 82	677 215 406	677 260 491	677 227 428
3-12-74	83 83	677 215 406	677 260 491	677 227 428
4-12-74	84 84	677 215 406	677 260 491	677 227 428
5-12-74	85 85	677 215 406	677 260 491	677 227 428
6-12-74	86 86	677 215 406	677 260 491	677 227 428
7-12-74	87 87	677 215 406	677 260 491	677 227 428
8-12-74	88 88	677 215 406	677 260 491	677 227 428
9-12-74	89 89	677 215 406	677 260 491	677 227 428
10-12-74	90 90	677 215 406	677 260 491	677 227 428
11-12-74	91 91	677 215 406	677 260 491	677 227 428
12-12-74	92 92	677 215 406	677 260 491	677 227 428
13-12-74	93 93	677 215 406	677 260 491	677 227 428
14-12-74	94 94	677 215 406	677 260 491	677 227 428
15-12-74	95 95	677 215 406	677 260 491	677 227 428
16-12-74	96 96	677 215 406	677 260 491	677 227 428
17-12-74	97 97	677 215 406	677 260 491	677 227 428
18-12-74	98 98	677 215 406	677 260 491	677 227 428
19-12-74	99 99	677 215 406	677 260 491	677 227 428
20-12-74	100 100	677 215 406	677 260 491	677 227 428

Figure 1-2 Individual patient radiotherapy prescription chart, a schematic presentation of the patient treatment position (top) and treatment planning information used for the fields reconstruction (bottom). The varied fractionation scheme (0.66Gy, 1.31Gy, 2.22Gy etc.) can be seen in the red box in bottom right.

This information and the original simulation films were used to reconstruct the treatments for 91 cases and 278 controls for each patient individually without

knowing whether the patient was a case or a control. The block borders, indicated on the simulation films (Figure 1-3), were used as a guide to reconstruct the fields in the modern treatment planning software. Most patients required two mantle fields, one anterior (AP) and one posterior (PA), however, some patients required additional para-aortic or “inverted-Y” fields. Bringing the total number of fields for which reconstruction was needed to up to 8 for some patients and to about 1150 in total. Due to the large number of fields required reconstruction, various template fields were created to improve the efficiency of the planning process. These templates were then used as the starting point for each patient and then adjusted, reducing the amount of time required for each plan but at the same time maintaining the individuality for each patient. For some patients who received mediastinal and para-aortic fields, it was common clinical practice at that time, to shift the inferior field border of the mediastinal field up and down during treatment, usually in the middle of the total treatment duration, to minimize the dosimetric uncertainties and hot spots of the field junction with the para-aortic field. This was incorporated in the reconstruction technique as the junctions often included the apex of the heart. An example of a simple mantle field reconstruction can be seen in (Figure 1-3).

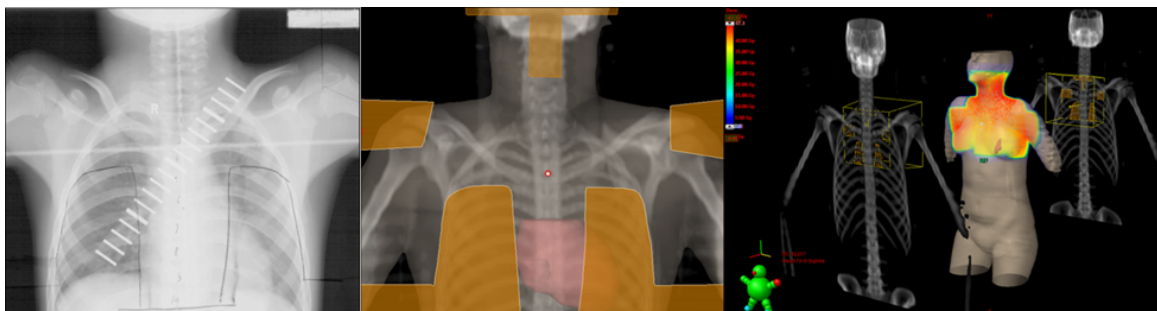


Figure 1-3 An example of original and reconstructed field for mantle field HL radiotherapy. The original simulation films were used for patient position verification during HL radiotherapy treatment from the 1960s to 1990, the lung block borders marked in black (left). The reconstructed field using Eclipse TPS on the substitute CT data set was overlaid on a digitally reconstructed radiograph, block borders marked in orange (middle). The two fields, anterior and posterior and dose distribution seen on the patient in a 3D reconstruction with high and low dose distributions represented in red and yellow respectively (right).

The dose distributions from all fields were then summed and cardiac doses were extracted for each patient individually. MHD and mean left ventricular doses (MLVD) were calculated. The volume of the whole heart and left ventricle receiving at least 20 or 30 Gy (V20 and V30 respectively) were also calculated and expressed in percentages. When neither the radiation chart nor the simulation film was available, MHD and MLVD were imputed with an average value derived from the rest of the patients based on hospital, treatment period, sex, and radiation field. Imputation was needed for 120 individuals; therefore, a sensitivity analysis was performed.

1.3.2 Dose calculation

The Anisotropic Analytical Algorithm (AAA) photon dose calculation model in Eclipse TPS (Palo Alto (CA): Varian Medical Systems) was used to calculate the dose distributions for patients who received RT using a linear accelerator (95.0%). The pencil beam convolution (PBC) algorithm dose calculation model was used for the patients who received RT using a cobalt-60 unit (5.0%). The AAA is a more accurate algorithm than the PBC in calculating dose distributions especially in heterogeneous and low density tissue such as lung, as it accounts for lateral electron transfer.¹³ However, cobalt-60 is an older treatment and AAA algorithm for it was not available in Eclipse TPS.

1.3.3 Data export

Due to the large number of dose volume histograms (DVHs) that needed to be exported, an automated process was devised. Dose cubes were exported for all patients from the TPS as Digital Imaging and Communications in Medicine (DICOM) files. The DICOM files were then imported into the CERR platform (www.cerr.info)

in MATLAB software (The MathWorks, Natick, MA; version 8.4 release: R2014b) to produce DVHs for the whole heart and the left ventricle.

1.3.4 Dose adjustment for fractionation and dose distribution.

The DVHs provided the physical doses for the whole heart and left ventricle for each patient. However, fractionation and prescribed dose varied considerably in historical treatments. Fraction size variation was observed even within one individual treatment course (Figure 1-2) which increased the complexity and volume of calculation needed.

Fractionation size is known as an important determinant for late effects.¹⁴ Therefore, the physical mean dose was converted into equivalent dose in 2-Gy fractions ($EQD2_{\alpha/\beta}$) according to the linear quadratic (LQ) model, for each fraction separately and then summed. $EQD2_{\alpha/\beta}$ accounts for the fraction dose as well as the tissue specific α/β ratio. The α/β ratio determines the shape of the cell survival curves in the LQ model and it accounts for the differences in reaction to radiation between early responding (tumours) and late responding tissue (normal organs at risk).^{14–18} Late responding tissues have a ratio between 1-4 Gy while for early responding tissue the ratio is closer to 10 Gy.¹⁵ $EQD2_{\alpha/\beta}$ was used for the analyses to produce the dose-response models.

An additional consideration in the dose correction was the fact that, in the past, mantle RT was administered anteriorly and posteriorly on separate days with the patient changing from supine to prone position, rather than delivering both fields at the same day as in modern RT. To account for this variation in dose distributions, the physical dose was converted into $EQD2_{\alpha/\beta}$ for each field separately and for each sub-volume of the whole heart or relative substructure. These quantities were then

summed extending over all dose bins in the structure DVH and in 0.1 Gy steps.^{16,18}

The equations used can be seen below:

$$(EQD2_{\alpha/\beta}) = Di \times \frac{(di + \alpha/\beta)}{2 + \alpha/\beta} \quad \text{Equation 1-1}$$

$$BED = Di \times \left[1 + \left(\frac{di}{\alpha/\beta} \right) \right] \quad \text{Equation 1-2}$$

where D_i the total absolute dose to the relevant organ, d_i the dose per fraction and α/β was assumed to be 2 for late cardiac effects.¹⁹

The summation ($EQD2_{\text{sum}}$) of the $EQD2_i$ to the relative organ's sub-volume v_i for number n of 0.1 Gy steps was:

$$EQD2_{\text{sum}} = \sum_{i=1}^n (EQD2_i * v_i) \quad \text{Equation 1-3}$$

When fraction size varied during treatment, $EQD2_{\alpha/\beta}$ was calculated separately for each fraction before summation.

1.3.5 Beam Model

Most patients in the study were treated with a linear accelerator using 8 MV beam energy and 5% of them were treated with a Cobalt-60 unit. Lack of the original beam characterisation data may introduce further uncertainties in the dose reconstruction. The TPS used for the dose reconstruction (Eclipse) did not have a commissioned 8 MV beam data model installed and this initially was identified as a potential source of uncertainty. Therefore an 8 MV model (Oxford BM) was produced by interpolation between the standard 6 MV and 10 MV Varian beam models. Before any planning work was undertaken for this study the Oxford BM model was compared with two clinically commissioned 8 MV beam models. The full dataset of the original 8 MV beam model used from the early 1980s during treatment for some of the patients in this cohort (Dutch BM) was retrieved from one of the treating hospitals in the Netherlands (Leiden University Medical Centre). The second 8 MV beam model

used in the comparison was acquired from Varian Medical Systems, Palo Alto, CA and had been produced by measurements using modern dosimetry equipment.

1.4 Dosimetry results

1.4.1 Beam model validation results

Percentage depth dose (PDD) curves for field sizes of 5x5, 10x10, 20x20 and 30x30 cm² were compared between the three models. Beam profiles were also compared for the same field sizes in depths of 2 cm, 5 cm, 10 cm and 20 cm. A sample of the results for the most commonly field sizes in this study is shown in Figure 1-4 and Figure 1-5, the full results are presented in appendix A, in “Further beam model analysis”. The agreement between the beam profiles and PDDs for the three beam models was within 3% for all relevant field sizes and depths which is within acceptable dosimetric levels of accuracy even in modern clinical RT.²⁰ Thus it was assumed that the interpolated beam model did not introduce any significant inaccuracies in the dose calculation compared to the original beam model.

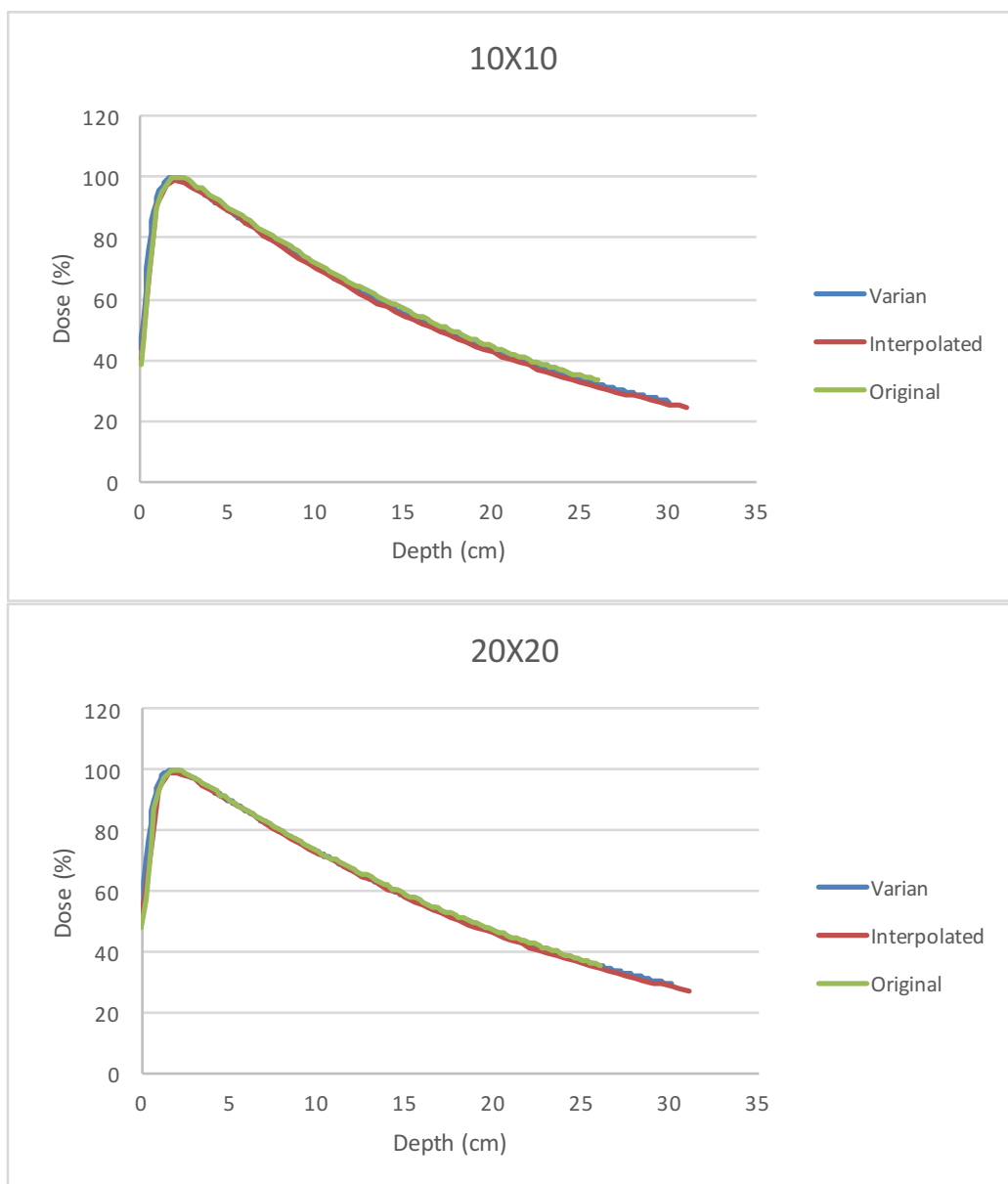


Figure 1-4 Percentage depth dose curve comparison between three 8 MV beam models. Square field size of 10X10 cm² (top) and 20X20 cm² (bottom) both at 100cm source to surface distance (SSD).

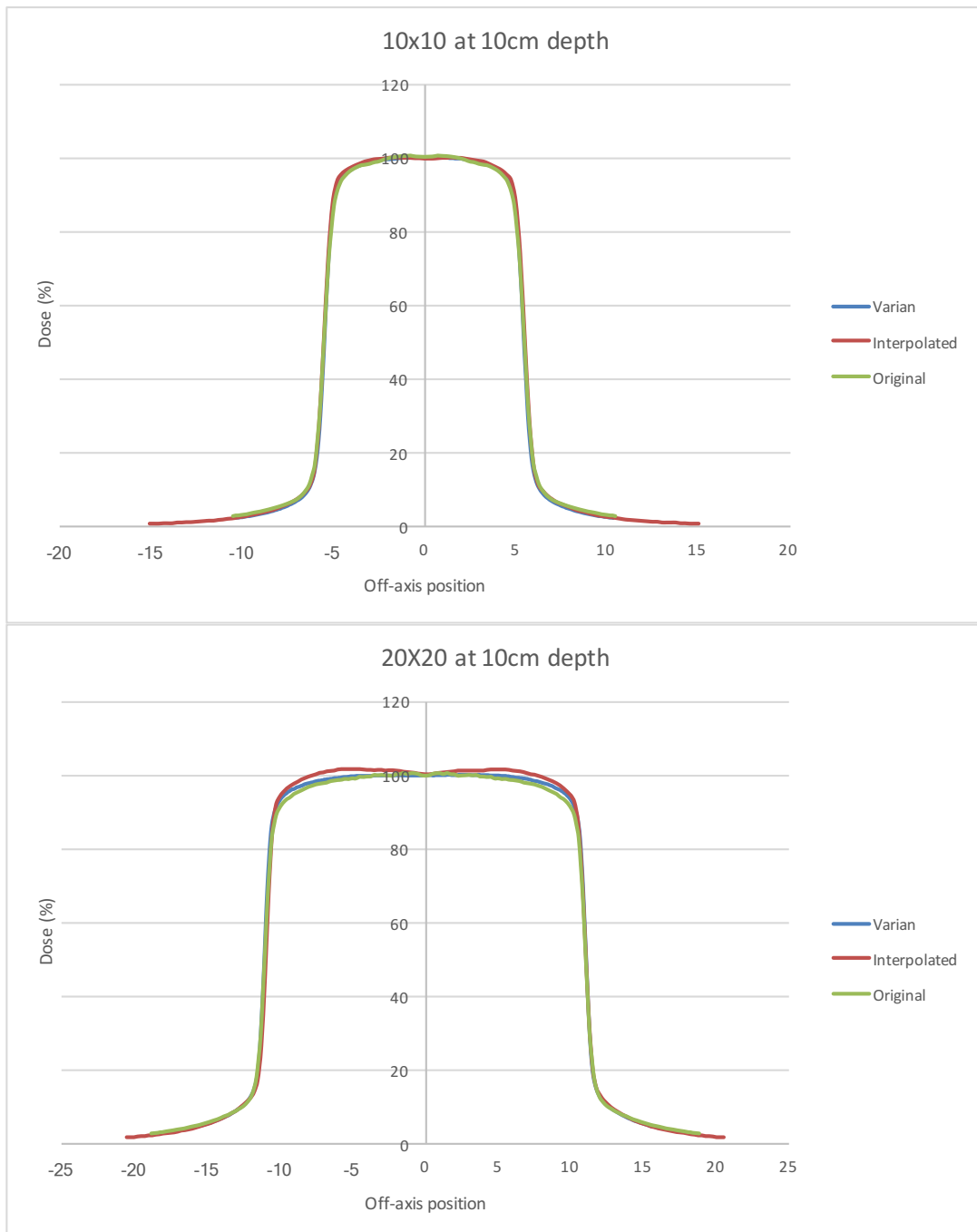


Figure 1-5 Beam profile comparison between three 8 MV beam models. Square field size 10X10 cm² (top) and 20X20 cm² (bottom) at 10 cm depth.

1.4.2 Radiation dosimetry results

For patients given mediastinal RT, the median prescribed dose was 36.2 Gy, the median MHD was 23.3 Gy whilst the median MLVD was 15.4 Gy. The median V30 and V20 for the left ventricle were 40.8 % and 49.7 % respectively. Detailed dosimetry results for cases and controls separately can be seen in (Table 1-1).

Table 1-1 Dosimetry results for all cases and controls

Dosimetric Parameter	Cases (n=91)		Controls (n=278)	
Prescribed mediastinal dose				
Average Gy (SD)	32.7	12.2	29.8	(14.6)
Median Gy (IQR)	37	32-40	36	(30-40)
MHD (EQD2)				
Average Gy (SD)	23.2	(9.6)	20.1	(10.0)
Median Gy (IQR)	25.8	(18.8-30.0)	22.5	(16.7-27.2)
MLVD (EQD2)				
Average Gy (SD)	16.7	(8.8)	13.8	(7.9)
Median Gy (IQR)	16.5	(11.9-21.9)	15.1	(8.4-19.1)
V30 for the left ventricle (%) [¶]				
Average % (SD)	40.8	(24.7)	33.9	(23.7)
Median % (IQR)	42.8	(24.8-54.7)	40.1	(13.1-49.4)
V20 for the left ventricle (%) [¶]				
Average % (SD)	49.2	(26.3)	41.6	(26.4)
Median % (IQR)	53.2	(33.3-63.3)	48.5	(26.9-57.2)

MHD: Mean heart dose, MLVD: Mean left ventricular dose, SD: standard deviation; IQR: Interquartile range; EQD2: 2-Gray equivalent dose; [¶] V30 and V20 are the percentages of the left ventricle volume that received at least 30 and 20 Gy respectively

The MHD and the MLVD were strongly correlated (cor. coefficient = 0.93) and the MLVD was consistently lower than MHD for both cases and controls (Figure 1-6).

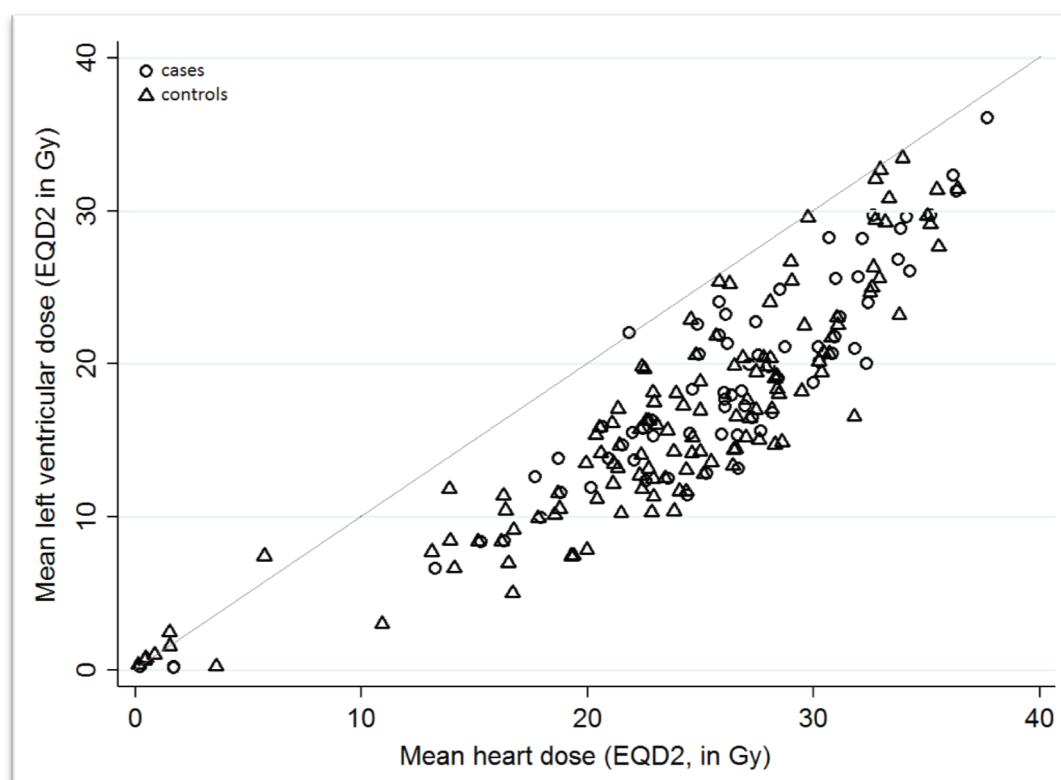


Figure 1-6 Scatterplot of mean left ventricular dose versus MHD (EQD2)

Since MHD and MLVD were imputed for some patients for whom radiation charts and sim films were not available, a sensitivity analysis was performed. The risks for CHF were re-estimated including only patients for whom radiation charts and sim films were available and the results were similar with the original analysis. (see Appendix A, Supplemental Document, Table 3 and Supplemental Figure 2)

1.5 Combining the dosimetry results with the epidemiological data

1.5.1 Dose-response relationships

The reconstructed cardiac doses from this cohort were used to estimate dose-response relationships between radiation dose (MHD and MLVD) and risk of CHF. Rate ratios (RRs) for CHF were estimated using logistic regression, conditional on sets of individual cases and their matched controls. Some of the patients were used both as cases and controls for a different case. The dose-response was estimated by modelling CHF rate as $K_m * (1 + \beta * d)$ where K_m is a constant specific to each matched set, d is radiation dose and β is the increase in excess CHF relative rate per unit increase in dose. Nonlinearity was evaluated by including an exponential term: $K_m * [1 + \beta * d * e^{(\delta d)}]$ and goodness of fit assessed by likelihood ratio tests. Significance tests were two-sided and $p \leq 0.05$ was taken to indicate statistical significance. Analyses were performed using STATA statistical software version 13.0 (STATA corp. 2013) and Epicure version 1.8 (Hirosoft International).

For all five dosimetric parameters, CHF rate increased with increasing dose for all different dose categories. (Table 1-2) Prescribed mediastinal dose: $p_{\text{trend}}=0.027$, MHD: $p_{\text{trend}}=0.002$, MVLD: $p_{\text{trend}} < 0.001$), V30: $p_{\text{trend}}=0.021$ and V20: $p_{\text{trend}}=0.006$. The trend test was based on median value of the radiation dose in each dose category.

Table 1-2 Association between dosimetric parameters and CHF risk.

Dosimetric Parameters	Cases (n=91)		Controls (n=278)		RR*	95%CI
Radiotherapy	<i>N</i>	%	<i>N</i>	%	$p_{\text{trend}}^{\wedge} = 0.020$	
No RT to mediastinum or PAO	7	7.7	33	11.9	1.00	0.40-2.50
PAO-RT, no mediastinal RT	2	2.2	16	5.8	0.66	0.15-2.98
Mediastinal RT, no PAO-RT	39	42.9	126	45.3	1.87	1.27-2.75
Mediastinal RT & PAO-RT	43	47.2	103	37.0	2.59	1.80-3.72
Prescribed mediastinal dose	<i>N</i>	%	<i>N</i>	%	$p_{\text{trend}}^{\wedge} = 0.027$	
0 Gy (no mediastinal RT)	9	9.9	49	17.6	1.00	0.45-2.23
20-34 Gy (median 32 Gy)	15	16.5	45	16.2	2.35	0.85-6.46
35-39 Gy (median 36 Gy)	34	37.4	113	40.7	2.10	0.86-5.13
≥40 Gy (median 40 Gy)	33	36.3	71	25.5	3.02	1.23-7.40
MHD	<i>N</i>	%	<i>N</i>	%	$p_{\text{trend}}^{\wedge} = 0.002$	
0 Gy	7	7.7	29	10.4	1.00	0.39-2.55
1-20 Gy (median 16 Gy)	21	22.2	70	24.4	1.43	0.83-2.50
21-25 Gy (median 23 Gy)	20	22.2	102	37.1	1.03	0.63-1.67
26-30 Gy (median 28 Gy)	27	30.0	57	20.7	2.78	1.69-4.59
≥31 Gy (median 33 Gy)	16	17.8	20	7.3	4.16	2.14-8.10
MLVD	<i>N</i>	%	<i>N</i>	%	$p_{\text{trend}}^{\wedge} < 0.001$	
0 Gy	7	7.7	29	10.4	1.00	0.39-2.55
1-15 Gy (median 13 Gy)	36	39.5	144	51.8	1.27	0.86-1.89
16-20 Gy (median 19 Gy)	20	22.0	68	24.5	1.65	0.98-2.77
21-25 Gy (median 23 Gy)	16	17.6	23	8.3	3.84	1.97-7.47
≥26 Gy (median 30 Gy)	12	13.2	14	5.1	4.39	2.00-9.65
V30 for the left ventricle (%)[¶]	<i>N</i>	%	<i>N</i>	%	$p_{\text{trend}}^{\wedge} = 0.021$	
0%	9	9.9	35	12.6	1.00	0.48-2.10
1-24% (median 12%)	17	18.7	60	21.6	0.95	0.52-1.71
25-49% (median 40%)	33	36.3	121	43.5	1.05	0.70-1.58
50-74% (median 60%)	23	25.3	51	18.3	1.80	1.12-2.91
75-100% (median 84%)	9	9.9	11	4.0	3.22	1.32-7.86
V20 for the left ventricle (%)[¶]	<i>N</i>	%	<i>N</i>	%	$p_{\text{trend}}^{\wedge} = 0.006†$	
0%	8	8.8	32	11.5	1.00	0.45-2.23
1-24% (median 5%)	4	4.4	33	11.9	0.27	0.06-1.11
25-49% (median 39%)	28	30.7	87	31.3	1.38	0.89-2.14
50-74% (median 58%)	35	38.5	98	35.3	1.51	0.99-2.28
75-100% (median 86%)	16	17.6	28	10.1	2.50	1.33-4.69

MHD: Mean heart dose, MLVD: Mean left ventricular dose, RT: radiotherapy; PAO: para-aortic; RR: rate ratio.

[¶] V30 and V20 are the percentages of the left ventricle volume that received at least 30 and 20 Gy respectively

For MHD there was a statistically significant linear dose-response relationship ($p=0.006$) and allowing for curvature improved the fit significantly ($p<0.001$) (Figure 1-7, top). For MLVD, there was a statistically significant linear dose-response relationship ($p=0.004$) and allowing for curvature did not significantly improve the fit ($p=0.09$) (Figure 1-7, bottom). There was little evidence of an

increase for MHDs in the range of 1-25 Gy but increased steeply with MHDs of ≥ 25.0 Gy. For MLVD, there was little increase for doses up to 15.0 Gy but also increased steeply for MLVD > 15.0 Gy. The risk estimates were performed for the following dose categories: MHD: 0 Gy, 1-20 Gy, 20-25 Gy, 26-30 Gy, ≥ 31 Gy; MLVD: 0 Gy, 1-15 Gy, 16-20 Gy, 21-25 Gy, ≥ 26 Gy. They were plotted at the median dose in each dose category (0 Gy, 16.0 Gy, 23.0 Gy, 28.0 Gy, and 33.0 Gy for MHD and 0 Gy, 13.0 Gy, 19.0 Gy, 23.0 Gy, and 30.0 Gy for MLVD). Vertical lines representing the 95% confidence intervals (CI) were also plotted on the dose-response relationships (Figure 1-7). When the analysis was repeated omitting patients for whom neither radiation chart nor simulation films were available the results were similar.

The only other factor significantly associated with CHF rate apart from radiation dose was whether or not anthracyclines-containing chemotherapy was used. Potential interaction between radiation and anthracyclines was investigated but no significant multiplicative interaction was observed. The association with other classical CVD risk factors such as diabetes mellitus and obesity was also examined however no significant association was found.

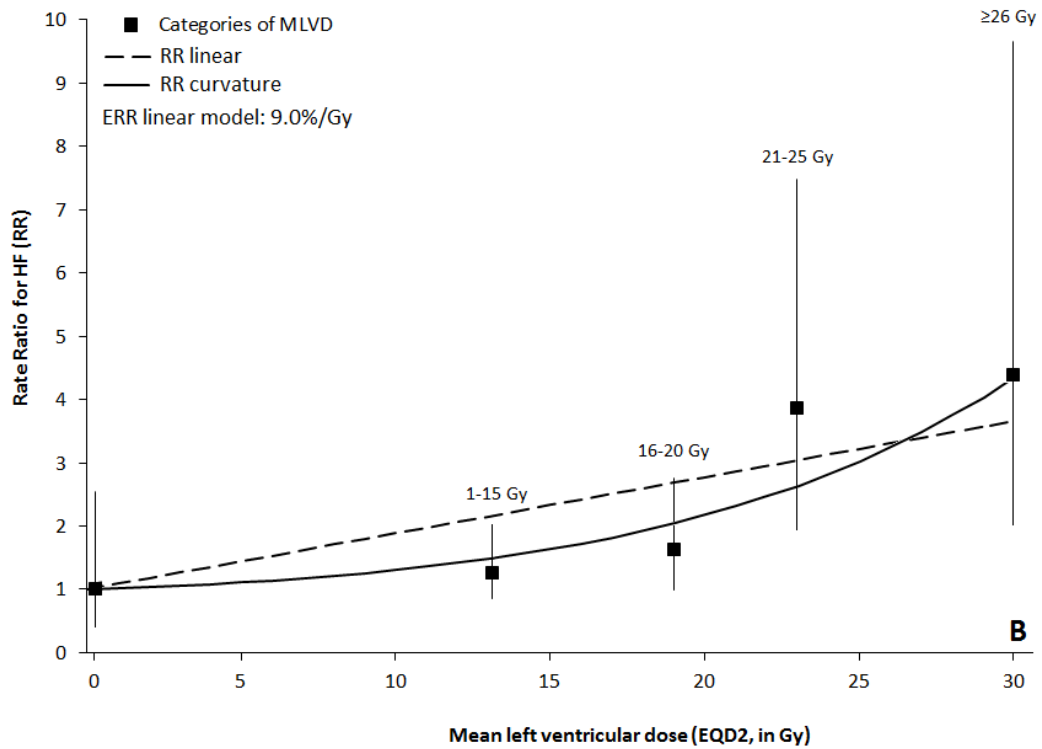
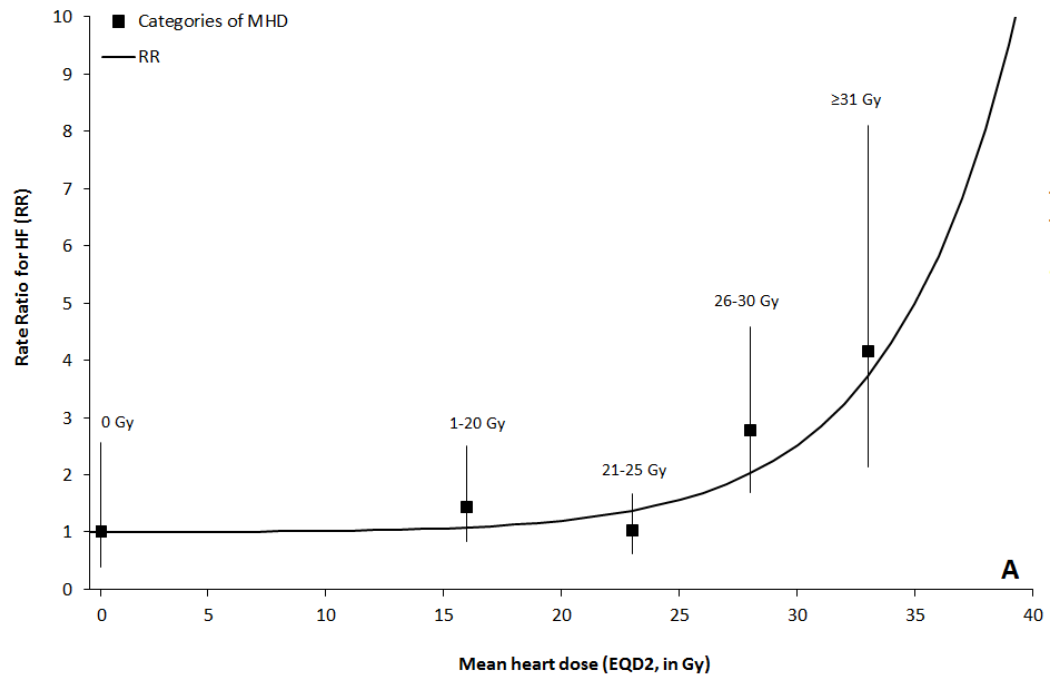


Figure 1-7 Relationship between RRs for CHF by MHD (top) and by MLVD (bottom) in Gy compared with no radiation exposure.

1.5.2 Cumulative risk of congestive heart failure

Cumulative risk of CHF rates was estimated based on three broad categories of MLVD: 0-15 Gy, 16-20 Gy, and ≥ 21 Gy and whether or not anthracyclines had been given, with the assumption that the multiplicative increase in CHF rate with anthracyclines did not differ according to MLVD. For the resulting six groups the RRs are given on Table 1-3.

Table 1-3 Estimated congestive heart failure rates by mean left ventricular dose and anthracycline treatment

	No anthracyclines (N=279)		With anthracyclines (N=90)	
MLVD	RR	95%CI	RR	95%CI
0-15Gy	1.00	0.68-1.47	2.60	1.21-5.58
16-20Gy	1.43	0.85-2.44	3.74	1.31-10.73
≥ 21 Gy	3.10	1.87-5.14	8.06	3.05-21.32

MLVD: Mean left ventricular dose; RR: Rate ratio; CI: Confidence intervals

Approximate cumulative incidence curves for CHF as first cardiac event among five-year survivors of HL by time since initial HL treatment, were derived for patients in these six groups. Cumulative risks were calculated with other heart disease or death as a competing risk. Further details are given in the main article in Appendix A. In patients treated without anthracyclines, 25-year cumulative risks of CHF following MLVDs of 0-15 Gy, 16-20 Gy, and ≥ 21 Gy were 4.4%, 6.2% and 13.3%, while in patients treated with anthracyclines the 25-year cumulative risks were 11.2%, 15.9% and 32.9%, respectively. For patients treated without anthracyclines, 35-year cumulative risks of CHF following MLVDs of 0-15 Gy, 16-20 Gy, and ≥ 21 Gy were 7.2%, 10.2%, 21.8%, respectively (Figure 1-8). Patients treated with anthracyclines have not yet been followed for long enough to estimate risks beyond 25 years.

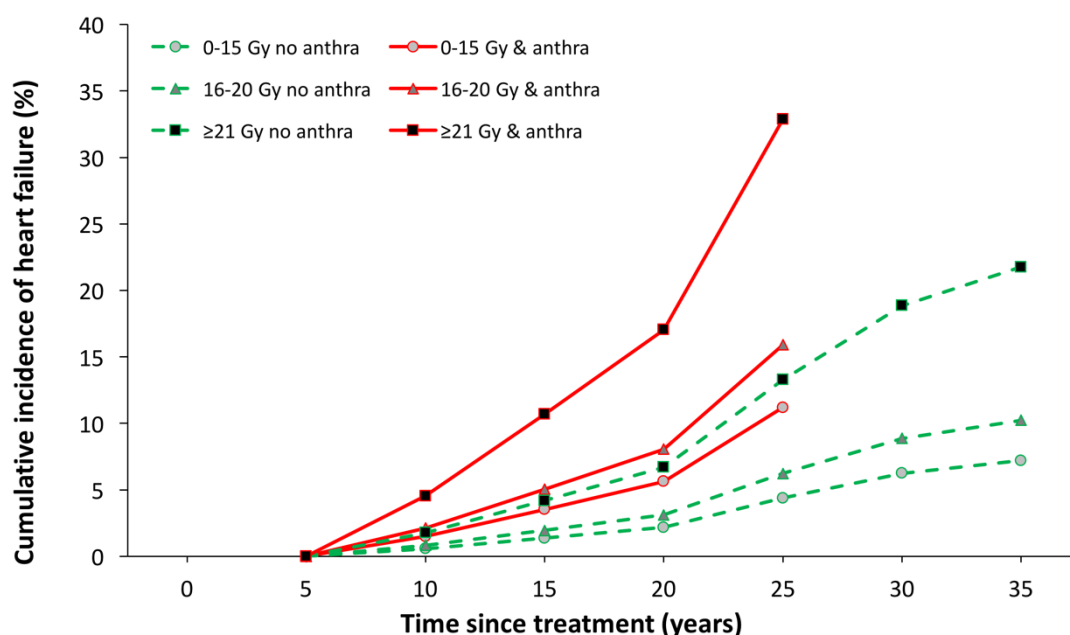


Figure 1-8 Approximate cumulative risks of CHF by mean left ventricular dose and whether treatment with anthracyclines was given. Lines indicate estimated cumulative incidences for dose categories (0-15 Gy, 16-20 Gy and ≥ 21 Gy) with and without anthracycline exposure

1.6 Discussion

This study has derived, for the first time, dose-response relationships for CHF rate based on cardiac radiation exposure in 5-year survivors of adolescent or adult HL. Analysis was conducted based on estimates of both MHD and MLVD derived from individual RT plans. Both measures of dose suggested that there was little increase in CHF risk for doses – up to 25 Gy MHD or up to 15 Gy MLVD – but that CHF rates increased rapidly at higher doses.

1.6.1 Dosimetric aspects

Patient specific estimates of dosimetric parameters such as MHD, MLVD, V20 and V30 derived from individual RT plans for most cases and controls. The MHD of 20.9 Gy reported here for a median prescribed dose of 36.2 Gy, was comparable to other studies who reported MHD of 24.2 Gy ²¹ and 27.5 Gy ²² for patients planned with

mantle field RT at 35.0 Gy and 36.0 Gy prescribed dose respectively. No studies reporting MLVD from mantle field RT could be found in the literature.

One of the strengths of the dosimetry method was that instead of using the prescribed radiation dose from the patients' RT charts to predict radiation-related CHF risks, individually estimated cardiac dosimetric doses were used for each patient. A series of validation tests were performed on the dose reconstruction method to ensure that errors are minimised as practically as possible in a retrospective dose reconstruction process. Another strength was that the physical MHD and MLVD extracted by the TPS, were converted into EQD2 taking into account variation in fractionation and dose distribution. The reason for this is that radiation-induced normal tissue toxicities do not simply depend on the cumulative physical organ dose calculated by the TPS, but are also related to fraction size and radiation dose distribution within the organ of interest.¹⁸ EQD2 also enables comparison of doses delivered by various treatment regimens and introduces consistency when compared to radiation dose-response relationships for other cardiac endpoints in HL survivors such as valvular and coronary heart disease.^{3,4} Additionally, when dose-response relationships are used to estimate risks for current or future patients, their TPS-extracted doses can also be converted in to EQD2 so that risk predictions can be based on consistent dosimetric parameters even when RT regimens are changing over time.

One limitation of the dosimetry method was that although detailed RT information was collected for each patient, those patients were treated before the era of CT-based treatment planning that started in the late 90's. Dose reconstructions were therefore carried out using representative CT datasets, and these cannot consider patient-specific variations in mediastinal separation, heart

size, shape and position. However, the effect of dose reconstruction errors on the dose-response relationships will be investigated in Chapter 2 and the development of a methodology to account for those errors will be explored. Additionally, for a proportion of patients, both the RT chart and the simulation film were missing and the MHD and MLVD were estimated based on the rest of the cohort rather than reconstructed. However, a sensitivity analysis including only patients for whom MHD and MLVD were reconstructed, showed similar results (see Appendix A, Supplemental Table 3 and Supplemental Figure 2). The EQD2 transformations accounted for fractionation size and for the fact that the delivery of the anterior and posterior fields was performed on different days. However, they did not account for the fact that the original posterior fields were delivered with the patient positioned in prone position, resulting in heart displacement compared to when the patient was positioned in supine position. The representative CTs used for the reconstruction were taken in supine position and the posterior field was simulated by gantry rotation rather than patient re-positioning. Lastly, the EQD2 corrections did not account for the effect of the differences in overall treatment time between patients. Even though this limitation may be important only when investigating acute effects rather than late effects such as cardiac toxicity, treatment time factors could affect late effects indirectly i.e. time-dependent acute effects could predispose to consequential late effects ^{16,18}.

1.6.2 Congestive heart failure in HL survivors

A radiation dose-response relationship for self-reported CHF has previously been observed in the CCSS ^{9,23}. In that cohort, CHF risk was increased by factors of 1.6, 3.1 and 10.5 following MHDs of 5-14, 15-34 and ≥ 35 Gy respectively, compared with patients who did not have any cardiac radiation exposure. These proportional

increases were somewhat higher than those in the present study, possibly due to the patients' younger ages at cancer treatment: 82.4% of the CCSS cohort were aged less than 15 years at cancer diagnosis compared with only 3.5% in the present study. The strengths of this study include that it was performed in a complete, multi-institutional population with long-term, detailed follow-up, including information from cardiologists and GPs. The outcome (CHF) was GP-reported and, if necessary, confirmed by cardiologists, which is an important advantage in comparison with studies relying on patient-reported outcomes or registry data.^{8,24–26}

One limitation of the study was that it included only cases for whom CHF was the first cardiovascular diagnosis to minimise the effects of other CVD such as CHD or VHD on the risk of developing CHF. However, in a previous study⁶, it was shown that CHF occurred frequently subsequent to CHD or VHD, rather than as a first event. Additional research is needed to study the influence of previous CVD and to identify additional risk factors for developing multiple CVD. Another limitation of the study was that patients were included in this study only if they had survived at least 5 years after HL diagnosis. However, recent studies in oesophageal cancer trials have shown an excess risk of cardiac related deaths as early as 8 months from diagnosis.²⁷

1.6.3 Future perspectives

For patients treated today, MHD and MLVD will usually be well below the median values of 23.3 Gy and 15.4 Gy than in this study which reported on patients treated with mantle field RT. In modern RT both treatment volumes and prescribed doses are reduced. Involved field RT has been reported to give median MHD of 17.2 Gy for prescribed doses of 35 Gy. Involved node radiotherapy (3D-CRT or IMRT) leads to even lower doses, median MHDs between 7.7-12.0 Gy for prescribed doses of

36 Gy.^{21,22,28,29} Additionally, many patients are prescribed today on doses between 20 Gy to 30 Gy which will result in even lower doses to normal tissues. Technological advancements in RT can achieve an even further reduction in normal tissue exposure. A study looking at cardiac dose reduction when using passive scattering proton beam therapy showed a median MHD of 8 Gy (RBE)²⁸ and a similar study showed a further reduction of MHD when using PBS proton therapy, with a median MHD of 5.4 Gy (RBE).³⁰ A study presented in this thesis in Chapter 3 showed a median MHD of 7.7 Gy (RBE) for patients also treated with PBS proton therapy. In all studies above, there were a small number of patients who received MHD between 20-26 Gy, even when modern involved node RT was used. Therefore, even if patients treated today are on average at a substantially lower risk of CHF, there is still a subgroup of patients who will be at a higher risk of developing radiation-related heart disease. Those patients will need to be referred for treatment using the most advanced RT techniques, such as proton RT, to keep the cardiac radiation doses as low as practically achievable. Regular follow up and monitoring for cardiac disease after treatment of HL is also advised.

Studies in larger populations of HL survivors treated more recently would be helpful in characterizing the risks from modern treatments more precisely. More accurate dosimetry based on a patient's individual CT scan may also help to determine whether MHD, MLVD, mean dose to other cardiac substructures or another dosimetric parameter is the best measure to predict radiation-related CHF risk. However, in the absence of more precise measures, these dose-response relationships for MHD and MLVD can be used to estimate CHF risk both in patients treated today, and in survivors treated in more recent decades, as in Chapter 4.

1.7 Conclusion

Cardiac radiation exposure and treatment with anthracyclines are important risk factors for the development of CHF in HL survivors. This study has provided the first ever dose-response relationship for risk of CHF in adult HL survivors. These findings are important as they further improve our understanding of radiation-related heart disease overall. It will enable more accurate prediction of cardiac risks for HL patients based on their individual cardiac doses. It will improve HL patient care by adapting treatment regimens for future patients and by defining appropriate follow-up care for HL survivors who have received high cardiac doses in the past.

1.8 References

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Chapter 2 Cardiac radiation dose reconstruction in the study of late effects: A comparison of different methods

2.1 Introduction

Radiation-related CVD can occur several decades after RT. Cardiac radiation dose information is not available for most historic patient cohorts. Therefore, to obtain dose-response relationships for radiation-related cardiac late effects in epidemiological studies, it is necessary to reconstruct the radiation doses delivered to the heart retrospectively, often without individual CT planning scans. The reconstructed doses can then be used to derive dose-response relationships that describe ways in which the risk of CVD is related to the radiation dose received by the whole heart or by specific cardiac structures. HL patients treated with RT are of particular interest, due to the wide range of cardiac doses received during RT and their long post-treatment survival, during which they are at risk of heart disease. Therefore, a number of epidemiological studies using reconstructed doses have been conducted in populations of HL patients.

In these studies, the reconstructed doses are subject to various sources of uncertainty including: errors in the reconstruction methods due to the availability and quality of imaging of the patient anatomy, the reconstruction process of the original RT treatment plan, the characterisation of the original radiation source and the calculation of the dose distributions within the organs of interest.¹ Another source of uncertainty in the reconstructed doses is introduced by changes in the patient anatomy and by positioning errors throughout their treatment, which introduces additional uncertainty between the planned dose and the actually delivered. This can be particularly relevant to patients treated decades ago when patient immobilisation and image-guided RT were not practiced. Daily variation in patient set-up for such historical treatments has been shown to result in up to 15%

tumour coverage positioning error which can be an indicator of the scale of variation in the doses to surrounding organs.^{2,3}

Reconstructed estimates of cardiac dose are subject to both systematic and random errors when compared to the doses that would have been obtained from the patient's own CT scan. One way to assess several aspects of the errors arising from a reconstruction method is to reconstruct doses for a series of patients for whom a more accurate estimate of the doses is also known (termed "true doses" for the purpose of this thesis). The true doses are usually calculated on the patients' own CT scans. Systematic errors in the reconstructed doses can bias the estimated risks per unit of dose in either direction (i.e. overestimate or underestimate the risk) while random errors will tend to attenuate the dose-response relationship.^{1,4,5} Both types of error need to be assessed and taken into account when estimating dose-response relationships based on the reconstructed doses. The effect of the systematic errors on the dose-response relationships can be assessed using regression analysis, while the effect of the random errors can be assessed using regression calibration.⁶ If these errors are small, they will have little effect on a dose-response relationship derived using the reconstructed doses. However, if the errors are large, a dose-response relationship derived using the reconstructed doses will be distorted unless they are taken explicitly into account.^{1,5}

Several dose reconstruction methods for HL patients have been described⁷⁻¹³ and although their dose prediction accuracy has at times been questioned, it has not previously been investigated. It is important to understand how dosimetry uncertainties might affect the results of dose-response analyses and how they should be accounted for.

In this chapter the accuracy of five methods of dose reconstruction has been investigated. These methods will be presented in increasing order of time spent on cardiac dose reconstruction per patient. The first, and the simplest, reconstruction method has been described by Maraldo et al.¹¹ It comprises a field superposition method based on reconstructed fields which estimates cardiac doses and doses in other OAR as a percentage of the prescribed dose. This method can be used to estimate doses for patients treated several decades ago provided that treatment field and prescribed dose information are available and it has been used to reconstruct cardiac doses and to derive hazard ratios (HR) for cardiovascular events for a cohort of HL patients.¹⁴ For the purpose of this thesis the method will be called “%Prescribed”.

The second reconstruction method was described by van Nimwegen et al.¹⁰ This method can be used when 2D simulation x-ray films and prescription dose information are available. It is a simple patient-specific approach, where the MHD is estimated from the percentage cardiac area exposed within the 2D simulation fields. It was used to reconstruct the MHD for a retrospective study which reported a radiation dose-response relationship for the risk of coronary heart disease in HL survivors.¹⁵ For the purpose of this thesis the method will be called “%Heart”.

The third reconstruction method was described by Stovall et al.⁸ This method can estimate the absorbed dose for a series of OAR inside and outside the treatment field and is based on a combination of measurements in an anthropomorphic phantom and analytical dose calculations. The method is the most widely used reconstruction method and has provided dose estimates for a number of large retrospective studies and different organs of interest. One of the studies for which cardiac doses were reconstructed was an analysis of cardiac outcomes in a

cohort of adult survivors of childhood and adolescent cancer performed within the CCSS cohort.¹⁶ For the purpose of this thesis the method will be called “Phantom”.

The fourth reconstruction method evaluated was described in Chapter 1 and it is a representative CT technique based on male and female anatomical data sets. The method can estimate the absorbed dose for a series of OARs including the heart and cardiac substructures. The doses are reconstructed on the representative CT using a treatment planning system (TPS) and by extracting anatomical and treatment information from patient records and 2D simulation films. This method was used to reconstruct MHD, MLVD and dose to the cardiac valves in two case-control studies that derived dose-response relationships for CHF (Chapter 1) and VHD in HL survivors.^{9,17} For the purpose of this thesis the method will be called “RepCT”.

The fifth and final reconstruction method evaluated here, has been previously described in detail by Ng et al.^{12,18} This method uses an advanced deformable image registration and navigator channels (NCs) adaptation technique to reconstruct 3D organ volumes and doses based on 2D simulation films. This method was used to reconstruct MHD and dose to the coronary arteries in a study examining the contributions to risk prediction of the dosimetric parameters of the coronary arteries and whole heart.¹⁹ For the purpose of this thesis the method will be called “Navigator”.

The five methods were used to reconstruct MHD and where possible MLVD in a group of fourteen HL patients. The reconstructed doses from all five methods were compared to the true doses derived from the patients’ own CT scans. The effect of the cardiac dose reconstruction uncertainties on the risk estimates from studies of the late effects of RT was evaluated. Models to predict the true doses were derived

for each reconstruction method using regression analysis, to quantify the effect of the systematic errors on the dose-response relationships, whilst regression calibration was used to quantify the likely effect of the random errors. All statistical analysis was performed using Stata 14.2 (Stata Corp LLC).

Table 2-1 Summary of the reconstruction methods used in this study

Reconstruction methods					
Name	%Prescribed	%Heart	Phantom*	RepCT	Navigator ^o
Relevant Study	Maraldo et al. ¹¹	Nimwegen et al. ¹⁰	Stovall et al. ⁸	Cutter et al. ⁹	Ng et al. ^{12,18}

*The methodology details and reconstructed doses presented below were kindly provided by Prof Rebecca Howell, Associate Professor of Radiation Physics, The University of Texas (MD Anderson Cancer Centre)

^o The reconstructed doses were kindly provided by Prof David Hodgson, University of Toronto, Department of Radiation Oncology, Princess Margaret Hospital for the purpose of this study and the methodology has been previously described in detail by Ng et al.¹⁸

The doses using the %Prescribed, the %Heart and the RepCT methods were reconstructed by the candidate

2.2 Methods

2.2.1 Dose reconstruction

Fourteen patients treated with CT-based RT for mediastinal HL were selected for this study. Details of these patients have been described previously by Ng et al.¹⁸ Briefly, the patients were treated between 1999 and 2008 and were selected consecutively to avoid possible bias. As these patients were treated during the modern era of CT-based RT, 2D simulation films, as were used for patients treated during the 2D planning era were not available. However, 2D digitally reconstructed radiographs (DRRs) were reconstructed by the TPS to mimic simulation films. The heart was highlighted on the DRRs, based on manually delineated heart contours. In retrospective studies on historically treated patients, the heart would also be highlighted on the simulation films retrospectively as shown on Figure 2-1. Two examples of the patient information used for the reconstruction can be seen in Appendix B.

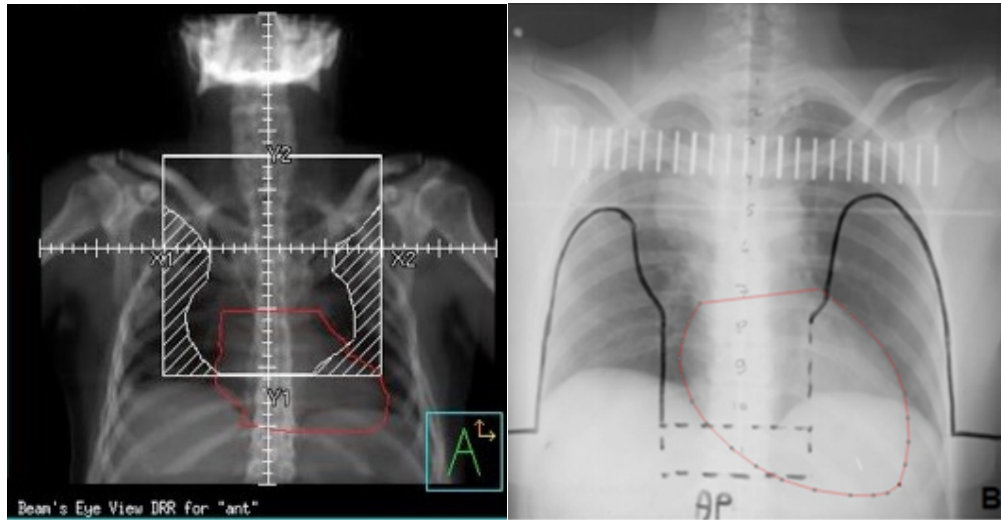


Figure 2-1 Two-dimensional (2D) digitally reconstructed radiographs (DRRs) (left) were used to mimic simulation films from historical HL RT treatments (right). (NB: different patient) Cardiac contours are displayed in red in both images.

2.2.1.1 %Prescribed reconstruction method

The various treatment fields used in this method (mantle, mediastinal, right/left neck, right/left axillary etc.) were used to reconstruct the MHD (Figure 2-2). The MHD for each field combination, expressed as a percentage of the treatment prescribed dose, was used to estimate the MHD for the patients in this group (Table 2-2). The original prescribed doses and the DRRs were used to identify the subfields for each patient and to combine them in order to estimate the total MHD by superimposing the relevant fields, based on Figure 2-2. All patients in this study were assigned a MHD of 65.1% of the prescribed dose according to their field arrangements. The reconstructed doses were then compared to the true doses obtained directly from the patients' own CT scans.

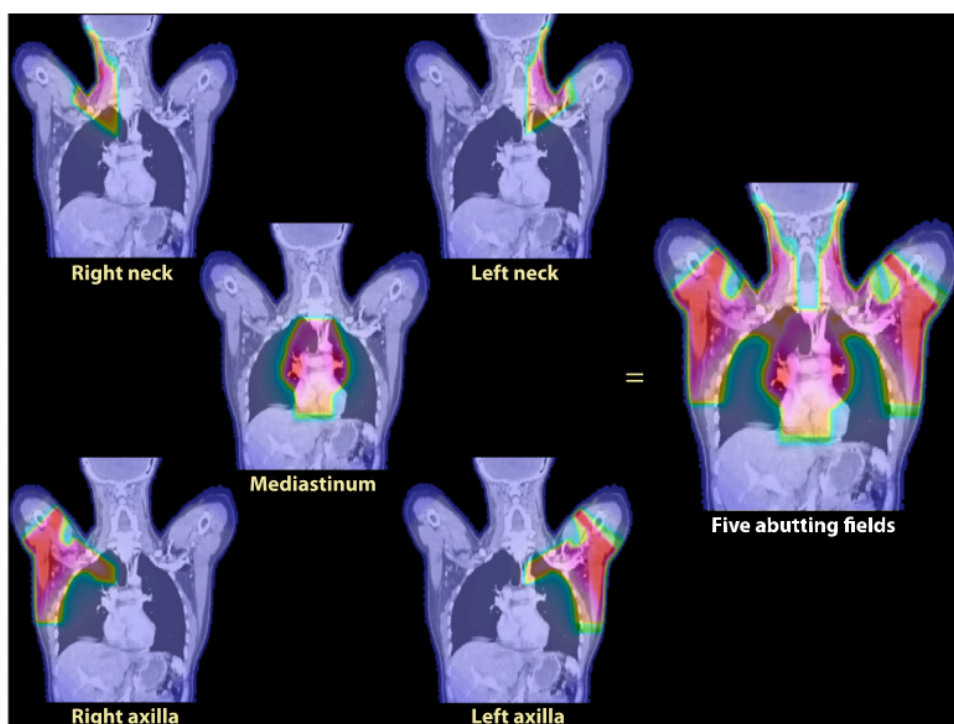


Figure 2-2 Example of the field superposition process. A final mantle field was simulated from five individual fields. Image taken by Maraldo et al.¹¹

Table 2-2 The mean heart dose estimates for the 17 most common combinations of RT fields expressed as % of prescribed dose.¹¹

Most common field combinations	MHD as % of prescribed dose
Mantle field	65.1
Mantle field and spleen irradiation	77.8
Mediastinum	65.1
Mediastinum and right neck	65.1
Mediastinum and left neck	65.1
Mediastinum and both right and left neck	65.1
Mediastinum and both right and left neck and axilla	65.1
Left neck only	4.6
Right neck only	4.6
Left and Right neck	4.8
Right neck and right axilla	5.6
Left neck and left axilla	5.8
Right axilla only	5.6
Left axilla only	5.8

MHD: Mean heart dose

2.2.1.2 %Heart reconstruction method

The heart was contoured on the DRRs of this group to mimic the methodology used on simulation films by van Nimwegen et al.¹⁰ The Image J software package²⁰ was then used to delineate and calculate the percentage of the heart area within the field (%Heart) on the DRRs. The MHD was estimated for each patient by multiplying the %Heart area inside the field by the patient's prescription dose. In the original paper the authors suggested that the MHD calculated this way was 14% higher on average than the MHD based on individual CT-based dosimetry and needed to be multiplied by a correction factor of 0.88 (i.e. 1/1.14). Therefore, the MHD estimated for this group was also divided by the same correction factor. The MHD was converted into EQD2²¹ assuming an α/β ratio of 2 for late cardiac effects²² as in the original method.

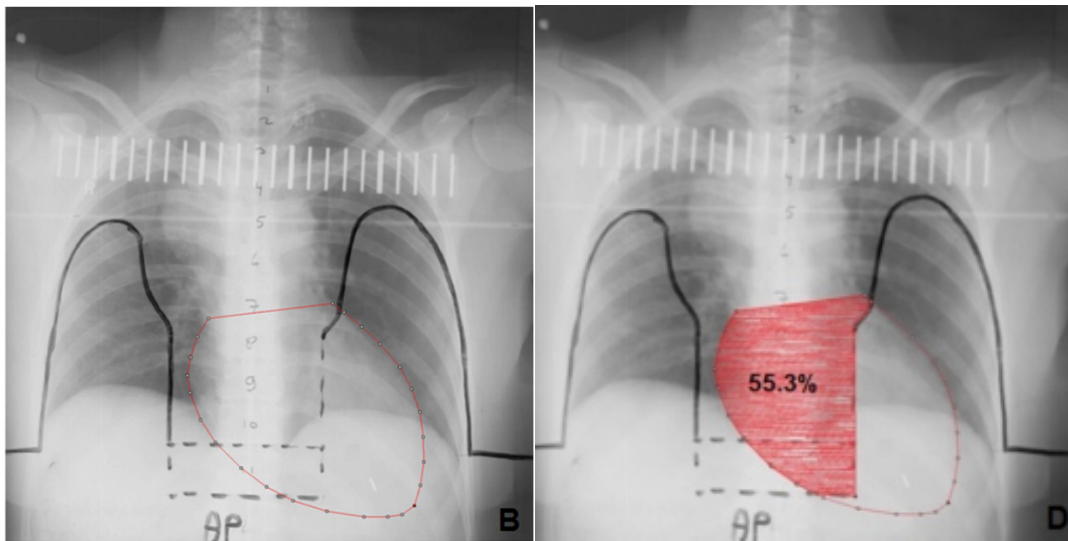


Figure 2-3 Delineation of %Heart contour within the field. Left: delineation of the whole heart on the simulation film. Right: irradiated proportion of heart surface in the field. The MHD can be calculated as $[(\%Heart * Prescribed\ dose) * correction\ factor]$ ¹⁰

2.2.1.3 Phantom reconstruction method

For the Phantom reconstruction method, each patient record was abstracted by an experienced dosimetrist for RT details necessary for dose reconstruction. Specifically, prescription, date, and treatment field parameters, including dose, orientation, energy, field size, weighting, blocking, and anatomical borders (or field central axis coordinates) were coded. A separate form for each treatment field or pairs of parallel-opposed fields were also coded. Each field and/or sub-field was assigned a dose based on the field weighting indicated in the treatment plan records.

The patient DRRs, which showed a contour of the heart as in Figure 2-1, were used to code the superior and inferior aspect of the heart contour with respect to the thoracic vertebrae. Most of the fields were coded as an anterior or posterior mantle or T-mantle field, or as a small rectangular chest field (for the field-in-field sub-fields). For each patient, the treatment fields were reconstructed on an adult computational phantom.⁸ The phantom was divided into rectangular sections for head, neck and trunk, each of which are defined by a 3D grid of evenly spaced points (Figure 2-4). Various organs were defined by a grid of points within the phantom. The phantom had a standard heart comprised of 55 points with upper and lower borders at the thoracic vertebral bodies 5 (T5) and 9 (T9), respectively. For this study, 6 additional heart models were added to the phantom to account for the six, unique upper and lower border positions that were abstracted from the RT records. The additional hearts were added by shifting, stretching, or shrinking the standard 55-point heart. Therefore, there were 7 unique upper and lower border combinations, which are listed in Table 2-3. Each patient in this group was assigned one of the seven unique hearts for dose calculation.

For each field, points within the phantom were designated as in-beam, blocked, at the beam edge, or out-of-beam. For points that were in-beam, doses were computed based on coded field parameters (energy, field size, depth) and using data from British Journal of Radiology supplement no. 17.²³ For points under a block and at the beam edge doses were set to 10.0 % and 50.0 %, respectively. For points, outside the treated beam, the distance from the edge of the field to the point was calculated using analytical models. The analytical models were based on out-of-field dose measurements in water phantoms as a function of distance from the field edge and take into account depth, field size, and beam energy.⁸ This process was repeated for each individual treatment field. Finally, the MHD to the designated heart was determined by taking the arithmetic mean of the dose to all points (from all fields) defined within the heart.

Table 2-3 Seven unique heart models were used for dose calculation based on the upper and lower borders of the heart(span) in relation to the patient's thoracic vertebrae (T).

Unique heart model	Span	Number of patients
Heart_0	T5-T9	1
Heart_1	T5-T10	4
Heart_2	T5-T11	2
Heart_3	T6-T10	5
Heart_4	T6-T11	1
Heart_5	T7-T11	1
Heart_6	T7-T10	1

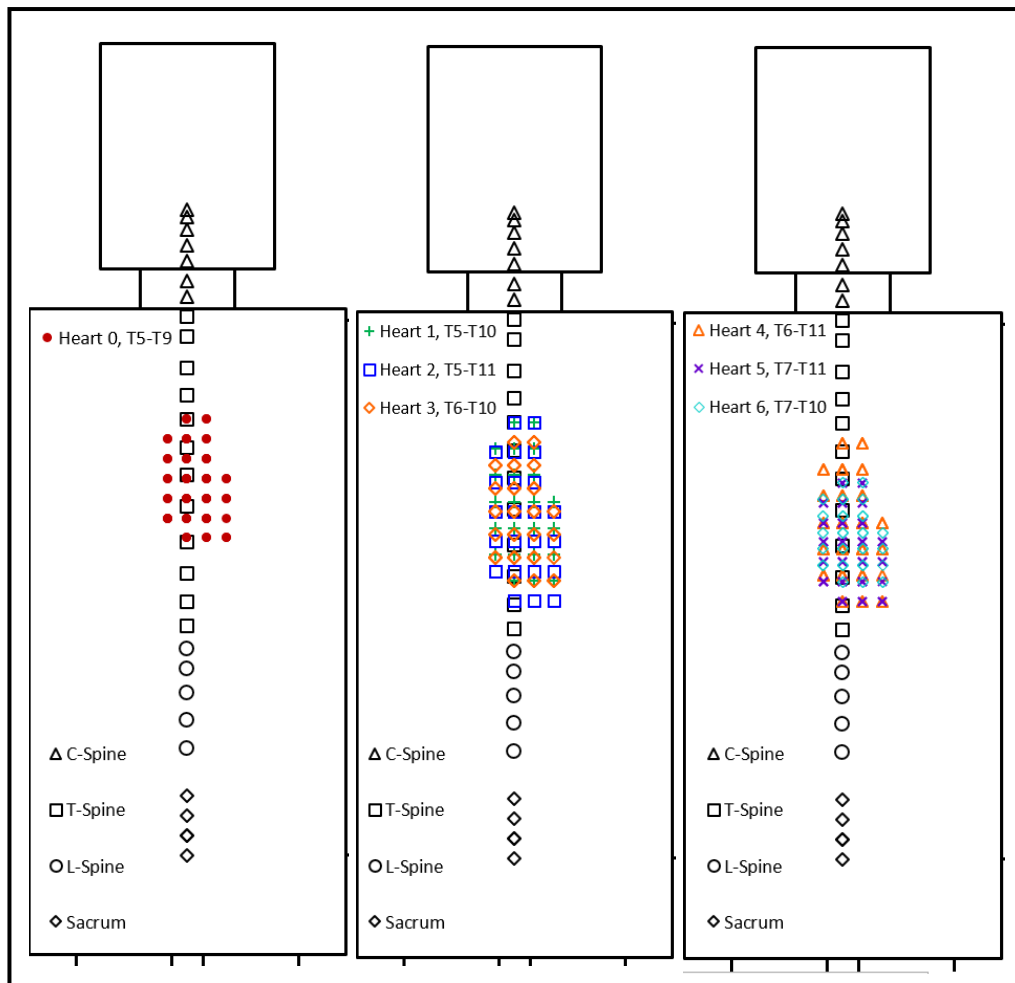


Figure 2-4 Adult computational phantom and the seven unique heart models created for the purpose of this study. C-Spine: Cervical spine, T-spine: thoracic spine. L-spine: lumbar spine. (Image courtesy of Rebecca Howell, Associate Professor of Radiation Physics, The University of Texas MD Anderson Cancer Center)

2.2.1.4 RepCT reconstruction method

The fourth reconstruction method evaluated was the RepCT method (described in detail in Chapter 1) and it was used to estimate both MHD and MLVD for each patient. In this method two substitute CT data sets (one for men and one for women) were used to reconstruct the original treatment plans for the fourteen patients based on their DRRs. The Eclipse treatment planning system (TPS) (Version 13.0.28, Varian Medical Systems, Palo Alto, CA) was used to reconstruct and calculate the cardiac doses for this study. Treatment planning variables such as prescribed dose, fractionation regime, beam arrangement, energy, field size and field shielding were extracted from the patients' planning report. As with previous methods, the DRRs

were used to reconstruct the field shape through blocks. Most patients were treated with two mantle fields, one anterior (AP) and one posterior (PA). However, some patients required additional field-in-field sub-fields.

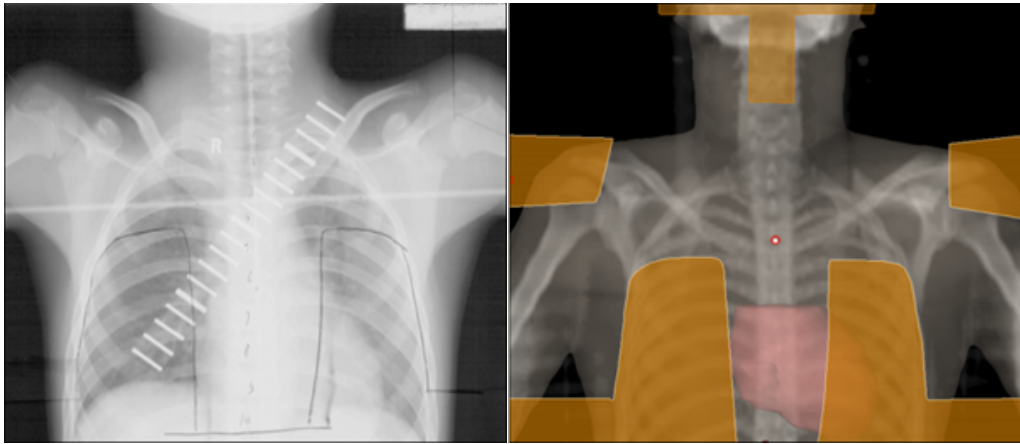


Figure 2-5 The original simulation films (left) were used for patient position verification during HL RT treatment from the 1960s to 1990, the lung block borders marked in black (left). The reconstructed fields on the representative CT data set were overlaid on a digitally reconstructed radiograph, block borders marked in orange (right).

The AAA photon dose calculation model in Eclipse TPS (Palo Alto (CA): Varian Medical Systems) was used to calculate the dose distributions. The dose distributions from all fields were then summed and cardiac doses (MHD and MLVD) were exported as DVHs. The physical mean dose was converted into $(EQD2_{\alpha/\beta})$ according to the LQ model for an α/β ratio of 2 as described in detail in section “1.3.4 Dose adjustment for fractionation and dose distribution” in Chapter 1.

2.2.1.5 Navigator reconstruction method

This Navigator method was also used to estimate both MHD and MLVD. This method used an advanced deformable image registration and navigator channels (NCs) adaptation technique to reconstruct 3D heart volumes and doses based on 2D simulation films from patients treated in the past. During the development of this method, twelve image sets (6 male, 6 female) were used to construct a male and a female population heart model, which was then registered to each patient according

to their gender. A series of rectangular regions of interest or NCs were then applied on the simulation films to quantify patient-specific heart structures based on differences in image intensity between the heart and other tissues, as shown in Figure 2-6. This patient-specific structural information was then adapted to the 3D population heart model using a combination of linear and bi-linear interpolation methods to generate a 3D patient-specific heart model. The MHD and MLVD were then calculated and extracted using a treatment planning system based on the new patient specific heart volume. Further details are given by Ng et al.¹⁸

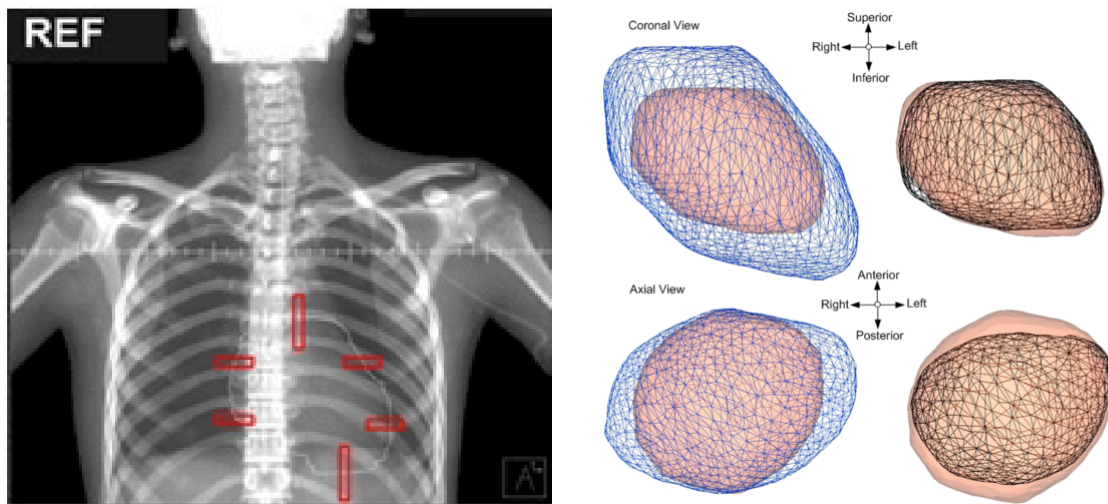


Figure 2-6 Graphical representation of the NCs technique and the adapted heart model. Left: six navigator channels (in red) were placed on the simulation film to capture structural differences and to define the heart contour of the original patient. Right: the 3D population heart model (in blue mesh) was then adapted (in black mesh) according to the heart contour (in pink) derived from the simulation film.¹⁹

2.2.2 Statistical Analysis

2.2.2.1 Regression analysis to assess systematic errors in the reconstruction methods

In order to assess the systematic errors, the relationship between the reconstructed doses and the true doses was evaluated using regression modelling for each reconstruction method. Initially, a simple linear regression of the reconstructed

doses (y_i) on the true doses (x_i) was performed. The regression model considered was:

$$y = \alpha + \beta x + \varepsilon \quad \text{Equation 2-1}$$

where the intercept (α) and the slope (β) are unknown parameters representing the systematic error in the reconstructed doses and ε represents the random error which is assessed in section 2.2.2.2. The fitted regression equation was:

$$\hat{y}_i = \hat{\alpha} + \hat{\beta} x_i \quad \text{Equation 2-2}$$

where

$$\hat{\beta} = \frac{\sum_{i=1}^n (x_i - \bar{x})(y_i - \bar{y})}{\sum_{j=1}^n (x_j - \bar{x})^2} \quad \text{Equation 2-3}$$

&

$$\hat{\alpha} = \bar{y} + \hat{\beta} \bar{x} \quad \text{Equation 2-4}$$

where

$$\bar{x} = \frac{\sum_{i=1}^n x_i}{n} \quad \text{Equation 2-5}$$

&

$$\bar{y} = \frac{\sum_{i=1}^n y_i}{n} \quad \text{Equation 2-6}$$

The variance of the random error was estimated from the sum of squares of the observations around the fitted regression model:

$$\hat{\sigma}_\varepsilon^2 = \frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{(n-p)} \quad \text{Equation 2-7}$$

where n is the number of observations and p the number of estimated parameters so that $n-p$ represents the degrees of freedom. In the case of a simple linear regression model, such as the one used here, the degrees of freedom are $n-2$ since there are two parameters estimated: intercept and slope. If, however, the regression is performed assuming the intercept (α) is zero, the degrees of freedom are $n-1$ as now only one parameter is being estimated.

In Equation 2-1 it was assumed that the values of the ε for different patients were mutually independent and had a normal distribution with mean zero and variance σ_ε^2 for all values of x_i (i.e. the random error was homoscedastic). If the assumption of homoscedasticity is violated, then the CI for the values of α and β in the simple linear regression model (equations 2.1 - 2.3 above) will be incorrect and significance tools will not give valid answers. In many cases where the assumption of homoscedasticity is violated, it can be achieved by carrying out a weighted linear regression. In this case the equations 2.3 to 2.6 are replaced by

$$\hat{\beta} = \frac{\sum_{i=1}^n \omega_i (x_i - \bar{x}_\omega)(y_i - \bar{y}_\omega)}{\sum_{j=1}^n \omega_j (x_j - \bar{x}_\omega)^2} \quad \text{Equation 2-8}$$

$$\hat{\alpha} = \bar{y}_\omega - \hat{\beta} \bar{x}_\omega \quad \text{Equation 2-9}$$

$$\bar{x}_\omega = \frac{\sum_{i=1}^n \omega_i x_i}{\sum_{i=1}^n \omega_i} \quad \text{Equation 2-10}$$

$$\bar{y}_\omega = \frac{\sum_{i=1}^n \omega_i y_i}{\sum_{i=1}^n \omega_i} \quad \text{Equation 2-11}$$

In order to examine whether it was appropriate to assume homoscedasticity (i.e. that σ_ε^2 is constant over all values of x_i), standardised residuals were calculated by dividing the simple residuals (r_i) by their estimated standard deviations (SD_i). Simple residuals are defined as:

$$r_i = y_i - \hat{y}_i \quad \text{Equation 2-12}$$

and the estimated SD of r_i is defined as:

$$SD_i = \hat{\sigma}_\varepsilon \sqrt{1 - h_i} \quad \text{Equation 2-13}$$

where h_i , known as the leverage of each observation i , was calculated as:

$$h_i = \frac{1}{n} + \frac{(x_i - \bar{x})^2}{\sum_{j=1}^n (x_j - \bar{x})^2} \quad \text{Equation 2-14}$$

The standardised residuals ($\text{Std}r_i = r_i / SD_i$) were then plotted versus the fitted values ($\hat{y}_i$). If the assumption of homoscedasticity was violated a weighted regression was performed, and the standardised residuals under this new model were re-examined.

An example of constant variance can be seen in the left plot in Figure 2-7. In the right plot, however, the variance increases with increasing fitted values, i.e. with increasing x_i . This shows that the assumption of homoscedasticity (i.e. σ_ε^2 constant for all values of x_i) is not appropriate. In this case it is necessary to introduce a set of weighting factors ω_i so that the variance of y_i becomes $\sigma_\varepsilon^2/\omega_i$. For situations such as that shown in the right-hand plot of Figure 2-7, a weighting factor such as ($\omega_i = \frac{1}{x_i^2}$) will often achieve homoscedasticity.

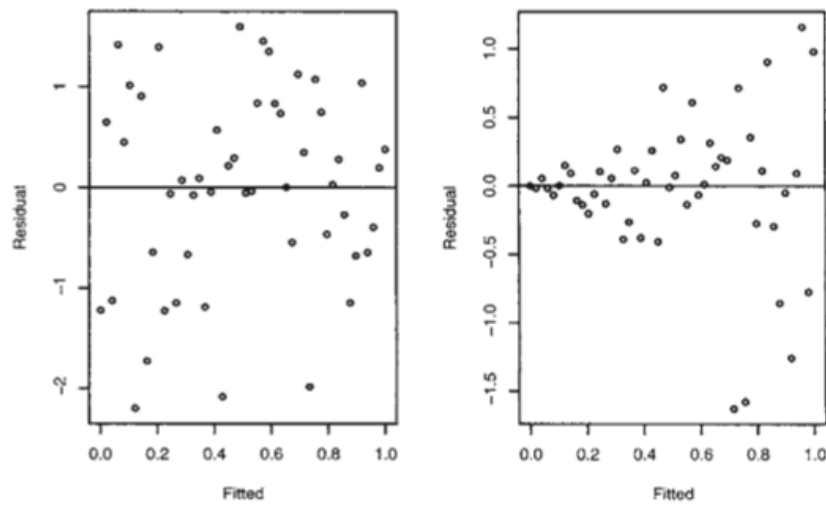


Figure 2-7 Plots of residuals versus fitted values. On the left plot the variance of y_i about x_i is constant (homoscedasticity) whilst on the right plot the variance increases with increasing fitted values (heteroscedasticity).²⁴

The final regression model for each method was selected after first achieving homoscedasticity and $\hat{\alpha}$ and $\hat{\beta}$ estimated using either equation (2.3 to 2.6) or (2.8 to 2.11) as appropriate. If there were no systematic errors in the reconstruction method, α in Equation 2-1 would be equal to 0 and β would be equal to 1. The significance of departures of $\hat{\alpha}$ from 0 and of $\hat{\beta}$ from 1 were therefore considered for each reconstruction method. (For further details see section 2.2.2.3)

2.2.2.2 Regression calibration to assess random errors in the reconstruction method

Random errors in the reconstructed doses (i.e. σ_{ϵ}^2) will attenuate any dose-response relationship that is derived using them. For random errors of a given magnitude, the extent of the attenuation is not constant but depends on the circumstances in which they are used. If the doses used to derive the dose-response relationship vary over a large range, then the attenuation in the dose-response relationship caused by random errors in the reconstructed doses will be smaller than if the dose-response relationship is derived using doses that vary over a small range.

The effect of the random errors in the reconstructed doses was assessed using the method of regression calibration.^{6,25} This method provides an exact correction for the effect of random error in the reconstructed doses when the dose-response being studied has been derived by simple linear regression, but has also been shown to work well in many other situations, including conditional logistic regression which is the method that has been used to derive the dose-response relationships of interest here.

Regression calibration corrects for attenuation due to random errors in the reconstructed doses by replacing each value of the reconstructed dose by the corresponding expected value of the true dose for a given value of the reconstructed dose. This requires an assumption about the statistical distributions of both the true and the reconstructed doses in the population for which the dose-response relationship for heart disease has been estimated. We assume that these two variables (i.e. true and reconstructed doses) are jointly normally distributed and that the true doses (x_i) have distribution:

$$x_i \sim N(\mu_x, \sigma_x^2) \quad \text{Equation 2-15}$$

and, conditional on the true dose x_i taking value x , the reconstructed doses (y_i) have distribution:

$$y_i | x_i = x \sim N(x, \sigma_\varepsilon^2) \quad \text{Equation 2-16}$$

With these distributional assumptions, it follows that the expected value (E) of the true dose given that the reconstructed dose takes value y_i is:

$$E(x_i | y_i = y) = \frac{\sigma_y^2}{\sigma_x^2 + \sigma_\varepsilon^2} \mu_x + \frac{\sigma_x^2}{\sigma_x^2 + \sigma_\varepsilon^2} y \quad \text{Equation 2-17}$$

The first term in Equation 2-17 is a constant and it can be shown that this will not affect the slope of a dose-response relationship derived using conditional logistic regression. The second term indicates the extent to which the random errors in the reconstructed doses attenuate the slope of the dose-response relationship. A correction can therefore be made for this attenuation by multiplying the slope by a factor f , where:

$$f = \frac{\sigma_x^2 + \sigma_\varepsilon^2}{\sigma_x^2} \quad \text{Equation 2-18}$$

2.2.2.3 Addressing systematic and random errors in dose-response relationships

Once a suitable regression model was derived for each reconstruction method, the extent of both systematic and random errors on the dose-response relationships was assessed and, where necessary, corrections to them were derived.

In order to adjust the dose-response relationships for systematic errors, the significance of departure of $\hat{\alpha}$ from 0 and of $\hat{\beta}$ from 1 in equation 2-1 was considered for each reconstruction method.

- If $\hat{\alpha}$ was not significantly different from 0 and $\hat{\beta}$ not significantly different from 1 the systematic error did not have an effect on the dose-response relationship ($y_i = x_i$).

- If $\hat{\alpha}$ was not significantly different from 0 but $\hat{\beta}$ was significantly different from 1 ($y_i = \hat{\beta} x_i$), the dose-response relationship was multiplied by $\hat{\beta}$ (i.e. the slope of the regression model).
- If $\hat{\alpha}$ was significantly different from 0 and $\hat{\beta}$ from 1 then the final regression model was ($y_i = \hat{\alpha} + \hat{\beta} x_i$) and the dose-response relationship was multiplied by the slope to adjust for the systematic error.

In order to adjust for random errors, the sample variance of the reconstructed doses which were used to derive the dose-response relationship in each study was considered. In most studies, only limited information about this was given, but the interquartile range (IQR) was normally available. Assuming that the reconstructed doses followed a normal distribution, the upper and lower quartiles were at -0.67σ and $+0.67\sigma$ and an estimate of the sample variance was: $(\text{IQR})/2 \cdot 0.67)^2$. This sample variance includes the random error, so is an estimate of $(\sigma_x^2 + \sigma_\epsilon^2)$ which is the numerator in Equation 2-17. The σ_ϵ^2 was estimated from the regression analysis, therefore, an estimate of σ_x^2 is $(\text{IQR})/2 \cdot 0.67)^2 - \sigma_\epsilon^2$. The estimated σ_x^2 and σ_ϵ^2 were then used to derive an approximate attenuation factor in Equation 2-18 which was then used to estimate the attenuation on the dose-response relationship due to the random error in the reconstructed doses.

2.3 Results

The true doses and the reconstructed MHD and MLVD derived using each method are listed in Table 2-4 and Table 2-5. The average true MHD was 15.2 Gy. The average reconstructed MHD estimated by the %Prescribed was 18.7 Gy, The %Heart method estimated the doses with an average MHD of 14.0 Gy. The MHD derived using the Phantom, RepCT and Navigator methods were 15.4, 15.5 and 15.2 Gy respectively. Phantom and RepCT overestimated the delivered MHD by only 0.2 and 0.3 Gy respectively whilst the Navigator method provided the same average MHD as the average of the true doses, the %Heart method underestimated the average MHD by 1.2 Gy and the %Prescribed overestimated the average dose by 3.5 Gy.

The RepCT and Navigator methods were the only methods which could estimate MLVD. The average true MLVD was 9.8 Gy whilst the RepCT and the Navigator method estimated it to be 11.1 and 9.9 Gy respectively. The regression analysis performed for each reconstruction method is described below.

Table 2-4 Reconstructed mean heart doses (MHD) derived by each method compared with the CT-based true doses (x_i)

Subject	sex	Prescribed dose/fractions	%Prescribed (Gy)	%Heart (Gy)	Phantom (Gy)	Rep CT (Gy)	Navigator (Gy)	True doses (Gy)
Patient 1	F	21 Gy in 14	13.7	4.6	7.0	5.8	6.3	5.5
Patient 2	M	20 Gy in 10	13.0	7.3	7.0	8.0	7.4	6.5
Patient 3	F	21 Gy in 12	13.7	6.6	7.6	7.3	7.0	7.2
Patient 4	M	30 Gy in 20	19.5	9.9	11.6	11.2	10.7	10.7
Patient 5	M	35 Gy in 20	22.8	10.6	13.0	12.6	10.4	11.6
Patient 6	F	20 Gy in 10	13.0	13.1	10.2	15.9	12.4	13.3
Patient 7	F	30 Gy in 20	19.5	11.7	14.8	15.4	12.1	13.8
Patient 8	F	30 Gy in 20	19.5	12.8	16.5	13.8	16.7	15.5
Patient 9	M	35 Gy in 20	22.8	17.8	14.5	18.9	17.8	19.2
Patient 10	M	35 Gy in 20	22.8	17.0	22.7	21.1	22.4	19.4
Patient 11	M	30 Gy in 20	19.5	19.3	23.0	20.4	23.8	21.7
Patient 12	F	35 Gy in 20	22.8	19.7	22.5	19.4	20.7	21.8
Patient 13	F	30 Gy in 17	19.9	23.0	18.1	19.7	22.6	23.2
Patient 14	M	30 Gy in 20	19.5	22.3	27.5	27.2	23.0	23.9
Average MHD (Gy)			18.7	14.0	15.4	15.5	15.2	15.2
SD of MHD (Gy)			±3.8	±5.9	±6.6	±6.1	±6.5	±6.4
Average time spent per patient*			20 min	30 min	30min	1 hour	1.5 hour*	-

MHD: Mean heart dose, SD: Standard deviation

* Estimate for comparison purposes, time spent for initial coding and setting up of methodology was not included

Table 2-5 Reconstructed mean left ventricular doses (MLVD) derived by two methods compared with the CT-based true doses (x_i)

Subject	sex	Prescribed dose in fractions	Rep CT (Gy)	Navigator (Gy)	True doses (Gy)
Patient 1	F	21Gy in 14	1.8	2.6	1.2
Patient 2	M	20Gy in 10	4.5	2.4	2.5
Patient 3	F	21Gy in 12	3.3	2.7	3.5
Patient 5	M	30Gy in 20	6.1	2.9	3.7
Patient 4	M	35Gy in 20	6.2	3.5	4.1
Patient 9	F	20Gy in 10	12.3	8.1	9.1
Patient 7	F	30Gy in 20	10.8	7.6	9.1
Patient 8	F	30Gy in 20	10.6	13.7	11.0
Patient 6	M	35Gy in 20	15.2	9.8	11.6
Patient 10	M	35Gy in 20	16.4	17.0	14.9
Patient 14	M	30Gy in 20	22.7	13.8	15.1
Patient 12	F	35Gy in 20	14.1	15.2	15.6
Patient 11	F	30.6Gy in 17	16.6	20.3	17.1
Patient 13	M	30Gy in 20	15.1	18.5	18.5
Average MLVD (Gy)			11.1	9.9	9.8
SD of MLVD (Gy)			6.1	6.5	6.0
Average time spent per patient*			1 hour*	1.5 hour*	-

MLVD: Mean left ventricular dose, SD: Standard deviation

* Estimate for comparison purposes, time spent for initial coding and setting up of methodology was not included

2.3.1 %Prescribed

A simple linear regression of the reconstructed versus the true doses was performed (Table 2-6) and the standardised residuals were plotted versus the fitted values (Figure 2-8). This did not suggest that the assumption of homoscedasticity was incorrect. The final regression model was therefore the simple linear regression. The constant $\hat{\alpha}$ was estimated to be equal to 12.70 and significantly different from 0 ($p=0.008$) whilst $\hat{\beta}$ was estimated to be 0.40 and significantly different from 1 ($p=0.001$). The estimated variance of the observations around the fitted line ($\hat{\sigma}_\varepsilon^2$) was 8.50. The final model is shown in Figure 2-9, where it can be seen to be a good fit to the reconstructed and the true doses.

Table 2-6 Simple linear regression of the reconstructed and the true doses

Simple linear regression	
$\hat{\sigma}_\varepsilon^2$	8.50
$\hat{\alpha}$ [95% Conf. Interval]	12.70 [0.12 - 0.67]
$\hat{\beta}$ [95% Conf. Interval]	0.40 [8.14 - 17.16]
Regression model: $\hat{y}_i = 12.70 + 0.40x_i$	

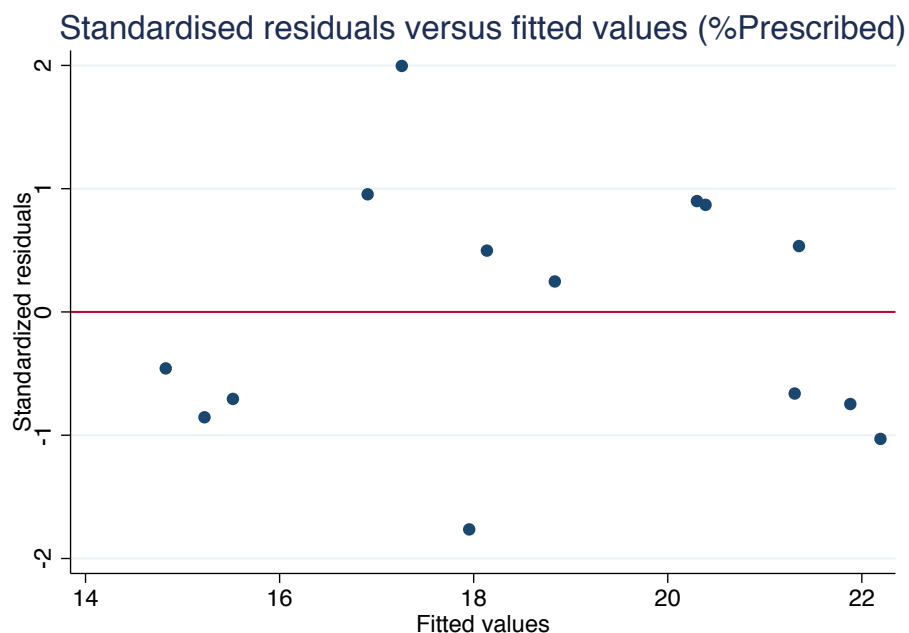


Figure 2-8 Standardised residuals versus fitted values, the assumption of homoscedasticity is confirmed.

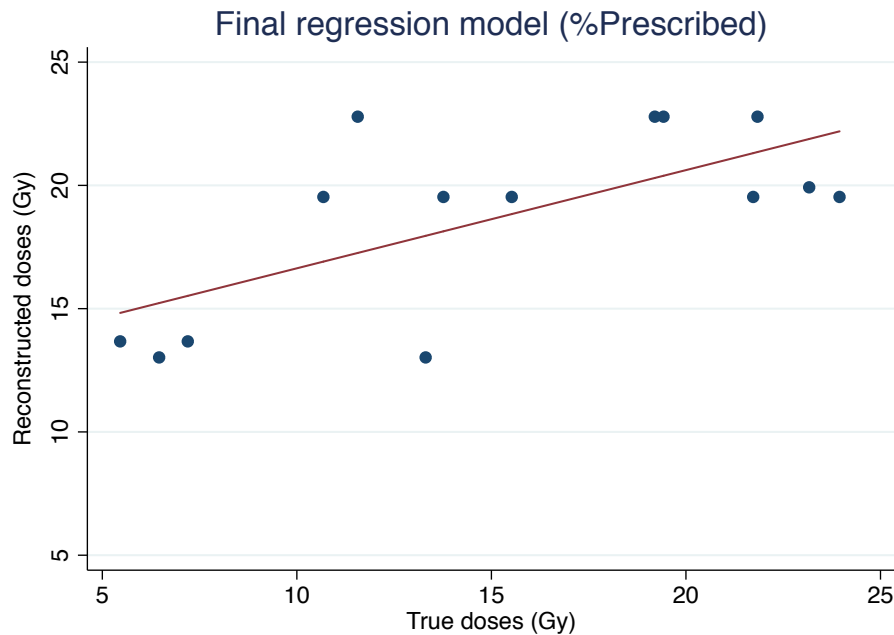


Figure 2-9 Final regression model: $\hat{y} = 12.70 + 0.40x$

2.3.1.1 Effect of errors on the dose-response relationship

The %Prescribed method has been used to derive a dose-response relationship by Maraldo et al.¹⁴ Based on Cox proportional Hazards model, the authors estimated that the cardiovascular events rate in HL patients increased by a hazard ratio of 1.015 [95% CI 1.006–1.024] i.e.

1.5% per Gy of MHD (95% CI: 0.6 to 2.4)

Systematic error

The effect of the systematic errors was taken into account by multiplying the dose-response relationship by the slope of the regression model of the reconstructed versus the true doses (i.e. 0.40). The same correction factor applied to the upper and lower bounds of the associated CI.

Random error

The reconstructed doses used to derive the dose-response relationship had a sample median of 23.30 [IQR: (7.8-26.2)] and therefore an approximate estimate of

the sample variance is $[(26.20-7.80)/(2 \times 0.67)]^2 = [13.73]^2 = 188.50$. From the regression analysis, the $\hat{\sigma}_\varepsilon^2$ was estimated 8.50, therefore: $\hat{\sigma}_x^2 = 188.50 - 8.50 = 180.00$.

Putting these two estimates into Equation 2-18 the attenuation factor f in the cardiovascular events rate due to random errors in the reconstructed doses becomes $188.50/180.00 = 1.05$. Hence the % increase in CV rate per Gy is attenuated by only 5.0 % and therefore had a negligible effect.

Corrected dose-response model

The rate will be therefore corrected as:

$(0.40 \times 1.5 \times 1.05)$ per Gy of MHD [95% CI: $(0.4 \times 0.6 \times 1.05)$ to $(0.4 \times 2.4 \times 1.05)$]

Providing with a corrected rate of:

0.6% per Gy of MHD [95% CI: 0.3 to 1.0]

2.3.2 %Heart

A simple linear regression of the reconstructed versus the true doses was performed (Table 2-7) and the standardised residuals were plotted versus the fitted values (Figure 2-10). This did not suggest that the assumption of homoscedasticity was incorrect. The constant $\hat{\alpha}$ was estimated to be equal to -0.002 and not significantly different from 0 ($p=0.998$) whilst $\hat{\beta}$ was estimated to be 0.92 and significantly different from 1 ($p=0.001$). The simple linear regression was repeated assuming the intercept was 0. The slope $\hat{\beta}$ was estimated again to be 0.92 and significantly different from 1 ($p=0.001$). The final regression model was therefore the simple linear regression with intercept 0. The estimated variance of the observations around the fitted line ($\hat{\sigma}_\epsilon^2$) was 0.77 and the final model is shown in Figure 2-11, where it can be seen to be a good fit to the reconstructed and the true doses.

Table 2-7 Simple linear regression of the reconstructed and the true doses.

Simple linear regression	
$\hat{\alpha}$ [95% Conf. Interval]	-0.002 [-1.415 - 1.412]
$\hat{\beta}$ [95% Conf. Interval]	0.92 [0.83 - 1.01]
Simple linear regression - intercept zero ($\hat{\alpha} = 0$)	
$\hat{\sigma}_\epsilon^2$	0.77
$\hat{\beta}$ [95% Conf. Interval]	0.92 [0.89 - 0.95]
Regression model: $\hat{y}_i = 0.92x_i$	

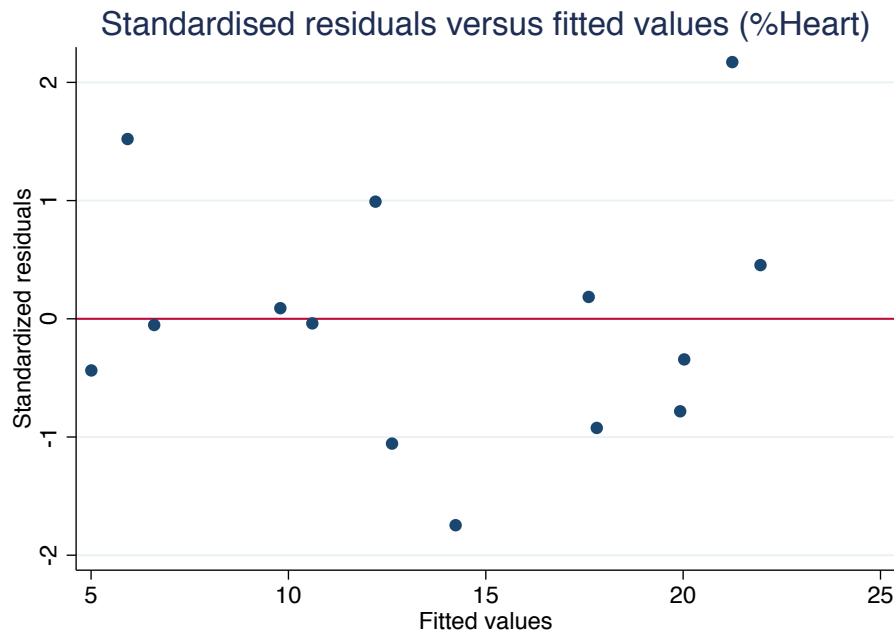


Figure 2-10 Standardised residuals versus fitted values, the assumption of homoscedasticity is confirmed.



Figure 2-11 Final regression model: $\hat{y} = 0.92x$

2.3.2.1 Effect of errors on the dose-response relationship

The %Heart method has been used to derive a dose-response relationship for risk of coronary heart disease in HL survivors by van Nimwegen et al.¹⁵ Based on

conditional logistic regression, the authors estimated that the excess relative risk (ERR) of coronary heart disease was increased by 7.4% per Gy of MHD:

ERR: 7.4% (95% CI 3.3% to 14.8%)

Systematic error

The effect of the systematic errors was taken into account by multiplying the dose-response relationship by the slope of the regression model (0.92). The same correction factor could be applied to the upper and lower bounds of the associated CI.

Random error

The reconstructed doses used to derive the dose-response relationship had a sample median of 20.2 [IQR: (17.5-24.8)] and therefore an approximate estimate of the sample variance is:

$$[(24.8-17.5)/(2 \times 0.67)]^2 = [5.45]^2 = 29.70$$

From the regression analysis, the $\hat{\sigma}_\varepsilon^2$ was estimated 0.77, therefore:

$$\hat{\sigma}_x^2 = 29.70 - 0.77 = 28.93$$

Putting these two estimates into Equation 2-18, the attenuation factor f in the ERR due to random errors in the reconstructed doses becomes $29.70/28.93 = 1.03$. Hence the ERR for coronary disease in HL patients is attenuated by only 3% due to the random errors in the reconstructed doses.

Corrected dose-response model

The rate will be therefore corrected as:

(0.92×7.4×1.03) per Gy of MHD [95% CI: (0.92×3.3×1.03 to (0.92×14.8×1.03]

Providing with a rate of:

ERR: 7.0% per Gy of MHD (95% CI 3.1 % to 14.0%)

2.3.3 Phantom

A simple linear regression of the reconstructed versus the true doses was performed (Table 2-8) and the standardised residuals were plotted versus the fitted values (Figure 2-12). This showed that the assumption of homoscedasticity was incorrect as the variance increased with increasing fitted values, i.e. with increasing MHD.

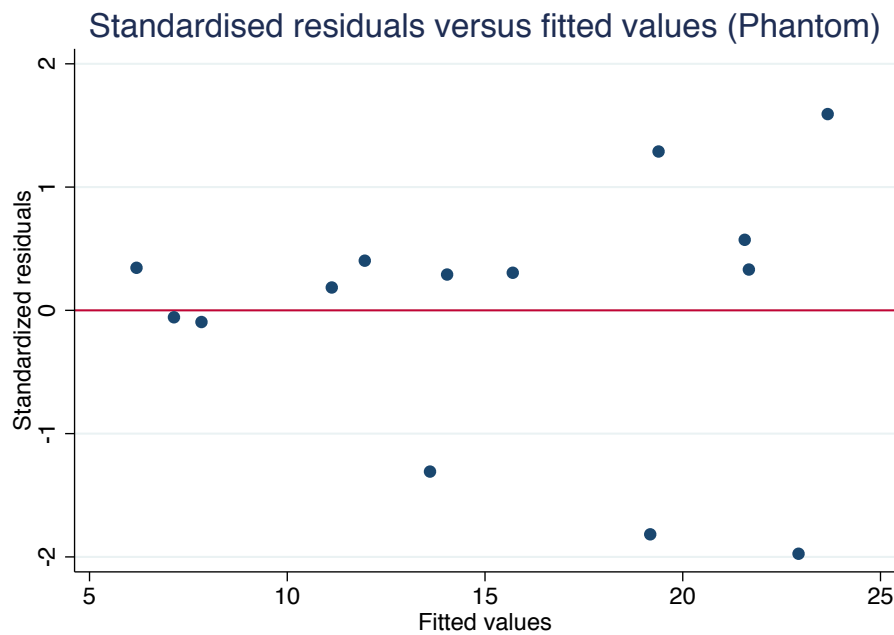


Figure 2-12 Standardised residuals versus fitted values, the assumption of homoscedasticity is not confirmed.

In order to achieve homoscedasticity, a weighted regression with weighting: $\omega_i = \frac{1}{x_i^2}$ was fitted and the standardised residuals were plotted versus the fitted values again. It can be seen on Figure 2-13 that homoscedasticity is now achieved. Therefore, the fitted model was estimated using the weighted regression. The constant $\hat{\alpha}$ was estimated to be equal to 1.51 and not significantly different from 0 ($p=0.120$) whilst $\hat{\beta}$ was estimated to be 0.91 and significantly different from 1 ($p=0.001$). The regression was repeated assuming the intercept as 0. The slope $\hat{\beta}$ was estimated to be 1.03 and still significantly different from 1 ($p=0.001$). The final

regression model was therefore the weighted linear regression and with intercept 0. The estimated variance of the observations around the fitted line ($\hat{\sigma}_\varepsilon^2$) was 7.24 and the final model is shown in Figure 2-14 where it can be seen to be a good fit to the reconstructed and the true doses.

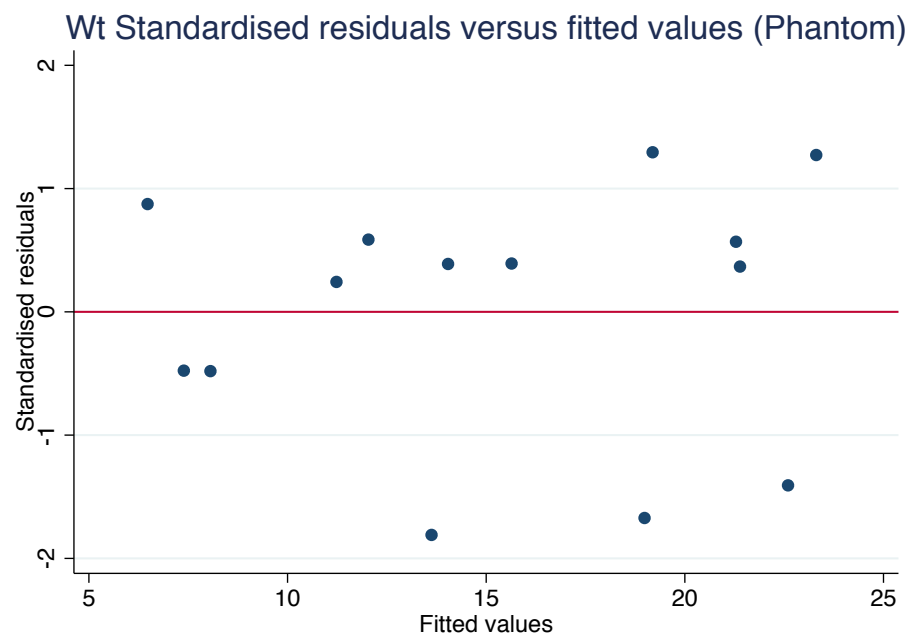


Figure 2-13 Standardised residuals versus fitted values following weighted regression, the assumption of homoscedasticity is confirmed

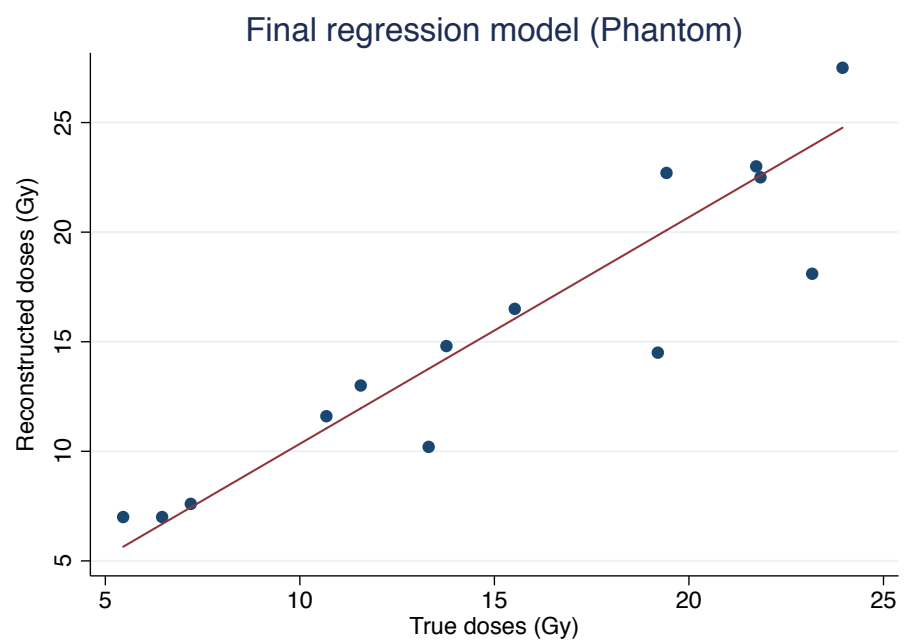


Figure 2-14 Final regression model: $\hat{y} = 1.03x$

Table 2-8 Weighted linear regression of the reconstructed and the true doses.

Weighted regression	
$\hat{\alpha}$ [95% Conf. Interval]	1.51 [-0.45 - 3.47]
$\hat{\beta}$ [95% Conf. Interval]	0.91 [0.73 - 1.09]
Weighted linear regression - intercept zero ($\hat{\alpha} = 0$)	
$\hat{\sigma}_{\varepsilon}^2$	7.24
$\hat{\beta}$ [95% Conf. Interval]	1.03 [0.94 - 1.13]
Regression model: $\hat{y}_i = 1.03x_i$	

2.3.3.1 Effect of errors on the dose-response relationship

The Phantom method has been used by Chow et al.²⁶ to derive RRs for risk of ischemic heart disease in survivors of childhood cancer. Based on a piecewise exponential regression, the authors estimated RRs for five categories of heart dose (Chow et al.²⁶ supplementary table A1)

Systematic error

The effect of the systematic errors was taken into account by multiplying the dose-response relationship by 1.03 (i.e. the slope of the regression model). The same correction factor could be applied to the upper and lower bounds of the CI.

Random error

The reconstructed doses used to derive the dose-response relationship (i.e. the RRs) had a sample variance of 98.60 (The median and IQR of the reconstructed doses were not provided by the authors, therefore, an estimation was performed using table 2 from Chow et al.²⁶) From the regression analysis, the $\hat{\sigma}_{\varepsilon}^2$ was estimated to be 7.24, therefore an approximate estimate of the sample variance is:

$$\hat{\sigma}_x^2 = 98.60 - 7.24 = 91.36$$

Putting these two estimates into Equation 2-18, the attenuation factor f in the RRs due to random errors in the reconstructed doses becomes $98.60/91.38=1.08$.

Hence the risk model for ischemic heart disease was attenuated by about 8% by the random errors in the dose estimates.

Corrected dose-response model

Therefore, after combining the effect of both systematic and random errors on the dose-response relationship, by multiplying each RR by 1.03 for the systematic error and by 1.08 for the random error, the corrected RRs are shown in Table 2-9.

Table 2-9 Multivariable Piecewise Exponential Regression Results for ischemic heart disease in the Childhood Cancer Survivor Study Cohort and corrected RRs

Heart Radiation dose (Gy)	RRs (95% CI)	Corrected RRs (95% CI)
No dose	1.00(referent)	1.0 (referent)
<5	0.8 (0.3 to 1.8)	0.9 (0.3 to 1.9)
5-14	2.4 (1.4 to 4.2)	2.7 (1.6 to 4.7)
15-34	3.7 (2.5 to 5.4)	4.1 (2.8 to 6.0)
≥ 35	7.8 (5.4 to 11.2)	8.7 (6.0 to 12.5)

2.3.4 RepCT

2.3.4.1 Mean heart dose reconstruction

A simple linear regression of the reconstructed versus the true doses was performed (Table 2-10) and the standardised residuals were plotted versus the fitted values (Figure 2-15). The graph suggested that the assumption of homoscedasticity was incorrect as the variance increased with increasing fitted values, i.e. with increasing MHD.

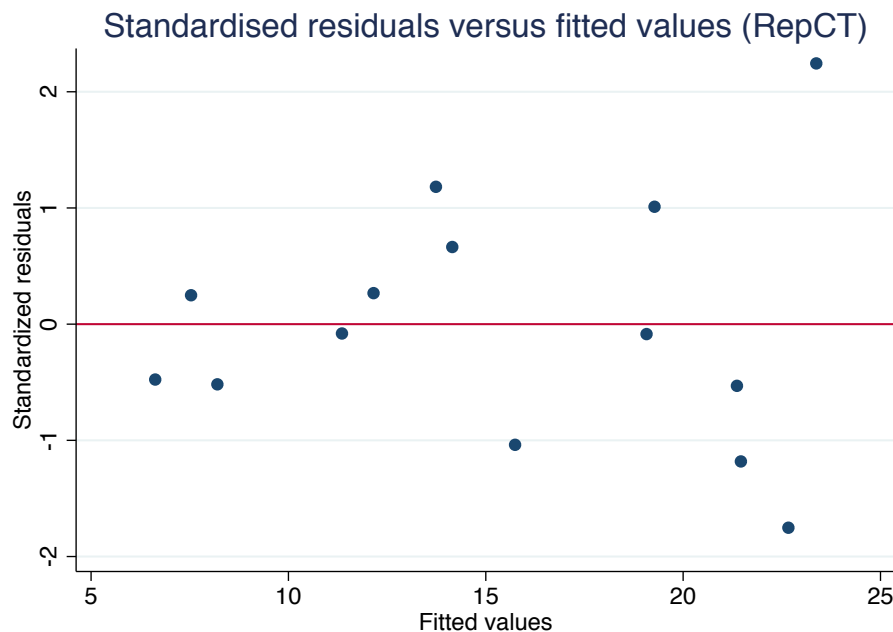


Figure 2-15 Standardised residuals versus fitted values, the assumption of homoscedasticity is not confirmed.

In order to achieve homoscedasticity, a weighted regression with weighting: $\omega_i = \frac{1}{x_i^2}$ was fitted and the standardised residuals were plotted versus the fitted values again. It can be seen on Figure 2-16 that homoscedasticity is now achieved. therefore, the fitted model was estimated using the weighted regression. The constant $\hat{\alpha}$ was estimated to be equal to 1.10 and not significantly different from 0 (p=0.123) whilst $\hat{\beta}$ was estimated to be 0.95 and significantly different from 1

($p < 0.001$). The regression was repeated assuming the intercept as 0. The slope $\hat{\beta}$ was estimated to be 1.04 and still significantly different from 1 ($p = 0.001$). The final regression model was therefore the weighted linear regression and with intercept 0. The estimated variance of the observations around the fitted line ($\hat{\sigma}_\varepsilon^2$) was 4.19. The final model is shown in Figure 2-17 with the reconstructed and the true doses, where it can be seen to be a good fit.

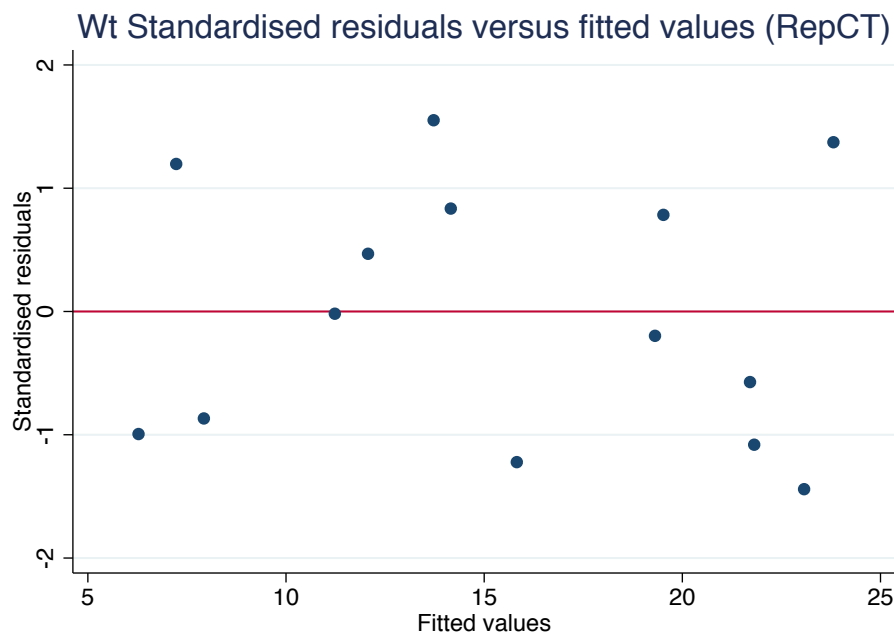


Figure 2-16 Standardised residuals versus fitted values following weighted regression, the assumption of homoscedasticity is now confirmed.

Table 2-10 Weighted linear regression of the reconstructed and the true doses

Weighted regression	
$\hat{\alpha}$ [95% Conf. Interval]	1.10 [-0.35 - 2.56]
$\hat{\beta}$ [95% Conf. Interval]	0.95 [0.81 - 1.08]
Weighted regression - intercept zero ($\hat{\alpha} = 0$)	
$\hat{\sigma}_\varepsilon^2$	4.19
$\hat{\beta}$ [95% Conf. Interval]	1.04 [0.97 - 1.11]
Regression model: $\hat{y}_i = 1.04x_i$	

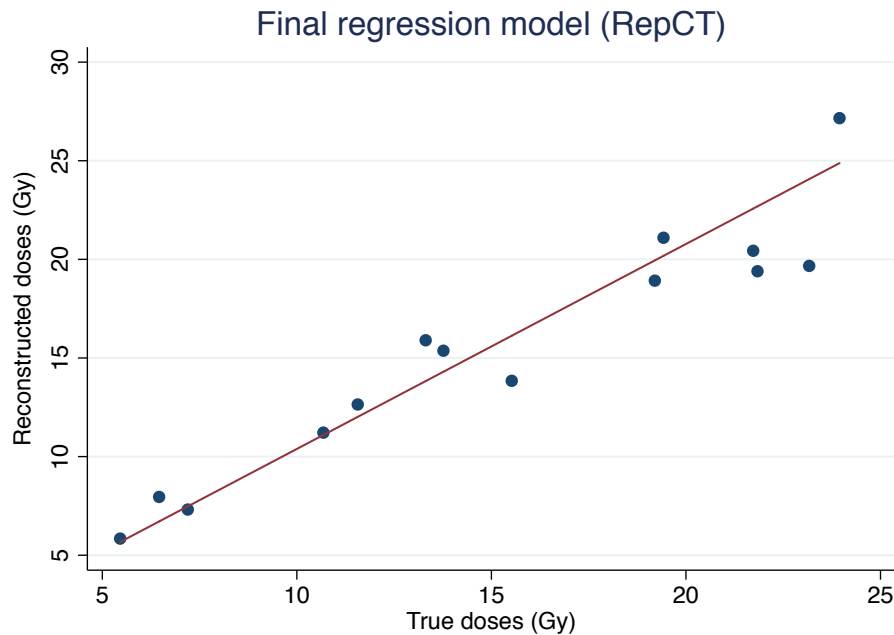


Figure 2-17 Final regression model: $\hat{y} = 1.04x$

The effect of the errors in MHD on a dose-response relationship was not assessed here in detail. However, if the linear dose-response relationship between MHD and the risk of CHF (ERR 7.0% per Gy) presented in Appendix A in supplemental Table 2 was considered, the systematic and random errors together would attenuate the dose-response relationship by only 2.0 %, therefore, the effect would be negligible. The effect however of the errors in this method was assessed using MLVD below.

2.3.4.2 Mean left ventricular dose reconstruction

A simple linear regression of the reconstructed versus the true doses was performed (Table 2-11) and the standardised residuals were plotted versus the fitted values Figure 2-18. As with MHD, a weighted regression needed to be performed to achieve homoscedasticity (Figure 2-19). The constant $\hat{\alpha}$ was estimated to be equal to 0.75 and not significantly different from 0 ($p=0.054$) whilst $\hat{\beta}$ was estimated to be 1.10 and significantly different from 1 ($p<0.001$). The regression was repeated with intercept 0. The slope $\hat{\beta}$ was estimated to be 1.25 and significantly different

from 1 ($p<0.001$). The final regression model is therefore the weighted linear regression with intercept 0. The estimated variance of the observations around the fitted line ($\hat{\sigma}_{\epsilon}^2$) was 11.93. The final model is shown in Figure 2-20 together with the reconstructed and the true doses, where it can be seen to be a good fit.

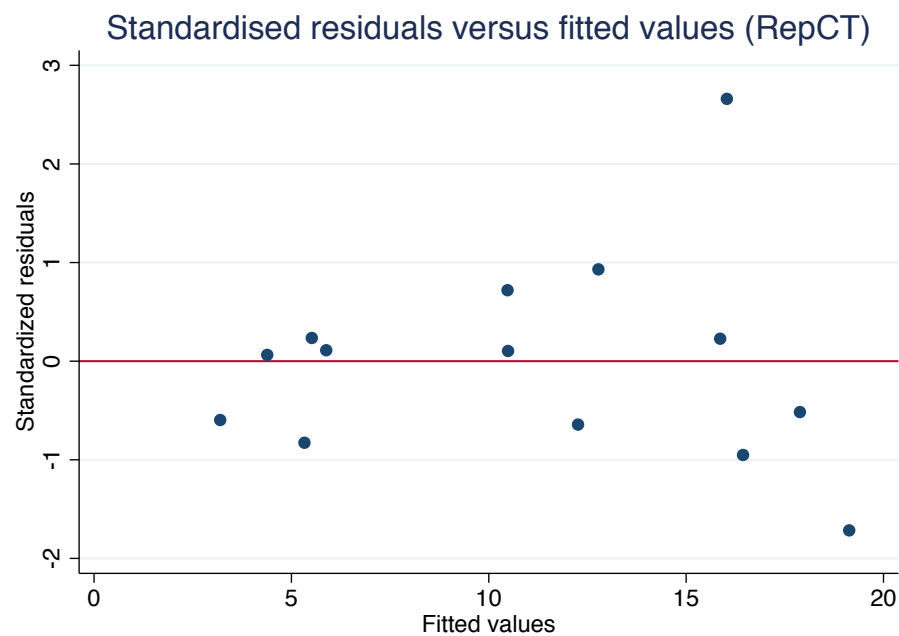


Figure 2-18 *Standardised residuals versus fitted values, the assumption of homoscedasticity is not confirmed.*

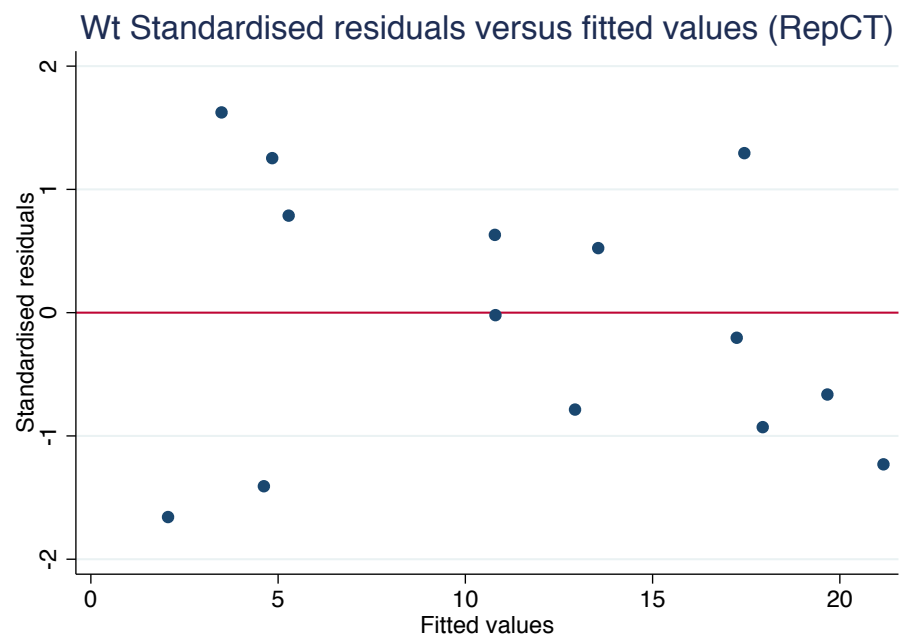


Figure 2-19 *Standardised residuals versus fitted values following weighted regression, the assumption of homoscedasticity is now confirmed.*

Table 2-11 Weighted linear regression of the reconstructed and the true doses

Weighted regression	
$\hat{\alpha}$ [95% Conf. Interval]	0.75 [-0.33 - 1.54]
$\hat{\beta}$ [95% Conf. Interval]	1.10 [0.87 - 1.33]
Weighted regression - intercept zero ($\hat{\alpha} = 0$)	
$\hat{\sigma}_{\varepsilon}^2$	11.93
$\hat{\beta}$ [95% Conf. Interval]	1.25 [1.07 - 1.43]
Regression model: $\hat{y}_i = 1.25x_i$	

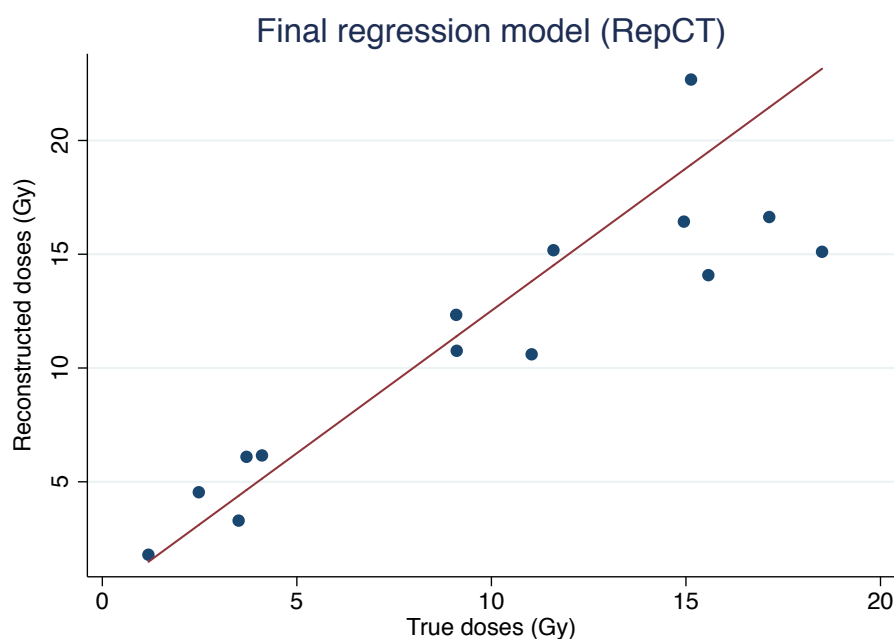


Figure 2-20 Final regression model: $\hat{y} = 1.25x$

2.3.4.3 Effect of errors on the dose-response relationship

The RepCT method has been used in the retrospective study described in Chapter 1 to derive a dose-response relationship for the risk of CHF in survivors of HL using reconstructed MHD and MLVD. The linear dose-response relationship between MLVD and the risk of CHF was used here to assess the impact of the errors. The ERR of CHF per Gy of MLVD reported in Chapter 1 was:

ERR: 9.0% per Gy of MLVD (95% CI 1.7% to 29.0%)

Systematic error

The effect of the systematic errors was taken into account by multiplying the dose-response relationship by 1.25 (i.e the slope of the regression model) The same correction factor can be applied to the upper and lower bounds of the CI.

Random error

The reconstructed MLVDs used to derive the dose-response relationship had a sample median of 16.2 [IQR: (11.9-21.9)] and a sample variance of:

$$[(21.9-11.9)/(2 \times 0.67)]^2 = [7.46]^2 = 55.65$$

From the regression analysis, the $\hat{\sigma}_\varepsilon^2$ was estimated 11.93, therefore:

$$\hat{\sigma}_x^2 = 55.65 - 11.93 = 43.72$$

Putting these two estimates into Equation 2-18, the attenuation factor f due to random errors in the reconstructed doses becomes $55.65/43.72=1.27$. Hence the dose-response relationship is attenuated by 27.0 % due to the random errors in the reconstructed doses.

Corrected dose-response model

The rate will be therefore corrected as:

$$(1.25 \times 9.0 \times 1.27) \text{ per Gy of MLVD [95\% CI: } (1.25 \times 1.7 \times 1.27 \text{ to } (1.25 \times 27.0 \times 1.27)]$$

Providing with a corrected rate of:

$$\text{ERR: } 14.3\% \text{ per Gy of MLVD (95\% CI 2.7\% to 42.9\%)}$$

2.3.5 Navigator

2.3.5.1 Mean heart dose reconstruction

The same analysis as above was performed for the Navigator method, the weighted regression results can be seen in Table 2-12 and the final regression model for MHD is shown in Figure 2-23 with the reconstructed and the true doses where it can be seen to be a good fit.

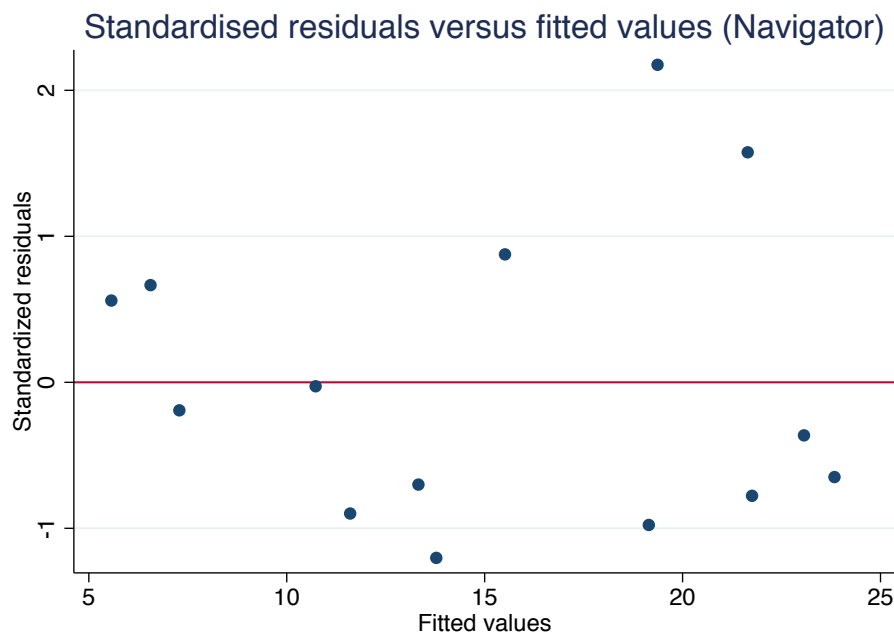


Figure 2-21 Standardised residuals versus fitted values, the assumption of homoscedasticity is not confirmed for the linear model.

Table 2-12 Weighted linear regression of the reconstructed and the true doses

Weighted regression	
$\hat{\alpha}$ [95% Conf. Interval]	0.85 [-0.37 - 2.08]
$\hat{\beta}$ [95% Conf. Interval]	0.94 [0.82 - 1.05]
Weighted regression - intercept zero ($\hat{\alpha} = 0$)	
$\hat{\sigma}_\varepsilon^2$	1.98
$\hat{\beta}$ [95% Conf. Interval]	1.01 [0.95 - 1.06]
Regression model: $\hat{y}_i = 1.01x_i$	

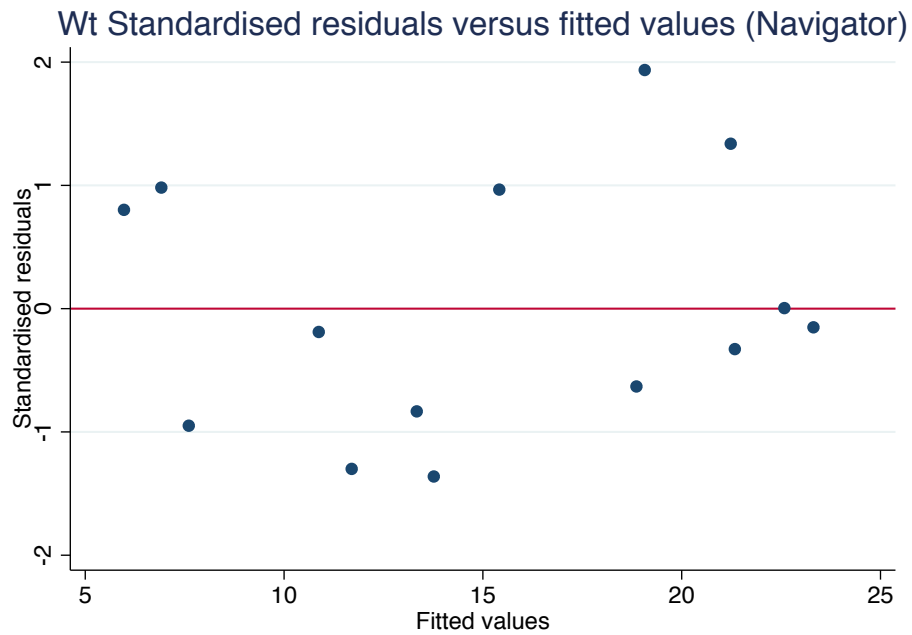


Figure 2-22 Standardised residuals versus fitted values following weighted regression, the assumption of homoscedasticity is now confirmed.

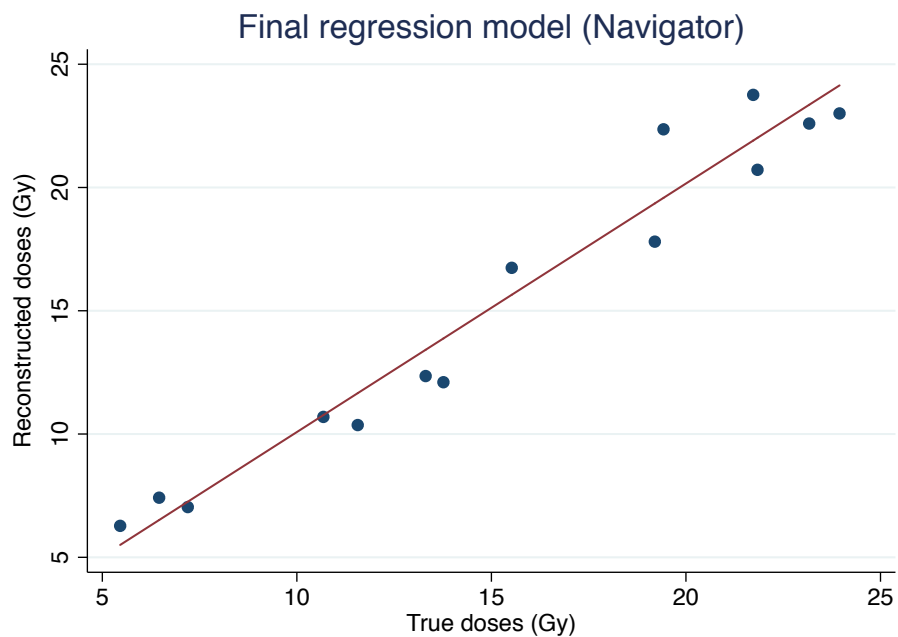


Figure 2-23 Final regression model: $\hat{y} = 1.01x$

2.3.5.2 Mean left ventricular dose reconstruction

The same analysis as above was performed for the MLVD and the final regression model can be seen in Figure 2-25.

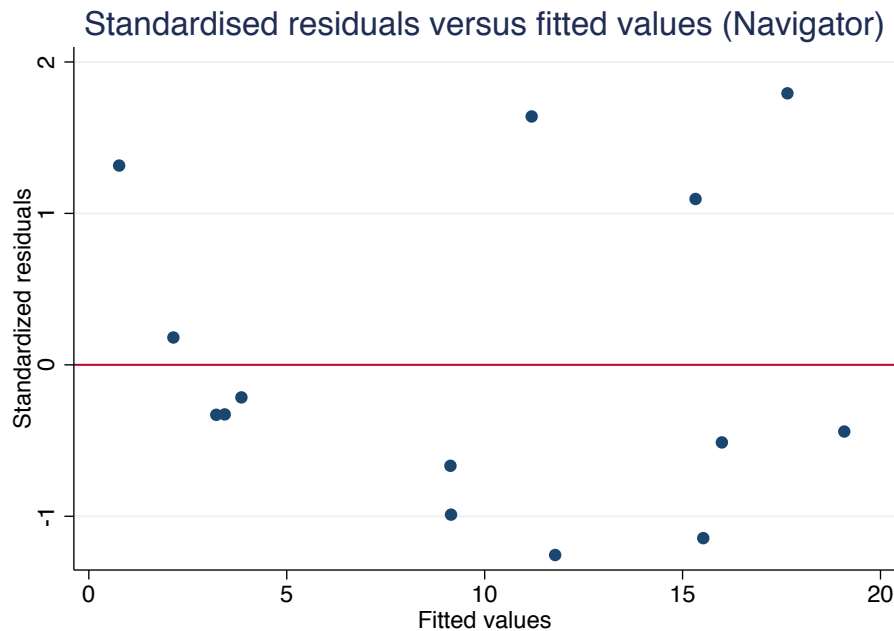


Figure 2-24 Standardised residuals versus fitted values, the assumption of homoscedasticity is confirmed for the linear regression.

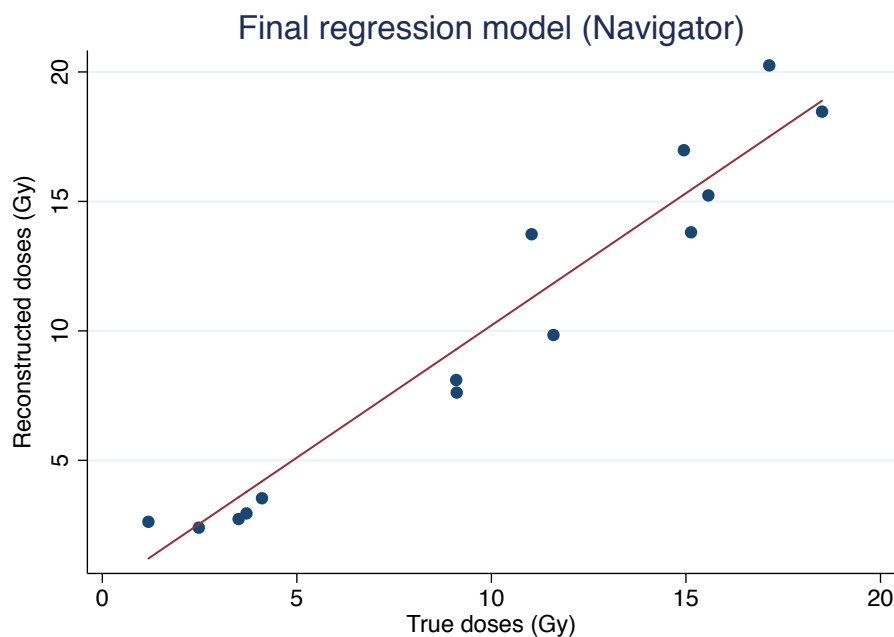


Figure 2-25 Final regression model: $\hat{y} = 1.02x$

Table 2-13 Simple linear regression of the reconstructed and the true left ventricular doses

Linear regression	
$\hat{\alpha}$ [95% Conf. Interval]	-0.49 [-2.34 - 1.37]
$\hat{\beta}$ [95% Conf. Interval]	1.06 [0.89 - 1.22]
Linear regression - intercept zero ($\hat{\alpha} = 0$)	
$\hat{\sigma}_{\epsilon}^2$	2.46
$\hat{\beta}$ [95% Conf. Interval]	1.02 [0.94 - 1.10]
Regression model: $\hat{y}_i = 1.02x_i$	

2.3.5.3 Effect of errors on the dose-response relationship

The Navigator method has been used to derive a dose-response relationship by Hahn et al. ¹⁹ Based on conditional logistic regression, the authors estimated that the cardiovascular events rate in HL patients increased by:

9% per Gy of MHD (95% CI: 2% to 16%)

Systematic error

The effect of the systematic errors was taken into account by multiplying the dose-response relationship by 1.01 (i.e. the slope of the regression model). The same correction factor can be applied to the upper and lower bounds of the associated CI. Since the slope was almost equal to 1 the effect of the systematic error was negligible.

Random error

The reconstructed doses used to derive the dose-response relationship had a sample median of 24.9 [IQR: (18.8-30.0)] and a sample variance of:

$$[(30.0-18.8)/(2 \times 0.67)]^2 = 69.9$$

From the regression analysis, the $\hat{\sigma}_{\epsilon}^2$ was estimated 1.98. Therefore:

$$\hat{\sigma}_x^2 = 69.9 - 1.98 = 67.9$$

Putting these two estimates into Equation 2-18, the attenuation factor f due to random errors in the reconstructed doses becomes $69.9/67.9 = 1.03$. Hence the cardiovascular events rate in HL patients is attenuated by 3.0 %.

Corrected dose-response model

The rate will be therefore corrected as:

$(1.01 \times 9.0 \times 1.03)$ per Gy of MHD [95% CI: $(1.01 \times 2.0 \times 1.03)$ to $(1.01 \times 16.0 \times 1.03)$]

Providing with a corrected rate of:

ERR: 9.4% per Gy of MHD (95% CI 2.1% to 16.6%)

2.4 Discussion

To the best of my knowledge, this is the first study to evaluate the accuracy and feasibility of several radiation dose reconstruction methods for use in retrospective cardiac dosimetry. It is also the first study to quantify the effect that the dose reconstruction errors had on published dose-response relationships and to provide a methodology for researchers to include those uncertainties in the dose-response models.

The %Prescribed was the least time-consuming method to use and required very basic software and computing resources. The average reconstructed MHD was overestimated by 19.0% compared to the average true MHD and the method had the largest systematic error compared to the other four methods, the effect of the random error, however, was negligible. The systematic error attenuated the associated dose-response relationship by 60% bringing the rate for cardiovascular events to 0.6% per Gy from the originally reported 1.5% per Gy.

The %Heart method was also simple to use and provided more accurate estimates for MHD compared to the %Prescribed, it underestimated the average MHD by 8.0%. The effect of the random error on the dose-response relationship was very low (3.0 %), however, the dose-response relationship was attenuated by 8.0% due to the systematic error in the reconstructed doses. The corrected ERR was estimated to be 7.0% per Gy of MHD, 0.4% lower than the originally reported ERR of 7.4% per Gy of MHD.

The Phantom is the most widely used method in the literature and has been used for various observational studies within the CCSS cohort.^{27,28} It is a more complex method than the previous two and requires specialised in-house software and trained staff. The average reconstructed MHD was overestimated by only 1.0%

and the effect of the systematic error on the dose-response model was negligible. The random error, however, caused an 8.0% attenuation of the dose-response relationship (RRs reported in Table 2-9).

The RepCT and Navigator methods are labour intensive and require specialized software and training. However, the RepCT is more accessible as it can be developed by any centre with a commercial TPS available and a library of HL CT scans. The Navigator method also requires sophisticated in-house software in addition to a TPS and is not widely available. Both methods estimated the average MHD very accurately (both within 1.0% of the average true doses) and the effect of the random and systematic errors on the dose-response relationships were negligible. However, the Navigator method performed better than the RepCT when used to reconstruct MLVD. RepCT overestimated the average MLVD by 11.0% whilst the Navigator method by only 1.0%. For the RepCT, the dose-response relationship for the risk of CHF per Gy of MLVD was attenuated due to the random error by 27.0% and due to the systematic error by 25.0% resulting in a corrected ERR of 14.3% from the original from 9.0%. The effect of the MLVD reconstruction errors on the dose-response relationship, could not be evaluated for the Navigator method as it has not been used to derive a risk model based on MLVD. However, based on the previous analysis, it is hypothesised that the Navigator would have a lower effect compare to the RepCT due to the lower reconstruction errors.

Among the methods studied, there is a clear trade-off between accuracy and time consumption. As expected, the more patient specific characteristics taken into consideration, the more accurate the dose estimates are. However, this is not always possible, or perhaps necessary, in some epidemiological studies. If MHD is the required dosimetric parameter for a large observational study and simulation

films are available, the %Heart method offers a good compromise as it is the quickest way of estimating the MHD relatively accurately and with minimum resources. However, it cannot provide volumetric dosimetry information and can only be used for the whole heart. Therefore, it is not suitable if doses to cardiac substructures are required. The %Prescribed is less accurate, however, very fast and it can provide MHD and dose estimates for a wide range of cardiac substructures and radiation field combinations, even when original patient imaging data (such as simulation films) are not available. This can be particularly useful for large observational studies in HL cohorts for which only the RT field arrangement and prescribed dose information is available. However, the derived dose-response relationships will need to be corrected due to substantial dose reconstruction errors as shown above.

The RepCT and the Navigator are the most accurate methods but also the most labour intensive. Therefore, they are more suitable for smaller patient cohorts. These methods can also estimate the dose to cardiac substructures and provide volumetric data. Dose-response relationships based on MHD from either method do not require any adjustment as the effect of the reconstruction errors is negligible. However, if the dose to substructures is used to derive them, the effect of the errors should be included. The Phantom method is arguably the most practical option for accurate MHD estimates in large patient cohorts (e.g. Childhood Cancer Survivor Study). It can also be used to estimate dose for cardiac substructures. However, its accuracy for estimating cardiac substructures was not evaluated in this study. Lastly, the Phantom method can be used even if simulation films are not available, however, in which case its reconstruction accuracy is expected to be compromised.

The selection of the volume of interest is crucial for epidemiological study design, the decision should be made based on the amount of patient data available and the dose reconstruction method to be used. It was shown that the reconstruction accuracy was reduced in dose estimates for cardiac substructures (e.g. left ventricle) compared to the whole heart. This is expected due to the larger variation of the position and size of cardiac substructures between patients and perhaps the ability to accurately delineate them even when modern imaging techniques are available. In a study of twenty-two detailed heart models created from heart CT-angiographies and inserted into representative patients' RT-planning CTs, Moignier et al.²⁹ reported that the coronary mean dose variation could be up to 40% between different coronary topologies, whereas the MHD variation was only up to 6%. However, dose to cardiac substructures might be a better risk predictor for some cardiac endpoints and therefore a more sophisticated reconstruction method that takes into account patient specific shape and size of the heart such as the Navigator method should be used. Furthermore, if the errors in the dose reconstruction are taken in to account, for example by using the method presented here, the derived dose-response relationships will still provide accurate risk estimates.

2.4.1 Strengths and limitation

One of the strengths of this study was that all five methods were compared against the same gold standard and for fifteen patients with a relatively large variation of heart positions and shapes. Additionally, the dose reconstruction was blind (i.e. the true doses were not known before the reconstruction was completed) and the same amount of patient information was used for all methods. The methods investigated here cover the vast majority of retrospective cardiac dosimetry methods used in

epidemiological studies for the prediction of radiation-related cardiac risks in literature. Furthermore, it is the first study to provide a methodology to account for dose-reconstruction errors in dose-response relationships, to specify and distinguish these errors between random and systematic and to identify the effect of each type of error independently.

Perhaps the most important limitation of this study was the relatively narrow range of cardiac doses in the HL patient group used in this study (MHD 5.5 Gy to 23.5 Gy and MLVD 1.2 Gy to 18.5 Gy). In historical treatments, the reported MHDs were up to 34-36 Gy^{17,30} due to the higher prescribed doses compared to the doses in this study. Therefore, a potential increase in dose reconstruction inaccuracies with increased dose would not be taken in to account. Only a limited amount of information was available regarding the distribution of doses used in the original cohorts to derive the dose-response models. Therefore, it was not possible to verify whether they followed a normal distribution precisely. This is a limitation of this study, however, modest departures from normality are unlikely to have a major effect in the conclusions of the regression calibration analysis. Another limitation was that, contrary to most epidemiological studies, DRRs were available for all patients in this study. In most epidemiological studies there is a number of patients with missing simulation films and their doses will therefore have to be imputed, bringing additional uncertainties. For that reason, the results here might slightly overestimate the reconstruction accuracy for all methods. However, the impact of imputed doses on the dose-response relationships when using the RepCT and %Heart methods have been shown to be negligible.^{15,17}

The particular strengths and limitations of each reconstruction method have been discussed in detail elsewhere^{8,10,11,18} and it is beyond the scope of this chapter.

However, the RepCT method was selected for the cardiac dose reconstruction in a case-control study described in Chapter 1 and thus more strengths and limitations of this particular method were described there.

2.4.2 *Future perspectives*

Similar comparisons to evaluate the reconstruction accuracy for more cardiac doses but also for doses in different OAR are required. Additionally, a larger group of patients with a wider range of cardiac doses would show whether reconstruction inaccuracies increase with lower or higher doses. The effect of the variation in mediastinal separation amongst patients on cardiac doses should also be investigated in future studies due to the potential effect on the absorbed cardiac doses. Lastly, with the increasing use of CT-based treatment planning in HL RT since the early 2000s, more accurate cardiac doses, based on a patient's individual CT scan, will be available in future observational studies. This will provide more accurate dose-response models and may also help to determine whether MHD, MLVD, mean dose to other cardiac substructures or another dosimetric parameter is the best measure to predict radiation-related risk of heart disease.

2.5 Conclusions

The reconstruction methods investigated in this study estimated cardiac doses with a range of 1.0% to 19.0% accuracy when compared to doses derived by CT-based dosimetry. These errors affected the derived dose-response relationships from as low as 2.0% for the more accurate reconstruction methods, to up to 60.0% for the less accurate. Methods to account for these errors when deriving dose-response relationships by using them were developed and presented in this study. Each reconstruction method has advantages and disadvantages, selection of the most appropriate method should be based on the organ or volume of interest for the specific epidemiological study, the amount of patients imaging data available, the end point of interest, availability of resources and the time taken as well as the size

of patient cohort. It is not necessarily true that the most sophisticated method is always the best choice.

2.6 Reference

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Chapter 3 Modern radiotherapy techniques for Hodgkin lymphoma, clinical pencil beam scanning vs advanced photon therapy

3.1 Introduction

The increased risk of radiation-related late effects in HL survivors and the association between these late effects and incidental radiation into OAR^{1–10}, has driven great technological advancements in RT and reductions in incidental radiation on healthy organs.

Modern photon RT techniques such as IMRT or advanced partial arc volumetric RT (PartArc) have achieved substantial dose reductions to OAR.^{11–14} An additional approach to achieving reductions in risks is proton beam therapy, where steep dose gradients allow further reductions in incidental radiation.¹⁵ In both photon and proton techniques, the delivery of RT in deep inspiration breath-hold (DIBH) can produce an even further decrease of OAR dose and risks.^{11,16}

A substantial number of planning studies have demonstrated dosimetric benefits of proton RT versus conventional or advanced photon RT for the treatment of HL. A recent comprehensive review on the use of proton RT for the treatment of HL performed by the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee, summarised the results from 14 planning studies.¹⁵ Overall, proton RT reduced the dose to most OAR when compared to conventional RT such as 3D-CRT or even advanced RT such as IMRT and Volumetric modulated arc therapy (VMAT). The mean dose reduction in the main OAR such as heart, lungs, breast, oesophagus etc. ranged on average between 1.0 and 4.0 Gy. The target volume coverage was most of the times superior with proton RT or at least as good as photon RT.

One of the main issues that Tseng et al.¹⁵ identified was the fact that it was not clear whether the “best plan” was used for each RT method in these planning studies. Proton and photon plans were created usually by the same centre with specialist clinical experience in either photon or proton RT, which might have introduced bias in either direction. Additionally, the proton RT field arrangement that was used in some studies might have not fully demonstrated the potential benefit from proton RT. For example, Andolino et al.¹⁷ used only posterior fields, which although reduced the breast dose, at the same time increased substantially the heart dose. However, the same argument could be used for proton RT centres with little experience in advanced photon RT treatment planning who might have not created clinically deliverable photon RT plans or at least not “the best” plan.

However, access to proton RT and especially delivered in DIBH is currently limited and demands a considerable increase in costs and training compared to conventional RT such as 3D-CRT. Hence, even in developed countries, referral for proton RT must be prioritised to patients at greatest risk of developing complications from conventional RT. In order to determine which patients should be treated using proton RT it is necessary to determine which patients will receive most benefit. Randomised trials to evaluate the benefits of proton RT haven not been developed yet and it is uncertain if they will due to the various challenges such as the long follow-up required for radiation-related effects (~10 years) combined with low rate of late effects in HL and the scarce availability of proton RT. Therefore, alternative selection processes should be developed, perhaps based on substantial dosimetric benefits in OAR and predicted risks of late effects.

One approach that has been adopted by the Health Council of the Netherlands has been described by Langendijk et al.¹⁸ In this model-based

approach, both photon and proton treatment plans are produced for a patient who is considered for proton RT. The results from the comparative study are then integrated into Normal Tissue Complication Probability (NTCP) models in order to estimate the potential side effects. The patients that benefit from protons compared to photons, in terms of NTCP-value reductions, are then chosen for proton RT. Whilst this is a thorough and scientifically sound approach, it can be time consuming and expensive, especially if it was to be applied to all RT patients.

In this chapter I aim to identify sub-groups of HL patients, who would be benefit substantially by PBS proton RT. One of the aims is to identify these patients based on their pre-chemotherapy extent of disease (i.e. before the decision for RT has been made and a treatment plan produced) with the aim of reducing the number of patients going through a detailed treatment planning assessment thus making the selection process more practical in a busy healthcare environment with scarce resources.

I will perform a detailed dosimetric comparison between clinically delivered PBS proton RT versus planned PartArc and 3D-CRT, all in DIBH and evaluate the potential dosimetric benefits or disadvantages. I will then investigate disease characteristics such as thoracic extent of the CTV, axillary involvement and target volume which could be used to identify HL patients for whom PBS would give the most substantial benefits compared to conventional or advanced photon RT.

3.2 Methods

3.2.1 Study population

A planning study was performed in a group of twenty-one HL patients treated between April 2015 and October 2016 in the Prague Proton Therapy Centre, Czech Republic. The patients (16 females and 5 males) were treated with involved site PBS proton RT at 30 Gy (RBE 1.1) in 15 fractions. The treatment was well tolerated with very few acute toxicities such as dysphagia and no severe toxicities. All patients were irradiated in supine position, arms alongside the body, with fixation via a 5-point head and neck mask with perforation for accessories needed for DIBH application (Figure 3-1). The planning CT was acquired using GE Optima CT 580W RT, in DIBH using SDX® system (Dyn'R-SDX version 2.06). The patient group characteristics can be seen in Table 3-1.

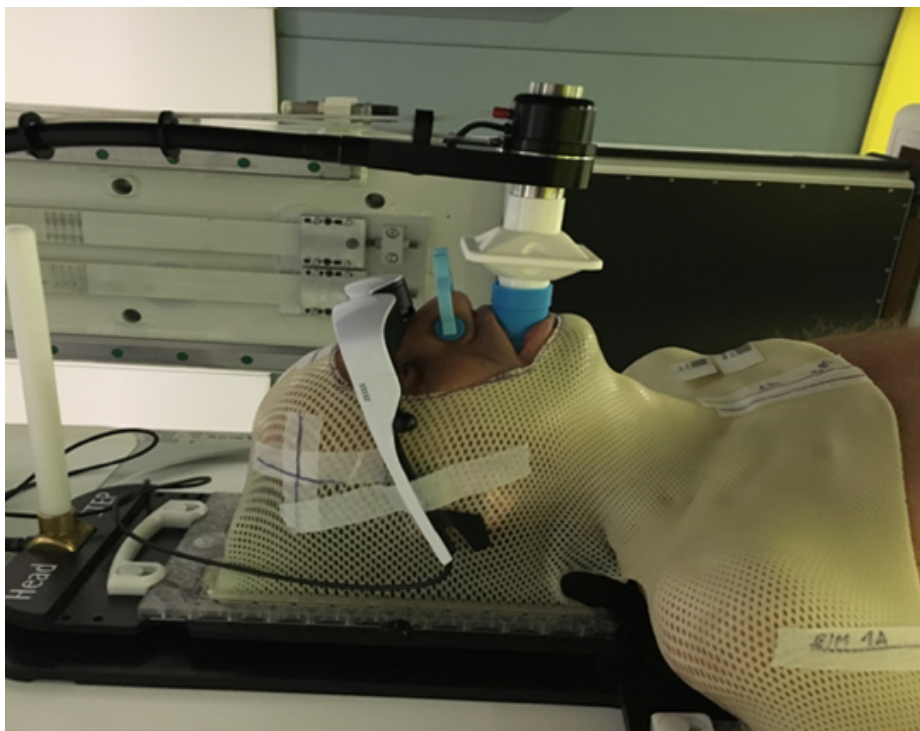


Figure 3-1 Five-point head and neck mask used for body fixation to reduce patient motion during treatment. A deep inspiration breath-hold SDX® system was used to monitor patients breathing during treatment. (Used with permission by the Prague Proton Therapy Center)

Table 3-1 Patient characteristics

Sex	N	%
Males	5	18
Females	16	82
Age at RT		
Median age 31years (range:18-48)		
Risk factors		
<i>Hypertension</i>		
No	20	95
Yes	1	5
<i>Smoking at time of HL diagnosis</i>		
No	16	82
Yes	5	18
HL Stage^o		
Early and intermediate (IIA/B)	18	86
Advanced (IIIB/IIISB)	3	14
Chemotherapy		
Median dose of anthracyclines 317.5 mg/m ² (range 255-420)		
6 x escalated BEACOPP	4	19
2 x escalated BEACOPP + 2 x ABVD	15	71
4 x ABVD	2	10
Total	21	100

HL: Hodgkin Lymphoma ^oHL stage according to Lugano classification¹⁹ RT: Radiotherapy

3.2.2 Treatment planning

The two photon techniques selected for the dosimetric comparison with PBS, were the PartArc technique and 3D-CRT. PartArc was developed for the purpose of this study, similar versions of the method presented in this chapter have been presented by Voong et al.¹³ also referred to as “butterfly VMAT” and by Filipi et al.¹⁴ However, a new approach was used here as described in section 3.2.2.3. PartArc was selected as it currently represents one of the most advanced photon RT methods for treatment of HL and can achieve significant dose reductions in OAR compared to other methods whilst not compromising significantly in target volume coverage.

3D-CRT was selected as it is still the standard photon RT method used in many RT centres worldwide. A total of 3 final plans per patient were compared. I used the Eclipse treatment planning system (TPS) (Version 13.0.28, Varian Medical System, Palo Alto, CA) to create the photon RT plans. The proton plans were created at the Prague Proton Centre using XiO TPS (Version V4.80.00.7, Elekta CMS, St. Louis, MO) and were delivered by an IBA Proteus®PLUS proton therapy system in the Prague Proton Therapy Centre.

3.2.2.1 Contouring

The proton plans were provided by the Prague Proton Centre with the target volumes already contoured by proton RT clinicians and dosimetrist with routine clinical practice experience. The international lymphoma radiation oncology group (ILROG) recommendations²⁰ were used for target volume delineation such as gross tumour volume (GTV), CTV and PTV for all treatment methods. For the purpose of this study, I contoured OAR such as lungs, spinal cord, breast, oesophagus for all patients, created a number of structures to improve the photon planning optimisation such as OAR minus PTV (e.g. Heart-PTV and body-PTV) as well as various other planning assisting structures. The heart and twelve cardiac substructures were contoured according to the heart atlas by Feng et al.²¹

For the proton RT plans the following clinical protocol was used: the CTV was divided into two parts, a neck and a mediastinal section. A margin of 5mm was added to the mediastinal section of the CTV to account for uncertainties for internal organ motion in the thoracic area such as the lungs and heart, this structure was named as the proton internal target volume (Proton-ITV). An additional uniform margin of 8mm was added to the Proton-ITV (including the neck section) to create the Proton-PTV which was the treated target volume.

For the photon RT plans, I created a Photon-PTV using different margins than those for protons, a uniform 10mm margin was added on the CTV, also following the ILROG guidelines, however, a larger margin was not added in the superior-inferior direction as advised by the guidelines, as the treatment would be delivered in DIBH.^{16,22} Around the supraclavicular and neck region the proton-PTV margins were usually smaller than the photon-PTV, (Figure 3-3 - top image), however the two PTVs very often overlapped near moving organs such as lungs and heart due to the increase margin of the proton-PTV near these organs. (Figure 3-3 - bottom image)

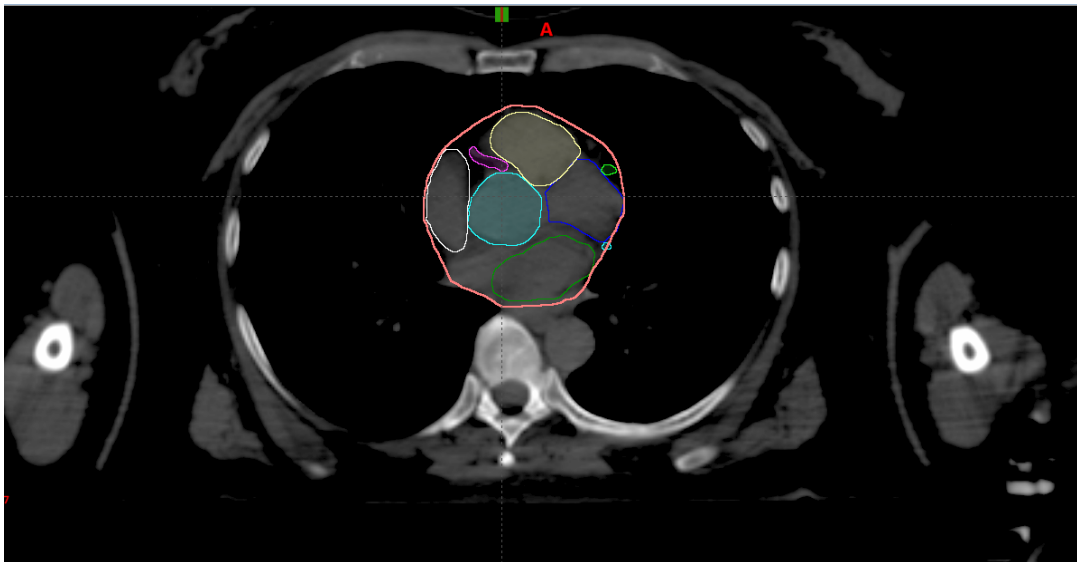


Figure 3-2 Transverse CT image of the heart and seven cardiac substructures. Heart (Pink), aortic valve (turquoise), left anterior descending (light Green), left atrium (dark green), left ventricle (blue), right atrium (white), right coronary artery (magenta), right ventricle (yellow).

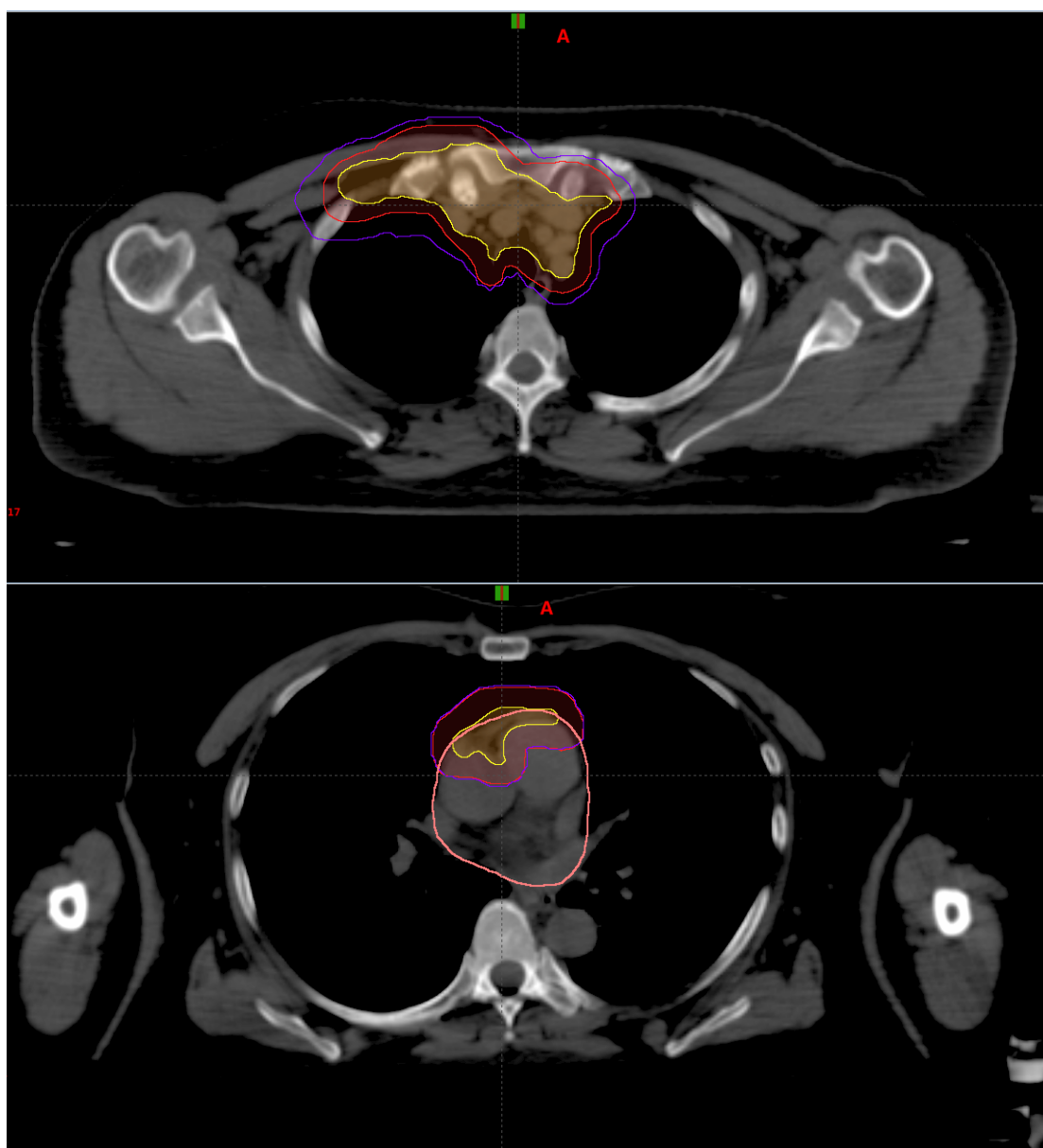


Figure 3-3 Transverse CT image of the supraclavicular and mediastinum area and target volumes contoured in different colour scheme. Top figure: CTV (yellow contour), proton-PTV (red contour) and photon-PTV (purple contour). Bottom image: heart (pink contour) CTV (yellow), the proton-PTV and photon-PTV overlapped creating a magenta contour.

3.2.2.2 PBS planning

The proton plans were generated in Prague using the following approach: A single anterior field with gantry angle 0° was used for upper-mediastinal involvement (Figure 3-4). When neck nodes were involved, a three-field solution was used, two fields (60° and 300°) were fitted to the neck section of the PTV and one field (0°) was fitted to the mediastinal section (Figure 3-5). A fourth field was introduced (180°) for cases with lower mediastinal involvement as well and a fifth or for some

cases a sixth field was introduced for axilla involvement (Figure 3-6). Those gantry angles varied slightly depending on the patient anatomy and the target volume location. The field arrangement was selected depending on the individual requirements for each patient and the number of fields was kept to minimum. The purpose of this strategy was to keep the dose to OAR as low as reasonably achievable. The field angles were also selected with OAR sparing as main priority, when for example it was crucial to keep the dose low in lungs or the heart, an anterior field was used. On the contrary, when sparing OAR in the neck area or breast was more important, posterior fields were used. When possible, beams were positioned so that their distal edge wouldn't aim directly at an OAR.

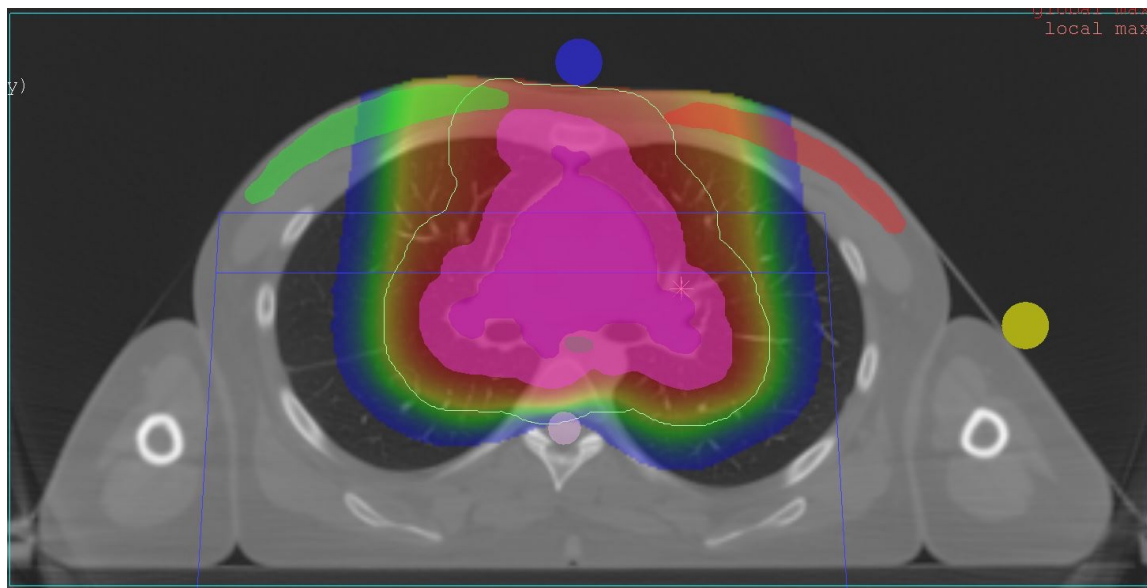


Figure 3-4 Example of patient with upper mediastinal involvement receiving proton radiotherapy using a single anterior field with gantry angle 0°. Gantry angles varied slightly depending on the patient anatomy and the target volume location.

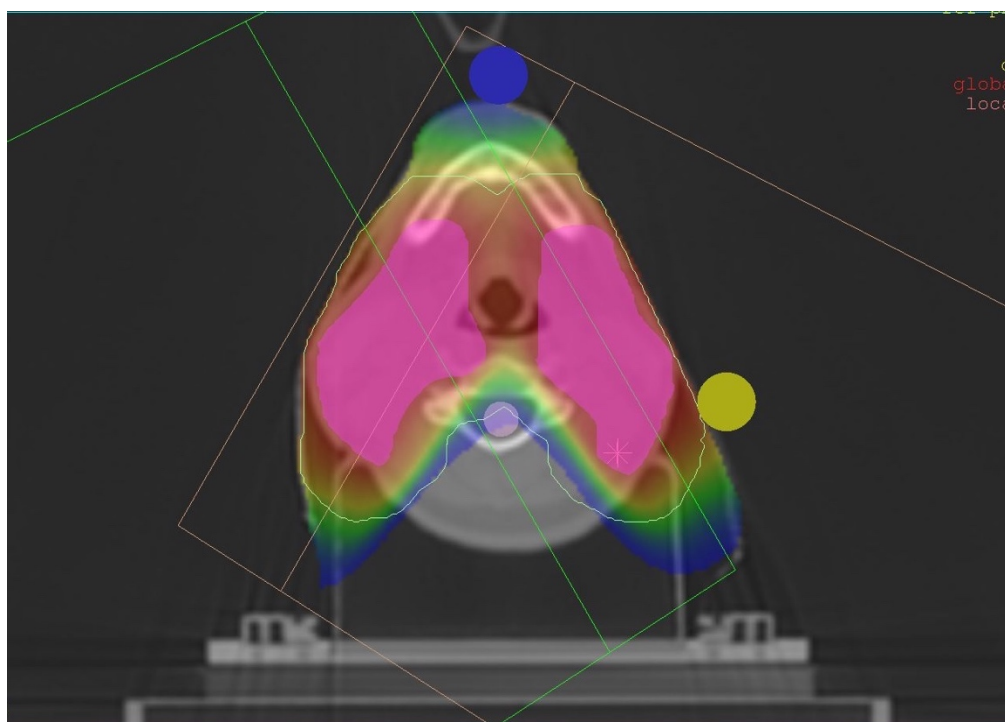


Figure 3-5 Example of patient with mediastinum and neck involvement receiving proton radiotherapy using a three-field solution of two anterior fields (60° and 300°) which were fitted to the neck section of the PTV and one field (0°) which was fitted to the mediastinal section (not seen here). Gantry angles varied slightly depending on the patient anatomy and the target volume location.

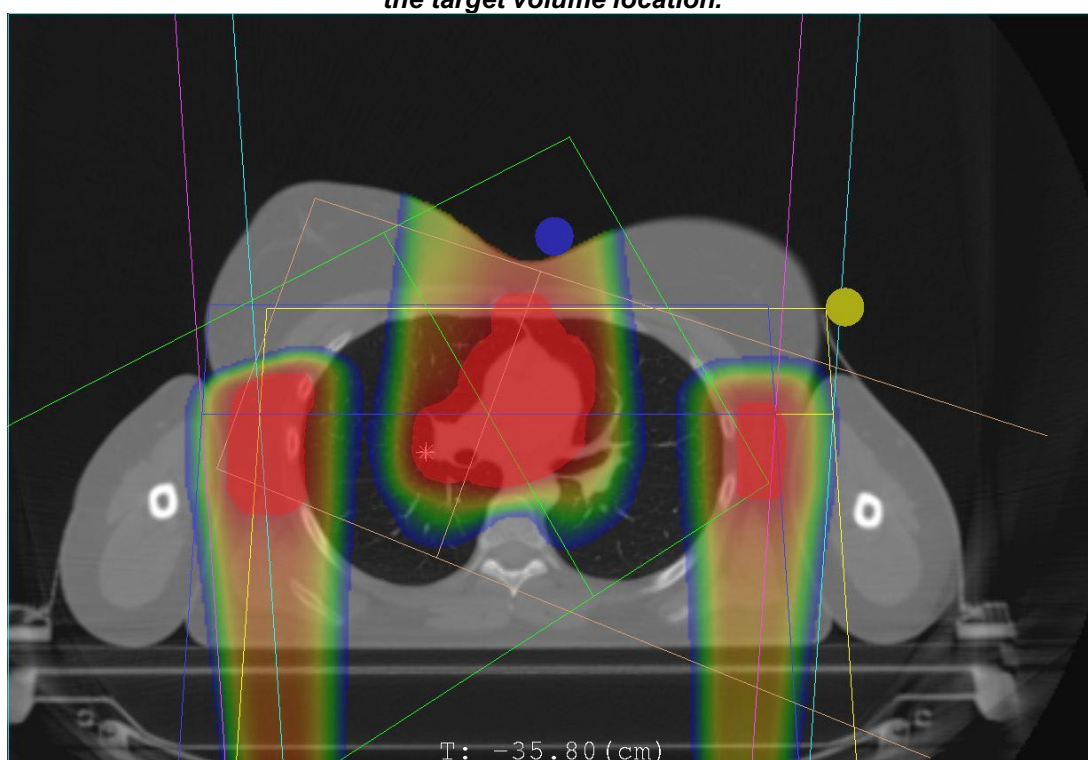


Figure 3-6 Example of patient with upper and lower mediastinum, neck and axilla involvement receiving proton radiotherapy using a six-field solution of two anterior fields (60° and 300°) which were fitted to the neck section of the PTV (not seen here), one field (0°) which was fitted to the upper mediastinal section, two posterior fields (180°) fitted to both axillae and one field (180°) which was fitted to the lower mediastinum (not seen here). Gantry angles varied slightly depending on the patient anatomy and the target volume location.

Iso-layered repainting was used to deliver the dose in the volume near the heart and lungs. A specified number of Monitor Units (MUs) was delivered in all planned positions during the first pencil beam scan and then repeated until all planned MUs were delivered before the next energy layer could be initiated. This repainting technique leads to different spot positions in each rescan as some spots will have received sufficient dose from previously completed scans. It leads to reduced dose inhomogeneity within the target volume.²³

3.2.2.3 PartArc planning

The PartArc approach consisted of one anterior and one posterior arc between 60° and 70° depending on the photon-PTV size and one non-coplanar arc of 60° with gantry rotation from 330° to 30° with couch rotation at 90° (Figure 3-7). The beam energy was 6 MV.

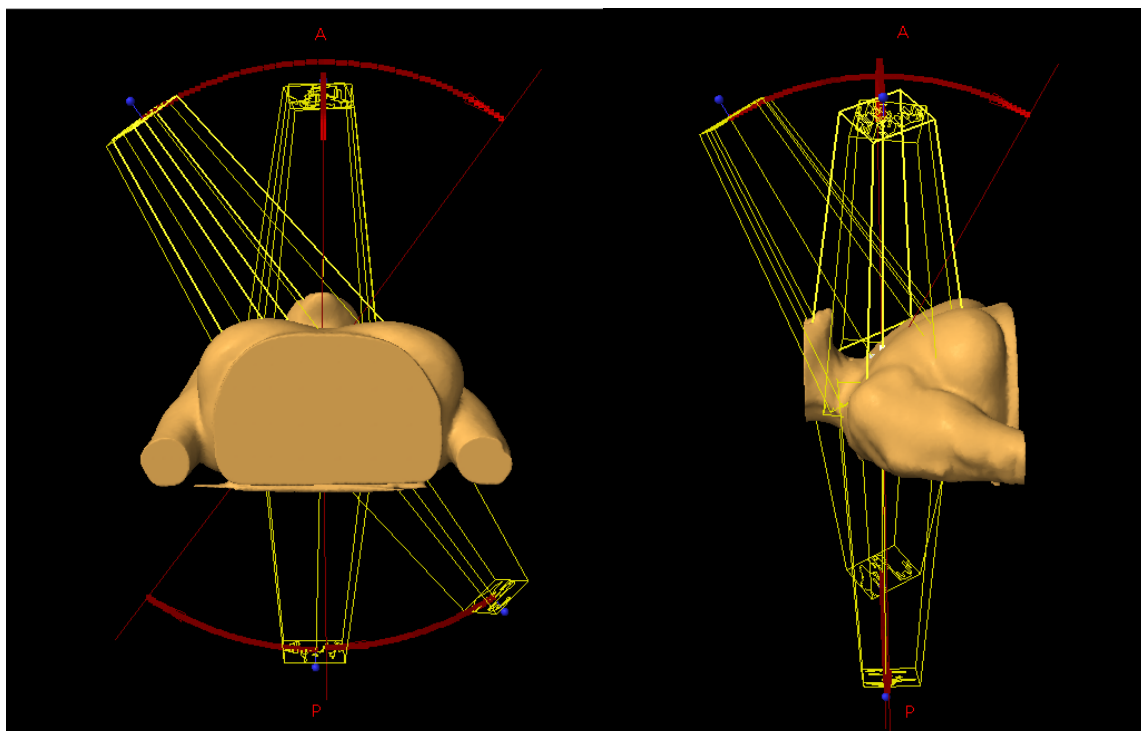


Figure 3-7 Arc arrangement in PartArc method. Left figure: transverse view of the patient, the anterior and posterior arcs can be seen in red outline above and below the patient contour. Right figure: lateral view of the patient, the non-coplanar arc can be seen in red outline above the patient contour.

When the photon-PTV extended to the neck area, it was challenging to maintain good coverage and dose conformity without sacrificing in whole body low dose or allowing for hot spots. As a compromise, an additional full arc of 360° (gantry rotation from 181° to 179°) that only covered the neck and upper supraclavicular area was added for 13 out of 21 patients (Figure 3-8). This improved PTV coverage and conformity and at the same time prevented a low dose bath for the rest of normal tissue and particularly the lungs compared to a full arc VMAT. To further increase conformity, the anterior and non-coplanar fields were run twice with a slightly altered collimator angle. The estimated treatment slot for PartArc was 30 minutes per patient which was comparable to similar advanced methods such as IMRT or full arc VMAT.

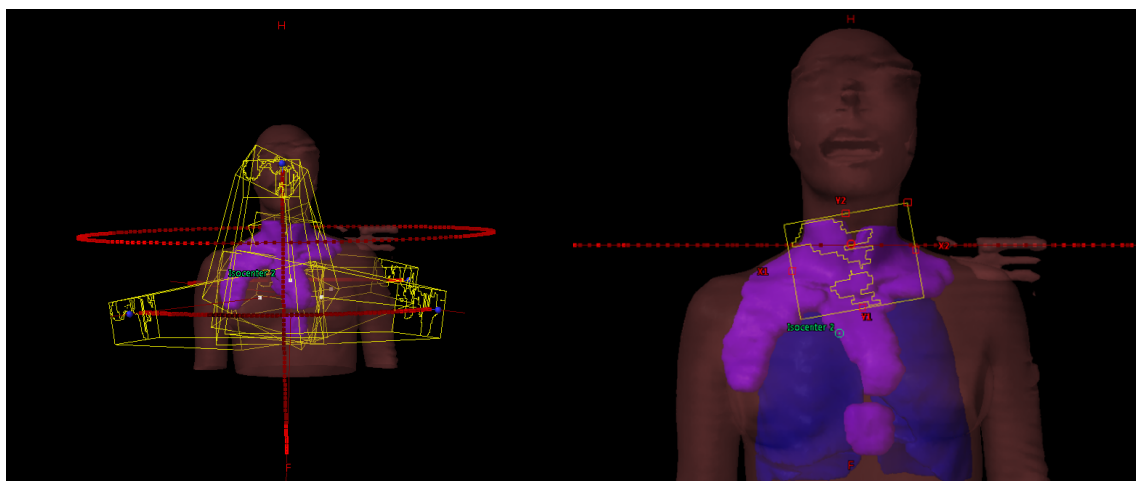


Figure 3-8 Arc arrangement in PartArc method with additional full arc around the neck and supraclavicular area. Left figure: anterior view of the patient, the standard PartArc arrangement and the added full arc can be seen in red outline around the patient contour. Right figure: Beam's eye view of the additional full arc, it can be clearly seen that the field only includes parts of the photon-PTV (purple) of the supraclavicular and neck area and avoids OAR such as lungs (blue) to reduce low dose bath.

The RapidArc inverse planning tool of Eclipse was used for planning optimisation. The dose coverage objectives for the photon-PTV and the dose constraints for OAR were set in the optimiser. Some of the dose constraints used can be seen on the “Aims” section in Table 3-2, Table 3-3 and Table 3-4. Additional structures were

created to assist with the planning optimisation such as OAR minus PTV (e.g. Heart-PTV). Isodoses, higher than 108% of the prescribed dose on initial plans were converted into 3D structures and then used in subsequent optimisations to reduce hot spots.

In order to ensure that the PartArc plans were clinically deliverable and that it was indeed one of the most superior photon RT techniques, it was compared to another advanced RT method used clinically at the Oxford University Hospital (OUH). OUH uses a hybrid photon RT method which combines full VMAT arcs and 3D-CRT fields. Three patients who have been treated at OUH were randomly selected and plans were created using PartArc and compared. PartArc performed better or at least equally compared to the OUH method, providing additional evidence that clinically deliverable PartArc plans were created for this study. (More details can be seen in Appendix C)

3.2.2.4 3D-CRT planning

The 3D-CRT technique included two main opposed fields, one anterior at 0° and one posterior at 180° as well as smaller sub-fields of the same angle. The beam energy was 6 MV. The main fields were initially shaped by adding multi-leaf collimators (MLCs) around the photon-PTV with a margin of 10mm, the sub-fields were created using the same method however the MLCs were manually pulled further within the photon-PTV to shield the volumes receiving doses at least 8% over the prescribed dose (108% hot spots - Figure 3-9). The relative beam weights of both main and sub-fields were manually adjusted to achieve a uniform dose distribution within the photon-PTV. For example, the weightings for the patient in Figure 3-9 were set as 60%, 35% and 5% for the main anterior, main posterior and sub anterior fields respectively. The beam energy of the sub-fields was adjusted to

10 MV for some patients when this improved PTV coverage, typically for patients with a large AP-PA separation at the level of the mediastinum.

3.2.2.5 Dose calculation algorithms

The AAA²⁴ was used for both photon techniques for dose calculation and the plans were normalised on the median for the PartArc and at 95% of the dose covering 95% of the photon-PTV for the 3D-CRT respectively. The Pencil Beam Algorithm²⁵ was used for the PBS plans. All treatment plans were approved by clinical oncologists and met minimum target volume coverage requirements of 95% of the prescribed dose covering at least 95% of the PTV volume.

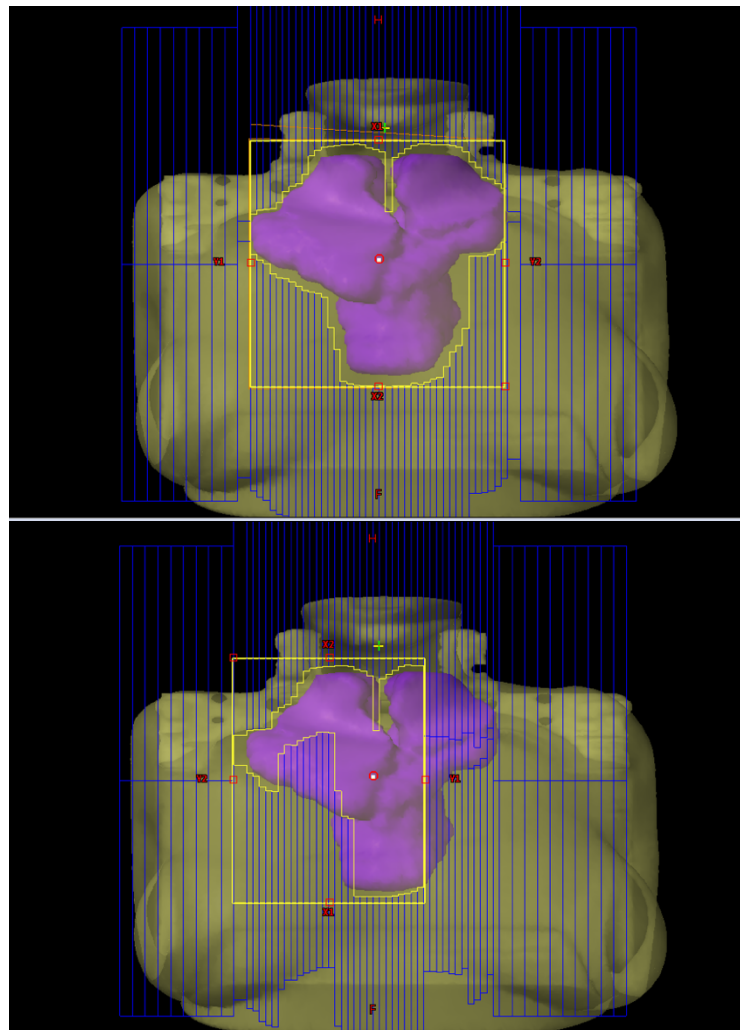


Figure 3-9 Beam's eye view of patient (yellow contour) through anterior 3D-CRT field. The multi-leaf collimators (blue blocks) are used to shield the normal tissue around the photon-PTV (magenta) on the top image. On the bottom image, several multi-leaf collimators have been pulled up to shield high dose areas in a sub-field.

3.2.3 Dosimetric analysis

Various dose measures were evaluated using DVHs for PTV and for OAR. D_{mean} (mean dose), $D_{2\%}$ (The dose received by the hottest 2% of the volume), D_{max} (maximum dose), $V_{107\%}$ (the volume that received dose $\geq 107\%$ of the prescribed dose), Clx (Conformity index) and HI (Homogeneity index) were used to evaluate the PTV coverage. The Clx was defined by RTOG guidelines²⁶ as $V_{95\%}/\text{PTV}_{\text{volume}}$ where $V_{95\%}$ was the body volume that received at least 95% of the prescribed dose. The HI was defined as $D_{2\%}-D_{98\%}/\text{prescribed dose}$. The mean dose to the whole body minus the target volume (Body-PTV) as well as the integral dose (Body-PTV*PTV_{volume}) were also calculated.

The D_{mean} , $D_{2\%}$, D_{max} , and volumetric parameters such as V_5 , V_{10} , V_{20} and V_{30} (The percentage volume of the OAR that received 5Gy, 10Gy, 20Gy and 30Gy respectively) were extracted for the heart, lungs, breast, oesophagus, larynx, thyroid, spinal cord and for 12 cardiac substructures. In an effort to identify subgroups of HL patients for whom protons provided additional dosimetric advantages or not, a number of dosimetric comparisons were performed for different disease volumes and/or anatomical distributions. Paired t-test was used to compare all dosimetric parameters for PartArc versus Protons and 3D-CRT versus protons. The statistical package used was Stata 14.2 (Stata Corp LLC).

The dose objectives during treatment planning for the PTV were: $D_{\text{mean}} = 30.0$ Gy, $D_{\text{max}} < 30.0$ Gy, $V_{95\%} > 95.0$, $\text{Clx} = 1.0$ and $\text{HI} = 0.0$. For OAR the dose constraints used were: heart ($D_{\text{mean}} < 10$ Gy, $D_{\text{max}} < 32$ Gy, $V_{30} < 10\%$), lungs ($D_{\text{mean}} < 12$ Gy, $V_5 < 50\%$, $V_{20} < 25\%$), breast ($V_5 < 20\%$, $V_{10} < 10\%$) spinal cord ($D_{\text{max}} < 35$ Gy), for all methods and can be seen in the “Aims” sections of Table 3-2, Table 3-3 and Table 3-4.

3.3 Results

Generally, the dose distributions from proton RT were more uniform and conformal compared to both PartArc and 3D-CRT. They also delivered lower doses to OAR. An example of two representative patient dose distributions for 3D-CRT, PartArc and PBS can be seen in Figure 3-10. The dose distributions for doses greater than 95% of the prescribed (28.50 Gy) are also shown in Figure 3-11. However, there were some instances that PBS did not provide significant dosimetric benefit or was inferior to PartArc for some dose metrics such as high dose regions within some OAR (Figure 3-13 and Table 3-3). The PBS treatment time was between 15 and 25 minutes per patient, depending on treatment specifications. the beam-on time varied between one to eight minutes according to the number of fields used. The number of breath holds varied between 2 and 15. The treatment time for the photon plans was estimated after discussions with treatment radiographers and dosimetrists from the London Bridge Hospital who clinically deliver a similar technique to PartArc. The PartArc plans were estimated to require between 30 to 35 minutes to be delivered on average and the conventional 3D-CRT between 5 to 10 minutes.

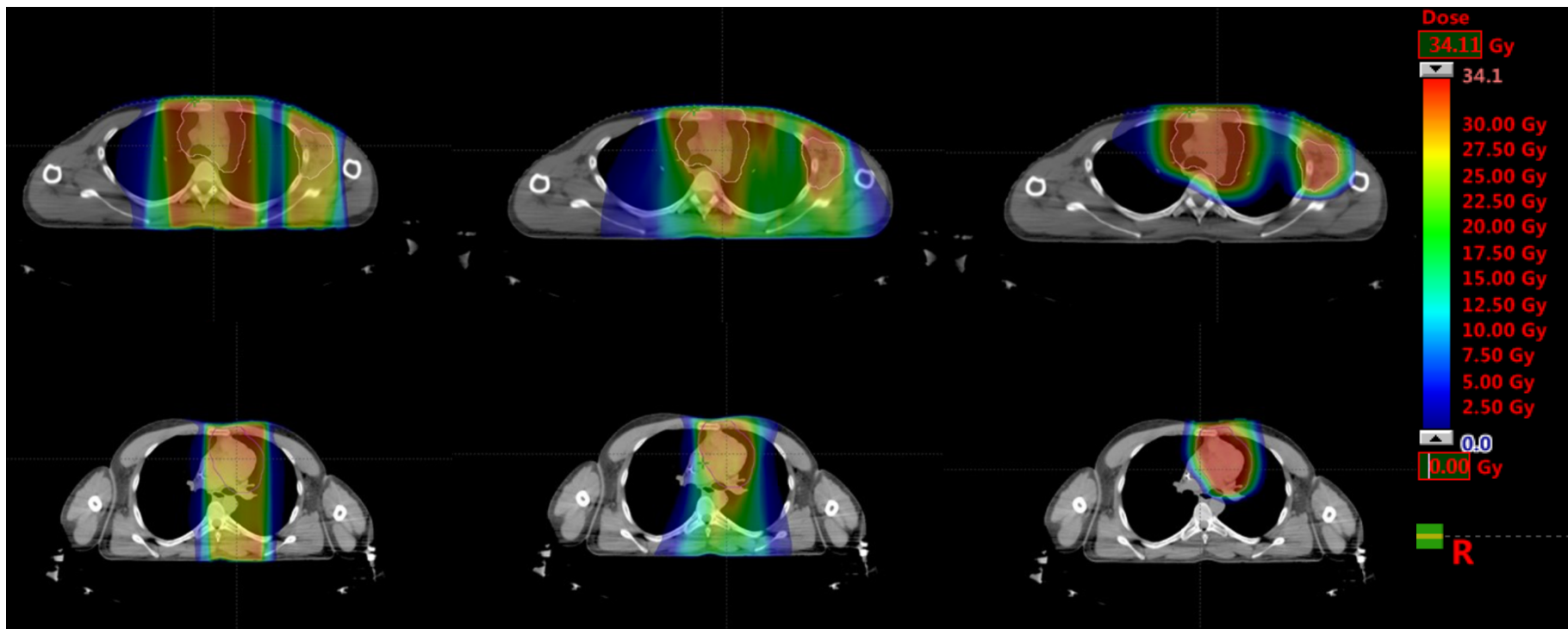


Figure 3-10 Top figures from left, 3D-CRT, PartArc and PBS treatment plans for female HL patient with mediastinum and right axilla involvement. Bottom figures from left, 3D-CRT PartArc and PBS treatment plans for male HL patient with mediastinal involvement. The dose distribution scale, explaining the relationship between colour and dose can be seen on the far right. the superior conformality of proton therapy can be clearly seen in the right images.

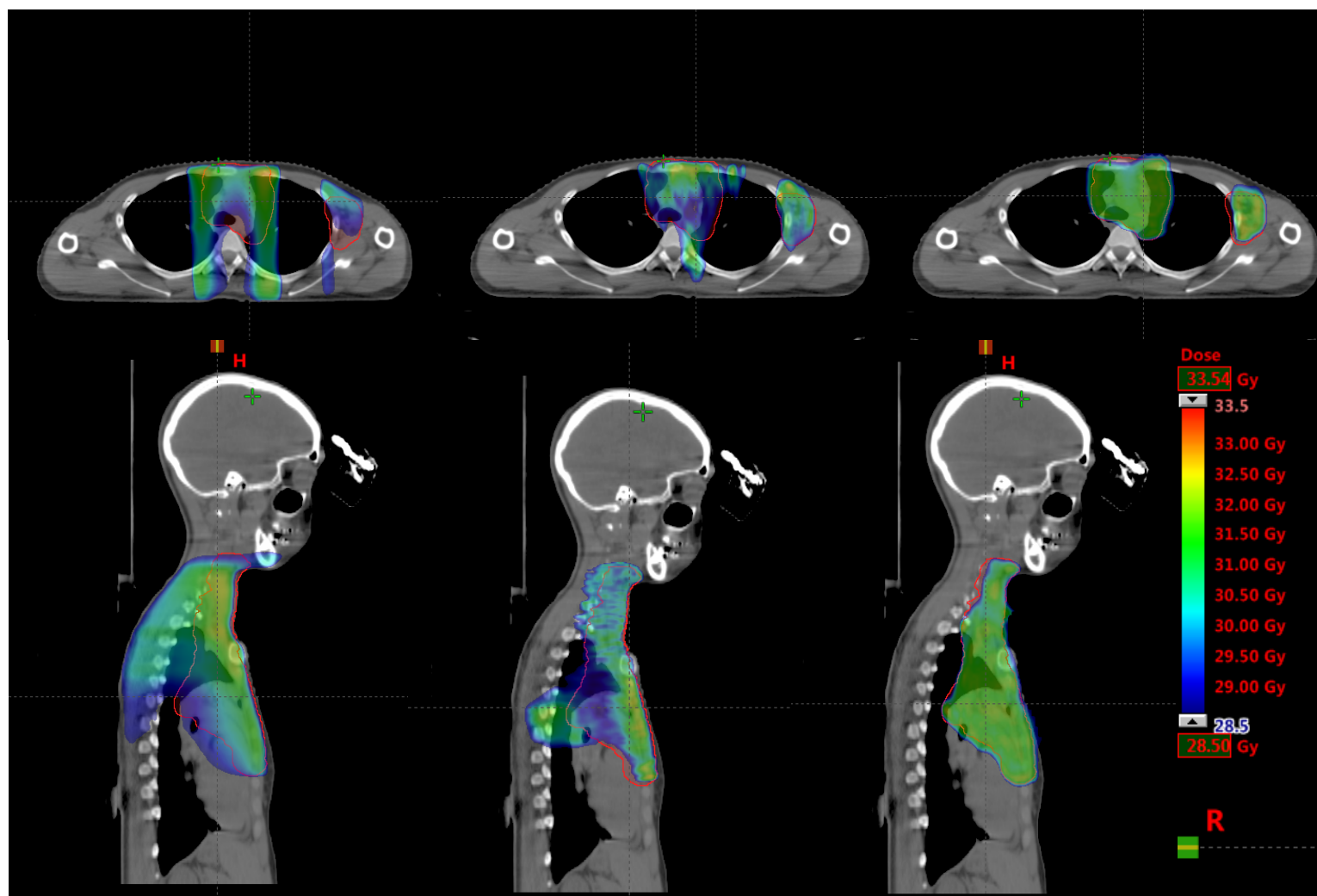


Figure 3-11 Transverse (top) and Sagittal (bottom) images of 3D-CRT PartArc and PBS treatment plans for female HL patient with mediastinum and right axilla involvement. The dose distribution scale, explaining the relationship between colour and dose can be seen on the far bottom right. The doses shown here are >28.5 Gy (95% of prescribed dose) the superior conformality of proton therapy can be clearly seen in the right images.

3.3.1 Target Volume

PTV coverage was acceptable for all techniques and approved by a radiation oncologist specialised in treatment of HL. When the 95%-isodose line did not cover 95% of the PTV volume (for 5 cases the coverage was between 90-94%), the minimum coverage requirement was reduced to 90%-isodose line covering 100% of the CTV. The PBS plans were superior with respect to both conformity and dose homogeneity as it can be seen from the conformity and homogeneity indexes (Table 3-2). PartArc and PBS performed similarly when comparing high dose regions within the target volume (Dmax and D2%) whilst larger hot spots were observed when using 3D-CRT.

Table 3-2 Comparison of dosimetric parameters between proton and photon therapy for planning target volume, (PBS versus 3D-CRT and PartArc).

Dose parameter	Aims	3D-CRT	PartArc	PBS
<i>Dmean Gy (Gy)</i>	30.0	31.3 ±0.6	29.9 ±0.3	30.8 ±0.3
<i>D2% (Gy)</i>	-	33.8 ±0.9	31.6 ±0.4	31.4 ±0.3
<i>Dmax (Gy)</i>	< 33.0	34.7 ±0.9	33.5 ±0.8	32.5 ±0.6
<i>V95% (%)</i>	> 95.0	94.9 ±1.1	95.9 ±2.6	98.9 ±1.0
<i>Conformity Index (CIx)</i>	1.0	2.94	1.38	1.30
<i>Homogeneity Index (HI)</i>	0.0	0.21	0.12	0.08
<i>Mean PTV Volume (cc)</i>	-	1519.6 ±579.3	1519.6 ±579.3	1587.3 ±600.0

SD:Standard deviation, PTV:Planning target volume

3.3.2 Normal tissues

The main dosimetric advantage of PBS over both photon techniques was observed in normal tissue dose reduction. PBS significantly reduced the average mean dose to most OAR compared to both photon methods for all patients. The thyroid dose was also reduced by PBS, but the decrease was not statistically significant. The mean dose to the carotids was increased with PBS compared to PartArc by 0.9Gy (Figure 3-12). The mean dose to the heart was reduced by 3.7 Gy and 1.7 Gy compared to 3D-CRT and PartArc respectively except for 4 patients for whom the

dose received by PBS was marginally higher than with PartArc. Similarly, the mean dose was reduced in lungs by 5.2 Gy and 3.8 Gy, breast by 1.5 Gy and 1.7 Gy, oesophagus by 4.6 Gy and 3.0 Gy, larynx by 2.1 Gy and 3.8 Gy and spinal cord by 15.8 Gy and 12.9 Gy (Table 3-3). The integral dose was significantly decreased when using PBS by 4.1 Gy and 3.1 Gy compare to 3D-CRT and PartArc respectively (Figure 3-12). PBS increased some of the high dose volumetric parameters compared to PartArc. The V30 and D2% for lungs heart and oesophagus were higher by 3.9%, 7.0% and 21.7% and 1.0Gy, 1.6Gy and 0.2Gy respectively (Table 3-4). The high dose spillage (>106%) with PBS in the cardiac area can be seen in Figure 3-13.

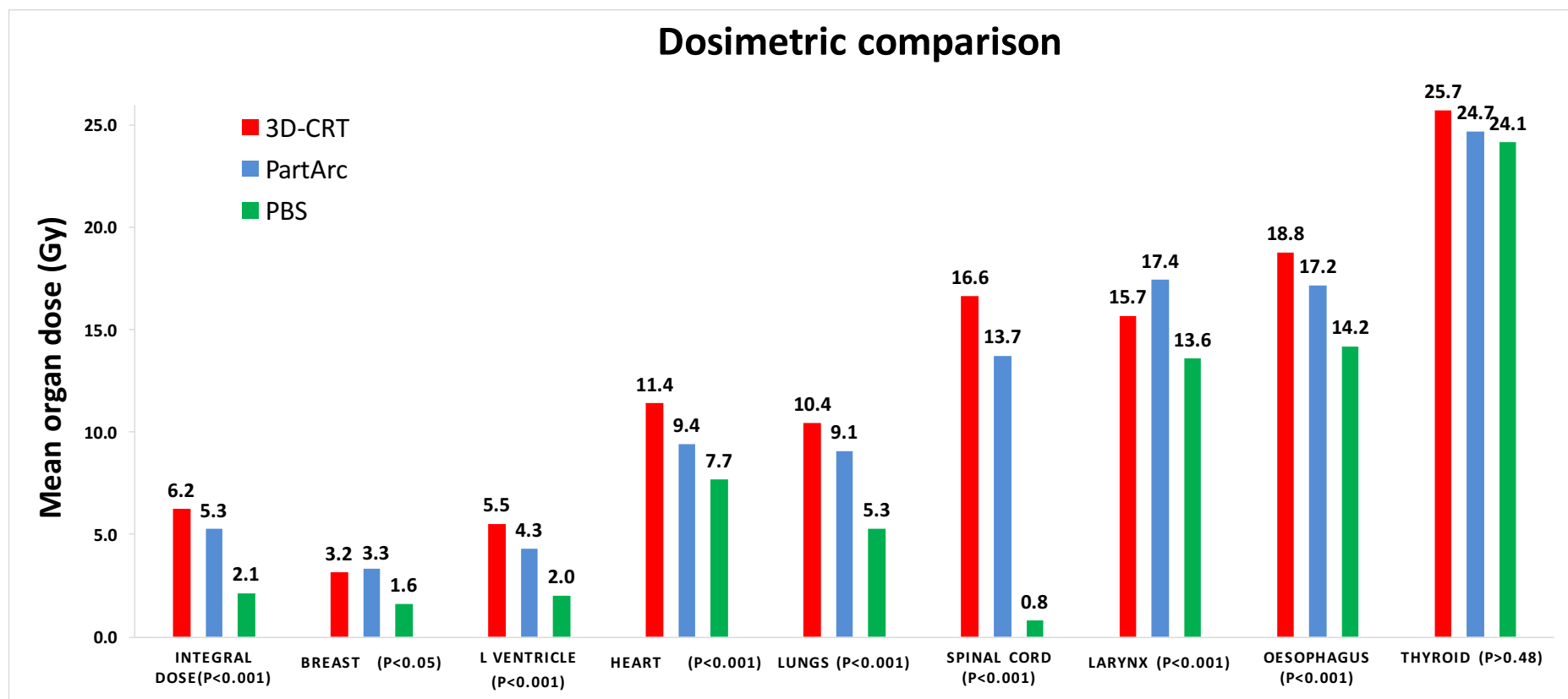


Figure 3-12 Mean integral dose and mean dose for various organs at risk compared for 3D-CRT, PartArc and PBS. *P* values represent paired *t*-test comparisons between both PBS vs PartArc and PBS vs 3D-CRT.

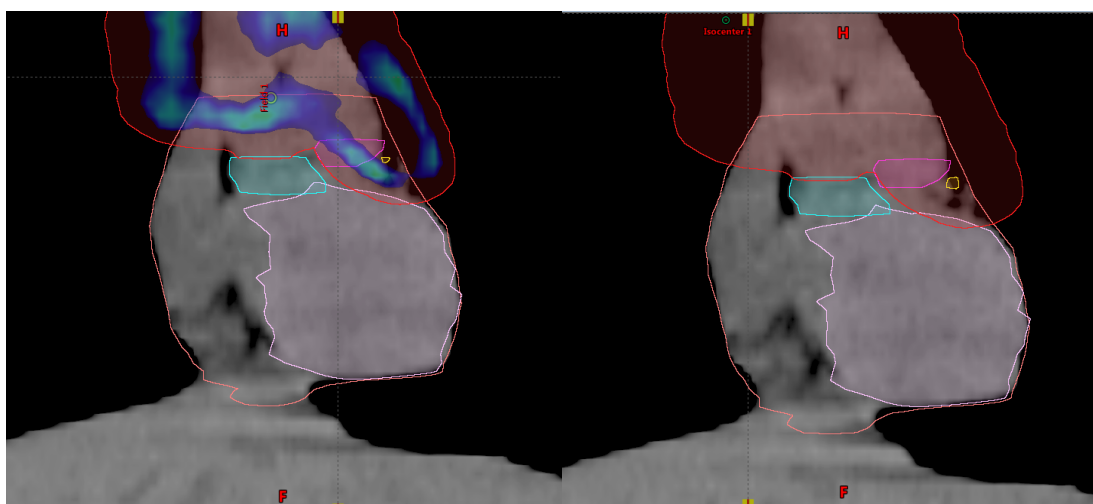


Figure 3-13 The 106% (31.8 Gy) of prescribed dose (30 Gy) colour wash can be seen on the PBS plan (left) in blue and green. There is no high dose spillage in the PartArc plan on this region. (right) The PTV (red) extends in the heart (pink) and includes the pulmonary valve (magenta) and the left anterior descending (yellow). High dose spots were more often seen in the cardiac area when using PBS compared to PartArc.

3.3.3 Dosimetric benefits for patient subgroups

3.3.3.1 Vertical extent of CTV

The relationship between MHD and the mediastinal extent of the CTV was examined. The mediastinal extent of the CTV was expressed as the level of the lowest thoracic vertebrae that the CTV extended to inferiorly. When MHD was plotted against the CTV thoracic level, PBS provided statistically significant lower MHDs compared to PartArc only for patients whose CTV extended below the 7th thoracic level (T) (reduction 2.9 Gy $p < 0.01$)

(Figure 3-14). For patient with the CTV located at and above T7, the difference between PBS and PartArc was not significantly different (0.6 Gy, $p = 0.22$). PBS provided statistically significant lower MHDs compared to 3D-CRT for both groups (5.4 Gy, $p < 0.001$) and PartArc (2.9 Gy, $p = 0.01$) (Figure 3-15).

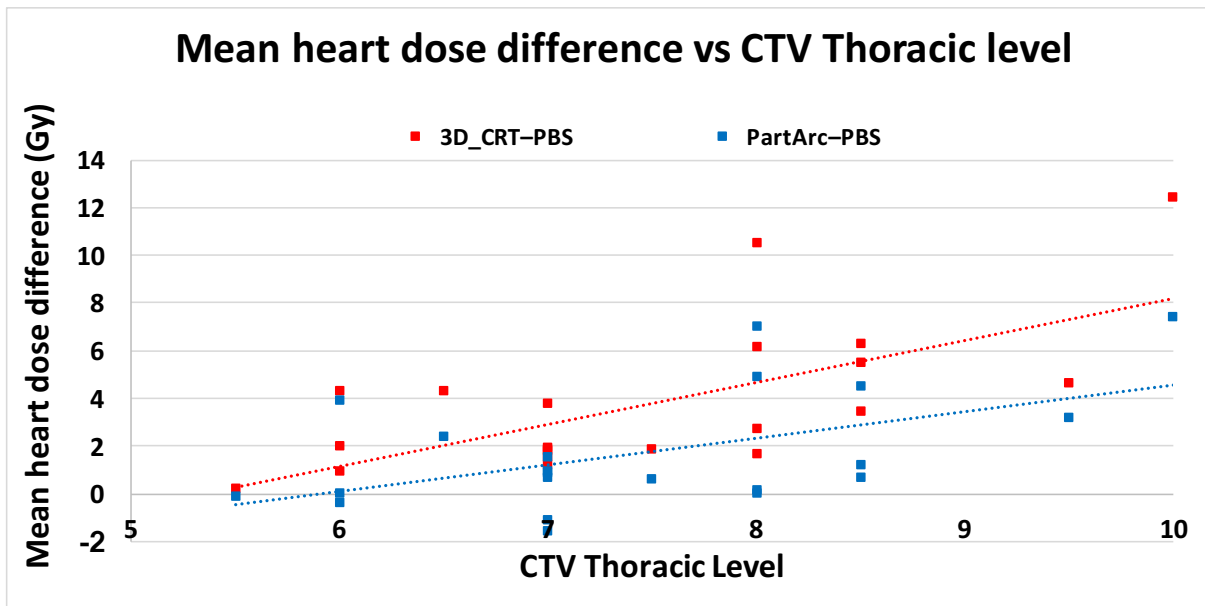


Figure 3-14 Mean heart dose versus CTV thoracic level. PBS provided statistically significant lower mean heart doses compared to PartArc only for patients whose CTV extended below the 7th thoracic level (T7). ($p=0.01$ for below T7, $p=0.23$ for at/above T7)

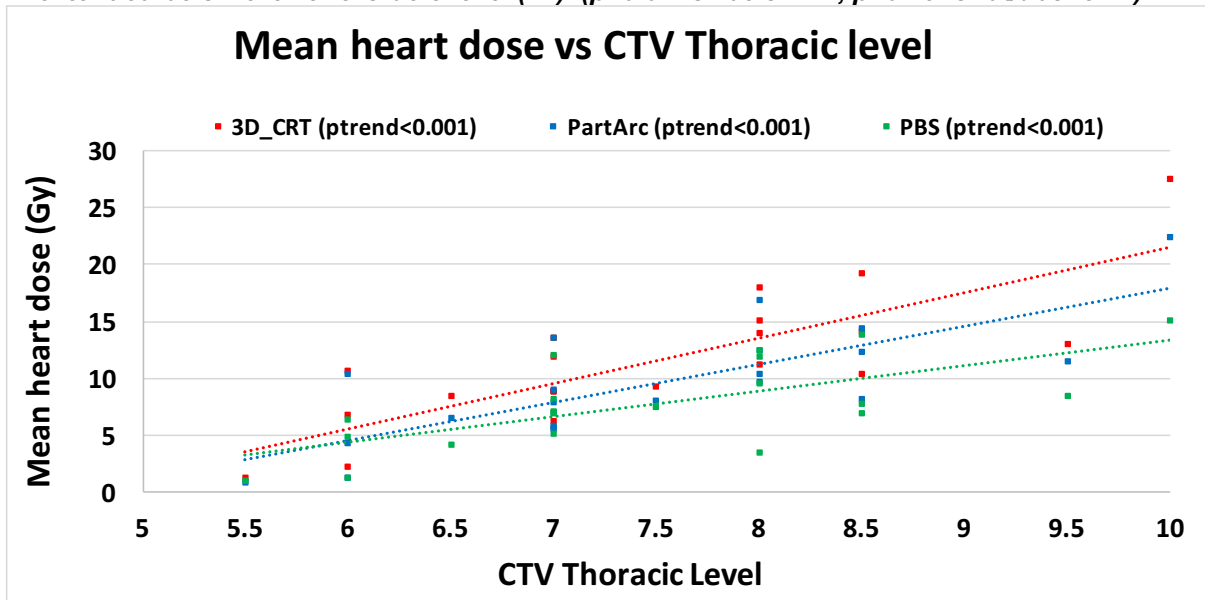


Figure 3-15 Mean heart dose difference between PBS and both 3D-CRT and PartArc. P_{trend} was estimated using linear regression.

The mean lung dose (MLD) was also plotted versus the CTV thoracic level and it can be seen in Figure 3-16. The effect of thoracic level was not as pronounced for MLD as for MHD. The increase in dose was not statistically significant ($p_{\text{trend}} > 0.05$) for any of the three techniques.

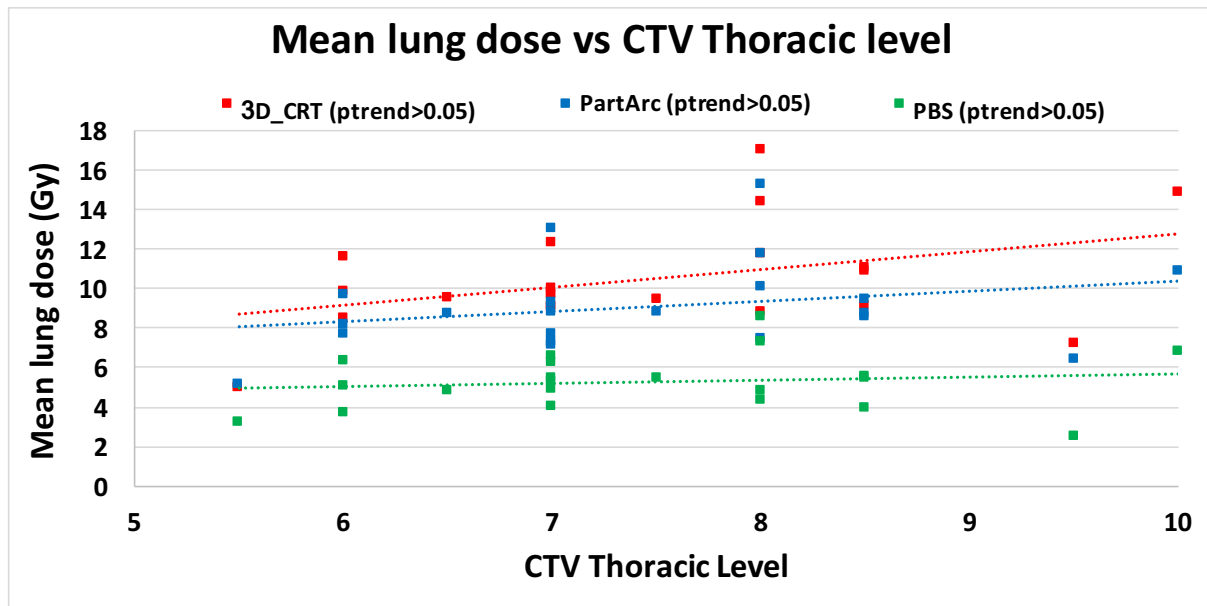


Figure 3-16 Mean lung dose versus CTV thoracic level. P_{trend} was estimated using simple linear regression.

3.3.3.2 Axillary involvement

The mean dose to lungs, heart and breast was assessed for patients with and without axillary involvement. The only OAR for which significant difference was observed between the two groups was breast. For women with axillary involvement (n=7) PBS significantly reduced the mean breast dose by an average of 2.7 Gy and 3.3 Gy compared to 3D-CRT and PartArc respectively. However, when only women without axilla disease (n=9) were examined, the mean breast dose difference between PBS and both photon techniques, despite lower, it was not statistically significant ($p>0.05$) (Figure 3-17).

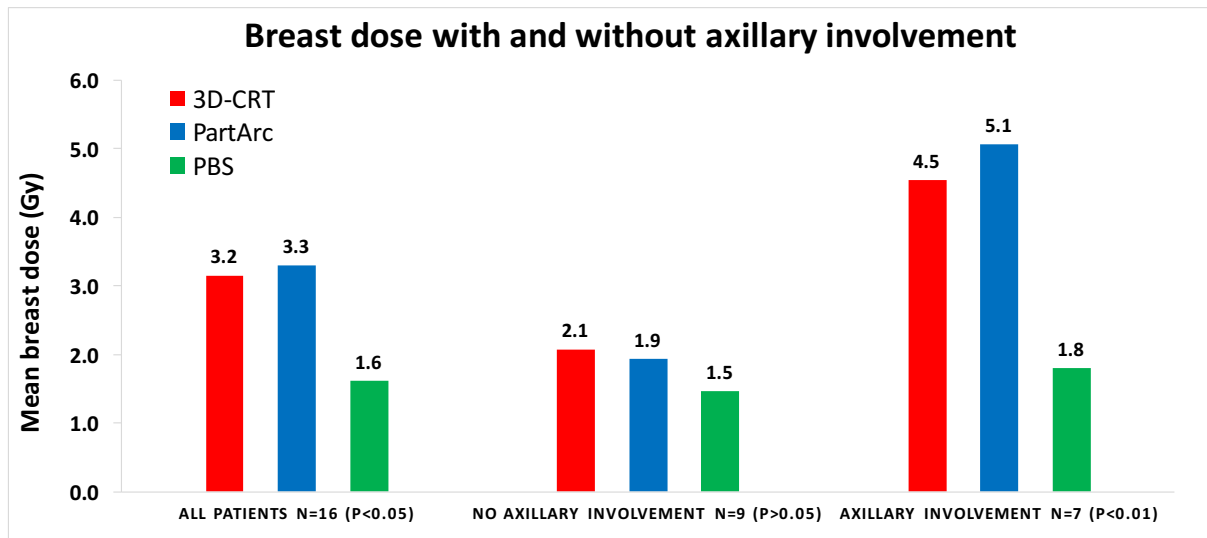


Figure 3-17 Mean breast dose comparison for patients with and without axillary involvement. P values represent paired t-test comparisons between both PBS vs PartArc and PBS vs 3D-CRT.

3.3.3.3 PTV volume

A potential increasing dosimetric benefit of PBS with increasing PTV volume was also examined. The integral body dose and the mean dose to the heart, breast and lungs were plotted against the PTV volume. Additionally, the MLD difference between PBS and both photon techniques was plotted against PTV volume. A significant linear trend was observed between MLD and PTV volume Figure 3-18 for both 3D-CRT and PartArc, whilst the dose was not increased with increasing volume for PBS. A significant trend was also seen in the dose difference plots (Figure 3-19). Therefore, for larger PTV volumes protons provided an even higher dosimetric advantage for MLD over photons.

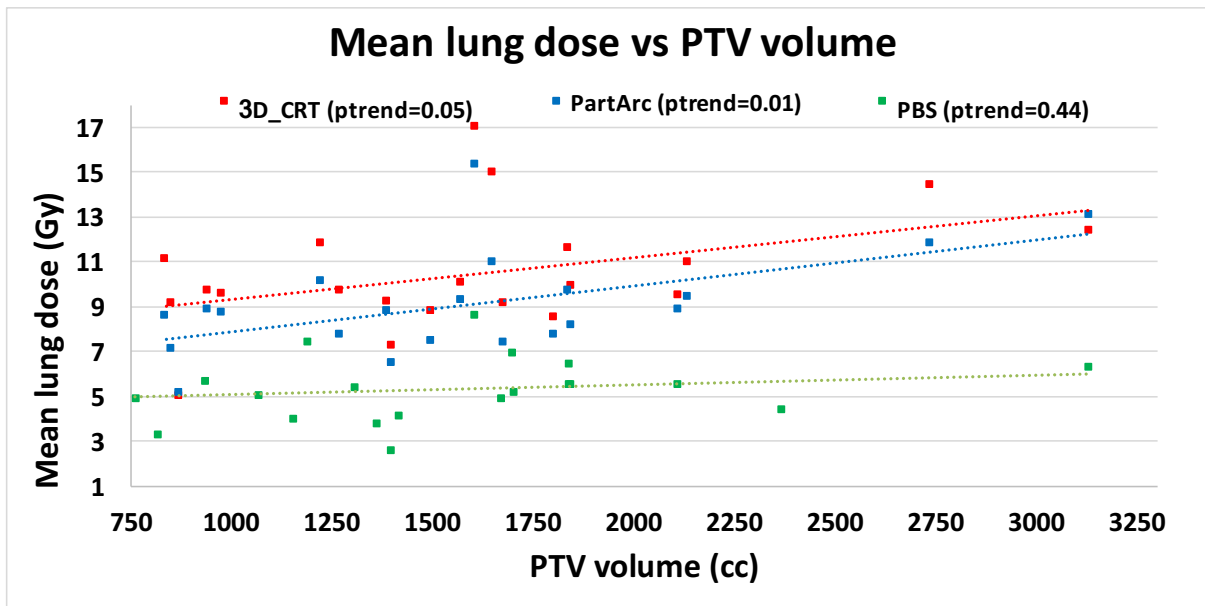


Figure 3-18 Mean lung dose plotted versus PTV volume. The dose increased with PTV volume for 3D-CRT and PartArc but not for PBS. P_{trend} was estimated using linear regression

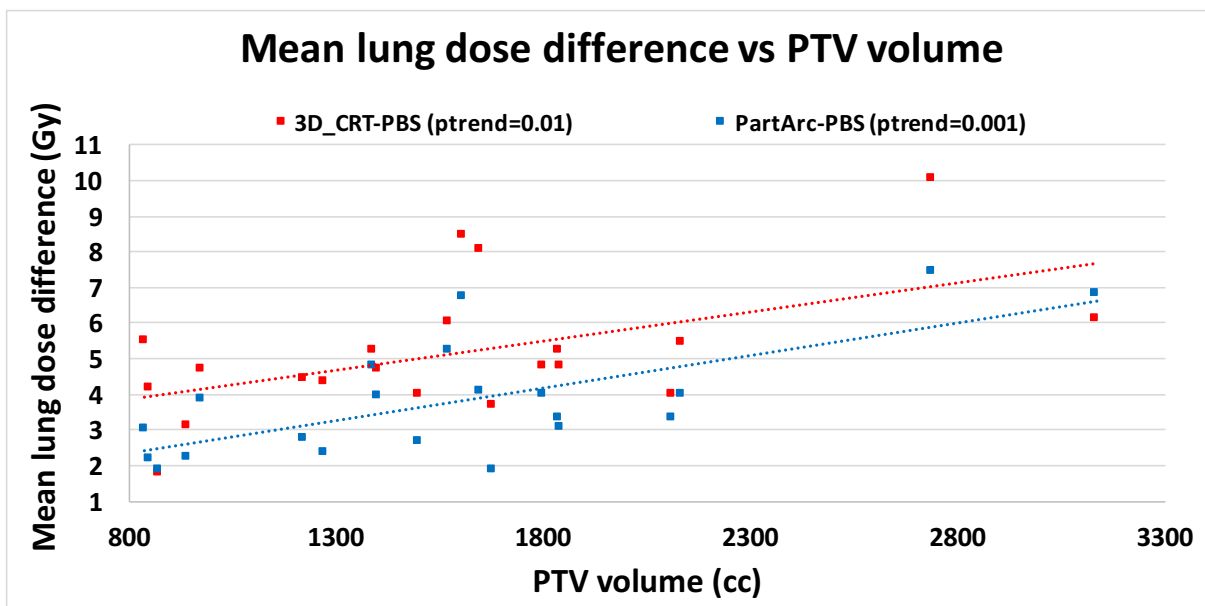


Figure 3-19 Mean lung dose difference between PBS and both photon techniques, plotted versus PTV volume. The dosimetric advantage of protons increased with increasing PTV volume. P_{trend} was estimated using linear regression.

Table 3-3 Comparison of mean dose, maximum dose and the dose received by the hottest 2% of the volume for organs at risk between proton and photon therapy.

Structure	Parameter	Aims	3D_CRT (A)	PartArc (B)	PBS (C)	A vs. C	B vs. C
Body-PTV	Dmean	-	6.2 (3-10)	5.3 (3-8)	2.1 (1-4)	-4.1**	-3.1**
	Dintegral Joules (J)	-	153.0 (87-288)	129.4 (71-236)	51.4 (19-92)	100.9**	76.1**
Heart	Dmean	< 10 Gy	11.4 (1-28)	9.4 (1-23)	7.7 (1-15)	-3.7**	-1.7*
	D2%	-	29.7 (14-33)	28.3 (6-32)	29.9 (16-32)	+0.2 [†]	+1.5*
	Dmax	< 32 Gy	31.7 (28-34)	31.3 (12-34)	31.4 (24-33)	-0.3 [†]	+0.1 [†]
Lungs	Dmean	<12 Gy	10.4 (5-17)	9.1 (5-15)	5.3 (3-9)	-5.2**	-3.8**
	D2%	-	31.8 (30-35)	30.0 (29-31)	30.9 (29-32)	-0.9**	1.0**
	Dmax	-	33.5 (32-36)	32.9 (32-35)	31.9 (31-33)	-1.6**	-1.0**
Breast	Dmean	-	3.2 (0-9)	3.3 (0-10)	1.6 (0-4)	-1.5*	-1.7*
	D2%	-	24.4 (2-34)	20.9 (5-34)	19.2 (1-30)	-5.2*	-1.7 [†]
	Dmax	-	33.5 (30-35)	31.3 (26-35)	29.2 (18-32)	-4.3**	-2.1*
Oesophagus	Dmean	-	18.8 (14-28)	17.2 (12-23)	14.2 (3-19)	-4.6**	-3.0**
	D2%	-	32.6 (29-34)	30.5 (29-31)	30.6 (20-32)	-1.9**	0.1 [†]
	Dmax	-	32.9 (30-35)	31.4 (30-32)	31.4 (27-32)	-1.5**	0.0 [†]
Thyroid	Dmean	-	25.7 (0-34)	24.7 (0-31)	24.2 (0-31)	-1.6 [†]	-0.5 [†]
	D2%	-	30.0 (0-35)	28.4 (0-33)	28.1 (0-32)	-1.9**	-0.3 [†]
	Dmax	-	30.3 (0-36)	29.1 (0-34)	28.6 (0-32)	-1.7**	-0.5 [†]
Larynx	Dmean	-	15.7 (0-31)	17.4 (0-29)	13.6 (0-30)	-2.1 [†]	-3.8*
	D2%	-	27.2 (0-34)	25.0 (0-31)	24.1 (0-31)	-3.1*	-0.9 [†]
	Dmax	-	28.2 (0-35)	26.7 (0-34)	26.0 (0-32)	-2.2*	-0.7 [†]
Spinal Cord	Dmean	-	16.6 (9-27)	13.7 (7-24)	0.8 (0-2)	-15.8**	-12.9**
	D2%	-	31.9 (29-34)	27.9 (23-31)	5.5 (0-17)	-26.4**	-22.3**
	Dmax	< 35 Gy	32.3 (30-34)	29.0 (25-32)	9.9 (0-21)	-22.4**	-19.1**
Carotid arteries	Dmean	-	27.9 (13-33)	26.4 (12-30)	27.3 (13-31)	-0.6*	+0.9**

The positive values indicate that PBS increased the dose compared to the respective photon technique.

[†]p>0.05, * p<0.05, ** p<0.001

The mean dose was reduced for 6 out of 12 cardiac substructures with PBS compared to PartArc and for 9 when compared to 3D-CRT. The mean dose to the left ventricle was reduced by 3.5 Gy and 2.3 Gy whilst the mean dose to the aortic and mitral valves was reduced significantly by 4.3 Gy and 6.1 Gy compared to PartArc and by 8.4 Gy and 9.6 compared to 3D-CRT respectively. There was a substantially smaller decrease in high dose parameters compared to mean dose when using PBS. Dmax and D2% were significantly lower with PBS compared to PartArc for only 4 out of 12 substructures whilst PartArc reduced the dose compared to PBS in 2 out of 12 substructures. For the rest the differences were not statistically significant (Table 3-5).

Table 3-4 Comparison of volumetric parameters between proton and photon therapy for the main organs at risk following HL radiotherapy.

Structure	Parameter	Aims	3D-CRT (A)	PartArc (B)	PBS (C)	A vs. C	B vs. C
Heart	V5 (%)	-	42	42	33	-8*	-9*
	V10 (%)	-	39	34	28	-11*	-6*
	V20 (%)	-	33	24	20	-13*	-4 [†]
	V30 (%)	<10	10	4	11	1 [†]	7**
Lungs	V5 (%)	<50	42	45	24	-18**	-21**
	V10 (%)	-	34	33	20	-14**	-14**
	V20 (%)	<25	27	21	14	-13**	-7**
	V30 (%)	-	13	2	6	-8**	4**
Breast	V5 (%)	<20	11	17	9	-2 [†]	-8*
	V10 (%)	<10	9	11	7	-2 [†]	-4 [†]
	V20 (%)	-	7	5	3	-3 [†]	-2 [†]
	V30 (%)	-	4	1	0	-4*	-1 [†]

The positive values indicate that PBS increased the dose compared to the respective photon technique.

[†]p>0.05,
* p<0.05, ** p<0.001

Table 3-5 Comparison of mean dose, maximum dose and the dose received by the hottest 2% of the volume for 12 cardiac substructures.

Structure	Parameter	3D-CRT (A)	PartArc (B)	PBS (C)	A vs. C	B vs. C
L Ventricle	Dmean	5.5	4.3	2.0	-3.5**	-2.3**
	D2%	19.9	14.3	11.5	-8.5**	-2.9*
	Dmax	25.1	20.0	18.6	-6.5**	-1.4*
Aortic Valve	Dmean	24.0	20.0	15.7	-8.4**	-4.3**
	D2%	26.5	25.0	25.3	-1.2 [†]	0.3 [†]
	Dmax	26.9	25.9	26.7	-0.1 [†]	0.8 [†]
Pulmonary Valve	Dmean	25.8	23.8	25.1	-0.6 [†]	1.3 [†]
	D2%	27.9	27.0	28.7	0.8 [†]	1.7*
	Dmax	28.3	27.6	29.0	0.7 [†]	1.4 [†]
Mitral Valve	Dmean	11.6	8.1	2.1	-9.6**	-6.1**
	D2%	15.4	11.4	4.2	-11.2**	-7.3**
	Dmax	16.4	12.3	5.0	-11.4**	-7.3**
Tricuspid Valve	Dmean	7.4	5.9	3.2	-4.2*	-2.7*
	D2%	10.7	8.9	6.1	-4.6*	-2.8*
	Dmax	11.4	9.6	7.3	-4.1*	-2.3 [†]
LAD	Dmean	10.4	9.0	9.1	-1.3 [†]	0.1 [†]
	D2%	23.1	18.9	19.0	-4.1*	0.1 [†]
	Dmax	25.5	20.5	20.2	-5.4 [†]	-0.3 [†]
L Coronary Art.	Dmean	25.8	21.7	20.3	-5.6*	-1.5 [†]
	D2%	27.6	24.7	23.1	-4.5*	-1.6 [†]
	Dmax	27.9	25.4	23.9	-4.1*	-1.5 [†]
R Coronary Art.	Dmean	16.1	13.7	15.3	-0.8 [†]	1.6 [†]
	D2%	25.7	24.9	25.9	0.3 [†]	1.1 [†]
	Dmax	26.1	25.5	26.5	0.5 [†]	1.0 [†]
L Atrium	Dmean	18.2	13.4	6.0	-12.2*	-7.4*
	D2%	25.3	23.3	17.8	-7.5*	-5.5*
	Dmax	26.6	24.8	21.9	-4.7*	-2.9 [†]
R Atrium	Dmean	14.2	11.2	10.0	-4.2*	-1.2 [†]
	D2%	26.6	26.6	27.1	0.5*	0.5 [†]
	Dmax	28.5	29.1	29.3	0.7*	0.2 [†]
R Ventricle	Dmean	8.5	6.8	6.7	-1.8*	-0.1 [†]
	D2%	25.3	23.8	26.0	0.7 [†]	2.2*
	Dmax	26.7	26.8	27.6	0.9*	0.8 [†]
L Circumflex	Dmean	10.4	8.5	5.7	-4.7**	-2.8**
	D2%	23.7	18.2	17.0	-6.7*	-1.2 [†]
	Dmax	24.5	19.6	18.4	-6.1*	-1.1 [†]

The positive values indicate that PBS increased the dose compared to the respective photon technique.

[†]p>0.05,

* p<0.05, ** p<0.001, LAD: Left Anterior Descending.

3.4 Discussion

To my knowledge, this is the largest group of HL patients treated with DIBH-PBS proton RT for whom a comprehensive dosimetric analysis have been reported. Additionally, this is the first attempt to identify HL patients based on specific disease characteristics for whom PBS can provide additional dosimetric benefits compared to the rest of HL patients. The results show that whilst the reduction in dose using PBS can be significant, not all patients benefit equally from this scarce treatment modality. The hypothesis that patients with specific disease characteristics could benefit substantially by PBS was confirmed for two patient subgroups and for patients with large target volume.

3.4.1 CTV extension and heart dose

Only when the CTV extended below T7, the difference in MHD was significant between PBS and PartArc. For patients with CTV at and above T7 the reduction in MHD was not statistically significant compared to PartArc.

3.4.2 Axillary involvement and breast dose

PBS reduced significantly the mean breast dose compared to either photon RT methods only in female patients with axillary disease. For patients with no axillary involvement, the dosimetric benefit of PBS versus either 3D-CRT or PartArc was not statistically significant.

3.4.3 PTV volume and lung dose

It was also shown that PBS provided an additional dosimetric advantage over photons for increasing PTV volume. When both photon RT methods were used, the MLD increased significantly with increasing PTV volume ($p_{\text{trend}} < 0.05$). However, the MLD did not increase significantly with increasing PTV volume ($p_{\text{trend}} = 0.44$).

These findings may provide useful information regarding disease anatomical indications for proton RT and assist in the referral process of HL patients for PBS proton RT. Generally, PBS was superior for most dosimetric parameters when compared to both photon RT techniques. PBS significantly reduced the mean dose to most OAR and the dose homogeneity within the target volume was higher. However, some high dose parameters and hot spots were increased with PBS compared to PartArc.

3.4.4 Heart and cardiac substructures

The mean dose to the whole heart and to most cardiac substructures was significantly reduced with PBS. Other volumetric and maximum dose parameters were also reduced, however, some high dose parameters such as the heart V30, were increased compared to PartArc. That can be explained due to the ability of PartArc to distribute the unintended high dose in larger volumes of lower dose.

In order to manage the effect of these high dose areas, planning optimisation and motion management is important to ensure that they do not include critical organs or cardiac substructures as the impact of hot spots within critical structures such as arteries would be predicted to increase risk. For example, inhomogeneity of dose within the heart and the dose to the coronary arteries were important predictors of late cardiotoxicity in a recent study by Hahn et al.²⁷ This is crucial especially for PBS considering the substantial RBE uncertainties at the distal edge of the SOBP.²⁸

Three research groups have previously assessed the cardiac dosimetric benefits in HL patients who received actual treatment with proton RT. A group from MD Anderson²⁹ reported cardiac dose reduction in a group of 10 HL patients treated with passive scattering proton RT. They reported that the MHD was reduced by 8.9

Gy compared to 3D-CRT as well as the volume for all volumetric parameters (V5, V10, V20 and V30) for both whole heart and coronary arteries. Their results were comparable to this study, however they showed greater dose reduction compared to this study. Researchers from the University of Florida Proton institute have investigated potential dosimetric benefits of using proton over photon RT in 3 studies.^{30–32} In two studies, 13 and 15 HL patients were treated with free-breathing passive scattering proton RT. In both studies, the mean dose to the heart was reduced compared to 3D-CRT (by 13.0 and 7.6 Gy) and compared to IMRT (by 4.0 Gy and 3.4 Gy).

The first study also reported the dose into cardiac substructures.³⁰ Proton RT reduced the mean dose to all four chambers of the heart compared to both 3D-CRT and IMRT and to three and two valves compared to 3D-CRT and IMRT respectively. In this study, the mean dose was also reduced for all four chambers compared to 3D-CRT but only in two chambers compared to PartArc. The mean dose to three out of four valves was reduced compared to both photon techniques. The third study³² also showed MHD reduction compared to IMRT, however it included only 3 patients and the study's aim was to evaluate the potential benefits of breath-hold technique compared to free breathing rather than dosimetric advantages of proton over photon therapy. A group from University of Pennsylvania presented a study³³ in 10 HL patients treated with free breathing PBS, the only other study, to report on clinical PBS proton RT for HL. They found that PBS provided the lowest MHD (5.8 Gy) in comparison with 3D-CRT (12.7 Gy), IMRT (10.4 Gy), and proton passive scattering (7.4 Gy) and the lowest V5, V10 and V20. However, the V30 was slightly increased compared to IMRT, similarly to this study. They used

only one anterior field for each patient which might explain the lower MHD by 1.9 Gy on average compared to this study.

Seven planning studies have assessed the potential dosimetric benefits of proton RT in HL patients treated with photon therapy and all reported MHD reduction. However, only four studies reported significant mean dose reduction^{34–37} and three reported that no significant dose reduction was achieved.^{38,17,39} Overall, this study and most previous studies have demonstrated significant dose reduction in the heart and substructures.

The importance of reducing the dose to the heart and the substructures in order to reduce risk of cardiac toxicity have been shown in multiple studies. In Chapter 4 I present a detailed analysis of risk predictions and the importance of cardiac dose reduction.

3.4.5 Lung

PBS reduced the dose to every lung dosimetric parameter compared to 3D-CRT and PartArc. The results here come to close agreement with three other studies of actual treatment with proton RT in terms of MLD reduction.^{29,31,33} Additionally, eight planning studies^{34–38,17,39,40} have also shown MLD reduction but of lower degree. This could be explained by the fact that in actual clinical plans, the field set up and planning arrangements are optimised compared to theoretical planning studies. Furthermore, patients referred for proton RT, are more likely to have been selected due to their bulky mediastinal disease. For example, in a study¹⁴ of 38 HL patients who were treated with a photon therapy technique similar to PartArc, only 5 of them had bulky disease and the average MLD was 5.9 Gy, substantially lower compared to the average of 9.1 Gy presented here. Reducing MLD and V5 in HL patients is particularly important for minimising the risk of radiation toxicities such as second

lung cancer and pneumonitis. MLD over 13.5 Gy and V5 over 55% predicted pneumonitis⁴¹ and radiation doses of 5.0 Gy or more are associated with an increased incidence of second lung cancer in HL patients.⁴²

3.4.6 Breast

When analysing all female patients, the dosimetric benefits for breast were limited with PBS. The mean breast dose was reduced by an average of 1.6 Gy compared to both photon techniques. On the contrary, when only women with axillary involvement were examined, the dose reduction was more than doubled, up to an average of 3.7 Gy compared to PartArc. Three clinical studies reported similar³¹ or lower^{29,33} dose reduction compared to this study. Planning studies also reported reduced doses between 0.2 and 3.65 Gy, the largest dose difference of 3.65 Gy between passive scattering and 3D-CRT was reported by Andolino et al.¹⁷ However, the authors only used breast-sparing posterior fields which resulted in increased MHD. Overall, PBS showed a substantial mean breast dose reduction only when axillary disease was present. For those women, the long-term benefits of proton RT could be important, particularly in reducing the risk of second breast cancer.^{1,7}

3.4.7 Body integral dose

There was a significant decrease in body integral dose with PBS, the average reduction was 66% (101.6 Joules) and 60% (78.0 Joules) compared to 3D-CRT and PartArc respectively. These results are comparable with previous studies reporting reduction on integral or mean body dose when using proton RT. The only other study that reported on integral dose in clinically delivered proton RT plans was performed by Hoppe et al.³¹ They reported that passive scattering proton RT reduced the integral dose in a group of 15 HL patients by an average of 57% (69.0

Joules) and 49% (50.0 Joules) compared to 3D-CRT and IMRT respectively. The mean integral dose following proton RT in that patient group (53.6 Joules) was in good agreement with the value reported in this study (51.4 Joules). Two planning studies reported on mean body dose. Horn et al³⁷ compared passive scattering proton plans with 3D-CRT and Tomotherapy for 14 HL patients and shown that protons could potentially reduce the dose by an average of 3.3 Gy and 2.9 Gy respectively. Chera et al³⁸ reported a mean body dose reduction of 1.35 Gy and 1.54 Gy, when comparing passive scattering proton plans to 3D-CRT and IMRT respectively. Reducing the integral dose received during RT may be important when considering second cancer risk. It has been shown that paediatric HL patients who received integral doses exceeding 150 Joules were in a 5.2-fold increased risk of death from carcinoma and a 12.5-fold increased risk of death from sarcoma.⁴³

3.4.8 Other organs at risk

The mean dose to the oesophagus following PBS was reduced by an average of 4.6 Gy and 3.0 Gy compared to 3D-CRT and PartArc respectively. Only four other studies reported on oesophageal dose with proton RT.^{29,31,37,44} The average mean dose reduction compared to 3D-CRT ranged from 1.7 Gy to 12.8 Gy and when compared to IMRT from 0.4 Gy to 3 Gy. The mean dose the carotid arteries was reduced marginally compared to 3D-CRT by 0.6 Gy but it was increased compared to PartArc by 0.9 Gy. The only other study in our knowledge reporting on dose to the carotids with proton RT by Maraldo et al.⁴⁵ However, in contrast to this study, they reported an increased mean carotid dose (average of left and right common carotid arteries) when using VMAT of 2.7 Gy and 1.1 Gy compared to 3D-CRT and Proton RT respectively.

The dose to the larynx was also reduced with protons, interestingly, only when compared to PartArc. Only one other study⁴⁶ reported on larynx dose, which also showed that VMAT increased the dose to the larynx compared to both 3D-CRT and proton RT. The largest dosimetric differences in this study were found in the spinal cord, both Zeng et al. and Horn et al.^{33,37} also found a significant dose reduction. Only Andolino et al.¹⁷ didn't report a significant difference which was possibly because only posterior fields were used and thus the spinal cord was in the entrance part of the proton beam. The prescription dose in HL is well below the conventional tolerance dose of the spinal cord and is therefore not generally considered as a concern when planning. However, keeping the dose as low as possible might be beneficial for patients needing re-irradiation. Finally, no significant dose reduction to the thyroid was found in this study, in agreement with 5 other studies.^{31,34,37,38,46}

3.4.9 Strengths of the study

In this study, the most advanced methods of both types of RT were used. Proton plans were created by proton RT specialist with routine clinical experience, all photon plans were created under the guidance of experts in DIBH photon RT from independent departments and PartArc was chosen amongst other advanced techniques by dosimetric comparison using real clinical data. Clinically realistic margins were used to create the PTVs for both photon and proton RT separately rather than using the same PTV.

Patients from a variety of disease volumes and field arrangements (AP only, AP-PA, PA only) were included in the study to account for potential bias. In our knowledge, no other study on HL patients has identified potential indicators for proton RT by reporting on mean dose to the heart, lungs or breast versus CTV

inferior border extension, PTV volume or axillary involvement respectively. I believe that the findings here provide new knowledge that could be used to identify subgroups of HL patients that would benefit significantly by proton RT and separate them from patients that photon therapy would result in similar dosimetric outcomes. Furthermore, it is the only clinical DIBH PBS study to my knowledge that reports the dose to most cardiac substructures. Twelve cardiac substructures were contoured and dosimetric information was provided for all of them.

The MHD is not the only dosimetric parameter to predict late effects. Due to the very often inhomogeneous dose distribution within the heart, the dose to substructures such as left ventricle³, valves⁴⁷, coronary arteries²⁷ can also be good predictors for specific cardiac endpoints.

3.4.10 Limitations of the study

Even though this was the largest number of HL patients treated with DIBH-PBS reported in literature, the patient number (21) was still low. More patients are needed to strengthen my conclusions about the dosimetric benefits of PBS and particularly for identifying specific patients. Additionally, the patients involved in this study were referred for proton RT, therefore they may not represent the average HL patient in terms of tumour volume. Higher tumour volumes usually result in higher OAR doses, therefore, the dosimetric benefit might have been inflated slightly compare to the average HL patient.

The PBS physical doses reported by the TPS were converted into RBE by using, the commonly used clinically, correction factor of 1.1. However, it has been reported from previous studies^{28,48} that proton RBE changes along the beam path and it can vary between 1.1 and 1.65, especially on the distal edge of the beam where the linear energy transfer (LET) increases due to the slowing down of

protons. This could have serious clinical implications as the increase in LET results in the increase of the effective range by 2.0 to 4.0 mm which can result in high LET regions extending beyond the planned target volume, in critical organs. However, the 1.1 RBE is routinely used in proton RT clinical practice, therefore, the results presented here are still clinically relevant.

Dosimetric comparison results depend on the margins used for target volumes. Even though different margins were used for protons and photons, the optimal proton margins are not known yet. Unless all proton uncertainties are quantified and included in the margins, at least to the extent that photon uncertainties currently are, there will always be an inherent uncertainty in dosimetric comparisons between protons and photons. Additionally, the reduced photon margins by 5mm in the superior-inferior CTV borders were decided considering that the plans were delivered in DIBH. Even though the use of DIBH is increasing in HL RT, the majority of centres worldwide are still delivering in free breathing.

The additional dose deposited by neutrons was not reported in this study as this was beyond the purpose of this thesis. However, studies have shown that the neutron dose during PBS was measured to be comparable if not less than that received by high energy photon RT.⁴⁹ Particularly for the purpose of this study, it is unlikely that including the additional neutron would have had a significant effect on the overall conclusions.

3.5 Conclusions

In summary, PBS can provide significant reductions in radiation dose to OAR for certain individuals receiving RT for HL. This would be expected to lead to reductions in the risk of late radiation-related toxicities and improved health for survivors. A further analysis on predicted treatment-related late effects for this group of patients is presented in Chapter 4 to investigate this hypothesis.

3.6 References

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Chapter 4 Risk prediction for clinical proton beam therapy and comparison with photon radiotherapy for Hodgkin lymphoma.

4.1 Introduction

Evidence that radiation-related CVD can occur in HL survivors following anthracycline-containing chemotherapy and RT has emerged from several observational studies.^{1–7} It has also been established that where normal tissues, including organs such as the lungs, breast and oesophagus, receive incidental radiation exposure during RT, patients are at increased risk of subsequent radiation-related cancers.^{8–11} Lastly, alkylating agent-containing chemotherapy has also been associated with increased risk of lung cancer.¹⁰

Cardiotoxicity and second cancers are of particular concern for patients with good prognosis, such as those with early breast cancer or HL. In addition, HL patients are often teenagers or young adults when diagnosed so, for those who are cured of HL, their natural life-expectancy is many decades, during which treatment-related long-term toxicities may affect their quality of life, cause years of excess morbidity¹² or result in an early death. Consequently, haematologists and oncologists may be willing to accept increased relapse rates, and the need for salvage therapy in those who do relapse, as a trade-off for omitting RT.¹³

In response to these concerns, RT techniques for the treatment of HL have evolved and reductions in the dose and volumes of irradiation have been achieved, reducing radiation doses to normal tissues whilst retaining efficacy. Modern RT techniques, such as the ones described in Chapter 3, have incorporated several technological advances that allow reduction of radiation exposure to the heart and other OAR.

As described in Chapter 3, PBS allows further reductions in incidental radiation compared to conventional or even advanced photon RT. However, access

to PBS and generally proton RT is currently limited and demands a considerable increase in cost compared to conventional RT. In addition, there are reimbursement issues from private or national healthcare providers. Hence, even in developed countries, patient referral must be prioritised for patients at greatest risk of developing complications from conventional RT that could be reduced using PBS. In order to achieve this, evidence-based recommendations on which patients will benefit more by PBS in terms of reduction in radiation-related toxicities are essential.

One way to investigate how the radiation dose reduction to an OAR provided by PBS or other advanced photon RT methods, reduces risk of late toxicities, is to use radiation dose-response relationships. These relationships, derived from observational studies, can be used to predict the risks for each RT method and allow them to be compared. Once those risks have been predicted and compared, referral to PBS could be recommended for those patients for whom the risks of late toxicities can be reduced substantially. For some patients, for whom the risks of late toxicities would be very high regardless of the RT technique used, the advice may be that they avoid RT entirely and receive treatment with chemotherapy alone.

In this chapter I have predicted cardiovascular and second cancer risks for 21 HL patients who were treated with PBS proton therapy between 2014 and 2016 at the Prague Proton Therapy Centre (described in Chapter 3). I have predicted 30-year cardiac mortality for each patient based on the cardiac doses they received during treatment and on published dose-response relationships.⁵⁻⁷ I have also predicted 30-year mortality from stroke^{14,15} and second cancers based on doses in the relevant OAR and the corresponding dose-response relationships.^{8,9,16} In order to investigate the potential risk reduction from using PBS compared to conventional

photon RT, I have also estimated 30-year cardiac mortality for each patient as if they had received photon RT, including 3D-CRT and volumetric arc therapy (PartArc). Mortality rates vary substantially from country to country. In order to investigate how that variation affects the predicted risks from RT, I have repeated the calculations using mortality rates from 4 geographical regions (USA, Western Europe, Eastern Europe and Japan).

4.2 Methods

30-year mortality risks from CHD, VHD, CHF and for the remaining cardiac diseases as a group denoted by “other cardiac” were predicted for each patient following treatment with chemotherapy and RT. The risks were then combined with the risk from stroke in order to predict the 30-year mortality risk from all treatment-related cardiovascular events. Treatment-related risks of death from breast, lung and oesophageal cancer were also predicted for each patient. A summary of the main patient characteristics is shown in Table 4-1.

Table 4-1 Patient characteristics

Sex	N	%
Males	5	18
Females	16	82
Age at RT		
Median age 31years (range:18-48)		
Risk factors		
<i>Hypertension</i>		
No	20	95
Yes	1	5
<i>Smoking at time of HL diagnosis</i>		
No	16	82
Yes	5	18
HL Stage°		
Early and intermediate (IIA/B)	18	86
Advanced (IIIB/IIISB)	3	14
Chemotherapy		
Median dose of anthracyclines 317.5 mg/m ² (range 255-420)		
6 x escalated BEACOPP	4	19
2 x escalated BEACOPP + 2 x ABVD	15	71
4 x ABVD	2	10
Total	21	100

HL: Hodgkin Lymphoma °HL stage according to Lugano classification¹⁷ RT: Radiotherapy

4.2.1 Background mortality risk

It was assumed that for each patient, their mortality rates in the absence of any treatment effects would be equal to the appropriate age-and-sex-specific population-based mortality rates in each geographical region of interest. These rates will be referred to in this thesis as background mortality rates. For each region the most recent mortality rates available were used, so that our predictions would be as relevant as possible to the likely future mortality for current patients. This is similar to the use of mortality rates that is commonly made in the construction of actuarial life tables and in calculations of life-expectancy.

Mortality rates were extracted from the WHO mortality database¹⁸ in 5-year age groups for female and male patients. Rates were extracted for each disease of interest for the latest year for which data were available for each country. The rates for Western and Eastern Europe were then derived by calculating the population-weighted average of the relevant countries shown in Table 4-2. The disease categories considered in this study and their respective International Statistical Classification of Diseases codes (ICD-10) are provided in Table 4-3. An example of population-based cardiac mortality rates for women and men in Western Europe can be seen in Table 4-4 and Table 4-5 respectively, mortality rates for the other regions can be seen in Appendix D.

Table 4-2 The countries comprising each geographical region and in parentheses the latest year that mortality rates were available for each country.

Western Europe: Austria (2014), Belgium (2014), Denmark (2014), Finland (2014), France (2014), Germany (2014), Ireland (2013), Italy (2012), Luxembourg (2014), Netherlands (2015), Norway (2014), Portugal (2014), Spain (2014), Sweden (2015), Switzerland (2013), United Kingdom (2013)
Eastern Europe: Bulgaria, Croatia (2015), Czech Republic (2015), Hungary (2014), Poland (2014), Romania (2015), Slovakia (2014)
USA (2014)
Japan (2014)

Table 4-3 Categorisation of diseases

Category of cardiovascular disease	ICD-10 codes
All cardiac diseases	I01, I02.0, I05-I09, I11, I13, I20-I25, I27, I30-I52
Ischaemic heart disease (IHD)	I20-25
Valvular heart disease (VHD)	I05-I08, I09.1, I34-39
Cardiomyopathy and congestive heart failure (CHF)	I01.2, I09.0, I11.0, I13.0, I13.2, I40-43, I50, I51.4-5, I51.7
Other cardiac	I01.0-1, I01.8-9, I02.0, I09.2-9, I11.9, I13.1, I13.9, I27, I30-33, I44-49, I51.0-3, I51.6, I51.8-9, I52
Stroke	I63-69
Category of second cancers	ICD-10 codes
Breast cancer	C50
Lung cancer	C34
Oesophageal cancer	C15

Table 4-4 Recent annual death rates per 100,000 for women in Western Europe* by age

	Year categories												
Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
<i>Cardiomyopathy/CHF</i>	0.2	0.3	0.4	0.5	0.8	1.1	2.1	3.2	6.1	10.2	17.6	41.7	109.0
<i>Ischaemic HD</i>	0.0	0.1	0.2	0.4	1.1	2.4	5.1	8.6	15.6	27.8	49.4	96.9	209.9
<i>Valvular disease</i>	0.0	0.0	0.0	0.1	0.1	0.3	0.4	0.7	1.1	2.5	5.4	11.9	30.6
<i>Other cardiac</i>	0.3	0.4	0.4	0.6	1.0	1.6	2.4	4.0	6.4	11.3	22.3	45.0	112.0
All Cardiac diseases	0.5	0.8	1.0	1.7	3.0	5.3	9.9	16.4	29.3	51.8	94.7	195.4	461.6
All causes of death	28.7	37.4	44.1	62.8	95.9	160.5	273.8	452.3	698.3	1039.7	1568.5	2538.4	4559.2
Population (1000s)	8913	9729	10457	11289	11812	12644	13447	12862	11603	10824	9489	8606	7721

* Population weighted average for 16 countries: Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom

Table 4-5 Annual death rates per 100,000 for men in Western Europe* by age

	Year categories												
Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
<i>Cardiomyopathy/CHF</i>	0.4	0.6	1.0	1.4	1.7	3.4	5.8	9.8	16.1	26.9	42.3	79.9	161.8
<i>Ischaemic HD</i>	0.1	0.3	0.8	2.1	4.5	11.5	23.6	44.3	75.9	117.8	173.9	290.4	493.6
<i>Valvular disease</i>	0.1	0.1	0.1	0.1	0.3	0.5	0.8	1.6	2.7	5.6	9.6	20.0	43.1
<i>Other cardiac</i>	0.5	0.6	0.9	1.4	2.2	3.9	6.3	10.3	16.8	25.8	41.2	71.8	147.0
All Cardiac diseases	1.0	1.7	2.8	4.9	8.7	19.3	36.4	66.0	111.6	176.1	266.9	462.1	845.5
All causes of death	59.9	101.8	115.5	137.6	181.3	289.9	491.2	833.8	1354.4	2094.7	3071.0	4806.0	7925.9
Population (1000s)	9392	10086	10596	11355	11922	12710	13479	12690	11210	10204	8718	7442	5978

* Population weighted average for 16 countries: Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom

The predicted 30-year background mortality risk of mortality for each patient for each of the specific diseases of interest and taking into account the probability of death from other causes (“competing risks”) was calculated as follows.

Let the annual death rate for the specific disease of interest during the n^{th} year after treatment be denoted by r_n^{sp} , and the corresponding death rate for all other causes of death be denoted by r_n^{oth} . Then the probability of death from the specific disease of interest during year n , given that the individual has survived up to the beginning of year n , is:

$$p_n^{sp} = 1 - e^{-r_n^{sp}} \text{ Equation 4-1}$$

also the probability that the individual died of either the specific disease of interest or of any other cause, given survival up to the beginning of year n is:

$$p_n^{sp+oth} = 1 - e^{-(r_n^{sp} + r_n^{oth})} \text{ Equation 4-2}$$

and the probability that the individual survived to the end of year n is:

$$q_n^{sp+oth} = 1 - p_n^{sp+oth} \text{ Equation 4-3}$$

Hence, the probability that the individual survived up to the beginning of year n is:

$$Q_{n-1}^{sp+oth} = Q_{n-2}^{sp+oth} \times q_{n-1}^{sp+oth} \text{ Equation 4-4}$$

where $Q_0^{sp+oth} = 1$

and the probability that the individual survived up to the beginning of year n and died during year n from the cause of interest is:

$$p_{-cr_n}^{sp} = p_n^{sp} \times Q_{n-1}^{sp+oth} \text{ Equation 4-5}$$

The cumulative probability that the individual dies of the cause of interest by the end of year n (n -year cumulative mortality) is therefore:

$$\sum_{i=0}^n p_{-cr_n}^{sp} \text{ Equation 4-6}$$

Predicted 30-year background mortality risks were calculated for each patient, based on gender and age at treatment for IHD, VHD, CHF, other cardiac, all cardiac disease, stroke, all cardiovascular (i.e. all cardiac disease plus stroke), breast cancer (female patients), lung cancer and oesophageal cancer. When estimating the risks for each cardiac disease individually, all other cardiac diseases were considered as competing risks of death as well as death from all other causes. For example, to adjust IHD for competing risks, all “other cardiac”, CHF and VHD were considered as competing risks of death, or to adjust breast cancer for competing risks all other causes of death were considered as competing risks.

4.2.2 Increased risk of cardiovascular and second cancer mortality following treatment

Mortality rates taking into account the likely effects of RT were derived for each disease category of interest using the dose-response relationships shown in Table 4-6 and the radiation doses shown in Table 4-7. For CHF the risks from anthracycline-containing chemotherapy, and for lung cancer the risks from alkylating-agents-containing chemotherapy were also considered. All the radiation dose-response relationships and the risks from chemotherapy were derived from case-control studies of patients treated in the past. For combined treatment (chemotherapy and RT) an additive rather than multiplicative relationship was observed in the original studies^{7,10}, therefore, the individual RRs from chemotherapy and RT were added as shown in Table 4-6

Predictions of the 30-year cumulative mortality risk for each disease of interest considering the likely effects of treatment, were then obtained in a similar fashion to that described above for the prediction of 30-year cumulative background mortality risks.

The measures of radiation dose used were: MHD to predict risks for IHD and MLVD to predict risk for CHF. For VHD a weighted sum of mean dose to the aortic valve (AVMean), mitral valve (MVMean) and tricuspid valve (TVMean) was used as described by Cutter et al.⁶ The dose to the pulmonary valve was not included in the weighted dose sum as there were no patients with pulmonary disease in the original study by Cutter et al.⁶ The weighted sum was:

$$\text{sumVD} = (\text{AVMean} * 0.553) + (\text{MVMean} * 0.368) + (\text{TVMean} * 0.079)$$

Since dose-response relationships were not available for the “other cardiac” diseases for HL patients, a different approach was followed to estimate the radiation-related risk for “other cardiac”. The RT-related excess risk was estimated by selecting one of the dose-response relationships for IHD, CHF or VHD to predict the risk for each other cardiac disease (shown in Table 4-3) individually. The selection was performed under the guidance of a clinician and based on the disease characteristics and how similar the damage mechanisms were with one of the three end points. For example, to predict radiation-related risk for “Ischemic cardiomyopathy (ICD10-I255)” the dose-response relationship for IHD was used. The allocation of each disease in one of the three dose-response relationship groups is shown in Appendix D. The radiation-related excess risk for each disease was then added up to form the “other cardiac” category. All cardiac doses were converted into EQD2 as described in Chapter 3 since the dose-response relationships for cardiac risks were derived based on EQD2.⁵⁻⁷

The mean dose to the common carotid arteries (MDCCA) was used to predict risk for stroke. Standardised incidence ratios (SIRs) for the risk of stroke in a cohort of HL survivors treated with mantle field RT, were published by De Bruin et al.¹⁴ However, a radiation dose-response relationship was not provided by the authors

and since the MDCCA for each patient were unknown a dose-response model could not directly derived. However, Maraldo et al.¹⁹ provided a retrospective dose reconstruction method (%Prescribed also shown in Chapter 2) for estimating MDCCA as a percentage of the prescribed dose for HL patients treated with mantle field RT. Since the cohort in the De Bruin et al.¹⁴ study also received mantle field RT, the %Prescribed method was used here to estimate the MDCCA for the cohort reported by De Bruin et al.¹⁴ to derive ERR/Gy of MDCCA. Details of the methodology to estimate the MDCCA based on this method are provided in Appendix D. Briefly, the SIRs reported in the De Bruin et al.¹⁴ study were divided by the estimated MDCCA in order to derive ERR/Gy of MDCCA for the risk of stroke.

To estimate risks for second cancers, the MLD was used for lung cancer, the mean breast dose (MBD) for breast cancer and the mean oesophageal dose (MOD) for oesophageal cancer. The dose-response relationships for second cancers were derived in studies based on point doses at the site of second cancer manifestation within the relevant organ at risk.^{8,9,20} However, since this is a prospective risk prediction study, the site of possible second cancer manifestation is not known precisely. Therefore, the mean dose to the appropriate OAR was used instead.

Table 4-6 Summary of the published dose-response relationships used in this chapter to estimate risks of cardiovascular disease and second cancers for Hodgkin lymphoma patients

Reference	Study population	Disease	Risk model
Cardiovascular			
<i>Van Nimwegen et al.</i> ⁵ (2015)	The Netherlands (hospital-based) 325 cases and 1,024 controls Median age_tx:32 y Treated 1965-1995	CHD	ERR/Gy=0.20 age_tx <28 y ERR/Gy=0.088 28≤ age_tx ≤36 y ERR/Gy=0.042 age_tx >36 y RR = 1 + ERR*MHD
<i>Cutter et al.</i> ⁶ (2015)	The Netherlands (hospital-based) 89 cases and 200 controls All patients age tx <41y Treated 1965-1995	VHD	RR=1+e ^(-5.02) * sumVD * e ^(0.075*sumVD)
<i>Van Nimwegen & Ntentas et al.</i> ⁷ (2017)	The Netherlands (hospital-based) 91 cases and 278 controls Median age_tx:28 y Treated 1965-1995	CHF	RR=1+e ^(-4.12) * MLVD * e ^(0.06*MLVD) +e ^{0.97} *d _{anthra} d _{anthra} =1 if anthracyclines are given d _{anthra} =0 if no anthracyclines are given
<i>De Bruin et al.</i> ¹⁴ (2009)	The Netherlands (hospital-based) 55 cases All patients age_tx <451y Treated 1965-1995	Stroke	*ERR/Gy = 0.10 age_tx <20 y *ERR/Gy = 0.08 20≤ age_tx ≤30 y *ERR/Gy = 0.04 30≤ age_tx ≤40 y *ERR/Gy = 0.01 age_tx >40 y RR=1+ ERR*MDCCA
Second cancers			
<i>Travis et al.</i> ⁸ (2003)	International population-based 105 cases and 266 controls Median age_tx:22 y Treated 1965-1994	Breast cancer	ERR/Gy = 0.15 RR=1+(0.15*MBD)
<i>Travis et al.</i> ¹⁰ (2002) & <i>Gilbert et al.</i> ²⁰ (2003)	International population-based 227 cases and 455 controls Median age_tx:50 y	Lung cancer	RT:ERR/Gy = 0.15 Chemo: RR = 4.3

	Treated 1965-1994		$RR=1 + (0.15*MLD) + ((4.3-1) * d_{alka})$ $d_{alka}=1$ if alkylating agents are given $d_{alka}=0$ if no alkylating agents are given
<i>Morton et al.</i> ⁹ (2014)	International population registry 36 cases and 71 controls Median age_tx:34 y Treated 1943-1992	Oesophageal cancer	ERR/Gy=0.38 RR= 1+(0.38*MOD)

* Standardised incidence ratios by De Bruin et al. were used in conjunction with the dose reconstruction methodology by Maraldo et al.¹⁹ to estimate ERR/Gy (Appendix D)
Abbreviations: CHD (coronary heart disease), VHD (valvular heart disease), CHF (congestive heart failure), y (years), age_tx (age at treatment), RR (relative risk), ERR (excess relative risk), Gy (Gray), MHD (mean heart dose), sumVD (summation of dose to the valves), MLVD (mean left ventricular dose), MDCCA (mean dose to the common carotid arteries), MBD (mean breast dose), MLD (mean lung dose) MOD (mean oesophageal dose).

Table 4-7 Mean organ doses used to derive CVD and second cancer risks

Structure	Parameter	3D_CRT (A)	PartArc (B)	PBS (C)	A vs. C	B vs. C
Heart	Dmean	11.4	9.4	7.7	-3.7**	-1.7*
Lungs	Dmean	10.4	9.1	5.3	-5.2**	-3.8**
Breast	Dmean	3.2	3.3	1.6	-1.5*	-1.7*
Oesophagus	Dmean	18.8	17.2	14.4	-4.6**	-3.0**
Carotid arteries	Dmean	27.9	26.4	27.3	-0.6*	+0.9**
L Ventricle	Dmean	5.5	4.3	2.0	-3.5**	-2.3**
Aortic Valve	Dmean	24.0	20.0	15.7	-8.4**	-4.3**
Mitral Valve	Dmean	11.6	8.1	2.1	-9.6**	-6.1**
Tricuspid Valve	Dmean	7.4	5.9	3.2	-4.2*	-2.7*

The positive values indicate that PBS increased the dose compared to the respective photon technique. †p>0.05,

* p<0.05, ** p<0.001

4.3 Results

Predicted cardiovascular and second cancer mortality risks for the group of 21 HL patients are presented below.

4.3.1 Cardiovascular mortality

4.3.1.1 Background 30-year cumulative cardiovascular mortality

The background cardiovascular mortality rates varied substantially between the 4 geographical regions. The patients studied here are from the Czech Republic and Slovakia. Therefore, it was assumed that their background mortality rates would be similar to the rates in Eastern Europe. The 30-year cumulative background mortality risk from cardiac diseases or stroke was three times higher for Eastern Europe than for group with the same age and sex characteristics in Western Europe and about double that of a group in the USA. A Japanese group had the lowest background risk (Figure 4-1).

The percentage contribution of each cardiac disease and stroke towards the overall risk of CV mortality is presented in Figure 4-2 for each geographical region. IHD is the main cause of cardiovascular-related mortality for all regions and it accounts for more than half of the cardiovascular-related deaths in Western Europe and USA. The way in which the cumulative background mortality risk develops over the 30 years after treatment for each CVD individually (IHD, CHF, other cardiac diseases, stroke and VHD) as well as for all cardiac disease and all cardiac disease plus stroke is shown in Figure 4-3.

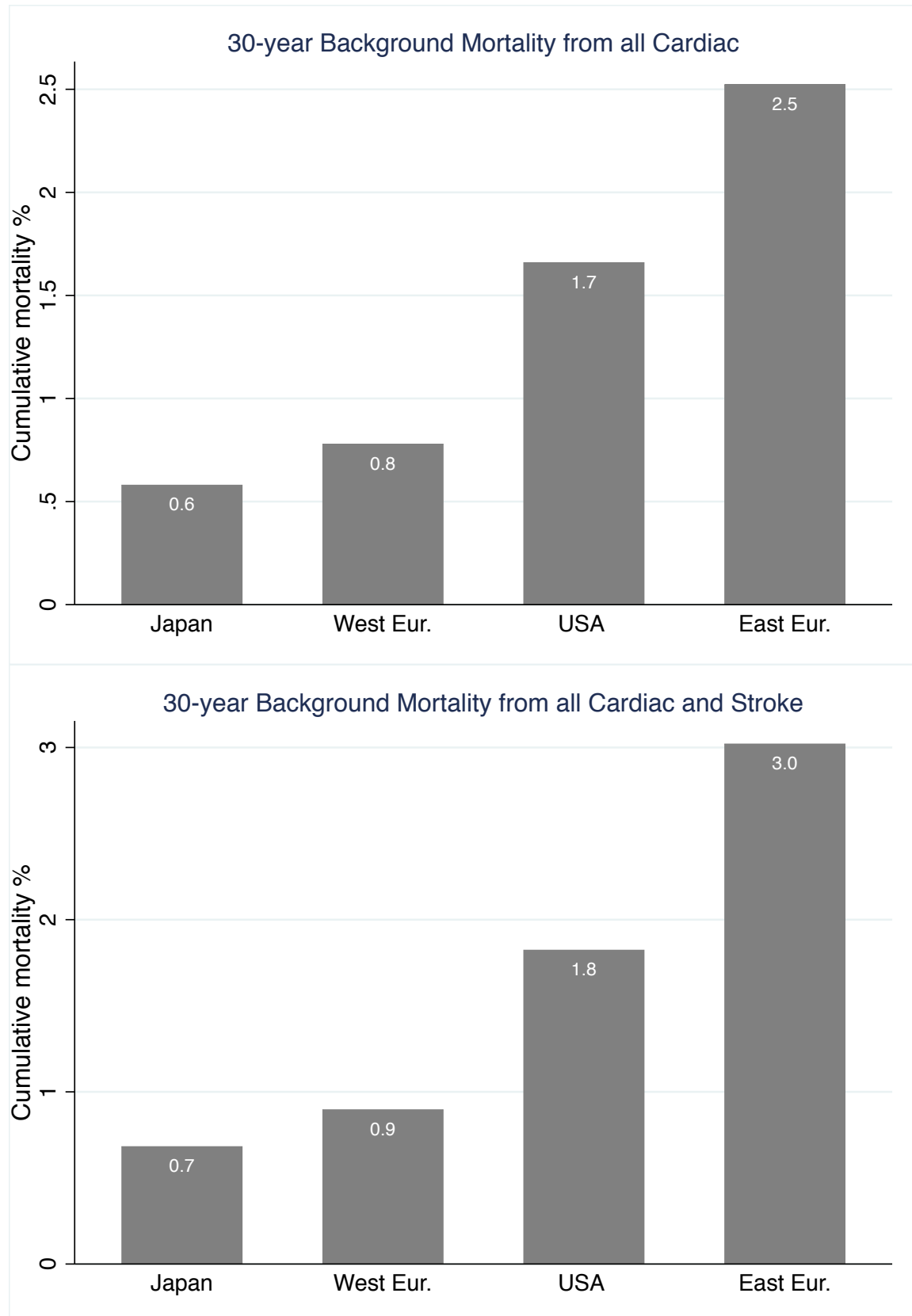


Figure 4-1 Cumulative 30-year background mortality risk from all cardiac diseases (top graph) and from all cardiac diseases and stroke (bottom graph) for each geographical region and accounting for deaths from other causes as competing risks. Calculations are for a population with distribution over categories of sex and age at entry, the same as the distribution over sex and age at treatment of the patient group

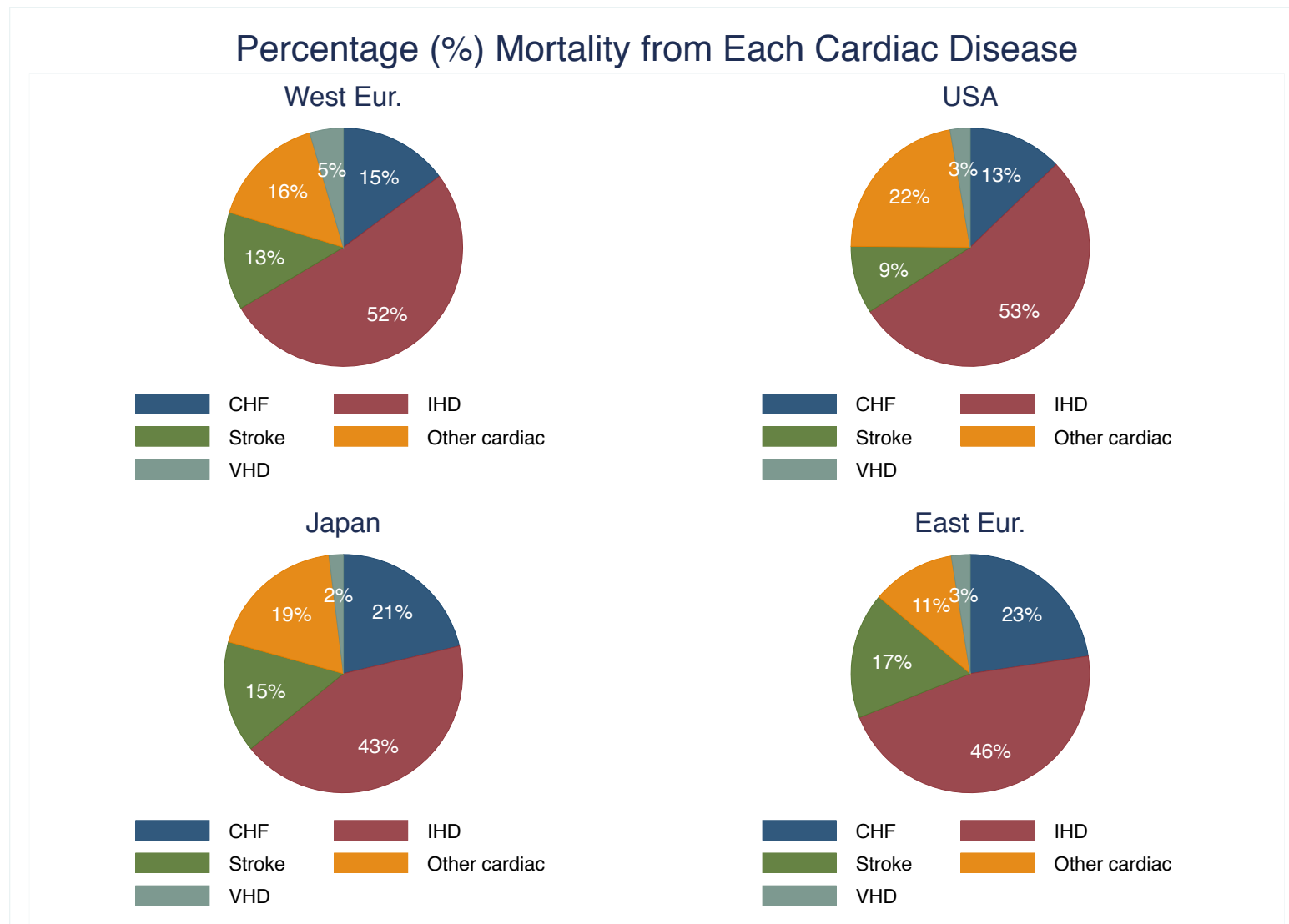


Figure 4-2 Percentage contribution of each cardiac disease and stroke to the overall 30-year cumulative risk of mortality from all cardiac diseases and stroke. CHF: Congestive heart failure, IHD: Ischemic heart disease, VHD: Valvular heart disease

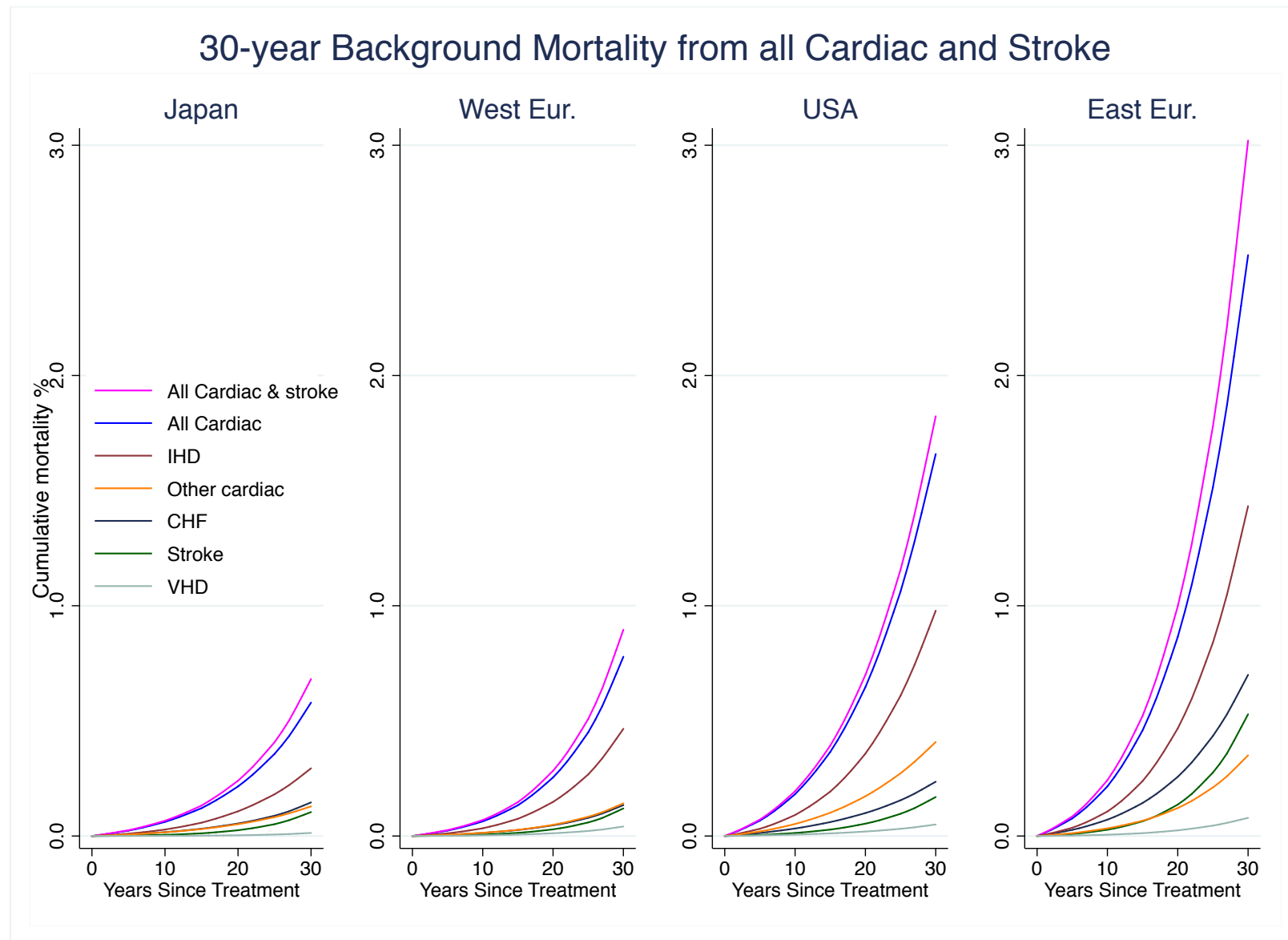


Figure 4-3 Cumulative background mortality from cardiac diseases and stroke over the 30 years after treatment for all 4 regions.

4.3.1.2 Predicted cardiovascular mortality following treatment for HL

The excess cardiovascular mortality risk following treatment with anthracycline-containing chemotherapy and each of the three different RT methods, can be seen in Table 4-8, Figure 4-4 and Figure 4-5 for each of the four geographical regions. The overall 30-year cumulative risk of death from any cardiac disease or stroke varied substantially between the different regions. On average, a HL patient from Eastern Europe who receives RT and chemotherapy will have a three times higher risk of dying from cardiac disease or stroke compared to a patient from Western Europe. The differences between the four regions were driven principally by the background risk, but both chemotherapy and RT contributed to the overall mortality risk.

When comparing the 3 RT methods within each of the four regions, PBS carried a lower mortality risk from CVD compared to either conventional or advanced photon RT techniques. However, the benefit of PBS varied with the background risk. For example, on average for patients in Eastern Europe, the risk was reduced by 0.5% (from 6.5% to 6.0%). However, for Japanese patients the risk was reduced by only 0.1% if PBS is used instead of 3D-CRT (from 1.6% to 1.5%). The highest CVD risk reduction achieved by PBS was a 2.1% decrease in risk when compared to 3D-CRT (7.6% and 9.7% respectively). For some patients, however, PartArc performed as well or even reduced slightly the CVD risk compared to PBS. For example, for a female patient of 31 years old at age of treatment, PartArc reduced the CVD risk by 0.2% compared to PBS (3.6% and 3.8% respectively).

Table 4-8 Predicted 30-year cumulative mortality risk from all cardiac diseases and stroke following chemotherapy and RT for HL. Risks were calculated for all 4 regions and for 3 RT methods

Region	Background	Chemo	Chemo&3D-CRT	Chemo&PartArc	Chemo&PBS
Japan	0.7% (0.1-2.9)	1.0% (0.2-5.0)	1.6% (0.3-7.1)	1.5% (0.3-6.9)	1.5% (0.3-6.6)
Western Eur.	0.9% (0.1-4.3)	1.2% (0.2-6.1)	1.9% (0.3-8.9)	1.8% (0.3-8.5)	1.7% (0.3-7.9)
USA	1.8% (0.3-7.3)	2.3% (0.5-8.8)	3.9% (1.0-12.7)	3.6% (0.9-12.2)	3.4% (0.9-11.4)
Eastern Eur.	3.0% (0.3-12.6)	4.2% (0.6-16.5)	6.5% (1.2-22.8)	6.2% (1.0-22.0)	6.0% (1.1-21.1)

Average of predicted risks for 21 patients based on sex, age at treatment, radiation dose to the whole heart and the relevant cardiac substructures and accounting for deaths from other causes as competing risks.

Chemo: Anthracycline containing chemotherapy (BEACOPP &/or ABVD), 3D-CRT: 3D conformal radiotherapy, PartArc: Partial arc volumetric radiotherapy, PBS: Pencil beam scanning radiotherapy

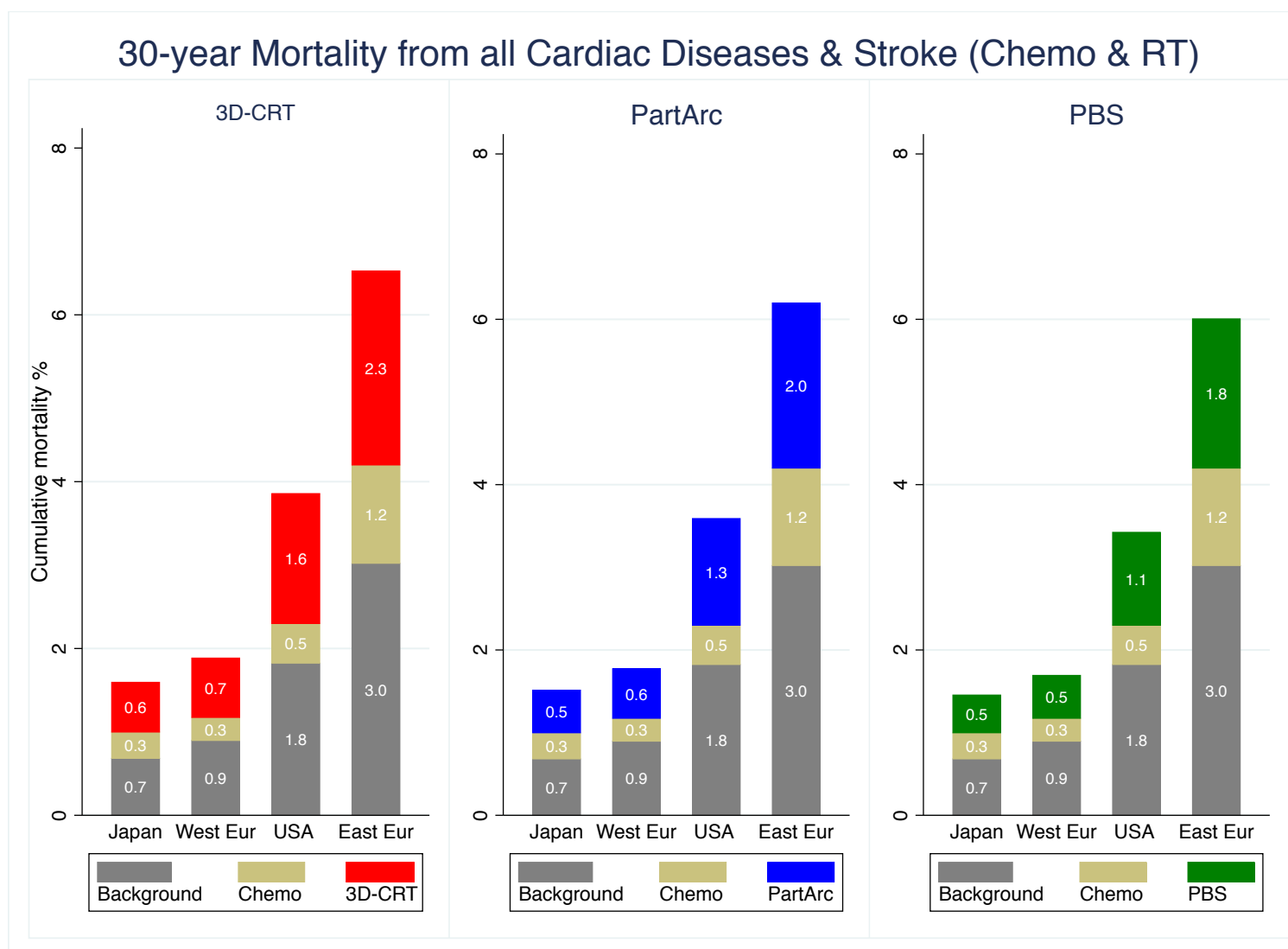


Figure 4-4 Predicted 30-year background cumulative mortality risks from all cardiac diseases and stroke. Background (grey bar), excess risk after chemotherapy (yellow bar), excess risk after 3D conformal RT (3D-CRT) (red bar), partial arc volumetric RT (PartArc) (blue bar) and pencil beam scanning (PBS) (green bar)

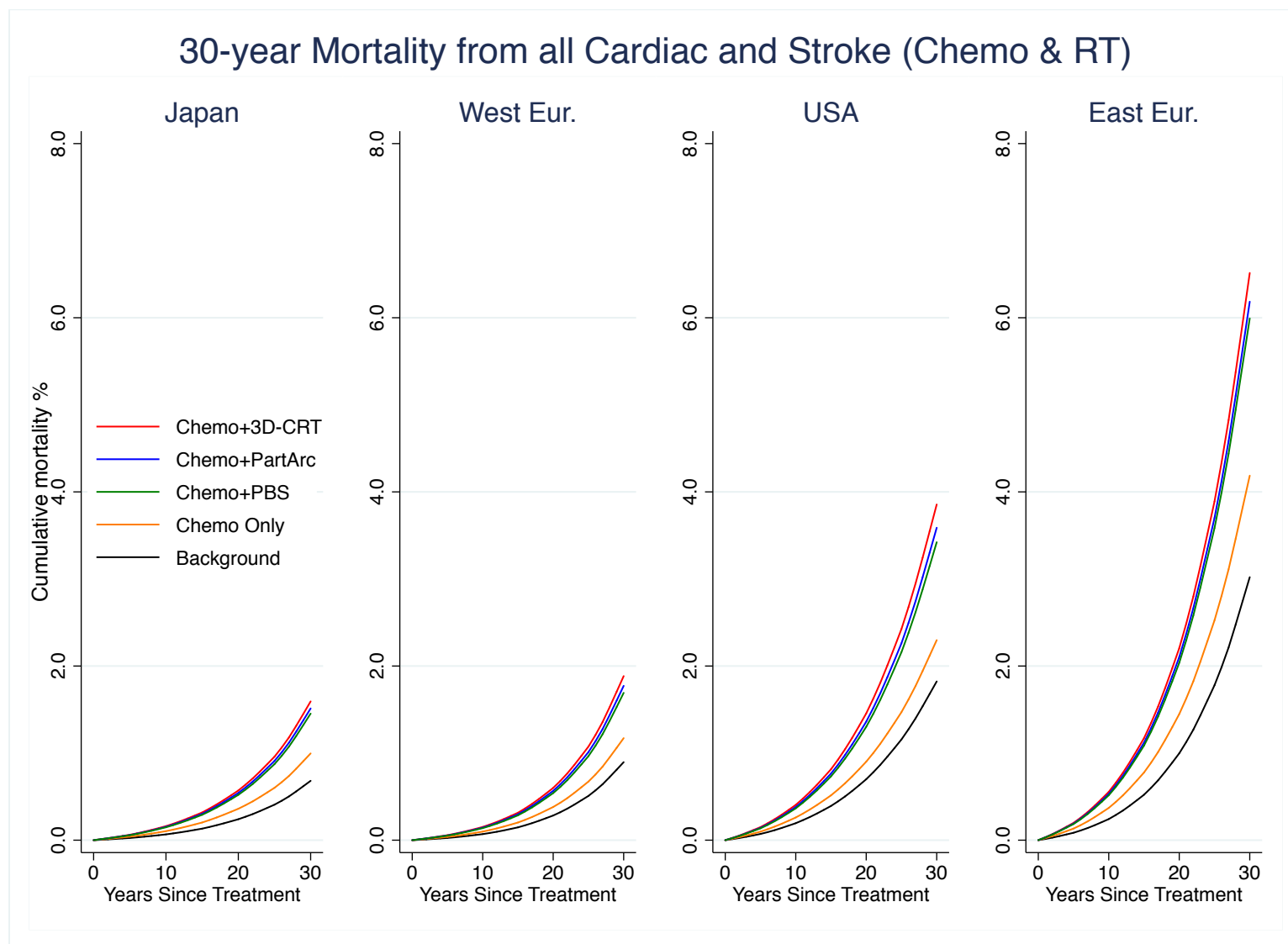


Figure 4-5 Predicted cumulative mortality risk from all cardiac diseases and stroke after RT and chemotherapy over 30 years after treatment for HL. Chemo: chemotherapy 3D-CRT: 3D conformal RT, PartArc: Partial arc volumetric RT, PBS: Pencil beam scanning.

4.3.2 Mortality from second cancers

The predicted background risk from second cancers as well as the excess mortality risks from second cancers following chemotherapy and RT is presented below.

4.3.2.1 Background 30-year cumulative cancer mortality

30-year background cancer mortality rates were calculated for all patients and can be seen in Figure 4-6 and Figure 4-7 for all and for female patients respectively. The background rates did not differ between regions as much as the CVD rates seen above. Risk of death from lung cancer was similar for people across Europe and the USA. However, Japanese patients had half the risk of dying from lung cancer compared to the other regions. The differences between regions were even smaller for breast and oesophageal cancer. The estimated background risk of dying from oesophageal cancer for this group of patients was about one tenth of the risk from lung cancer.

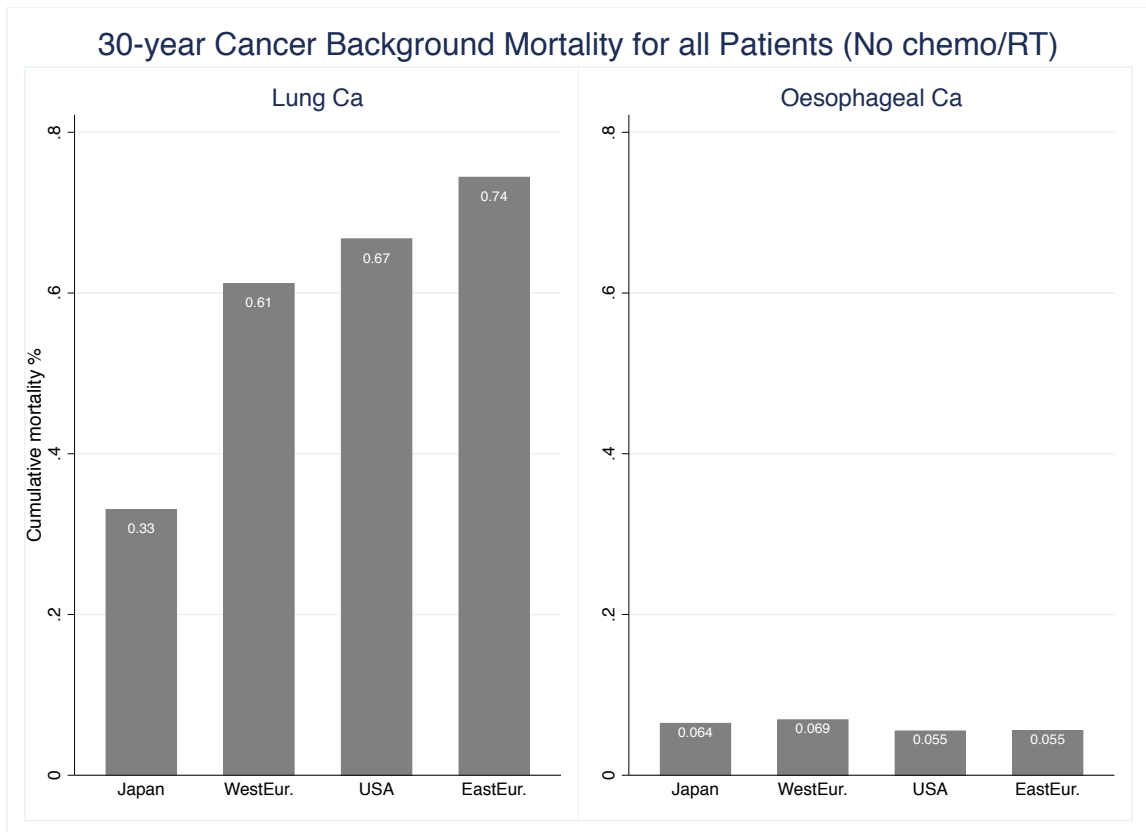


Figure 4-6 30-year cumulative background mortality from lung and oesophageal cancer calculated for all patients based on sex and age at treatment and adjusted for competing risks.

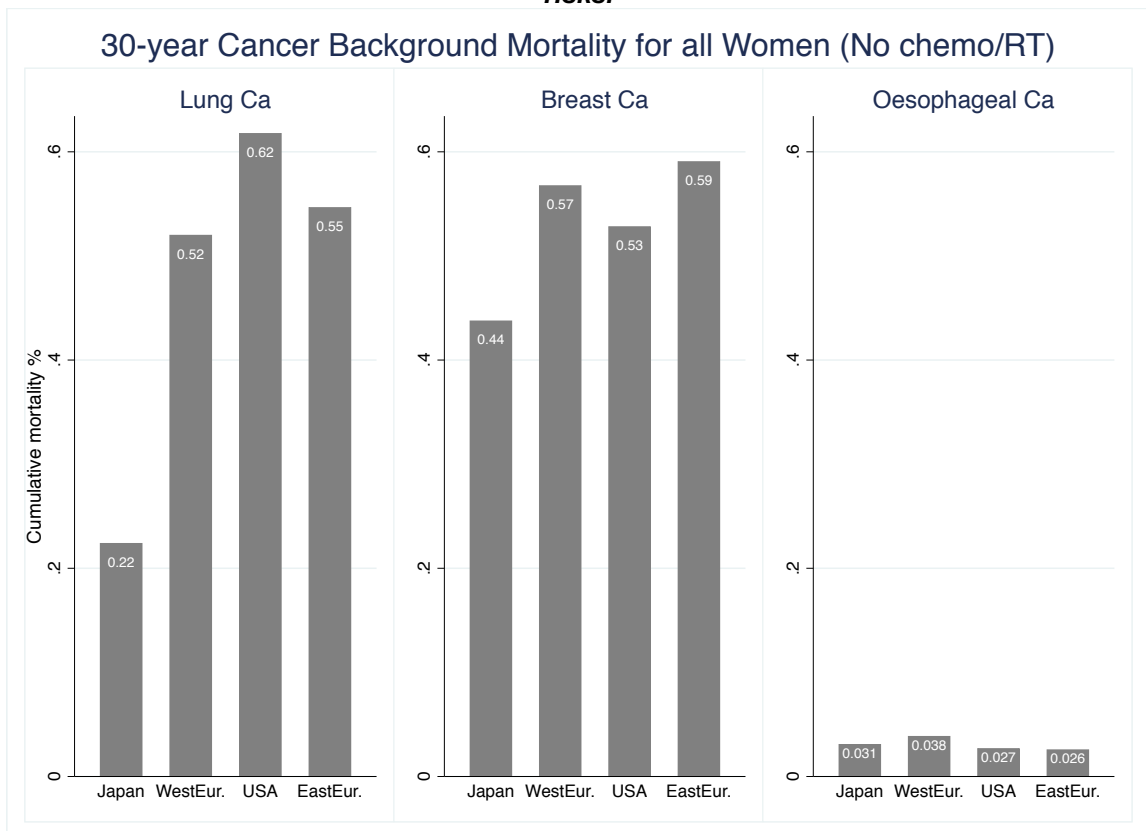


Figure 4-7 30-year cumulative background mortality from lung, breast and oesophageal cancer calculated only for female patients (n=16) based on age at treatment and adjusted for competing risks.

4.3.2.2 Predicted lung cancer mortality following treatment for HL

The 30-year cumulative mortality risks from lung cancer following treatment with chemotherapy and RT for all four geographical regions and for the three different RT methods can be seen in Table 4-9. The proportional increase in risk due to chemotherapy is substantially higher for lung cancer than for CVD. For patients in Eastern Europe, their risks from chemotherapy and RT will be almost identical if they are treated with 3D-CRT (1.67% vs 1.71%). However, PBS reduced their radiation-related lung cancer risk to 1.2%, 0.5% lower than the risk from chemotherapy (Figure 4-8).

As it was seen in Chapter 3, PBS reduced the MLD by an average of 5 Gy compared to 3D-CRT (Table 4-7). This resulted in a risk reduction of 0.5% for the patients from Eastern Europe i.e. for the group as a whole, for each reduction of 1 Gy in MLD there was a 0.1% reduction in 30-year risk. The MLD reduction achieved by PBS varied between 1.0 and 10.0 Gy.

Table 4-9 Predicted 30-year cumulative mortality risk from lung cancer following chemotherapy and RT for HL. Risks were calculated for all 4 regions and for the 3 RT methods.

Region	Background	Chemo	Chemo&3D-CRT	Chemo&PartArc	Chemo&PBS
Japan	0.3% (0.03-2.1)	1.1% (0.1-6.9)	1.9% (0.2-11.6)	1.8% (0.2-11.4)	1.6% (0.2-10.0)
Western Eur.	0.6% (0.1-2.6)	2.0% (0.2-8.5)	3.4% (0.4-14.1)	3.3% (0.3-14.0)	3.0% (0.3-12.3)
USA	0.6% (0.1-2.4)	2.0% (0.2-7.8)	3.7% (0.4-13.1)	3.6% (0.4-13.0)	3.3% (0.3-11.5)
Easter Eur.	0.7% (0.1-3.5)	2.4% (0.2-11.2)	4.1% (0.5-18.6)	4.0% (0.4-18.4)	3.6% (0.4-16.2)

Average of predicted risks for 21 patients based on sex, age at treatment, mean lung radiation dose and accounting for deaths from other causes as competing risks. Chemo: Alkylating agent-containing chemotherapy (BEACOPP &/or ABVD), 3D-CRT: 3D conformal radiotherapy, PartArc: Partial arc volumetric radiotherapy, PBS: Pencil beam scanning radiotherapy

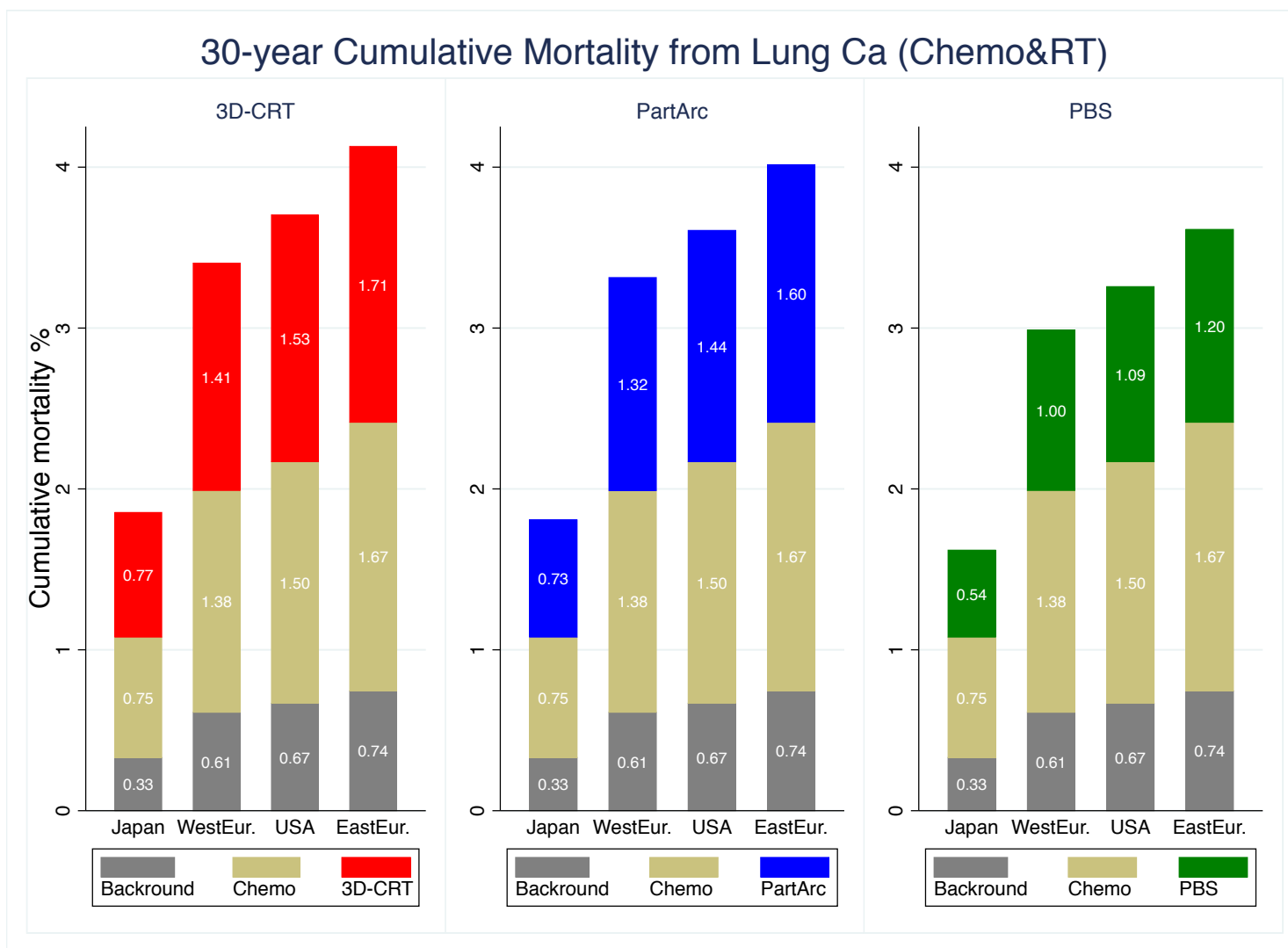


Figure 4-8 Predicted 30-year background cumulative mortality risks from lung cancer. Background (grey bar), excess risk after chemotherapy (yellow bar), excess risk after 3D conformal RT (3D-CRT) (red bar), partial arc volumetric RT (PartArc) (blue bar) and pencil beam scanning (PBS) (green bar)

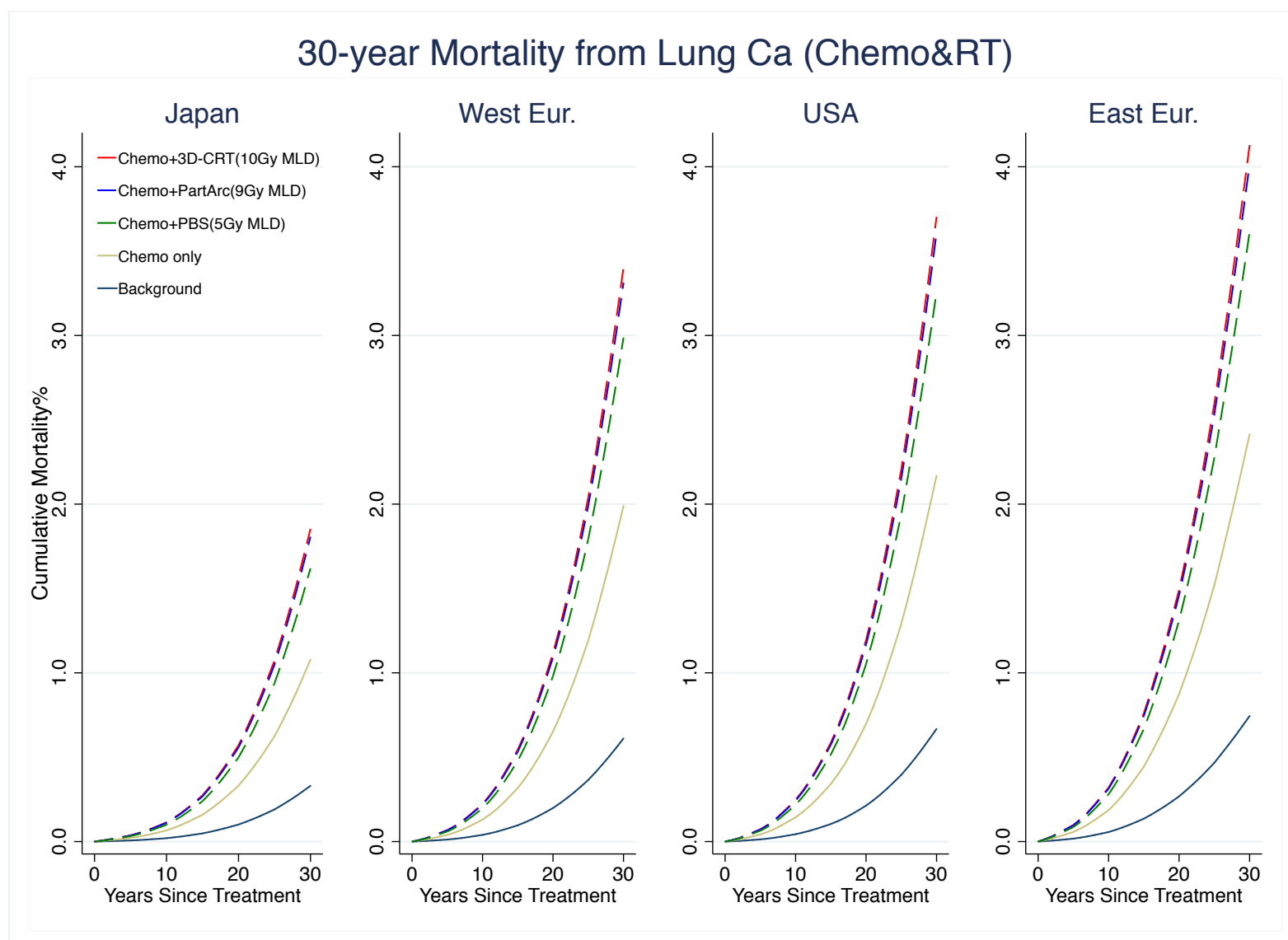


Figure 4-9 Predicted cumulative mortality risk from lung cancer over 30 years after treatment for HL (Chemotherapy & RT). 3D-CRT: 3D conformal RT, PartArc: Partial arc volumetric RT, PBS: Pencil beam scanning MLD: Mean lung dose

4.3.2.3 Predicted breast cancer mortality following treatment for HL

The background mortality risk for breast cancer and the radiation-related excess mortality risks were estimated in a similar fashion to that for lung cancer and can be seen in (Table 4-10).

The mortality from breast cancer was lower than that for lung cancer and differences between regions in background mortality were also smaller. The excess mortality risk due to RT was also lower than for lung cancer despite the ERR/Gy being identical, (Table 4-6) due to the lower MBD compared with the MLDs. The excess 30-year cumulative mortality risk from second breast cancer was 1/3 of the background mortality for 3D-CRT and PartArc and only 1/6 for PBS, i.e. the radiation-related risk was halved when using PBS compared to either photon RT method.

Table 4-10 Predicted 30-year cumulative mortality risk from breast cancer following chemotherapy and RT. Risks were calculated for all 4 regions and for the 3 RT methods.

Region	Background	Chemo&3D-CRT	Chemo&PartArc	Chemo&PBS
Japan	0.4% (0.1-0.91)	0.6% (0.2-1.40)	0.6% (0.2-1.52)	0.5% (0.2-1.05)
West Eur.	0.6% (0.2-1.45)	0.8% (0.2-2.00)	0.8% (0.2-2.19)	0.7% (0.2-1.52)
USA	0.5% (0.2-1.26)	0.7% (0.2-1.79)	0.8% (0.2-1.95)	0.6% (0.2-1.35)
East Eur.	0.6% (0.2-1.47)	0.8% (0.2-2.10)	0.8% (0.2-2.30)	0.7% (0.2-1.60)

Average risks from 21 patients predicted for each patient individually based on sex, age at treatment, mean radiation dose to the breast and were adjusted for competing risks. Chemo: Anthracycline containing chemotherapy (BEACOPP &/or ABVD), 3D-CRT: 3D conformal radiotherapy, PartArc: Partial arc volumetric radiotherapy, PBS: Pencil beam scanning radiotherapy

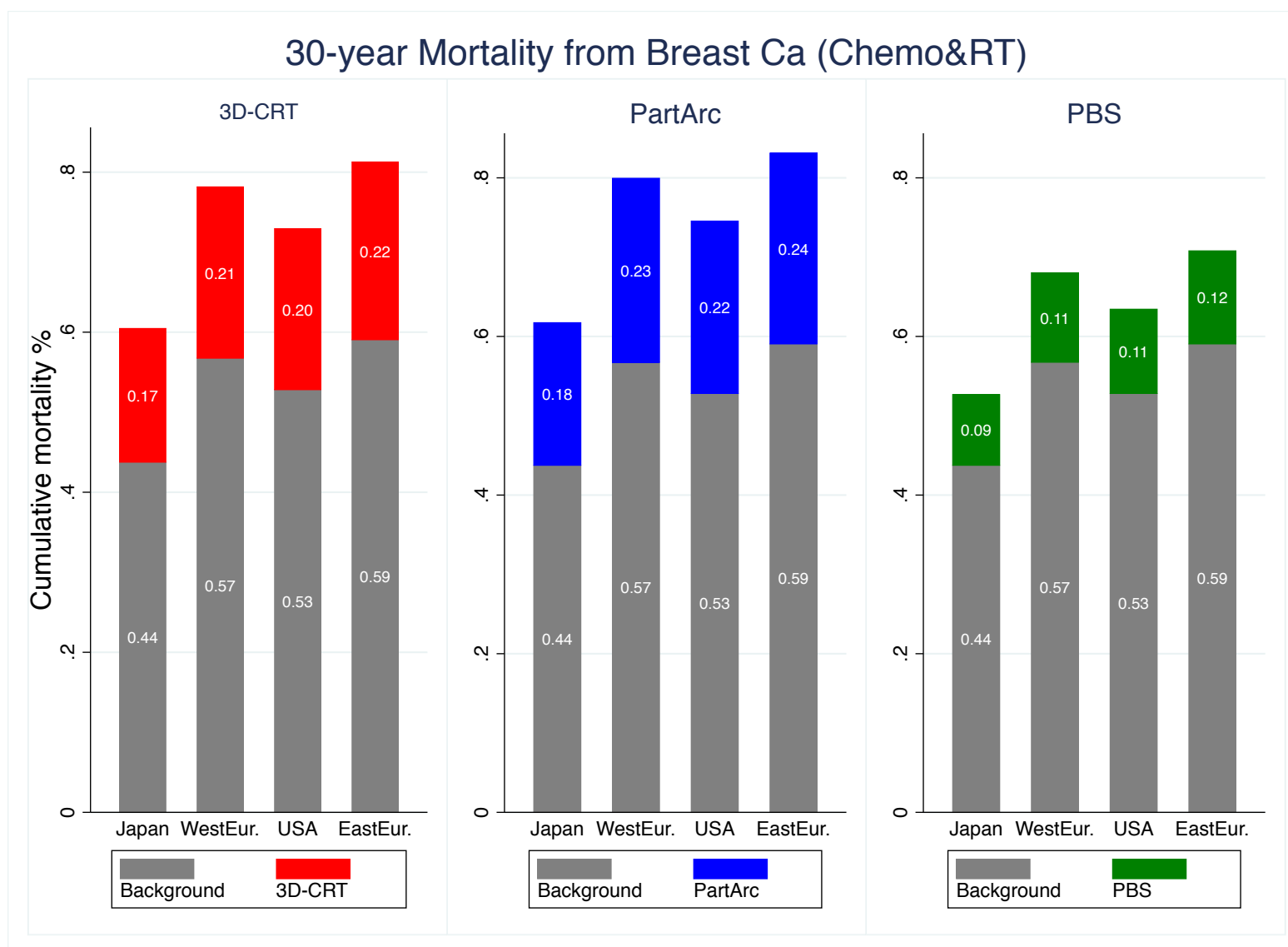


Figure 4-10 Predicted 30-year background cumulative mortality risks from breast cancer. Background (grey bar), excess risk after 3D conformal RT (3D-CRT) (red bar), partial arc volumetric RT (PartArc) (blue bar) and pencil beam scanning (PBS) (green bar)

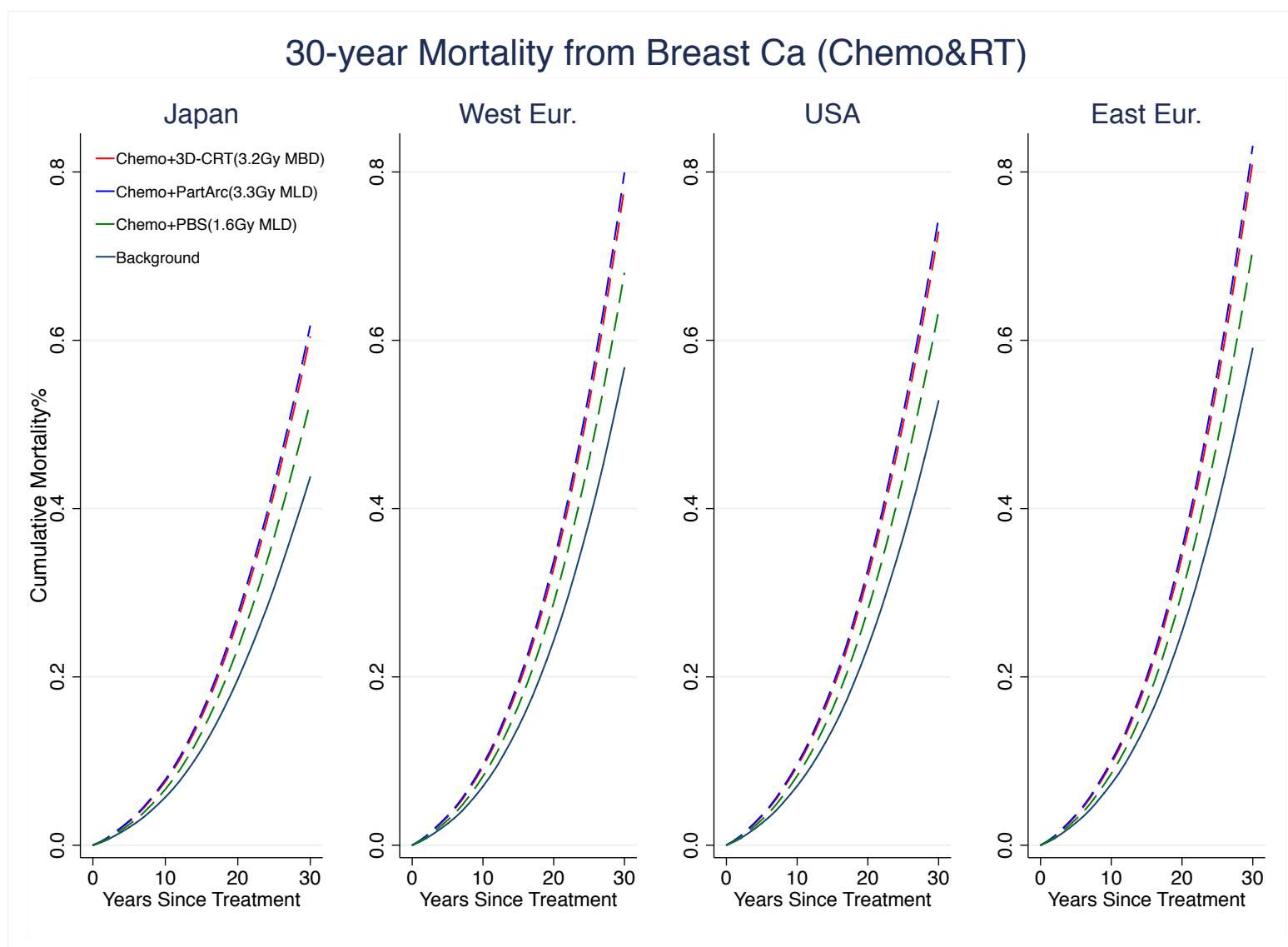


Figure 4-11 Predicted cumulative mortality risk from breast cancer over 30 years after treatment for HL. 3D-CRT: 3D conformal RT, PartArc: Partial arc volumetric RT, PBS: Pencil beam scanning MBD: Mean breast dose

4.3.2.4 Predicted oesophageal cancer mortality following treatment for HL

Lastly, the background and the radiation-related excess mortality risks from oesophageal cancer were estimated (Table 4-11). The background mortality rates from oesophageal cancer were much lower than for breast and lung cancer and were similar in all regions. However, the risk increased substantially with RT from 0.06% to up to 0.52% for East Europe when using 3D-CRT. The excess risk from RT was between 5 and 6 times higher than the background risk, depending on RT method.

Table 4-11 Predicted 30-year cumulative mortality risk from oesophageal cancer for all patients following RT and chemo. Risks were calculated for all regions and for 3 RT methods.

Region	Background	Chemo&3D-CRT	Chemo&PartArc	Chemo&PBS
Japan	0.06% (0.00-0.54)	0.41% (0.04-3.57)	0.39% (0.04-3.32)	0.32% (0.03-2.80)
Western Eur.	0.07% (0.01-0.44)	0.52% (0.03-2.95)	0.49% (0.03-2.73)	0.40% (0.03-2.3)
USA	0.06% (0.00-0.38)	0.41% (0.03-2.52)	0.38% (0.03-2.34)	0.32% (0.03-1.98)
Eastern Eur.	0.06% (0.00-0.34)	0.52% (0.02-2.26)	0.48% (0.02-2.10)	0.40% (0.02-1.80)

Average of predicted risks for 21 patients based on sex, age at treatment, mean breast radiation dose and accounting for deaths from other causes as competing risks. Chemo: Alkylating agent-containing chemotherapy (BEACOPP &/or ABVD), 3D-CRT: 3D conformal radiotherapy, PartArc: Partial arc volumetric radiotherapy, PBS: Pencil beam scanning radiotherapy

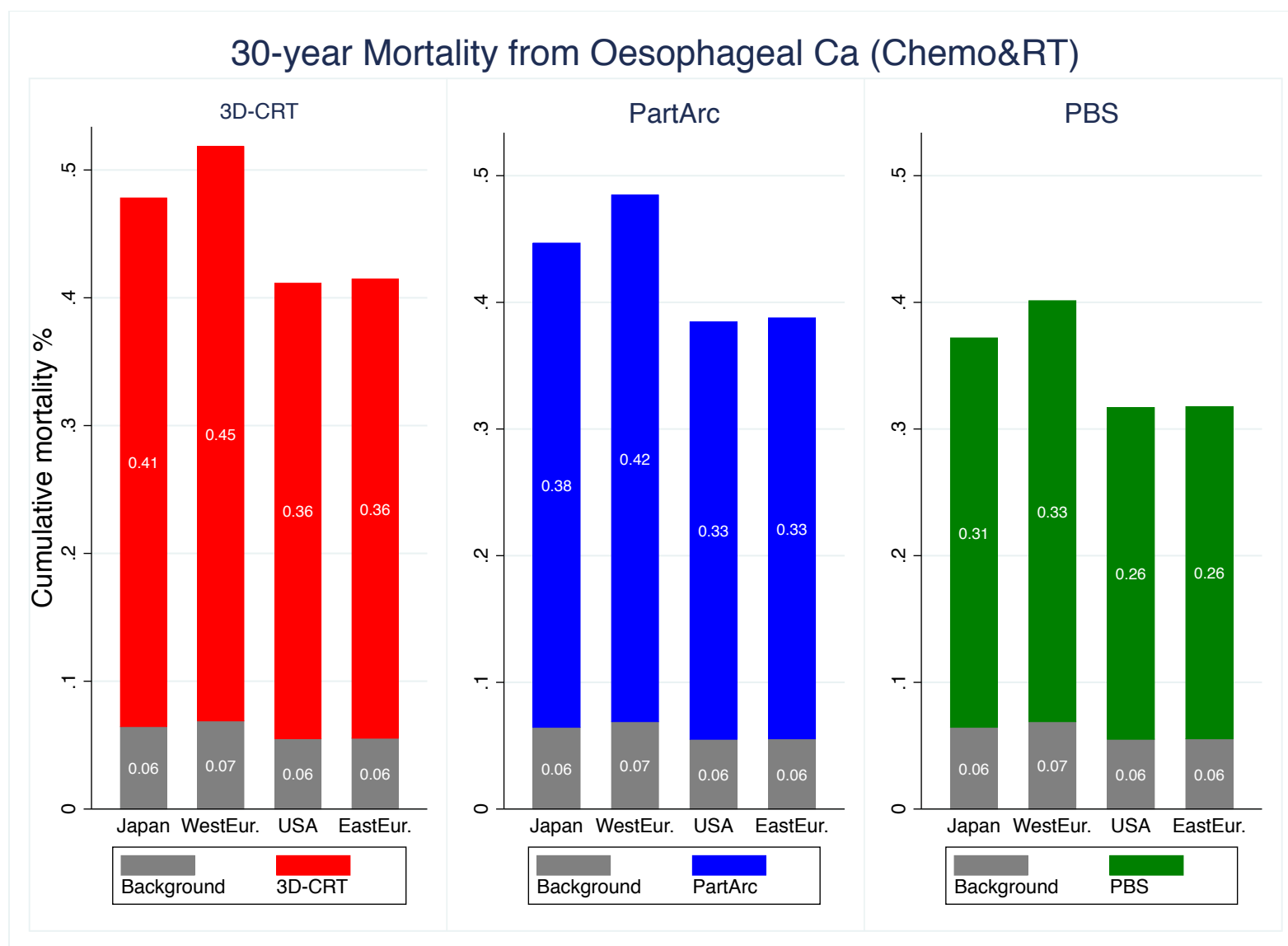


Figure 4-12 Predicted 30-year background cumulative mortality risks from oesophageal cancer. Background (grey bar), excess risk after 3D conformal RT (3D-CRT) (red bar), partial arc volumetric RT (PartArc) (blue bar) and pencil beam scanning (PBS) (green bar)

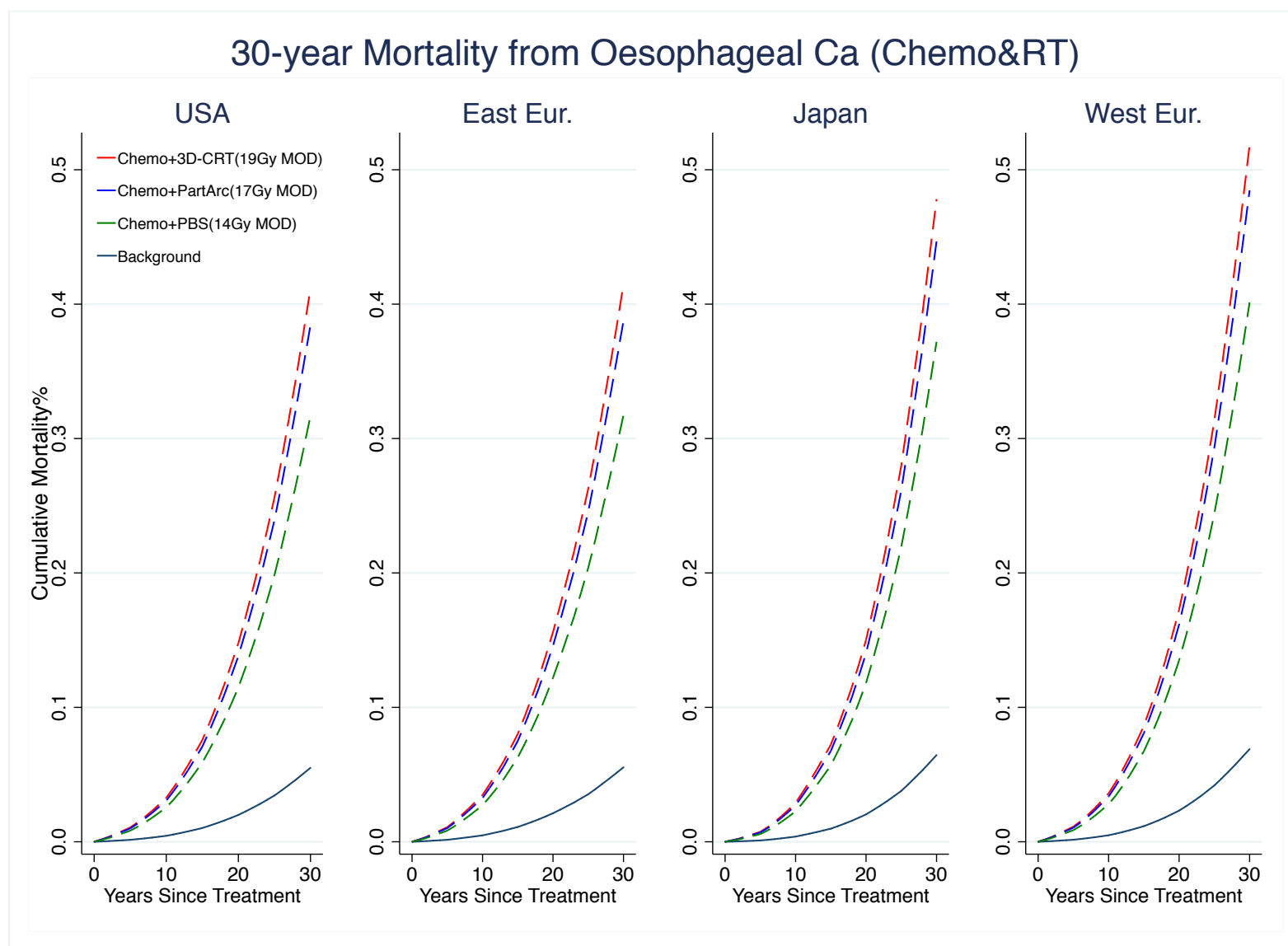


Figure 4-13 Predicted cumulative mortality risk from oesophageal cancer over 30 years after treatment for HL. 3D-CRT: 3D conformal RT, PartArc: Partial arc volumetric RT, PBS: Pencil beam scanning MOD: Mean oesophageal dose.

4.4 Discussion

To my knowledge, this is the first study to estimate cardiovascular and second cancer risks for a group of HL patients who were treated with DIBH-PBS proton RT, and to compare the risks from PBS to the risks from DIBH-PartArc. Furthermore, it is the first study to use the recently derived cardiac disease-specific radiation dose-response relationships from large epidemiological studies to produce overall cardiac mortality risks by combining them. Lastly, it also, as far as I am aware, the first time that regional background mortality rates have been taken into account in predicting risks for patients that have been treated with proton RT. It was assumed that the mortality rates for the patient group studied here were best represented by Eastern European rates since the patients originated from Slovakia as well as the Czech Republic and were treated in Prague. The risks for Western Europe, USA and Japan, represent the risks that an identical in terms of patient characteristics as described in Table 4-1 group of HL patients from these regions would have.

The results suggest PBS reduced the risks from both radiation-related CVD and second cancers when compared to either of the photon RT methods. However, the risk reduction achieved by PBS varied substantially depending on the patient's background risk, their burden of disease and the comparison photon RT method. In some cases, the differences in background risk between regions dwarfed those between RT methods within the same region. For example, the typical background 30-year CVD mortality risk for a patient from the USA was higher than the background risk plus the excess risk from RT and chemotherapy together for a patient from Western Europe. These findings demonstrate the importance of considering background risk and life-style risk factors in patient-specific risk prediction.

The most recent background mortality rates for CVD and second cancers from 26 countries were used to estimate 30-year cumulative background mortality for the 4 different geographical regions and the rates were adjusted for competing risks. The fact that background mortality risk was shown to have such a prominent effect on the treatment-related risks shows that it is important to take background risks into account when predicting treatment-related risks. The substantial differences between geographical regions and their impact on risks indicate that additional life-style risk factors such as smoking, obesity, exercise and other chronic diseases should also be taken in to account when predicting risks.

4.4.1 Cardiovascular Risks

It is well known that cardiovascular mortality varies substantially between different countries and geographical regions.^{21,22} A similar variation was observed when 30-year cumulative CVD background mortality risk was calculated for the patient group in this study for the 4 different regions. The 30-year background risk of CVD mortality for Eastern Europe was 3.0% which is more than three times that for Western Europe (0.9%) and almost twice that for the USA (1.8%). Japanese patients had the lowest cumulative background risk of dying from CVD (0.7%).

Since radiation and chemotherapy-related CVD mortality risks multiply the background mortality risk, the absolute magnitude of the excess treatment-related risk is affected. It was, however, surprising that the differences in overall mortality between the four regions were much greater than the differences between the three RT methods within the same region. This demonstrated how the effect of life-style risk factors can in some cases dwarf the risk reduction by using advanced RT methods instead of conventional RT. For example, for the patients in this study, the radiation-related excess 30-year cumulative mortality risk of CVD was reduced by

0.5% and 0.2% if patients were treated with PBS instead of 3D-CRT or PartArc respectively (PBS: 1.8%, 3D-CRT: 2.3% and PartArc 2.0%). However, the risk reduction for a Japanese group was only 0.1%.

The magnitude of the chemotherapy-related CVD risk varied from 0.3% to 1.2%, depending on geographical region of interest and was due to the almost 3-fold increased risk of CHF following chemotherapy reported in the case-control study in Chapter 1 and Appendix A. No other cardiac disease contributed to the overall CVD risk following chemotherapy. Increased risk of VHD has also been reported in previous studies.⁴ However, in the most recent study on VHD which was used here to derive treatment-related risks of VHD no evidence of chemotherapy-related increased risk was found.⁶

In summary, the average predicted 30-year cumulative risk of CVD mortality for this patient group following chemotherapy and PBS proton RT, was estimated to be 6.0% based on Eastern European mortality rates, whilst the risks were 3.4%, 1.7% and 1.5% for patients from the USA, Western Europe and Japan respectively. If the patients had been treated with 3D-CRT or PartArc they would have had a 6.5% (range: 1.2% to 22.8%) or 6.2% (1.0% to 22.0%) increased risk of CVD respectively. The biggest reduction in CVD risk achieved by PBS for one of the patients in this group was a 2.1% decrease in risk when compared to 3D-CRT (7.6% and 9.7% respectively). However, for some patients (n=8), PartArc performed as well or even reduced slightly the CVD risk compared to PBS. For example, for a female patient of 31 years old at age of treatment, PartArc reduced the CVD risk by 0.2% compared to PBS (3.6% and 3.8% respectively). This demonstrated that for some patients, referral to proton RT can be beneficial whilst for others, using photon RT methods would result in equal, if not lower, CVD risks.

4.4.2 Second cancers

The background mortality risks for second cancers did not vary between the geographical regions as much as in CVD, except for Japanese patients who had half the risk of dying from lung cancer compared to patients from other regions. Therefore, the variation in the overall treatment-related cumulative mortality risks was not as large as for CVD.

The radiation-related mortality risk from lung cancer was reduced by 0.5% with PBS compared to 3D-CRT and by 0.4% compared to PartArc. When considering that PBS reduced the MLD by 5 Gy compared to 3D-CRT and by 4 Gy compared to PartArc, it can be assumed that for this patient group as a whole, for each reduction of 1 Gy in MLD there was a 0.1% reduction in 30-year risk. The risk reduction achieved for breast cancer was smaller which was expected due to the smaller dosimetric differences between the three RT methods. The radiation-related risk for oesophageal cancer was increased from 5 to 6 times that of background risk, due to the higher mean radiation doses received by the oesophagus and the increased ERR/Gy. However, oesophageal cancer is relatively rare, and the 30-year cumulative mortality risk for oesophageal cancer was reduced by only 0.1% when using PBS compared to either photon RT method.

Alkylating agent-containing chemotherapy for treatment of HL has been associated with risk of lung cancer.^{8,23} The risk was estimated to be 1.67%, almost identical to the radiation-related risk if the patients were treated with 3D-CRT (1.67% vs 1.71%). However, since this group was treated with PBS their excess risk from RT was estimated to be 1.2%, 0.5% lower than the chemotherapy-related risk. The RRs for lung cancer related to alkylating agent-containing chemotherapy used in this study to estimate the above risks were originally derived in epidemiological

studies on patients treated with older chemotherapy regimens (e.g. MOPP) which contained higher doses of alkylating agents than the modern chemotherapeutic regimens used for the patients in this study (BEACOPP and/or ABVD). Therefore, the chemotherapy-related risk for lung cancer might have been overestimated for these patients. However, it is uncertain whether the lower doses used in modern regimens will result in a decrease in risk and there is, as yet, no published data to confirm or reject this hypothesis.

4.4.3 Strengths and limitations

The main strength of this study is that the risk prediction models developed to estimate CVD risks are based on HL patient data from epidemiological studies with long-term follow-up combined with patient-specific cardiac doses such as MHD and dose to substructures. This is the first time that these recently published results have been used to predict risks for individual cardiac diseases and for all CVD together. Additionally, the cardiac radiation doses received by the patient group here, were converted into EQD2 rather than using the extracted doses from the treatment planning system, since the dose-response relationships for cardiac risks were derived based on EQD2.

Another strength of this study is that it is the first time that CVD and second cancer risks are predicted for patients treated with PBS proton RT for HL and that those risks were compared to advanced PartArc RT, both delivered in DIBH. The use of proton PBS-RT has been growing rapidly worldwide and is expected to continue during the next decades²⁵ and evidence for the use of PBS in HL patients is crucial. However, these advanced RT methods are not widely used in clinical practice yet, therefore, the risks estimated here might be lower than the risks from

more conventional RT methods. Perhaps the risks following 3D-CRT presented here could provide a better estimate for more conventional RT methods.

A limitation of the study is that the accuracy of the risk prediction model for “other cardiac” diseases and stroke might be compromised due to the fact that they were not based on published dose-response relationships but instead, on dose-response estimates as described above. However, since the “other cardiac” category includes 125 cardiac diseases for which no dose-response relationships are available the approach followed here to estimate risk from “other cardiac” diseases provides a pragmatic solution to the issue, especially when considering that they comprise less than 20% of the “all cardiac” risk.

Another limitation to the study was that second cancer risks were predicted using dose-response relationships derived in studies based on point doses at the site of second cancer manifestation within the relevant organ at risk.^{8,9,20} However, since this is a prospective risk prediction study, the site of a possible second cancer manifestation is not known. Therefore, the mean dose to the appropriate OAR was used instead. Additionally, these dose-response relationships were derived from HL cohorts who received higher prescribed doses and larger radiation fields than commonly used today. Therefore, it is possible that the second cancer risks reported here might be overestimated. However, a recent study by Schaapveld et al.²⁴ showed that although radiation treatment fields and alkylating agent-containing chemotherapy have been reduced in most recent treatment era, the risks persisted for solid cancers.

4.4.4 Future perspectives

As the proportion of HL patients surviving for many years after treatment is already very high, increasing effort will be required to individualise treatment by considering the potential late effects of therapy. As illustrated in this chapter and in Chapter 3, age, sex, background risks, the anatomic distribution of disease and doses to OAR are all factors that need to be considered if sophisticated decisions are to be made regarding the trade-offs between choice of treatment and the risks of late toxicity²⁶. Those decisions can be assisted by risk prediction models, however, they need to be accurate and evidence-based.

The risk models presented here are a first step towards individualised and evidence-based risk prediction, and have provided new knowledge about the risks after advanced proton and photon RT. The risks comparisons were performed for the whole group of patients and on average the results demonstrate moderate reduction with PBS. A further analysis should be performed with a focus to identify subgroups of HL patients who would benefit substantially from PBS. It would be interesting, for example, to investigate whether the dosimetric benefits for the subgroups identified in Chapter 3, are also translated into substantial risk reductions.

The use of dose-response models for more cardiac diseases and based on cardiac substructure radiation doses from more recently treated patients will increase the risk-prediction accuracy. Additionally, dose-response models for second primary cancers based on mean organ doses rather than point doses will increase accuracy. However, the long follow up required to perform such observational studies and the fact that RT is evolving much faster than epidemiological timescales, makes this task challenging. In this study the risk of

second lung, breast and oesophageal cancer were estimated, however, the risk of leukaemia or thyroid cancer were not evaluated. It is important that in future work the risk of leukaemia and thyroid cancer versus integral and thyroid dose respectively is considered.

The risk prediction models could be further refined by taking into account more risk factors such as smoking, obesity, chronic diseases and if possible, other life-style factors such as exercise. Additionally, it is important to predict CVD and second cancer incidence in addition to mortality, as developing these diseases can substantially affect patients' quality of life as well as putting extra financial pressure on healthcare systems. Therefore, if treatment-related incidence or mortality is to be avoided by for example, tailoring the treatment regimen, referring selected individuals for specialised therapies such as proton RT or by suggesting lifestyle changes that reduce the risks, it is essential that patients at high risk can be accurately identified.

Even though this is the largest group of HL patients treated with DIBH-PBS that has reported in literature to date, the patient numbers ($n=21$) are still too small to provide definite conclusions regarding the distribution of potential benefit across the entire HL patient population. More patients need to be included in future studies, in order to identify patients with increased potential benefit from proton RT. However, this is also challenging due to the limited availability of patient data from those treated with PBS proton RT.

4.5 Conclusions

This chapter provides new knowledge in the study of late effects in patients treated with advanced proton RT. PBS proton RT can achieve significant radiation dose reductions and decrease the mortality risk from CVD and second cancers for some

HL patients. However, this is not the case for all HL patients and, for some patients, the risks would be similar if advanced or even conventional photon RT were used. Therefore, sophisticated risk modelling, based on individualised patient radiation dosimetry and risk factors, should be utilised whilst patients are being considered for RT treatment. This will enable oncologists to reassure patients for whom there is little risk and to identify those at appreciable risk, including smokers or obese patients, and consider referring them for advanced treatment such as PBS proton RT.

4.6 References

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General discussion

The research presented in the Chapter 1 shows that HL survivors treated between the 1960s and the 1990s are at increased risk of radiation and anthracycline-related CHF. This study has derived, for the first time, a dose-response relationship for CHF based on cardiac radiation exposure in 5-year survivors of adolescent or adult HL. Analysis was conducted based on estimates of both MHD and MLVD derived from individual RT plans. A non-linear dose-response relationship for the risk of radiation-related CHF versus MHD and a linear dose-response relationship versus MLVD were described. Both measures of dose suggested that there was little increase in CHF risk for doses – up to 25.0 Gy MHD or up to 15.0 Gy MLVD – but that CHF rates increased rapidly at higher doses. A radiation dose-response relationship for CHF based on MHD has previously been observed in childhood cancer survivors.^{1,2} In that cohort, CHF risk was increased by factors of 1.6, 3.1 and 10.5 following MHDs of 5-14, 15-34 and ≥ 35.0 Gy respectively, compared with patients who did not have any cardiac radiation exposure. These proportional increases were somewhat higher than those in the present study, possibly due to the patients' younger ages at cancer treatment: 82.4% of the CCSS cohort were aged less than 15 years at cancer diagnosis compared with only 3.5% in the present study.

The accuracy of dose-response relationships for risks of CVD, such as those presented in Chapter 1 and in other epidemiological studies^{1,3,4}, has been questioned due to the possible effect of errors in cardiac dose reconstruction on the dose-response relationships derived using them. In Chapter 2, new findings were presented regarding the accuracy of five cardiac dose reconstruction methods and the effect of the reconstruction errors on dose-response relationships derived using them. In this study, the ratio of the doses estimated by the different reconstruction

methods compared to the CT-based estimates, varied from 1.0% to 19.0%. For linear dose-response relationships the reconstruction errors affected the risk per Gy as little as 2.0% for the more accurate reconstruction methods, to up to 60.0% for the less accurate. The results in Chapter 2, however, demonstrated that the linear dose-response relationships based on MHD, shown in Chapter 1, for the risk of CHF and the study by van Nimwegen et al.³ for the risk of CHD, were not affected substantially by dose-reconstruction errors (2.0% and 5.0% respectively in the risk per Gy).

The effect of errors in the estimated doses on the dose-response models based on MLVD, was shown to be greater than the effect on dose-response models based on MHD. When the effect that errors in the reconstructed MLVD had on the dose-response relationship for risk of CHF was evaluated, it was shown that the initially reported ERR of 9.0% per Gy of MLVD was attenuated by 37.0% due to the reconstruction errors. The ERR after applying the correction was 14.3% per Gy of MLVD. To a certain extent, this was expected since representative CT-based dosimetry methods, like the RepCT used in Chapter 1, cannot fully take into account patient-specific variations in heart size, shape and position. There is a greater source of uncertainty when estimating dose in cardiac substructures, compared to MHD, especially for those near the field edge. Therefore, the estimates for MLVD may not be as robust as those for MHD and dose-response models based on cardiac substructures should be used with more caution unless the accuracy of the reconstruction method has been validated or the effect of the errors has been taken into account.

Each reconstruction method has advantages and disadvantages and selection of the most appropriate method should be based on various factors.

Selection should be based on the organ or volume of interest for the specific epidemiological study, the amount of patient imaging data available, the end points of interest, the measure of dose to be used (e.g. MHD, MLVD etc.), the availability of resources and time taken as well as the size of patient cohort. It is not necessarily true that the most sophisticated method is always the best choice.

In Chapters 3 and 4 the research focus moved towards modern RT methods for HL and specifically on the potential benefits of using proton RT versus photon RT. The results in Chapter 3 showed that clinical PBS can provide significant reductions in incidental radiation dose to OAR compared to photon RT. These results were in agreement with other studies which, even though were not on clinical PBS, they provided dosimetric comparisons between proton and photon RT methods.⁵ It was also shown that whilst the reduction in radiation dose to most OAR using PBS can be significant, not all patients benefitted equally from this currently scarce and expensive treatment modality. For example, women with axillary involvement received significantly lower MBD with PBS compared to both photon RT methods. However, women with no axillary involvement received similar MBD with all RT methods. Additionally, in all patients, the difference in MHD was significant between PBS and PartArc only when their disease extended below T7. For patients with CTV at and above T7 the reduction in MHD was not statistically significant compared to PartArc. Lastly, when both photon RT methods were used, the MLD increased significantly with increasing PTV volume ($p_{\text{trend}} < 0.05$). However, with PBS the MLD did not increase significantly with increasing PTV volume ($p_{\text{trend}} = 0.44$), which showed that PBS provided an increasing dosimetric advantage for increasing PTV volume.

PBS was superior for most dosimetric parameters when compared to photon RT techniques, it significantly increased the dose homogeneity within the target volume and reduced the mean dose to most OAR. This was, therefore, expected to lead to reductions in the risk of late toxicities such as radiation-related CVD and second cancers. This hypothesis was confirmed in Chapter 4 where it was shown that PBS proton RT substantially decreased the cumulative mortality risk from CVD and second cancers compared to both photon RT methods.

The risk reductions achieved by PBS varied substantially depending on the patient's background risk, the extent of the disease and the photon RT method used as comparison. For example, in this patient group the highest reduction in CVD risk achieved by PBS for one of the patients was 2.1% when compared to 3D-CRT (7.6% and 9.7% respectively). For some patients, however, PartArc performed as well or even reduced slightly the CVD risk compared to PBS. For example, for a female patient of 31 years old at age of treatment, PartArc reduced the CVD risk by 0.2% compared to PBS (3.6% and 3.8% respectively).

The results in Chapter 4 demonstrated that for some patients, referral to proton RT can be beneficial, especially when adding up all the risk reductions together (CVD and second cancers) as well as those that were not included in this study such as for other second cancers or other late effects.⁶ However, for some patients, photon RT would result in equal, if not lower, risks. It was also shown that, although the patients in this study had substantially lower predicted mortality risk due to treatment-related toxicities compared to patient treated in the past, they were still at increased risk compared to the general public.

A new approach to risk comparison following RT was presented in Chapter 4. The treatment-related risks were put into perspective when regional variation in

background risk was taken in to account. It was shown that in some cases the background risk differences between geographical regions dwarfed the differences in risk between RT methods. For example, for a patient from the USA the typical background 30-year CVD mortality risk on its own was higher than the background risk plus the excess risk from RT and chemotherapy together for a patient of the same age and sex from Western Europe.

These findings demonstrate the importance of taking into account background risk and life-style risk factors when selecting the appropriate treatment based on patient specific risk prediction, as these risks could exceed any benefit from advanced RT methods. PBS is a superior RT treatment modality, but, it is expensive and access to it is limited. Therefore, it is important for patient referral to be prioritised for those who really need it.

Future perspectives

HL survivors who were treated in the past are at increased risk of developing treatment-related heart disease and second primary cancers. Therefore, it is crucial that these risks be taken into account when organising survivorship care for these patients. Regular follow-up and monitoring for cardiac disease and second cancers is advised.

Patients treated today are, on average, at a substantially lower risk of treatment-related heart disease and second cancers compared to patients treated a few decades ago. However, there are still some patients who will be at a considerable risk. Those patients will need to be referred for treatment using the most advanced RT techniques, such as proton RT, to keep the doses to OAR and thus the risk of late toxicities, as low as practically achievable. Patient selection can be assisted by sophisticated and evidence-based risk prediction models. The risk

prediction models presented here are a first step towards individualised and evidence-based risk prediction, and have provided new knowledge about the risks after advanced proton and photon RT. However, they need to be even further refined by taking into account more risk factors such as smoking, obesity, chronic diseases and if possible, other life-style factors such as exercise. Additionally, apart from mortality, it is important to predict CVD and second cancer incidence risk, as developing these diseases can substantially affect patients' quality of life as well as putting extra financial pressure on healthcare systems. The use of dose-response models based on more recently treated patients and on individual patient CT-based dosimetry would have increased the risk-prediction accuracy. However, due to the long follow up required to perform such observational studies and the fact that RT is evolving much faster than epidemiological timescales, makes this task extremely challenging. With the increasing use of CT-based treatment planning in HL RT since the early 2000s, however, more accurate cardiac doses, based on a patient's individual CT scan, will be available in future observational studies. This might provide more accurate dose-response models and may also help to determine whether MHD, MLVD, mean dose to other cardiac substructures or another dosimetric parameter is the best measure to predict radiation-related risk of heart disease. Lastly, novel methods such as the voxel-by-voxel analysis reported by McWilliams et al.⁹ which correlates dose in each voxel of the patients CT scan against overall survival could provide an alternative and more efficient data-mining based retrospective risk prediction method.

Future work along the lines of the study presented in Chapter 4 but with larger numbers of patients would be helpful in order to identify subgroups of patients with increased potential benefit from proton RT. Such studies could investigate whether

the dosimetric benefits for the subgroups identified in Chapter 3, are likely also to be translated into substantial risk reduction.

Concluding remarks

This thesis has provided new knowledge in the study of late effects in HL patients who were treated decades ago as well as for patients treated recently with advanced RT methods. The results here can be used to facilitate progress towards personalised RT in terms of choosing the appropriate RT method, by integrating individualised risk prediction in advanced RT treatment planning. The research here provides the basis for further work towards evidence-based case selection for HL patients for the first NHS proton therapy centres in the UK, opening in 2018-2021.

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Appendix A

Research dissemination

Published manuscripts

- 1) van Nimwegen*, F.A. & Ntentas*, G., Darby, S.C., et al. 2017. *Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines*. Blood, 129(16), pp.2257-2265. *(Shared first authorship)

Papers in preparation

- 1) Ntentas, G., Dědečková, K., Aznar, M.C., et al. *Clinical intensity modulated proton therapy for Hodgkin lymphoma: which patients benefit the most?*
- 2) Ntentas, G., Darby, S.C., K., Aznar, M.C., et al. *Cardiac radiation dose reconstruction in the study of late effects: a comparison of different methods*.
- 3) Ntentas, G., Darby, S.C., Dědečková, K., et al. *Predicted cardiac and second cancer risks in Hodgkin lymphoma patients treated with advanced proton beam therapy*.

Invited talks

1. “Radiation dose reconstruction using the representative CT method” Late Effects Research Group, MD Anderson Cancer Centre, Houston, USA (2017)
2. “Protons in lymphoma treatment” UK-LRG workshop of advanced RT techniques in Lymphoma, London, UK (2016)

Main conference presentations

- “Predicted Cardiac and Second Cancer Risks in HL Patients Treated with Advanced Proton Beam Therapy Compared to Photon Radiotherapy” American Society for Radiation Oncology, 59th Annual Meeting, San Diego (Oral Pres. 2017) & International Conference on Malignant Lymphoma, Lugano (Poster Pres. 2017)
- “Cardiac Radiation Dose Reconstruction in the Study of Late Effects: A Comparison of Different Methods” American Society for Radiation Oncology, 59th Annual Meeting, San Diego (Poster Pres. 2017)

LYMPHOID NEOPLASIA

CME Article

Risk of heart failure in survivors of Hodgkin lymphoma: effects of cardiac exposure to radiation and anthracyclines

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Key Points

- Risk of HF increases following cardiac radiation doses above 20 Gy.
- Anthracyclines increase HF rate by threefold independently of radiation.

Hodgkin lymphoma (HL) survivors treated with radiotherapy and/or chemotherapy are known to have increased risks of heart failure (HF), but a radiation dose-response relationship has not previously been derived. A case-control study, nested in a cohort of 2617 five-year survivors of HL diagnosed before age 51 years during 1965 to 1995, was conducted. Cases (n = 91) had moderate or severe HF as their first cardiovascular diagnosis. Controls (n = 278) were matched to cases on age, sex, and HL diagnosis date. Treatment and follow-up information were abstracted from medical records. Mean heart doses and mean left ventricular doses (MLVD) were estimated by reconstruction of individual treatments on representative computed tomography datasets. Average MLVD was 16.7 Gy for cases and 13.8 Gy for controls ($P_{\text{difference}} = .003$). HF rate increased with MLVD: relative to 0 Gy, HF rates following MLVD of 1-15, 16-20, 21-25, and ≥ 26 Gy were 1.27, 1.65, 3.84, and 4.39, respectively ($P_{\text{trend}} < .001$). Anthracycline-containing chemotherapy increased HF rate by a factor of 2.83 (95% CI: 1.43-5.59), and there was no significant interaction with MLVD ($P_{\text{interaction}} = .09$). Twenty-five-year cumulative risks of HF following MLVDs of 0-15 Gy, 16-20 Gy, and ≥ 21 Gy were 4.4%, 6.2%, and 13.3%, respectively, in patients treated without anthracycline-containing chemotherapy, and 11.2%, 15.9%, and 32.9%, respectively, in patients treated with anthracyclines. We have derived quantitative estimates of HF risk in patients treated for HL following radiotherapy with or without anthracycline-containing chemotherapy. Our results enable estimation of HF risk for patients before treatment, during radiotherapy planning, and during follow-up. (*Blood*. 2017;129(16):2257-2265)

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Disclosures

Associate Editor Laurie H. Sehn served as an advisor or consultant for AbbVie, Amgen, Roche/Genentech, Celgene, Janssen, Lundbeck, Seattle Genetics, and TG Therapeutics. CME questions author Laurie Barclay, freelance writer and reviewer, Medscape, LLC, owns stock, stock options, or bonds from Alnylam, Biogen, and Pfizer. The authors declare no competing financial interests.

Learning objectives

1. Distinguish the risk for heart failure (HF) in patients with Hodgkin lymphoma (HL) related to radiation exposure vs no exposure, based on a case-control study.
2. Distinguish the risk for HF in patients with HL related to anthracycline exposure.
3. Determine the clinical implications regarding the risk for HF in patients with HL related to radiation and anthracycline exposure.

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Introduction

With 10-year survival rates >80%, Hodgkin lymphoma (HL) is a model of a curable malignancy.¹ The efficacy and safety of treatments continue to improve, but late effects, including cardiovascular diseases, have caused substantial treatment-related morbidity and mortality in HL survivors treated in the past. It has been shown that mediastinal radiotherapy and/or anthracycline-containing chemotherapy increase the risk of coronary heart disease (CHD), valvular heart disease (VHD), and heart failure (HF) in HL survivors.²⁻⁹

We previously found a linear dose-response relationship for the risk of radiation-related CHD in HL survivors with the excess rate increasing by 7.4% per Gy,¹⁰ and a nonlinear dose-response relationship for VHD, with 1.4-, 3.1-, 5.4-, and 11.8-fold increased VHD rates for doses of ≤30 Gy, 31-35 Gy, 36-40 Gy, and >40 Gy, respectively.³ Mediastinal radiotherapy has also been associated with HF in survivors of both HL and childhood cancer.^{9,11} However, the shape of the radiation dose-response relationship has not previously been described, either for patients who received radiotherapy alone or for patients who received radiotherapy in combination with anthracyclines. Radiotherapy use has declined but still remains an important component of HL treatment. Anthracyclines have been commonly used since the early 1980s and remain the backbone of HL chemotherapy regimens used today.

With this study, we aimed to determine the radiation dose-response relationship for HF in long-term survivors of adolescent and adult HL, to estimate cumulative risk of HF after radiotherapy given with and without anthracyclines, and to assess other determinants of HF risk.

patients were treated with orthovoltage therapy or cobalt-60; from the 1970s onwards, linear accelerators were used. Individual blocks were used to shield normal tissues as much as possible. Patients usually received 40 Gy in fractions of 1.5 to 2.0 Gy when they were treated with radiotherapy only and 30 to 36 Gy when they also received chemotherapy. Mantle field irradiation (including mediastinal, axillary, and neck nodes) was the most commonly applied radiation from the early 1970s to the late 1980s. Since the late 1980s, a growing number of patients received more limited radiation fields (involved fields). Treatment of recurrences was generally less standardized.

From the 1960s to 1980s, chemotherapy consisted mainly of MOPP (mechlorethamine, vincristine, procarbazine, prednisone). In the 1980s, anthracycline-containing regimens such as MOPP/ABV (MOPP/doxorubicin, bleomycin, vinblastine) and ABVD (ABV and dacarbazine) were introduced as part of primary treatment. Anthracycline dose was estimated in milligrams anthracycline per square meter body surface, based on number of cycles received times the standard anthracycline dose in the corresponding chemotherapy regimen during that time period. Standard doses of anthracycline per regimen per cycle were 25 mg/m² at days 1 and 15 for ABVD and alternating MOPP-ABVD and 35 mg/m² at day 8 for MOPP-ABV hybrid.

A detailed description of patient selection, data collection, and treatments has been published previously^{2,9,13-15} as well as assessment of cardiovascular events during follow-up.⁹ Patients were eligible for this study if (1) they survived at least 5 years after HL diagnosis; (2) they were diagnosed with HL before the age of 51 years; (3) HL was their first primary malignancy (except for nonmelanoma skin cancer or carcinoma in situ of the cervix uteri or the breast); and (4) radiotherapy for HL was the only radiotherapy given to the neck or trunk prior to the cutoff date, which was defined as date of HF for the cases, whereas for each control it was defined as date of HL diagnosis plus a time interval equal to the interval from date of HL diagnosis to date of HF diagnosis of the corresponding case.

Cases and controls

Cases (n = 91) were patients who developed HF in the form of either symptomatic congestive HF or cardiomyopathy, with an ejection fraction of <50% (or a ≥10% drop from baseline) or a fractional shortening of <24% (based on a combination of the Common Terminology Criteria for Adverse Events versions 3.0 and 4.0; grade ≥2; see supplemental Text 1, available on the *Blood* Web site)¹⁶ as their first clinically significant heart disease. Cases were identified from medical records or postal questionnaires completed by the patient's general practitioner (GP)⁹ and verified using cardiac notes from either the GP or the treating cardiologist. The data abstraction forms and coding instructions were developed in collaboration with physicians, and it has been shown that the Common Terminology Criteria for Adverse Events can be used to properly grade cardiovascular events from medical records.¹⁷ A total of 53 further cases of HF were excluded (see supplemental Table 1 for reasons). Follow-up was complete to October 2013. For each case with HF, we attempted to select 4 controls from the cohort, individually matched on

Methods

Study population

A nested case-control study was conducted within an existing multicenter hospital-based cohort (N = 2617) of HL survivors treated in The Netherlands between 1965 and 1995 before the age of 51 years, who had survived ≥5 years after HL diagnosis. The cohort was identified through hospital-based cancer registries in 4 large university hospitals and 1 cancer center. Over time, a wide variety of treatments was used in the cohort. The majority of patients were treated according to European Organization for Research and Treatment of Cancer Lymphoma Group protocols for primary treatment.¹² Briefly, in the 1960s,

sex, age at HL diagnosis (≤ 1 year), and date of HL diagnosis (≤ 3 years). Controls had to be free of any cardiac disease grade ≥ 2 at the cutoff date. In total, 278 controls were matched to the cases. Cases were eligible to be controls up to the date they developed HF, and controls were selected with replacement.

Data collection

Detailed treatment information, including radiation doses and fields and cumulative chemotherapy doses, was collected from medical records. Copies of original radiotherapy prescription sheets and simulation films were obtained. Where original prescriptions were unavailable, information about radiotherapy, including dates, anatomical areas, dose, fractionation, and treatment energy, was abstracted from other clinical notes. If cumulative chemotherapy doses were not available, regimen-specific standard doses were multiplied by the number of cycles that a patient received. Cardiotoxicity equivalence ratios of 0.50 for daunorubicin and epirubicin to doxorubicin were used.^{18,19} Vital status and dates of death were obtained up to July 2013 by linkage with the Dutch Central Bureau of Genealogy. In The Netherlands, the law requires that GP and hospital records must be kept throughout a patient's lifetime and for at least 15 years after their death. Detailed data on medical history, smoking, and established cardiovascular risk factors, both at diagnosis of HL and at diagnosis of HF (or cutoff date for controls), could therefore be collected for all patients from GP questionnaires in 2004 (for 94% of the cohort) and in 2013 (for 83% of the cohort), and from hospital records. In addition, a questionnaire on established cardiovascular risk factors and lifestyle was mailed to all patients in the cohort still alive in 2013 ($n = 475$; response rate: 70%), resulting in questionnaire data for 45 cases and 186 controls. Further details are given elsewhere.^{2,10,20} This study was approved by the ethics review board of The Netherlands Cancer Institute.

Retrospective radiation dosimetry methods

The radiation dosimetry method is described elsewhere.³ Radiotherapy regimens were reconstructed using the Eclipse treatment planning system (Version 13.0.28; Varian Medical System, Palo Alto, CA). Two substitute computed tomography (CT) data sets (for men and women, respectively) were chosen from a library of 50 to be representative regarding average anatomy and estimated heart dose from a standardized mantle field. The heart and substructures of the heart were outlined as per published guidelines.²¹ Treatment planning was performed for each individual patient using variables such as beam arrangement, energy, prescribed dose, field size, and field shielding, which were extracted from each patient's original radiotherapy prescription charts and simulation films. Standard mantle fields, as well as paraaortic and splenic fields for patients who received such treatments, were created. The dose distributions from all fields were then summed, and cardiac doses were extracted. Mean heart dose (MHD) and mean left ventricular dose (MLVD) were calculated and converted into equivalent dose in 2-Gy fractions (EQD2) and biologically effective dose.^{22,23} When fraction size varied during treatment, EQD2 and biologically effective dose were calculated separately for each fraction size before summation (supplemental Text 2). V20 and V30 (volume of structure receiving at least 20 or 30 Gy, respectively) were calculated for the heart and left ventricle and expressed in percentages.

For patients with neither radiation chart nor simulation film (22 cases and 103 controls), MHD and MLVD were estimated, for each combination of hospital, treatment period, sex, and radiation field, as the average value for patients with either a chart or a film.

Statistical analysis

Rate ratios (RRs) for HF for different levels of each factor were estimated using logistic regression, conditional on sets of individual cases and their matched controls. Confidence intervals (CIs) for factors with 2 levels were based on the Wald method. CIs for factors with >2 levels used the amount of information in each category, including the reference category.²⁴ Multiple regression was used to control for confounding and to assess the combined effect of radiation dose and other factors. The dose-response was estimated by modeling HF rate as $K_m(1 + \beta d)$, where d is radiation dose, K_m is a constant specific to each matched set, and β is the increase in excess HF relative rate per unit increase in dose. Nonlinearity was evaluated by including an exponential term: $K_m[1 + \beta d \exp(\delta d)]$,

Table 1. Characteristics of cases and controls

	Cases		Controls	
	N	%	N	%
Total	91	100	278	100
Sex*				
Males	47	51.6	139	50.0
Females	44	48.4	139	50.0
Age at HL diagnosis*				
Median age, y (IQR)	28.3	(21.9-37.7)	28.2	(22.9-37.7)
5-25†	38	41.8	107	38.5
26-35	24	26.4	86	30.9
36-50	29	31.9	85	30.6
Age at HF diagnosis/cutoff date				
Median age, y (IQR)	47.9	(41.2-57.7)	48.2	(41.5-57.6)
27-40	21	23.1	59	21.2
41-60	42	46.1	127	45.7
≥ 61	28	30.8	92	33.1
Year of diagnosis HL diagnosis*				
1965-1974	30	33.0	98	35.3
1975-1984	35	38.5	114	41.0
1985-1995	26	28.6	66	23.7
Time to HF diagnosis/cutoff date				
Median time, y (IQR)	20.6	(13.7-25.2)	20.6	(14.0-25.0)
5-10	14	15.4	43	15.5
11-20	33	36.3	101	36.3
21-30	38	41.8	121	43.5
≥ 31	6	6.6	13	4.7
Deceased at end of follow-up				
Median time (IQR) in years after cutoff	3.6	(0.2-5.6)	8.2	(4.6-14.4)
No	39	42.9	171	61.5
Yes	52	57.1	107	38.5

*Matching variables used in the selection of controls.

†Four cases and 9 controls (3.5% of the population) were aged <15 y at time of HL diagnosis.

and goodness of fit was assessed by likelihood ratio tests. Approximate cumulative risks of HF for categories of radiation dose were estimated from the HF RRs together with the cumulative risk of HF for the entire cohort (supplemental Text 3). Significance tests were 2-sided, and $P \leq .05$ was taken to indicate statistical significance. Analyses were performed using STATA statistical software version 13.0 (STATAcorp 2013)²⁵ and Epicure version 1.8 (Hirosoft International).²⁶

Results

In the 91 cases, HF occurred after a median interval of 20.6 years (interquartile range [IQR]: 13.7-25.2) (Table 1). The majority of HF diagnoses were grade 2 (44%) or 3 (43%) (supplemental Table 1). The median age at HL diagnosis was 28.3 years (IQR: 21.9-37.7). Fifty-seven percent of the HF cases had died by the end of follow-up, with median time from HF to death of 3.6 years (IQR: 0.2-5.6).

Radiotherapy, chemotherapy, and splenectomy

For patients given mediastinal radiotherapy (cases: 90.1%; controls: 82.3%; $P_{\text{difference}} = .078$), the average prescribed dose was 30.5 Gy (cases: 32.7 Gy; controls: 29.8 Gy; $P_{\text{difference}} = .088$), whereas the average MHD was lower at 20.9 Gy (cases: 23.2 Gy; controls: 20.1 Gy; $P_{\text{difference}} = .009$), and the average MLVD was even lower, at 14.5 Gy (cases: 16.7 Gy; controls: 13.8 Gy; $P_{\text{difference}} = .003$). MHD and MLVD were strongly correlated (correlation coefficient: 0.93; supplemental Figure 1).

For all 3 measures of dose, HF rate increased with increasing dose (prescribed mediastinal dose: $P_{\text{trend}} = .027$; MHD: $P_{\text{trend}} = .002$;

Table 2. Associations between treatment and HF risk

Treatment factor	Cases (total: 91)			Controls (total: 278)			RR*	95% CI	P _{trend} †
	N	%		N	%				
Radiotherapy									
No RT to mediastinum or PAO	7	7.7		33	11.9		1.00	0.40-2.50	
PAO-RT, no mediastinal RT	2	2.2		16	5.8		0.66	0.15-2.98	
Mediastinal RT, no PAO-RT	39	42.9		126	45.3		1.87	1.27-2.75	
Mediastinal RT and PAO-RT	43	47.2		103	37.0		2.59	1.80-3.72	.020
Prescribed mediastinal dose									
Average (SD)	32.7	(12.2)		29.8	(14.6)				
Median (IQR)	37	(32-40)		36	(30-40)				
0 Gy (no mediastinal RT)	9	9.9		49	17.6		1.00	0.45-2.23	
20-34 Gy (median 32 Gy)	15	16.5		45	16.2		2.35	0.85-6.46	
35-39 Gy (median 36 Gy)	34	37.4		113	40.7		2.10	0.86-5.13	
≥40 Gy (median 40 Gy)	33	36.3		71	25.5		3.02	1.23-7.40	.027
MHD									
Average (SD)	23.2	(9.6)		20.1	(10.0)				
Median (IQR)	25.8	(18.8-30.0)		22.5	(16.7-27.2)				
0 Gy	7	7.7		29	10.4		1.00	0.39-2.55	
1-20 Gy (median 16 Gy)	21	22.2		70	24.4		1.43	0.83-2.50	
21-25 Gy (median 23 Gy)	20	22.2		102	37.1		1.03	0.63-1.67	
26-30 Gy (median 28 Gy)	27	30.0		57	20.7		2.78	1.69-4.59	
≥31 Gy (median 33 Gy)	16	17.8		20	7.3		4.16	2.14-8.10	.002‡
Mean dose to the left ventricle (MLVD)									
Average (SD)	16.7	(8.8)		13.8	(7.9)				
Median (IQR)	16.5	(11.9-21.9)		15.1	(8.4-19.1)				
0 Gy	7	7.7		29	10.4		1.00	0.39-2.55	
1-15 Gy (median 13 Gy)	36	39.5		144	51.8		1.27	0.86-1.89	
16-20 Gy (median 19 Gy)	20	22.0		68	24.5		1.65	0.98-2.77	
21-25 Gy (median 23 Gy)	16	17.6		23	8.3		3.84	1.97-7.47	
≥26 Gy (median 30 Gy)	12	13.2		14	5.1		4.39	2.00-9.65	<.001‡
V30 for the left ventricle (%)§									
Average (SD)	40.8	(24.7)		33.9	(23.7)				
Median (IQR)	42.8	(24.8-54.7)		40.1	(13.1-49.4)				
0%	9	9.9		35	12.6		1.00	0.48-2.10	
1-24% (median 12%)	17	18.7		60	21.6		0.95	0.52-1.71	

MHDs and MLVDs are EQD2 Gy (see "Methods"). Treatment variables include both primary and salvage treatment. anthra, anthracyclines; CT, chemotherapy; PAO, paraortic; RT, radiotherapy; ST, salvage therapy.

*RRs were estimated conditionally on the matched sets.

†P_{trend} based on median value of the treatment factor in each category.

‡P_{trend} after adjusting for treatment with anthracyclines: MHD < .001; mean dose to the left ventricle, .001; V30 of the left ventricle, .004; V20 of the left ventricle, .006.

§V30 and V20 are the percentages of the left ventricle volume that received at least 30 and 20 Gy, respectively.

||Six cycles of MOPP-ABV hybrid contain 210 mg/m² anthracycline (35 mg/m² per cycle); 6 cycles of ABVD contain 300 mg/m² anthracycline (50 mg/m² per cycle). There was no significant difference between the HF rate in the 2 dose categories <280 mg/m² and ≥280 mg/m² (P = .97).

*Most patients who received anthracyclines received either 6 ABVD (prescribed anthracycline dose 300 mg/m²) or 8 MOPP-ABV hybrid (prescribed anthracycline dose 280 mg/m²).

†P_{trend} after adjusting for mean dose to the left ventricle, .015.

**Includes mainly patients who did not receive mediastinal RT at all, or received mediastinal RT only for salvage treatment, or received anthracyclines for both primary and salvage treatment.

Table 2. (continued)

Treatment factor	Cases (total: 91)		Controls (total: 278)		RR*	95% CI	$P_{\text{trend}}^{\dagger}$
	N	%	N	%			
25-49% (median 40%)	33	36.3	121	43.5	1.05	0.70-1.58	
50-74% (median 60%)	23	25.3	51	18.3	1.80	1.12-2.91	
75-100% (median 84%)	9	9.9	11	4.0	3.22	1.32-7.86	.021‡
V20 for the left ventricle (%)*							
Average (SD)	49.2	(26.3)	41.6	(26.4)			
Median (IQR)	53.2	(33.3-63.3)	48.5	(26.9-57.2)			
0%	8	8.8	32	11.5	1.00	0.45-2.23	
1-24% (median 5%)	4	4.4	33	11.9	0.27	0.06-1.11	
25-49% (median 39%)	28	30.7	87	31.3	1.38	0.89-2.14	
50-74% (median 58%)	35	38.5	98	35.3	1.51	0.99-2.28	
75-100% (median 86%)	16	17.6	28	10.1	2.50	1.33-4.69	.006‡
Chemotherapy							
No chemotherapy	23	25.3	82	29.5	1.00	0.65-1.55	
CT, but no anthracyclines	37	40.6	137	49.3	0.93	0.63-1.37	
CT with anthracyclines	31	64.1	59	21.2	2.83	1.43-5.59	.043
Cumulative anthracycline dose†							
0 mg/m ²	60	65.9	219	78.8	1.00	0.57-1.74	
<280 mg/m ² (median 210 mg/m ²)	7	7.7	12	4.3	2.99	1.05-8.50	
≥280 mg/m ² (median 300 mg/m ²)†	24	26.4	47	16.9	2.93	1.30-6.59	.006#
Salvage therapy							
PT: mediastinal RT, no anthra, ST: none or no anthra	51	56.0	170	61.2	1.00	0.67-1.47	
PT: mediastinal RT, anthra, ST: none or no anthra	13	14.3	31	11.2	2.30	1.02-5.21	
PT: mediastinal RT, no anthra, ST: anthra	12	13.2	14	5.0	3.85	1.59-9.36	
Other**	15	16.5	63	22.7	0.59	0.31-1.14	
Splenectomy							
No	60	66.7	176	63.8	1	ref	
Yes	30	33.3	100	36.2	0.85	0.49-1.45	.54
Unknown	1	1.1	2	0.7	—	—	

MHDs and MLVDs are EQD2 Gy (see "Methods"). Treatment variables include both primary and salvage treatment.

anthra, anthracyclines; CT, chemotherapy; PAO, paraortic; PT, primary therapy; RT, radiotherapy; SD, standard deviation; ST, salvage therapy.

*RRs were estimated conditionally on the matched sets.

†Trend test based on median value of the treatment factor in each category.

‡ P_{trend} after adjusting for treatment with anthracyclines: MHD < .001; mean dose to the left ventricle, .001; V30 of the left ventricle, .004; V20 of the left ventricle, .006.

#V30 and V20 are the percentages of the left ventricle volume that received at least 30 and 20 Gy, respectively.

||Six cycles of MOPP-ABV hybrid contain 210 mg/m² anthracycline (35 mg/m² per cycle); 6 cycles of ABVD contain 300 mg/m² anthracycline (50 mg/m² per cycle). There was no significant difference between the HF rate in the 2 dose categories <280 mg/m² and ≥280 mg/m² ($P = .97$).*Most patients who received anthracyclines received either 6 ABVD (prescribed anthracycline dose 300 mg/m²) or 8 MOPP-ABV hybrid (prescribed anthracycline dose 280 mg/m²).# P_{trend} after adjusting for MHD, .011; after adjusting for mean dose to the left ventricle, .015.

**Includes many patients who did not receive mediastinal RT at all, or received mediastinal RT only for salvage treatment, or received anthracyclines for both primary and salvage treatment.

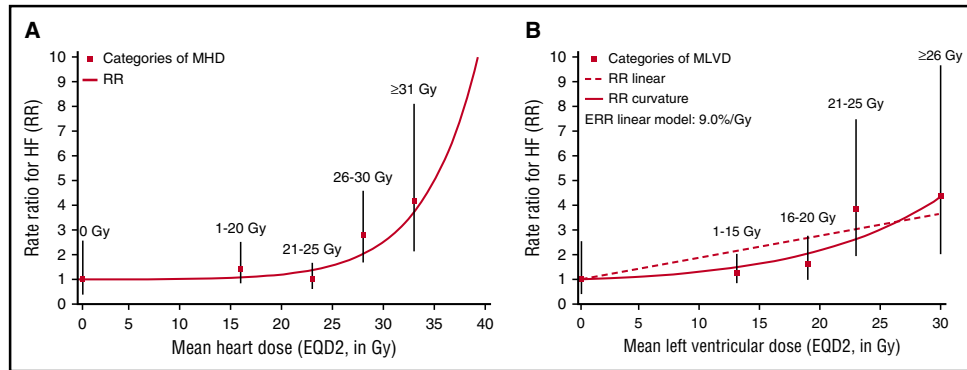


Figure 1. Relationship between HF rate and cardiac dose. RRs for HF by MHD (A) and by MLVD (B) in Gy compared with no radiation exposure. RRs are calculated conditionally on matched sets after adjustment for anthracycline-based chemotherapy (yes/no). Squares indicate anthracycline-adjusted estimates for the following dose categories: MHD: 0 Gy, 1-20 Gy, 21-25 Gy, 26-30 Gy, ≥ 31 Gy; MLVD: 0 Gy, 1-15 Gy, 16-20 Gy, 21-25 Gy, ≥ 26 Gy, and are plotted at the median dose in each category (0 Gy, 16 Gy, 23 Gy, 28 Gy, and 33 Gy for MHD; 0 Gy, 13 Gy, 19 Gy, 23 Gy, and 30 Gy for MLVD). Vertical lines are 95% CIs. For MHD, there was a statistically significant linear dose-response relationship ($P = .006$) and allowing for curvature improved the fit significantly ($P \leq .001$). For MLVD, there was a statistically significant linear dose-response relationship ($P = .004$), and allowing for curvature did not significantly improve the fit ($P = .09$). Further details are given in supplemental Table 2.

MLVD: $P_{\text{trend}} < .001$; Table 2). For MHD, the dose-response relationship was nonlinear ($P_{\text{curvature}} = .029$; supplemental Table 2), with little evidence of an increase for MHDs in the range 1 to 25 Gy, but increasing steeply with MHDs of ≥ 25 Gy (Figure 1A). For MLVD, there was no significant departure from linearity ($P_{\text{curvature}} = .09$) (Figure 1B). HF rate also increased with increasing V30 and V20 for the left ventricle (Table 2). When the analysis was repeated omitting patients with neither radiation chart nor simulation film, results were similar (supplemental Table 3; supplemental Figure 2).

Chemotherapy without anthracyclines was not significantly associated with HF (RR: 0.93; 95% CI: 0.63-1.37). However, for anthracycline-based chemotherapy, the HF rate was increased by a factor of nearly 3 (RR: 2.83; 95% CI: 1.43-5.59). Among those who received anthracyclines, HF rates were similar for those with cumulative doses < 280 mg/m² and those with cumulative doses ≥ 280 mg/m² ($P_{\text{difference}} = .97$). HF rates were similar among those with and without splenectomy (RR: 0.85; 95% CI: 0.49-1.45). Among those

who received mediastinal RT as primary therapy, HF rates did not differ significantly between those who received anthracyclines only as primary therapy and those who received anthracyclines only as salvage therapy (RR: 2.30; 95% CI 1.02-5.21 versus RR: 3.85; 95% CI 1.59-9.36; $P_{\text{difference}} = .4$) (Table 2). Only 2 patients received anthracyclines for primary as well as salvage treatment; both were cases.

HF RRs in individuals with MHD or MLVD ≥ 26 Gy relative to 0 to 25 Gy did not differ significantly according to use of anthracycline chemotherapy ($P_{\text{interaction}} = .45$ for MHD, .09 for MLVD) or with splenectomy ($P_{\text{interaction}} = .71$ for MHD, .62 for MLVD).

Classical cardiovascular disease risk factors

None of the known classical cardiovascular disease risk factors differed significantly between HF cases and matched controls. Diagnosis of diabetes mellitus between HL and cutoff was associated with a nonsignificantly increased HF rate (RR: 1.59; 95% CI 0.63-4.05)

Table 3. Estimated HF rates by radiotherapy dose and anthracycline treatment

	Treated without anthracyclines				Treated with anthracyclines			
	No. of cases	No. of controls	RR	95% CI	No. of cases	No. of controls	RR	95% CI
MHD (EQD2)								
0-25 Gy	28	153	1.00	0.67-1.48	20	48	2.92	1.35-6.30
26-30 Gy	22	49	2.43	1.51-3.91	5	8	7.09	2.56-19.67
≥ 31 Gy	10	17	3.67	1.86-7.25	6	3	10.71	3.51-32.67
MLVD (EQD2)								
0-15 Gy	26	133	1.00	0.68-1.47	17	40	2.60	1.21-5.58
16-20 Gy	17	60	1.43	0.85-2.44	3	8	3.74	1.31-10.73
≥ 21 Gy	17	26	3.10	1.87-5.14	11	11	8.06	3.05-21.32
V30 left ventricle, %								
0-24	9	51	1.00		4	16	3.36	1.57-7.22
25-100	51	168	2.57	1.25-5.29	27	43	8.65	2.83-26.41
V20 left ventricle, %								
0-49	26	118	1.00		14	34	2.84	1.36-5.97
50-100	34	101	1.58	0.94-2.67	17	25	4.50	1.85-10.98

There was no significant interaction on a multiplicative scale between anthracycline treatment and either MHD or MLVD (see supplemental Table 5A-B). Therefore, estimates of HF rates by radiotherapy dose and anthracycline treatment were calculated under the assumption that there was no multiplicative interaction between the 2. Estimates allowing for an interaction between radiotherapy dose and anthracycline treatment are given in supplemental Table 6.

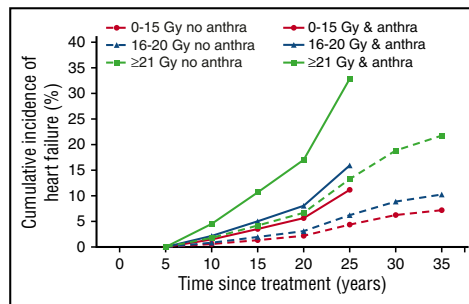


Figure 2. Approximate cumulative risks of HF by MLVD and whether treatment with anthracyclines was given. Modeled cumulative risk of HF as first cardiac event among 5-year survivors of HL by time since initial HL treatment of categories of MLVD (Gy). Lines indicate estimated cumulative incidences for dose categories (0-15 Gy, 16-20 Gy, and ≥ 21 Gy) with and without anthracycline exposure. Cumulative risks were calculated with other heart disease or death as a competing risk. Further details are given in supplemental Text 3.

compared with those not diagnosed with the disease (supplemental Table 4). When taking into account all risk factors that were diagnosed before the end of follow-up, instead of only those diagnosed prior to HF/cutoff date, hypertension (RR: 1.80; 95% CI: 0.73-4.44), diabetes mellitus (RR: 1.83; 95% CI: 0.96-3.47), and having at least 1 risk factor (RR: 1.53; 95% CI: 0.93-2.52) were all associated with nonsignificantly increased HF rates, whereas patients with a high level of physical activity (≥ 3 hours per week) at time of follow-up had a nonsignificantly lower HF rate than those who were not (< 1 hour per week) (RR: 0.59; 95% CI: 0.32-1.10).

HF RRs in individuals with MHDs or MLVDs ≥ 26 Gy relative to 0-25 Gy did not differ significantly according to presence of at least 1 cardiovascular risk factor, sex, age at HL diagnosis, or time since HL diagnosis (all $P_{\text{interaction}}$ values $> .50$; supplemental Table 5A-B).

Estimated HF rates and cumulative risks

Our analyses showed that the only factors significantly associated with HF rate were radiation dose and whether anthracyclines were used, with no significant multiplicative interaction between the 2. Summary HF rates were therefore estimated based on 3 broad categories of MHD or MLVD and whether anthracyclines had been given, with the assumption that the multiplicative increase in HF rate with anthracyclines did not differ according to MHD or MLVD (Table 3). Based on these estimates, approximate cumulative incidence curves for HF were derived for patients in these 6 groups (Figure 2). In patients treated without anthracyclines, 25-year cumulative risks of HF following MLVDs of 0-15 Gy, 16-20 Gy, and ≥ 21 Gy were 4.4%, 6.2%, and 13.3%, whereas in patients treated with anthracyclines, the 25-year cumulative risks were 11.2%, 15.9%, and 32.9%, respectively. For patients treated without anthracyclines, 35-year cumulative risks of HF following MLVDs of 0-15 Gy, 16-20 Gy, and ≥ 21 Gy were 7.2%, 10.2%, and 21.8%, respectively. Patients treated with anthracyclines have not yet been followed long enough to estimate risks beyond 25 years.

Discussion

In this study, we have examined, for the first time, dose-response relationships for HF rate based on cardiac radiation exposure in 5-year

survivors of adolescent or adult HL. We conducted analyses based on estimates of both MHD and MLVD derived from individual radiotherapy plans. Both measures of dose suggested that there is little increase in HF risk for lower doses, up to 25 Gy MHD or up to 15 Gy MLVD, but that HF rates increase rapidly at higher doses. We also found that treatment with anthracyclines increase the HF rate, approximately threefold, irrespective of cardiac radiation exposure.

A radiation dose-response relationship for self-reported HF has previously been observed in the Childhood Cancer Survivor Study (CCSS).^{11,27} In that cohort, HF risk was increased by factors of 1.6, 3.1, and 10.5 following MHDs of 5 to 14, 15 to 34, and ≥ 35 Gy, respectively, compared with patients who did not have any cardiac radiation exposure.²⁷ These proportional increases are somewhat higher than those in our present study, possibly due to the patients' younger ages at cancer treatment: 82.4% of the CCSS cohort were aged < 15 years at cancer diagnosis compared with only 3.5% in the present study. A clearly increasing HF risk with increasing anthracycline dose was also seen in the CCSS study, and risk was increased by factors of 2.1, 3.7, and 10.5 for cumulative anthracycline doses of < 100 , 100 to 249, and ≥ 250 mg/m² compared with those not exposed to anthracyclines.

In the CCSS, the therapy-associated risk of HF was potentiated by the presence of cardiovascular risk factors, such as hypertension and diabetes mellitus, and by lack of physical activity.^{28,29} In our current study, no such associations were apparent. However, the CCSS studies were based on patient-reported outcomes of cardiovascular risk factors, and probably also included risk factors diagnosed at the same time as or even after the cardiovascular disease of interest, possibly resulting in an overestimation of the strength of the associations. In contrast, our conservative approach of including only risk factors diagnosed prior to HF may have resulted in an underestimation. Despite this, it seems likely that risk factor control in high-risk patients who received cardiotoxic treatment may be important in risk-reduction strategies for cardiovascular diseases after HL treatment.

The strengths of our study include that it was performed in a complete, multi-institutional population with long-term, detailed follow-up, including information from cardiologists and GPs. The outcome (HF) was GP reported and, if necessary, confirmed by cardiologists, which is an important advantage in comparison with studies relying on patient-reported outcomes or registry data.^{6,30-32} Instead of using prescribed radiation dose, radiation-related HF risks were estimated using individual patient dosimetric parameters such as MHD and MLVD, which were converted into EQD2 and adjusted for dose distribution and varying fractionation schedules. Where available, individual cumulative anthracycline doses were analyzed, rather than protocol prescription chemotherapy doses.

A limitation of our study is that a total of only 90 patients were prescribed anthracyclines, all but 11 of whom also received mediastinal radiotherapy. Furthermore, the range of cumulative anthracycline doses was limited, with most patients being prescribed either 280 or 300 mg/m² doxorubicin equivalent, and follow-up for patients who received anthracyclines was shorter than for patients treated with radiotherapy alone. Therefore, our ability to study the interaction between radiation exposure of the heart and anthracycline exposure was limited, and we were unable to estimate a separate dose-response relationship for anthracyclines.

The results indicate that salvage therapy with anthracyclines following primary treatment with mediastinal radiotherapy would be more harmful than primary treatment with mediastinal radiotherapy and anthracyclines. However, the small number of patients treated with anthracyclines makes it impossible to draw any firm conclusions regarding the possible effect of the time elapsed between exposure of

the heart to anthracyclines and to radiation. It is hypothesized that this increased risk is associated with an increased radiation dose during primary treatment, and perhaps an increased anthracycline dose for salvage treatment, compared with the doses for combined primary treatment. Further research may indicate whether treatment sequence may influence HF risk, which may contribute to risk prediction models of cardiovascular disease in survivors who have been treated in the past.

Detailed radiotherapy information was collected for each patient, but radiotherapy was applied before the era of CT-based treatment planning. Dose reconstructions were therefore carried out using representative CT datasets, and these cannot take into account patient-specific variations in heart size, shape, and position. For a proportion of patients, both the radiotherapy chart and the simulation film were missing, and the MHD and MLVD were estimated rather than reconstructed (see "Methods"). However, a sensitivity analysis including only patients for whom MHD and MLVD were reconstructed showed similar results (supplemental Table 3; supplemental Figure 2). Our study includes only cases in which HF was the first cardiovascular diagnosis, in order to eliminate the effects of other cardiovascular diseases such as CHD or VHD on the risk of developing HF. However, in a previous study,⁹ we showed that HF occurred frequently subsequent to CHD or VHD, rather than as a first event. Additional research is needed to study the influence of previous cardiovascular diseases and to identify risk factors for developing multiple cardiovascular diseases.

For patients treated today, MHDs and MLVDs will usually be well below the average values of 20.9 Gy and 14.5 Gy reported in this study, due to reductions in both treatment volumes and prescribed doses. Involved field radiotherapy has been reported to give a median MHD of 17.2 Gy for prescribed doses of 35 Gy and involved node radiotherapy leads to even lower doses (median MHDs of 7.7-12.0 Gy for prescribed doses of 36 Gy).³³⁻³⁵ Also, anthracycline doses are nowadays frequently lower than the doses received by the majority of patients in our study. Therefore, patients treated today are likely to be at a substantially lower risk of treatment-related HF than the patients included in this study. Studies in larger populations of HL survivors treated more recently would be helpful in characterizing the risks from modern treatments more precisely. More accurate dosimetry based on a patient's individual CT scan may also help to determine whether MHD, MLVD, or another dosimetric parameter is the best measure to predict radiation-related HF risk. However, in the absence of more precise measures, these dose-response relationships for MHD and MLVD can be used to estimate HF risk both in patients treated today and in survivors treated in more recent decades.

In conclusion, cardiac radiation exposure and treatment with anthracyclines are important risk factors for the development of HF in

HL survivors. Our findings are important for clinicians to provide information regarding risks of HF before treatment, during radiation treatment planning, and during long-term follow-up of HL survivors, including patients treated in the past.

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Authorship

Contribution: F.A.v.N., G.N., S.C.D., M.S., F.E.v.L., D.J.C., and B.M.P.A. designed the study and concept; F.E.v.L., S.C.D., G.N., and D.J.C. provided financial support; P.J.L., C.P.M.J., L.D., and B.M.P.A. provided study materials or patients; F.A.v.N., G.N., P.J.L., C.P.M.J., and L.D. collected and assembled the data; G.N. and D.J.C. conducted the dosimetry; F.A.v.N., G.N., S.C.D., M.S., M.H., F.E.v.L., D.J.C., and B.M.P.A. analyzed and interpreted the data; F.A.v.N., G.N., S.C.D., M.S., M.H., P.J.L., C.P.M.J., L.D., F.E.v.L., D.J.C., and B.M.P.A. wrote the manuscript; and F.A.v.N., G.N., S.C.D., M.S., M.H., P.J.L., C.P.M.J., L.D., F.E.v.L., D.J.C., and B.M.P.A. gave final approval of the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Supplementary materials of the above paper

Supplemental Table 2: Dose-response relationships

	Linear model*						Non-linear model†						
	β _{radio}	Deviance	χ ² (1 df)†	p-value†	β _{anthra}	p _{anthra}	β _{radio1}	β _{radio2}	Deviance	χ ² (1 df) ¥	p-value¥	β _{anthra}	p _{anthra}
Mean heart dose													
All patients	0.07	233.89	7.50	0.006	1.05	0.006	-7.85	0.16	229.13	4.76	0.029	1.01	0.009
Only patients with simfilms	0.08	133.19	8.26	0.004	0.94	0.034	-5.37	0.10	129.23	3.95	0.047	0.97	0.034
Low dose range (up to 25 Gy)	0.01	895.83	0.164	>0.50	1.41	0.035	-0.69	-0.12	879.98	1.59	0.21	1.51	0.028
Mean left ventricular dose													
All patients	0.09	232.94	9.45	0.004	1.02	0.007	-4.12	0.06	230.95	1.99	0.09	0.97	0.012
Only patients with simfilms	0.12	131.12	10.33	0.001	0.86	0.053	-3.06	0.04	129.63	1.49	0.22	0.83	0.065
Low dose range (up to 20 Gy)	0.03	149.59	0.69	0.41	1.46	0.015	-79.9	3.78	147.69	1.90	0.17	1.48	0.014
* RR = 1+ β _{radio} *dose + β _{anthra}													
† for test of β _{radio} = 0													
‡ RR =1+ β _{radio1} *dose*exp(β _{radio2} *dose) + β _{anthra}													
¥ for test of model allowing for curvature versus linear model (i.e. test of β _{radio2} =0)													

* $RR = 1 + \beta_{\text{radio}} * \text{dose} + \beta_{\text{anthra}}$

† for test of $\beta_{\text{radio}} = 0$

‡ $RR = 1 + e^{(\beta_{\text{radio1}} * \text{MLVD} * e^{(\beta_{\text{radio2}} * \text{MLVD})})} + \beta_{\text{anthra}}$

¥ for test of model allowing for curvature versus linear model (i.e. test of $\beta_{\text{radio2}} = 0$)

Supplemental table 3: Associations between radiation doses and CHF risk based only on patients for whom cardiac doses could be reconstructed

Treatment factor	RR*	95%CI	P _{trend}
Mean heart dose (MHD)			
0 Gy	1.00	0.36-2.77	
1-20 Gy (median 16 Gy)	0.77	0.32-1.88	
21-25 Gy (median 23 Gy)	1.22	0.62-2.41	
26-30 Gy (median 28 Gy)	3.71	2.00-6.87	
≥31 Gy (median 33 Gy)	3.69	1.77-7.73	0.001
Mean dose to the left ventricle (MLVD)			
0 Gy	1.00	0.35-2.84	
1-15 Gy (median 13 Gy)	1.10	0.63-1.91	
16-20 Gy (median 19 Gy)	2.79	1.43-5.43	
21-25 Gy (median 23 Gy)	3.99	1.71-9.32	
≥26 Gy (median 30 Gy)	3.52	1.46-8.52	0.002

RR: rate ratio, CI: confidence interval, MHD: mean heart dose, MLVD: mean left ventricular dose.

Supplemental Table 4: Associations between patient-related risk factors and CHF risk

Risk factor	#cases	%	#controls	%	RR	95%CI	p
	(total: 91)		(total: 278)				
Risk factors present at HL diagnosis							
Obesity at HL diagnosis (BMI $\geq$ 30)	4	4.8	6	2.3	2.00	0.56-7.15	0.29
Smoking at time of HL diagnosis [¶]	40	45.5	117	43.7	1.12	0.67-1.90	0.65
Risk factors present at cut-off							
Smoking at cut-off [¶]	13	17.8	46	23.8	0.74	0.35-1.59	0.44
Recent smoker at cut-off (<5 years) [¶]	16	17.6	51	18.4	0.92	0.47-1.78	0.80
Risk factors present between HL diagnosis and cut-off [§]							
Hypertension	3	3.3	18	6.5	0.42	0.12-1.49	0.18
Hypercholesterolemia	2	2.2	10	3.6	0.63	0.13-3.11	0.57
Diabetes mellitus	7	7.7	13	4.7	1.59	0.63-4.05	0.33
Obesity (BMI $\geq$ 30)	10	11.0	28	10.1	1.09	0.51-2.34	0.83
At least one of the above risk factors	19	20.9	52	18.7	1.10	0.60-2.03	0.75
Risk factors ever diagnosed [¥]							
Hypertension	11	24.4	40	21.5	1.80	0.73-4.44	0.20
Hypercholesterolemia	7	15.6	39	21.0	0.86	0.32-2.30	0.76
Diabetes mellitus	18	19.8	34	12.2	1.83	0.96-3.47	0.06
Obesity (BMI $\geq$ 30)	12	13.2	28	10.1	1.36	0.65-2.83	0.41
At least one of the above risk factors	52	57.2	132	47.5	1.53	0.93-2.52	0.09
Ever smoked [†]	42	48.3	125	47.2	1.03	0.62-1.70	0.92
Physical activity at time of follow-up [‡]							
Not active (<1 hour a week)	22	48.9	83	44.6	1.00	0.61-1.63	
Moderately active (1-3 hours a week)	10	22.2	33	17.7	1.16	0.56-2.39	
Very active ($\geq$ 4 hours a week)	13	28.9	70	37.6	0.59	0.32-1.10	0.22*

RR: rate ratio, CI: confidence interval, HL: Hodgkin lymphoma, BMI: body mass index

Risk factors were defined as yes/no variables. RRs were estimated conditionally on the matched sets, except for analyses of physical activity at time of follow-up (see below). No further adjustments were made as no significant associations were identified.

*p for trend

[§]Patients were classified as having a risk factor if it was ever mentioned in the medical record, by the GP, or in the patient questionnaire. If no risk factors were mentioned in any of these data sources, patients were classified as not having a risk factor. Patients were diagnosed with one of the risk factors according to the medical guidelines effective at the moment of diagnosis. Risk factor information of xx patients is solely based on patient-reported outcomes.

[‡]Patients were classified as having a risk factor if it was ever mentioned in the medical record, by the GP or in the patient questionnaire. If no risk factors were mentioned, patients were classified as not having a risk factor. Patients diagnosed with one of the risk factors were diagnosed according to the medical guidelines effective at the moment of diagnosis.

[‡] Analysis conducted on the sub-population of patients who completed the risk factor questionnaire (45 cases and 186 controls), adjusted for the matching factors.

[¶] Smoking history at HL diagnosis was missing for 3 cases and 10 controls, smoking at time of cut-off was missing for 9 cases and 31 controls.

[†]Smoking history was missing for 3 cases and 6 controls.

Supplemental Table 5A: Interaction analyses for mean heart dose groups and CHF risk

	Mean heart dose from radiotherapy (EQD2)						P _{interaction}
	N Cases	N Controls	0-25 Gy RR (95%CI)	N Cases	N Controls	26+ Gy RR (95%CI)	
Anthracyclines							
No	28	153	1.00	32	66	3.13 (1.65-5.97)	0.45
Yes	20	48	3.65 (1.43-9.33)	11	11	7.15 (2.52-20.28)	
Splenectomy							
No	36	137	1.00	24	39	2.62 (1.38-5.00)	0.71
Yes	11	62	0.68 (0.32-1.45)	19	38	2.18 (1.03-4.62)	
Presence of at least one cardiovascular disease risk factor							
No	37	160	1.00	35	66	2.59 (1.45-4.62)	0.53
Yes	11	41	0.99 (0.45-2.17)	8	11	3.83 (1.37-10.67)	
Gender							
Male	29	105	1.00	18	34	2.48 (1.14-5.38)	0.72
Female	19	96	1.00*	25	43	3.03 (1.42-6.48)	
Age at HL diagnosis							
≤25 years	19	73	1.00	19	38	2.14 (0.94-4.85)	0.43
26-50 years	29	128	1.00*	24	39	3.31 (1.62-6.80)	
Time since HL diagnosis							
5-20 years	22	25	1.00	37	107	2.82 (1.36-5.89)	0.92
≥21 years	21	23	1.00*	94	40	2.67 (1.20-5.91)	

RR: Rate ratio.

* RRs cannot be estimated as these variables were matching variables and so do not vary with the matched sets

EQD2: equivalent dose in 2 Gy fractions

Supplemental Table 5B: Interaction analyses for mean left ventricular dose groups and CHF risk

	Mean left ventricular dose from radiotherapy (EQD2)						
	N Cases	N Controls	0-19 Gy RR (95%CI)	N Cases	N Controls	≥20 Gy RR (95%CI)	P _{interaction}
Anthracyclines							
No	39	189	1.00	21	30	3.90 (1.57-9.65)	0.09
Yes	19	44	4.03 (2.01-8.08)	12	15	5.76 (2.17-15.28)	
Splenectomy							
No	81	150	1.00	15	42	0.67 (0.34-1.32)	0.62
Yes	19	26	2.81 (1.32-5.99)	15	18	2.52 (1.16-5.50)	
Presence of at least one cardiovascular disease risk factor							
No	80	153	1.00	21	37	1.15 (0.62-2.12)	0.12
Yes	9	36	2.34 (1.19-4.61)	13	20	6.80 (2.64-17.48)	
Gender							
Male	13	34	1.00	18	121	3.15 (1.33-7.44)	0.95
Female	20	24	1.00*	27	112	3.03 (1.47-6.27)	
Age at HL diagnosis							
<25 years	140	93	1.00	33	25	2.85 (1.17-6.91)	0.82
26-50 years	27	18	1.00*	20	13	3.24 (1.59-6.60)	
Time since HL diagnosis							
5-20 years	113	120	1.00	29	29	3.13 (1.47-6.67)	0.96
≥21 years	21	24	1.00*	15	18	3.02 (1.34-6.85)	

RR: Rate ratio

* RRs cannot be estimated as these variables were matching variables and so do not vary with the matched sets

Supplemental Table 6: Estimate heart failure rates by radiotherapy dose and anthracycline treatment*

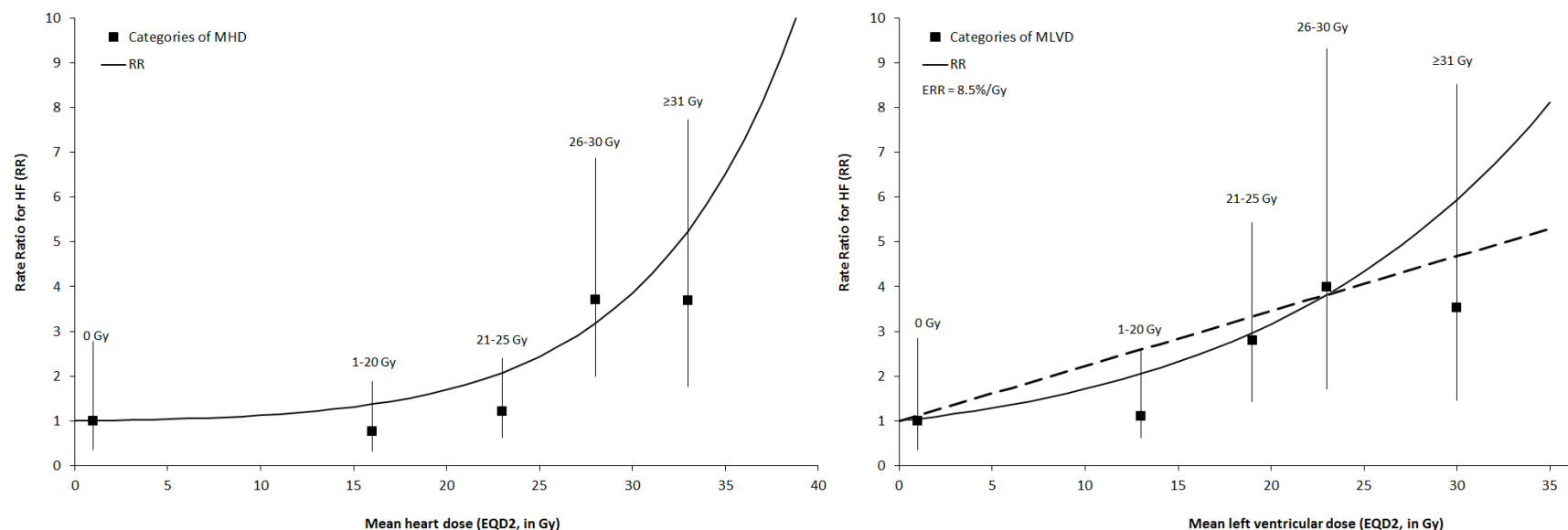
	Treated without anthracyclines					Treated with anthracyclines				
	#cases	#controls	RR	95%CI	p [‡]	#cases	#controls	RR	95%CI	p [§]
Mean heart dose (EQD2)										
0-25 Gy	28	153	1.00	0.62-1.63		20	48	3.55	1.60-7.86	
26-30 Gy	22	49	2.82	1.64-4.83		5	8	5.30	1.65-17.11	
≥31 Gy	10	17	3.99	1.86-8.54	<0.001	6	3	10.92	2.72-43.80	0.08
Mean left ventricular dose (EQD2)										
0-15 Gy	26	133	1.00	0.59-1.69		17	40	3.91	1.80-8.51	
16-20 Gy	17	60	1.70	0.94-3.08		3	8	3.81	0.93-15.62	
≥21Gy	17	26	4.21	2.31-7.66	0.002	11	11	7.12	3.04-16.66	0.33
V30 left ventricle (%)										
0-24%	9	51	1.00	0.42-2.41		4	16	3.46	1.11-10.78	0.11
25-100%	51	168	2.61	1.79-3.80	0.042	27	43	8.72	4.38-17.37	<0.001
V20 left ventricle (%)										
0-49%	26	118	1.00	0.60-1.66		14	34	3.27	1.48 -7.24	0.018
50-100%	34	101	1.72	1.09-2.71	0.10	17	25	4.43	2.21-8.88	0.001

*Estimates allow for an interaction between use of anthracyclines and radiotherapy

[‡]p (for variables with 2 categories) or p for trend (for variables with more than 2 categories) among patients treated without anthracyclines

[§]p (for variables with 2 categories) or p for trend (for variables with more than 2 categories) among patients treated with anthracyclines

Supplemental Figure 2: Relationship between heart failure rate and cardiac dose based only on patients for whom cardiac doses could be reconstructed*



*Rate ratios (RRs) for congestive heart failure (CHF) by mean heart dose (left panel) and by mean left ventricular dose (right panel) in Gy compared with no radiation exposure. RRs are calculated conditionally on matched sets after adjustment for anthracycline-based chemotherapy (yes/no). Squares indicate anthracycline-adjusted estimates for the following dose categories: mean heart dose: 0 Gy, 1-20 Gy, 20-25 Gy, 26-30 Gy, ≥ 31 Gy; mean left ventricular dose: 0 Gy, 1-15 Gy, 16-20 Gy, 21-25 Gy, ≥ 26 Gy, and are plotted at the median dose in each category (0 Gy, 16 Gy, 23 Gy, 28 Gy, and 33 Gy for mean heart dose; 0 Gy, 13 Gy, 19 Gy, 23 Gy, and 30 Gy for mean left ventricular dose). Vertical lines are 95% confidence intervals. For mean heart dose, there was a statistically significant linear dose-response relationship ($p=0.004$) and allowing for curvature improved the fit significantly ($p=0.047$). For mean left ventricular dose, there was a statistically significant linear dose-response relationship ($p=0.001$) and allowing for curvature did not significantly improve the fit ($p=0.22$)

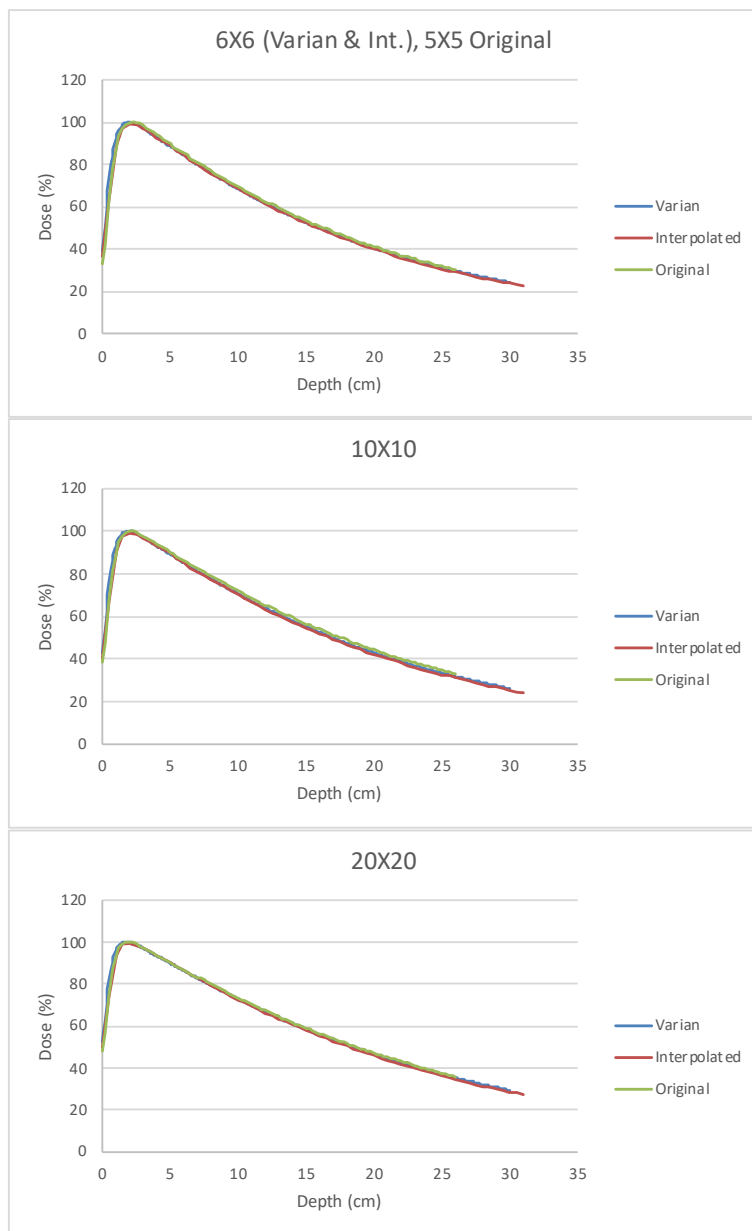
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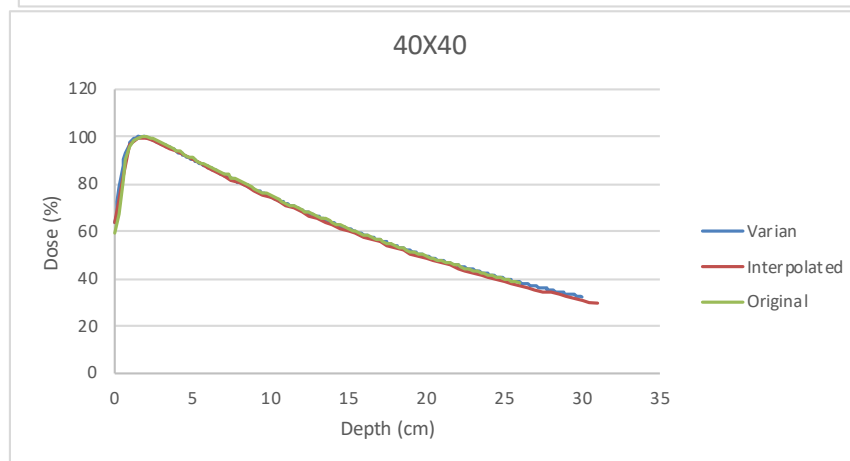
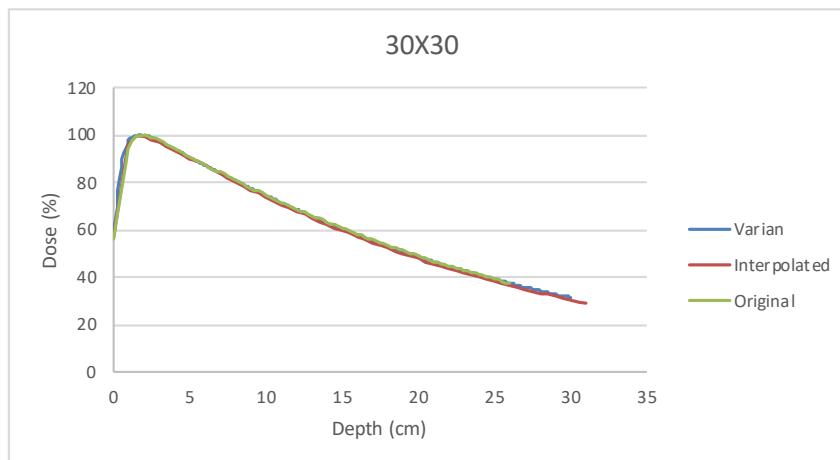
Section 2 Beam model validation

Percentage Depth Doses Comparison

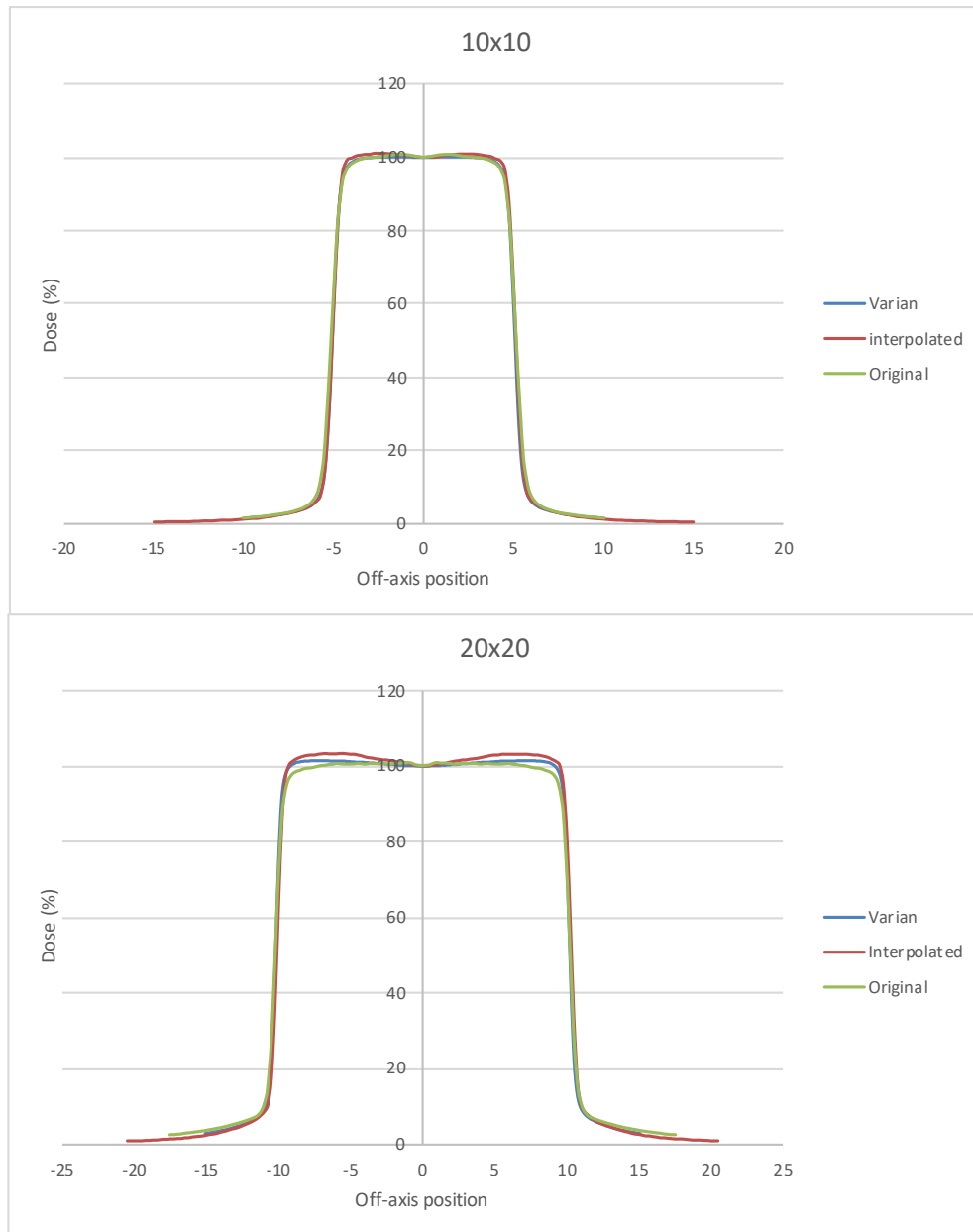
Open field

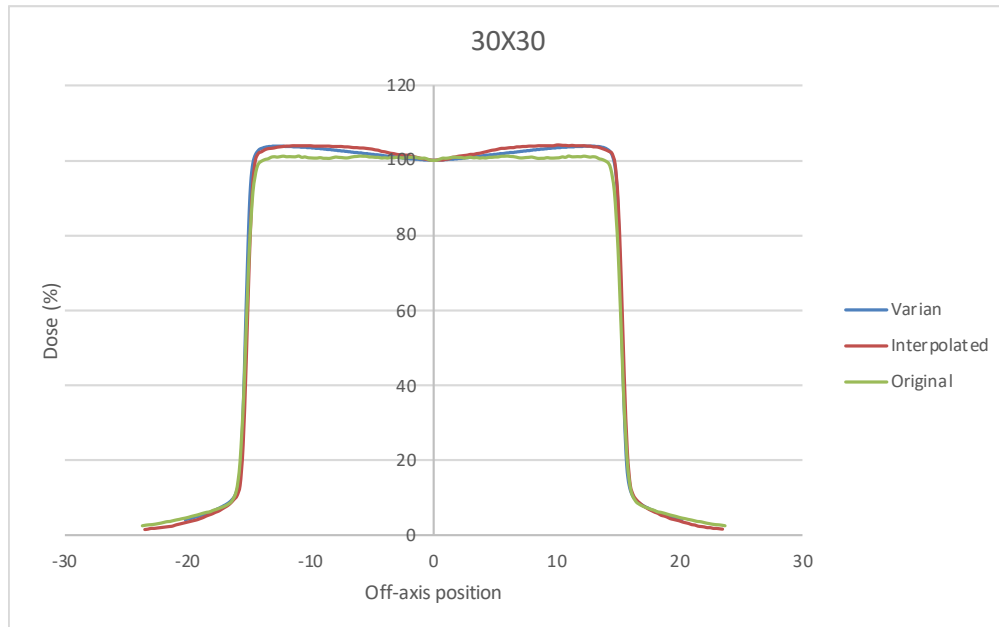
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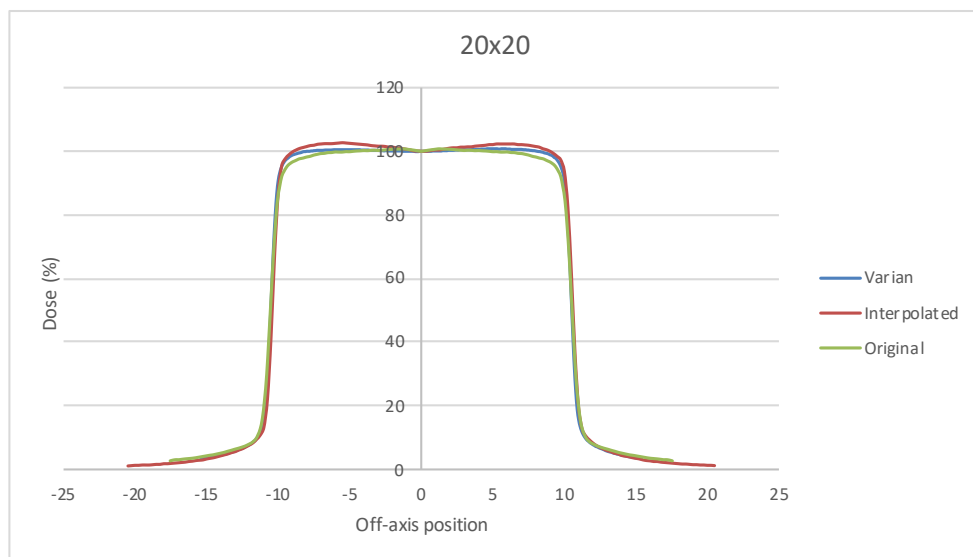
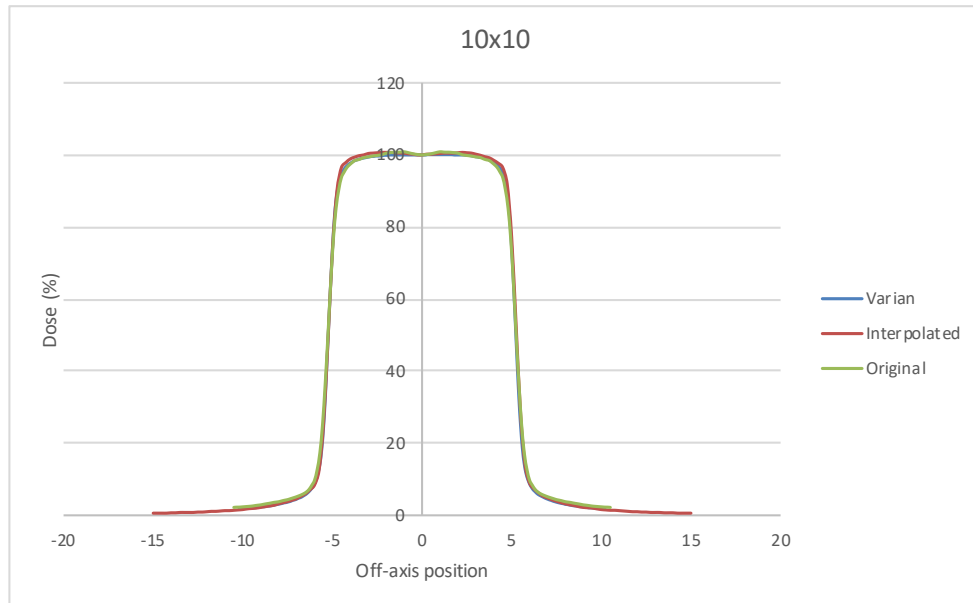


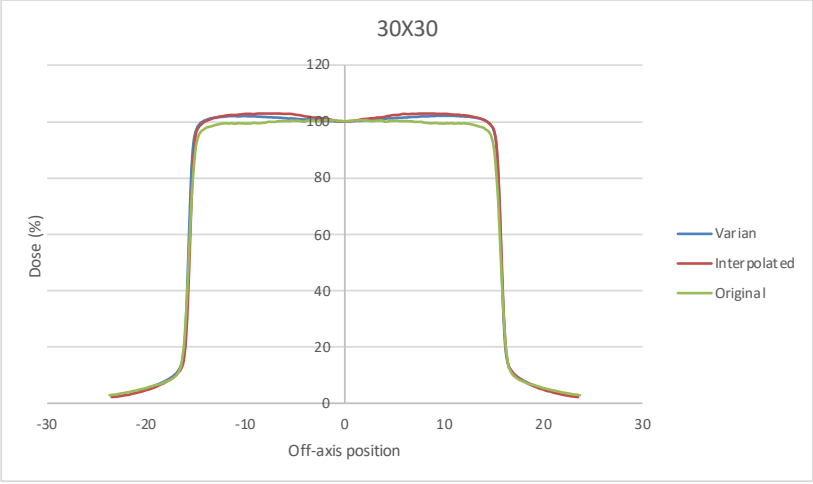
Beam Profiles Comparison at 2cm depth



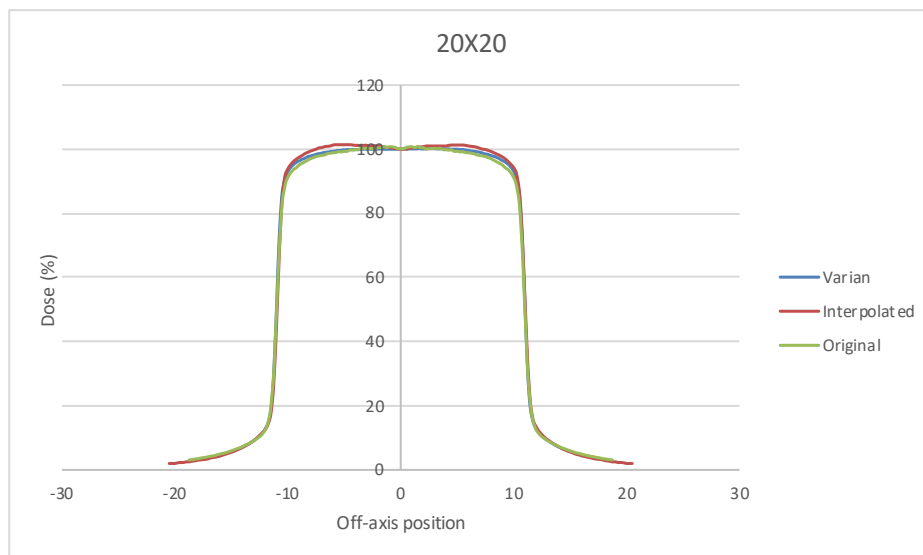
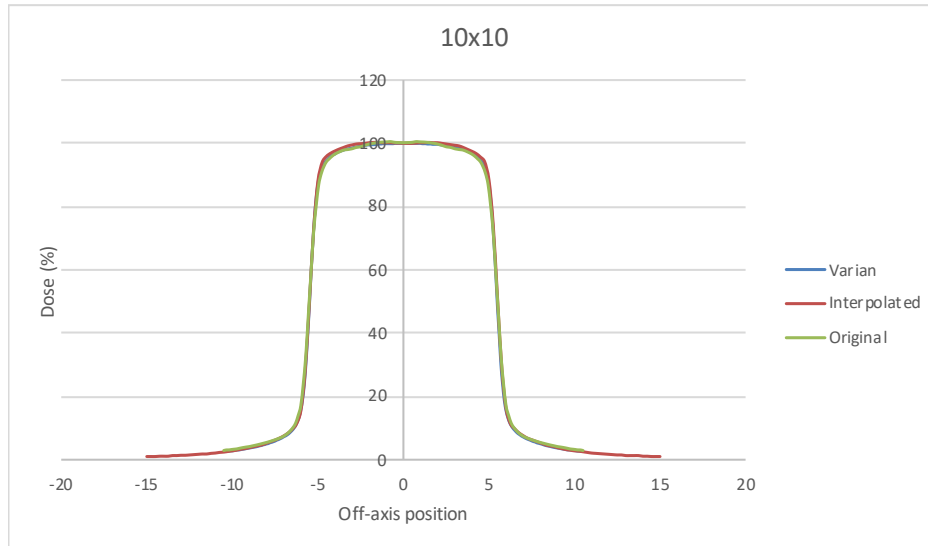


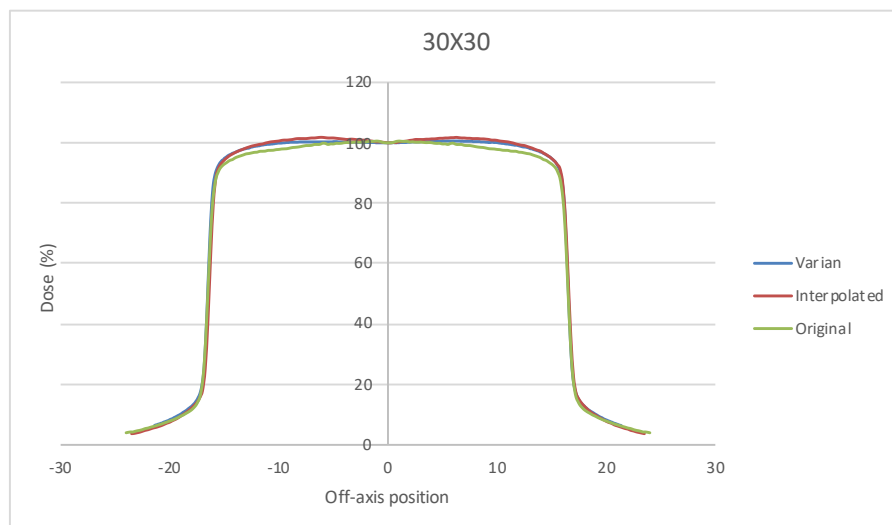
Beam Profiles Comparison at 5cm depth





Beam Profiles Comparison at 10cm depth





Appendix B

Examples of the patient information provided for 14 patients to be used for the cardiac doses reconstruction using five reconstruction methods in Chapter 2.

Subject 1

Gender: Female

Plan Summary Sheet

Beam Setup

<u>Beam</u>	<u>Machine</u>	<u>Energy</u>	<u>Modality</u>	<u>Prescription</u>	<u>Isocenter</u>	SSD (cm)	<u>MU Per Fraction</u>
						<u>Start / Avg</u>	
Ant	oldWV16	6 MV	Photons	mantle	iso	92.62 / 92.62	106
Post	oldWV16	6 MV	Photons	mantle	iso	93.19 / 93.19	110
ant seg	oldWV16	10 MV	Photons	mantle	iso	92.62 / 92.62	10
post seg	oldWV16	10 MV	Photons	mantle	iso	93.19 / 93.19	10

<u>Beam</u>	<u>Collimators (cm) (Control Pt 1)</u>				<u>Gantry</u>						
	<u>X1</u>	<u>X2</u>	<u>Y2</u>	<u>Y1</u>	<u>Start / Stop</u>	<u>Couch</u>	<u>Coll</u>	<u>Block</u>	<u>Wedge</u>	<u>Bolus</u>	<u>Comp</u>
Ant	9.4	10.6	18.0	9.1	0.0 / 0.0	0.0	0.0	Yes	None	No	No
Post	10.6	9.4	18.0	9.1	180.0/180.0	0.0	0.0	Yes	None	No	No
ant seg	9.4	10.6	3.0	9.1	0.0 / 0.0	0.0	0.0	Yes	None	No	No
post seg	10.6	9.4	3.0	9.1	180.0/180.0	0.0	0.0	Yes	None	No	No

Prescriptions

mantle

Prescribe 2000 cGy overall to 100 % of point dose at "icru a" in 10 fractions.
 Beam weights are proportional to monitor units.
 Actual point dose at "icru a" from all prescriptions/beams is 2004.65 cGy.
 4 beams are assigned to this prescription.

Isocenter

iso

Position patient such that lasers line up with patient marks.
 Move the table LEFT 0.03 cm (looking from foot of table.)
 Move the table UP 6.49 cm.
 No in/out table adjustment is required.

Primary Data Set Dimensions: 145 slices, 512 x 512 pixels
 CT to Density Table Name: *All RMP CT Scanners*

Patient Position: On back (supine) Head First
 Couch: Removed at Y = -102.11
 Body Board Angle: None

Number of Photon Beams: 4
 Number of Stereo Beams: 0
 Number of Electron Beams: 0

Number of Brachy Sources: 0

Outside-Patient Air Threshold: 0.60 g/cm³

	Dose Grid Geometry			
	<u>Lateral</u>	<u>Ant-Post</u>	<u>Sup-Inf</u>	<u>Units</u>
Resolution	0.400	0.400	0.400	cm
Dimension	76	45	55	Pixels
Origin	-14.373	-100.706	-35.209	cm

Top Slice of CT Extended: 0.00 cm
 Bottom Slice of CT Extended: 0.00 cm

Region of Interest Density Overrides:

ROI

Density

(no ROI density overrides in use)

	<i>Ant</i>	<i>Post</i>	<i>ant seg</i>
<u>Beam Setup</u>			
Machine Name	<i>oldWV16</i>	<i>oldWV16</i>	<i>oldWV16</i>
Machine Version	2007-07-01 00:00:00	2007-07-01 00:00:00	2007-07-01 00:00:00
Energy / Modality	6 MV Photons	6 MV Photons	10 MV Photons
SAD (cm)	100.0	100.0	100.0
Prescription	mantle	mantle	mantle
Isocenter	iso	iso	iso
<u>Beam Geometry</u>			
Couch Angle	0.0	0.0	0.0
Gantry Angle	0.0	180.0	0.0
Collimator Angle	0.0	0.0	0.0
SSD (cm)	92.62	93.19	92.62
SSD With Bolus (cm)	--	--	--
<u>Collimators (cm) (Control Pt 1)</u>			
X1 / X2 (X)	9.40 / 10.60 (20.00)	10.60 / 9.40 (20.00)	9.40 / 10.60 (20.00)
Y2 / Y1 (Y)	18.00 / 9.10 (27.10)	18.00 / 9.10 (27.10)	3.00 / 9.10 (12.10)
<u>Modifiers</u>			
Wedge Name	None	None	None
Wedge Orientation	--	--	--
Wedge Angle	None	None	None
Blocked / Tray #	Yes /	Yes /	Yes /
Bolus	None	None	None
Compensator	None	None	None
Opening Density Matrix	None	None	None
<u>Dose</u>			
Dose Engine	Adaptive Convolve	Adaptive Convolve	Adaptive Convolve
Model	All Field Sizes	All Field Sizes	All Field Sizes
Density Correction	Heterogeneous	Heterogeneous	Heterogeneous
Relative Weight (%)	44.79	46.81	4.20
Reference Point	<i>icru a</i>	<i>icru a</i>	<i>icru a</i>
Normalized Dose (ND) at Ref Pt	1.350	0.927	1.248
Collimator Output Factor (OFc)(Last CP)	0.996	0.996	1.001
Tray / Block & Tray Factor	0.9600 / 0.0384	0.9600 / 0.0384	0.9690 / 0.0388
Total Transmission Factor (TTF)	0.960	0.960	0.969
SPD/OAD (cm)	96.63 / 1.36	103.39 / 1.36	96.63 / 1.36
SSD to Ref Pt (cm)	92.88	93.01	92.88
Ref Pt Depth / Eff Depth (cm)	3.75 / 4.10	10.38 / 11.58	3.75 / 4.10
Unblk Equiv Sq (cm / %Blkd)(Last CP)	23.0 / 20.2%	23.0 / 23.5%	15.1 / 30.9%
Meas Ref Point Dose (cGy/MU)	--	--	--
Dose at Ref/Fraction (cGy)	106.7	76.0	10.3
Dose Rate (MU/min)	400	400	400
Number of Fractions	10	10	10
MU/Fraction	106	110	10

post seg

Beam Setup

Machine Name	<i>oldWV16</i>
Machine Version	2007-07-01 00:00:00
Energy / Modality	10 MV Photons
SAD (cm)	100.0
Prescription	mantle
Isocenter	iso

Beam Geometry

Couch Angle	0.0
Gantry Angle	180.0
Collimator Angle	0.0
SSD (cm)	93.19
SSD With Bolus (cm)	---

Collimators (cm) (Control Pt 1)

X1 / X2 (X)	10.60 / 9.40 (20.00)
Y2 / Y1 (Y)	3.00 / 9.10 (12.10)

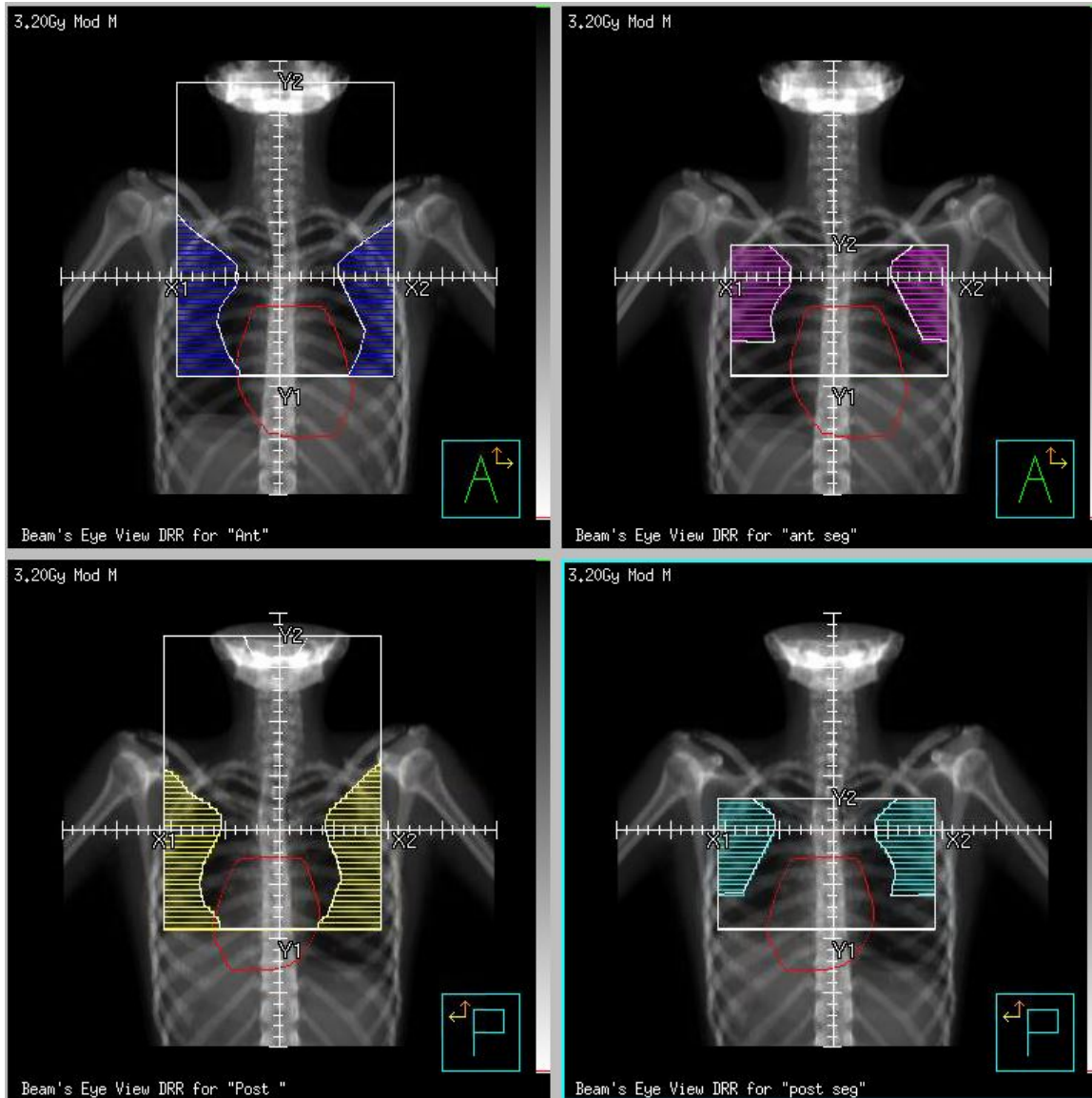
Modifiers

Wedge Name	None
Wedge Orientation	---
Wedge Angle	None
Blocked / Tray #	Yes /
Bolus	None
Compensator	None
Opening Density Matrix	None

Dose

Dose Engine	Adaptive Convolve
Model	All Field Sizes
Density Correction	Heterogeneous
Relative Weight (%)	4.20
Reference Point	<i>icru a</i>
Normalized Dose (ND) at Ref Pt	0.909
Collimator Output Factor (OFc)(Last CP)	1.001
Tray / Block & Tray Factor	0.9690 / 0.0388
Total Transmission Factor (TTF)	0.969
SPD/OAD (cm)	103.39 / 1.36
SSD to Ref Pt (cm)	93.01
Ref Pt Depth / Eff Depth (cm)	10.38 / 11.58
Unblk Equiv Sq (cm / %Blkd)(Last CP)	15.1 / 30.9%
Meas Ref Point Dose (cGy/MU)	---
Dose at Ref/Fraction (cGy)	7.5
Dose Rate (MU/min)	400
Number of Fractions	10
MU/Fraction	10

DRRs (actual CT plan)



Subject 2

Gender: Female

Plan Summary Sheet

Beam Setup

<u>Beam</u>	<u>Machine</u>	<u>Energy</u>	<u>Modality</u>	<u>Prescription</u>	<u>Isocenter</u>	SSD (cm)	<u>MU Per Fraction</u>
						<u>Start / Avg</u>	
ANT Mod MANTLE	oldWV16	6 MV	Photons	mod mantle	ISO	92.16 / 92.16	106
POST MOD MANTLE	oldWV16	6 MV	Photons	mod mantle	ISO	92.43 / 92.43	71
post seg	oldWV16	10 MV	Photons	mod mantle	ISO	92.43 / 92.43	15

<u>Beam</u>	<u>Collimators (cm) (Control Pt 1)</u>				<u>Gantry</u>		<u>Couch</u>	<u>Coll</u>	<u>Block</u>	<u>Wedge</u>	<u>Bolus</u>	<u>Comp</u>
	<u>X1</u>	<u>X2</u>	<u>Y2</u>	<u>Y1</u>	<u>Start / Stop</u>							
ANT Mod MANTLE	11.0	12.3	16.0	8.8	0.0 / 0.0		0.0	0.0	MLC	None	No	No
POST MOD MANTLE	2.3	11.0	15.0	8.0	180.0/180.0		0.0	0.0	MLC	None	No	No
post seg	4.5	5.0	3.5	8.0	180.0/180.0		0.0	0.0	MLC	None	No	No

Prescriptions

mod mantle

Prescribe 175 cGy per fraction to 100 % of point dose at "icru a" for 20 fractions.

Beam weights are proportional to monitor units.

Actual point dose at "icru a" from all prescriptions/beams is 3485.56 cGy.

3 beams are assigned to this prescription.

Isocenter

ISO

Position patient such that lasers line up with patient marks.

Move the table RIGHT 0.00 cm (looking from foot of table.)

Move the table UP 7.48 cm.

No in/out table adjustment is required.

Primary Data Set Dimensions: 193 slices, 512 x 512 pixels
 CT to Density Table Name: *All RMP CT Scanners*

Patient Position: On back (supine) Head First
 Couch: Removed at Y = -49.06
 Body Board Angle: None

Number of Photon Beams: 3
 Number of Stereo Beams: 0
 Number of Electron Beams: 0

Number of Brachy Sources: 0

Outside-Patient Air Threshold: 0.60 g/cm³

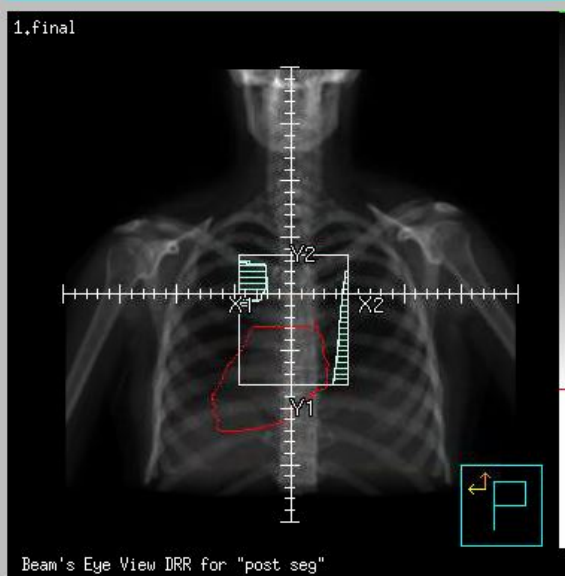
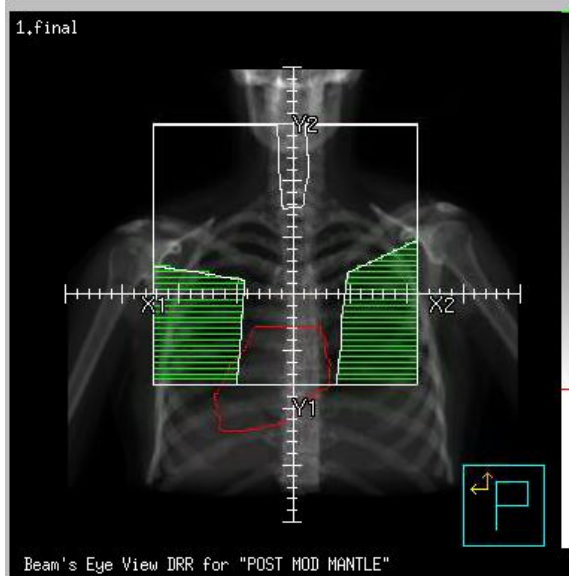
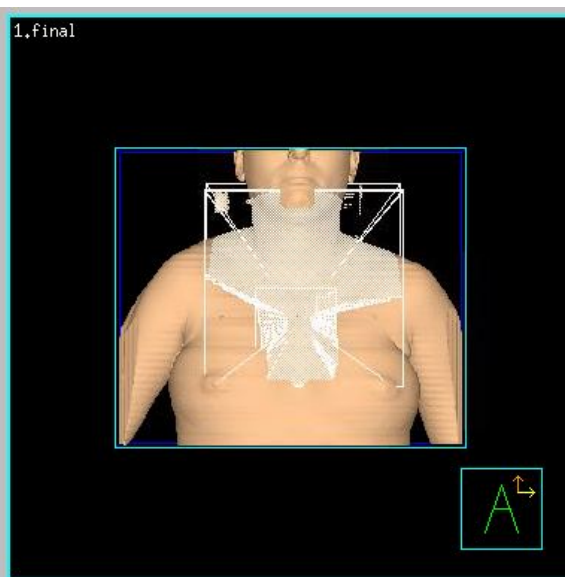
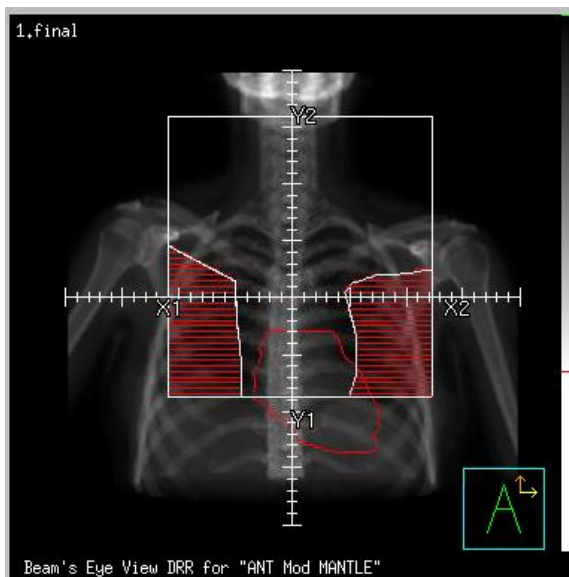
Dose Grid Geometry				
	<u>Lateral</u>	<u>Ant-Post</u>	<u>Sup-Inf</u>	<u>Units</u>
Resolution	0.400	0.400	0.400	cm
Dimension	88	61	95	Pixels
Origin	-16.731	-50.136	-20.592	cm

Top Slice of CT Extended: 1.00 cm
 Bottom Slice of CT Extended: 1.00 cm

Region of Interest Density Overrides:
ROI
Density
 (no ROI density overrides in use)

	<i>ANT Mod MANTLE</i>	<i>POST MOD MANTLE</i>	<i>post seg</i>
<u>Beam Setup</u>			
Machine Name	<i>oldWV16</i>	<i>oldWV16</i>	<i>oldWV16</i>
Machine Version	2007-07-01 00:00:00	2007-07-01 00:00:00	2007-07-01 00:00:00
Energy / Modality	6 MV Photons	6 MV Photons	10 MV Photons
SAD (cm)	100.0	100.0	100.0
Prescription	mod mantle	mod mantle	mod mantle
Isocenter	ISO	ISO	ISO
<u>Beam Geometry</u>			
Couch Angle	0.0	0.0	0.0
Gantry Angle	0.0	180.0	180.0
Collimator Angle	0.0	0.0	0.0
SSD (cm)	92.16	92.43	92.43
SSD With Bolus (cm)	---	---	---
<u>Collimators (cm) (Control Pt 1)</u>			
X1 / X2 (X)	11.00 / 12.30 (23.30)	12.30 / 11.00 (23.30)	4.50 / 5.00 (9.50)
Y2 / Y1 (Y)	16.00 / 8.80 (24.80)	15.00 / 8.00 (23.00)	3.50 / 8.00 (11.50)
<u>Modifiers</u>			
Wedge Name	None	None	None
Wedge Orientation	---	---	---
Wedge Angle	None	None	None
Blocked / Tray #	Yes/MLC	Yes/MLC	Yes/MLC
Bolus	None	None	None
Compensator	None	None	None
Opening Density Matrix	None	None	None
<u>Dose</u>			
Dose Engine	Adaptive Convolve	Adaptive Convolve	Adaptive Convolve
Model	All Field Sizes	All Field Sizes	All Field Sizes
Density Correction	Heterogeneous	Heterogeneous	Heterogeneous
Relative Weight (%)	55.20	36.80	8.00
Reference Point	<i>icru a</i>	<i>icru a</i>	<i>mu point</i>
Normalized Dose (ND) at Ref Pt	1.291	1.020	0.897
Collimator Output Factor (OFc)(Last CP)	0.997	0.996	1.000
MLC Transmission Factor (Last CP)	0.015	0.015	0.02
Total Transmission Factor (TTF)	1.000	1.000	1.000
SPD/OAD (cm)	97.61 / 1.43	102.41 / 1.43	102.65 / 5.75
SSD to Ref Pt (cm)	92.70	92.70	92.12
Ref Pt Depth / Eff Depth (cm)	4.91 / 5.31	9.71 / 9.39	10.53 / 11.80
Unblk Equiv Sq (cm / %Blkd)(Last CP)	24.0 / 25.6%	23.1 / 28.1%	10.4 / 12.7%
Meas Ref Point Dose (cGy/MU)	---	---	---
Dose at Ref/Fraction (cGy)	106.4	56.3	11.4
Dose Rate (MU/min)	400	400	400
Number of Fractions	20	20	20
MU/Fraction	106	71	15

DRRs (actual CT plan)



Appendix C

Section 1 Comparison of PartArc versus clinically delivered plans

Dosimetric comparison between PartArc and the HybridArc clinical RT method used at Oxford University Hospital. This analysis was performed as part of the validation of PartArc for use in the studies in Chapter 3 and Chapter 4. Results demonstrate that PartArc plans were clinically deliverable and even reduced some of the dosimetric parameters seen compared to the clinically delivered plans.

Table 1 Dosimetric comparison of PartArc versus clinical HybridArc

PTV		
	HybridArc	PartArc
Dmean (Gy)	30.44	29.98
D2% (Gy)	32.61	31.18
Dmax (Gy)	33.95	33.43
Body-PTV		
	HybridArc	PartArc
Dmean (Gy)	4.17	4.02
Heart		
	HybridArc	PartArc
Dmean (Gy)	16.40	13.67
V30 (%)	11.49	5.30
D2% (Gy)	30.70	30.43
Lungs		
	HybridArc	PartArc
Dmean (Gy)	10.73	9.31
D2% (Gy)	30.30	29.74
V5 (%)	53.27	50.06
V10 (%)	37.11	34.61
V30 (%)	3.65	1.42
Left Breast		
	HybridArc	PartArc
Dmean (Gy)	5.16	3.31
D2% (Gy)	29.98	25.54
Right Breast		
	HybridArc	PartArc
Dmean (Gy)	1.00	0.82
D2% (Gy)	6.43	6.21

Appendix D

Section 1: Estimating ERR/Gy for stroke

A radiation dose-response relationship for the risk of stroke versus carotid artery dose was not provided by De Bruin et al.¹ as the MDCCA for each patient were unknown. However, Maraldo et al.² provided a retrospective dose reconstruction method (%Prescribed) for estimating the dose to the right and left (R-CCA and L-CCA) as a percentage of the prescribed dose for HL patients treated with mantle field RT (supplementary table 5). Since the cohort in the De Bruin et al.¹ study also received mantle field RT, the %Prescribed method was used here to estimate the MDCCA for the patient cohort in the De Bruin et al (ref) study as it can be seen on Table 1.

Once the average MDCCA was estimated, the age-specific SIRs reported by De Bruin et al were converted into ERR ($ERR = SIR - 1$) and then divided by the average MDCCA to derive ERR/Gy of MDCCA as it can be seen on Table 2.

Table 1 Reconstruction of MDCCA using the %Prescribed method provided by Maraldo et al.²

	n	% of total receiving radio	%prescribed dose to R-CCA	%prescribed dose to L-CCA	Mean %prescribed dose to CCA	MDCCA (Gy)	Total dose to CCA (Gy)
All patients*	2160	91%					
Mantle field	1415	66%	88.6%	80.1%	84.4%	33.7	47742.1
Supraclavicular irradiation alone	52	2%	64.0%	50.4%	57.2%	22.9	1189.8
Neck + Mediastinal (no mantle field)	236	11%	88.6%	80.1%	84.4%	33.7	7962.6
Neck irradiation (no mediastinal irradiation)	84	4%	43.6%	54.7%	49.2%	19.7	1651.4
Mediastinal irradiation (no neck irradiation)	70	3%	64.0%	50.4%	57.2%	22.9	1601.6
Infradiaphragmatic irradiation alone	116	5%	0.0%	0.0%	0.0%	0.0	0.0
No radiotherapy	187	9%	0.0%	0.0%	0.0%	0.0	0.0
				Total dose (Gy)			60147.5
				Average dose to CCA per patient (Gy)			27.8

* The total number of patients reported by De Bruin et al.¹ was 2201, however, for 41 patients the treatment was unknown.

Table 2 Estimation of excess risk for stroke per Gy of MDCCA

Age at treatment	SIR	ERR	ERR/Gy of MDCCA
age_tx <=20	3.8	2.8	2.8/27.8 = 0.10
age_tx >20 & age_tx<=30	3.1	2.1	2.1/27.8 = 0.08
age_tx >30 & age_tx<=40	2.0	1.0	1.0/27.8 = 0.04
age_tx >40	1.4	0.4	0.4/27.8 = 0.01

References

1. De Bruin ML, Dorresteijn LDA, Van't Veer MB, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of hodgkin lymphoma. *J Natl Cancer Inst.* 2009;101(13):928-937. doi:10.1093/jnci/djp147.
2. Maraldo M V, Lundemann M, Vogelius IR, Specht L. A new method to estimate doses to the normal tissues after past extended and involved field radiotherapy for Hodgkin lymphoma. *Radiother Oncol.* 2015:1-6. doi:10.1016/j.radonc.2015.01.008.

Section 2 Mortality rates used in Chapter 4

Table 12 Annual death rates per 100,000 for women in 17 countries in Western Europe by age*

Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Cardiomyopathy/CHF	0.2	0.3	0.4	0.5	0.8	1.1	2.1	3.2	6.1	10.2	17.6	41.7	109.0
Ischaemic HD	0.0	0.1	0.2	0.4	1.1	2.4	5.1	8.6	15.6	27.8	49.4	96.9	209.9
Valvular disease	0.0	0.0	0.0	0.1	0.1	0.3	0.4	0.7	1.1	2.5	5.4	11.9	30.6
Other cardiac diseases	0.3	0.4	0.4	0.6	1.0	1.6	2.4	4.0	6.4	11.3	22.3	45.0	112.0
<i>All Cardiac diseases</i>	0.5	0.8	1.0	1.7	3.0	5.3	9.9	16.4	29.3	51.8	94.7	195.4	461.6
<i>All causes of death</i>	28.7	37.4	44.1	62.8	95.9	160.5	273.8	452.3	698.3	1039.7	1568.5	2538.4	4559.2
Population (1000s)	8913	9729	10457	11289	11812	12644	13447	12862	11603	10824	9489	8606	7721

* Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom

Table 13 Annual death rates per 100,000 for men in 17 countries in Western Europe by age

Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Cardiomyopathy/CHF	0.4	0.6	1.0	1.4	1.7	3.4	5.8	9.8	16.1	26.9	42.3	79.9	161.8
Ischaemic HD	0.1	0.3	0.8	2.1	4.5	11.5	23.6	44.3	75.9	117.8	173.9	290.4	493.6
Valvular disease	0.1	0.1	0.1	0.1	0.3	0.5	0.8	1.6	2.7	5.6	9.6	20.0	43.1
Other cardiac diseases	0.5	0.6	0.9	1.4	2.2	3.9	6.3	10.3	16.8	25.8	41.2	71.8	147.0
<i>All Cardiac diseases</i>	1.0	1.7	2.8	4.9	8.7	19.3	36.4	66.0	111.6	176.1	266.9	462.1	845.5
<i>All causes of death</i>	59.9	101.8	115.5	137.6	181.3	289.9	491.2	833.8	1354.4	2094.7	3071.0	4806.0	7925.9
Population (1000s)	9392	10086	10596	11355	11922	12710	13479	12690	11210	10204	8718	7442	5978

* Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom

Table 14 Annual death rates per 100,000 for women in USA by age

Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Cardiomyopathy/CHF	0.4	0.7	1.1	1.8	2.5	3.9	5.1	9.0	12.4	18.0	29.0	53.1	104.4
Ischaemic HD	0.1	0.2	0.5	1.7	4.2	9.2	16.6	32.5	51.0	79.5	124.7	209.7	358.0
Valvular disease	0.0	0.1	0.3	0.4	0.4	0.5	0.8	1.4	1.7	3.5	5.8	11.9	25.7
Other cardiac diseases	0.5	0.7	1.2	2.3	3.4	6.5	10.4	16.0	22.5	29.7	42.5	68.7	117.8
<i>All Cardiac diseases</i>	0.9	1.7	3.0	6.1	10.5	20.0	32.9	58.9	87.6	130.6	202.0	343.4	605.9
<i>All causes of death</i>	52.5	88.0	116.2	157.3	216.4	326.8	490.6	784.9	1127.1	1573.1	2336.6	3798.1	6161.6
Population (1000s)	10517	11174	10856	10395	10003	10085	10492	11162	10856	9590	7963	5785	4311

Table 15 Annual death rates per 100,000 for men in USA by age

Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Cardiomyopathy/CHF	0.8	1.4	2.5	4.0	5.2	7.7	10.9	16.1	23.8	35.0	52.7	93.8	153.3
Ischaemic HD	0.2	0.6	1.9	5.1	10.6	25.0	47.7	91.8	149.4	219.2	307.7	461.4	688.4
Valvular disease	0.1	0.2	0.2	0.6	0.7	0.9	1.5	2.3	3.9	5.7	8.7	16.2	30.8
Other cardiac diseases	0.5	1.3	2.1	3.8	6.5	11.1	17.9	29.1	41.4	56.6	71.1	101.5	146.7
<i>All Cardiac diseases</i>	1.6	3.5	6.7	13.4	23.0	44.6	78.0	139.3	218.5	316.4	440.2	672.9	1019.1
<i>All causes of death</i>	124.2	244.1	277.9	324.7	370.7	500.3	736.4	1204.9	1836.8	2606.7	3657.4	5698.6	8444.6
Population (1000s)	10992	11708	11239	10521	9982	10071	10669	11137	10452	8916	7098	4873	3535

Table 16 Annual death rates per 100,000 for women in 9 countries* in Eastern Europe by age

Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Cardiomyopathy/CHF	0.6	0.7	0.9	1.4	2.8	4.8	8.4	16.6	30.9	52.4	97.1	189.8	428.5
Ischaemic HD	0.1	0.3	0.6	0.5	2.1	5.6	11.5	22.7	46.0	87.8	163.1	323.3	666.5
Valvular disease	0.1	0.0	0.1	0.1	0.1	0.3	0.4	0.7	1.0	3.3	6.2	13.7	26.3
Other cardiac diseases	0.2	0.5	0.8	1.1	1.6	2.7	4.3	8.8	14.6	23.3	40.1	71.7	143.6
<i>All Cardiac diseases</i>	1.0	1.6	2.4	3.1	6.5	13.4	24.5	48.7	92.5	166.9	306.4	598.5	1264.9
<i>All causes of death</i>	44.4	48.6	60.0	79.7	136.7	235.8	408.6	705.3	1116.4	1726.7	2633.0	4354.7	7868.0
Population (1000s)	2840	3393	3979	4146	4387	3952	3631	3384	3694	3418	2518	1695	1338

* Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia, Slovenia

Table 17 Annual death rates per 100,000 for men in 9 countries* in Eastern Europe by age

Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Cardiomyopathy/CHF	1.4	2.4	2.6	4.6	8.4	17.9	33.1	59.7	101.8	151.0	227.4	347.4	624.7
Ischaemic HD	0.0	0.4	1.4	3.9	9.3	24.7	56.9	109.8	191.0	304.0	448.2	704.1	1093.8
Valvular disease	0.2	0.0	0.1	0.4	0.4	0.6	0.7	1.6	3.8	6.6	11.2	18.4	30.7
Other cardiac diseases	0.9	1.1	2.0	3.9	5.6	9.9	16.3	28.8	43.5	67.2	88.3	137.0	208.1
<i>All Cardiac diseases</i>	2.5	3.8	6.1	12.8	23.7	53.1	107.1	199.9	340.1	528.8	775.1	1207.0	1957.4
<i>All causes of death</i>	102.7	168.5	176.9	230.9	332.6	560.3	968.4	1687.4	2732.8	4085.3	5766.4	8560.5	12949.0
Population (1000s)	2840	3393	3979	4146	4387	3952	3631	3384	3694	3418	2518	1695	1338

* Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Slovakia, Slovenia

Table 18 Annual death rates per 100,000 for women in Japan by age

Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Cardiomyopathy/CHF	0.3	0.3	0.4	0.7	0.7	1.2	2.0	2.7	4.0	8.2	12.8	30.6	78.8
Ischaemic HD	0.1	0.1	0.2	0.5	0.9	1.7	3.2	5.1	8.6	15.3	26.8	55.0	115.9
Valvular disease	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.4	0.6	1.7	3.9	10.4
Other cardiac diseases	0.2	0.3	0.5	0.8	1.0	1.6	2.2	2.9	4.8	8.3	13.6	27.0	58.4
<i>All Cardiac diseases</i>	0.6	0.7	1.1	1.9	2.6	4.5	7.5	10.8	17.8	32.3	54.9	116.5	263.5
<i>All causes of death</i>	27.5	46.4	61.8	82.3	110.4	158.9	238.8	356.0	504.6	766.2	1120.6	1890.1	3577.9
Population (1000s)	4517	4491	4717	5554	6140	6987	6262	5977	5538	5778	5728	5213	4230

Table 2. Annual death rates per 100,000 for men in Japan by age

Disease category	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Cardiomyopathy/CHF	0.6	0.9	0.9	1.5	2.1	3.5	5.3	7.9	12.6	21.8	33.7	61.1	125.3
Ischaemic HD	0.1	0.5	1.0	2.1	4.6	10.2	16.7	28.9	41.3	69.6	94.9	142.1	231.9
Valvular disease	0.0	0.1	0.0	0.0	0.0	0.1	0.2	0.4	0.7	1.3	3.1	6.3	13.7
Other cardiac diseases	0.7	1.1	1.2	2.2	2.9	4.8	7.7	12.1	17.3	26.6	34.8	53.6	97.2
<i>All Cardiac diseases</i>	1.4	2.6	3.1	5.8	9.7	18.6	29.9	49.3	71.9	119.3	166.4	263.1	468.1
<i>All causes of death</i>	57.6	103.0	119.9	148.4	191.9	298.9	475.6	770.8	1165.3	1847.1	2738.8	4424.1	7557.6
Population (1000s)	4853	4847	4972	5767	6350	7218	6412	6048	5490	5566	5299	4453	3238

Section 3 Allocation of all cardiac diseases in subcategories

Allocation of cardiac disease in the group of ischemic heart disease (IHD), valvular heart disease (VHD) or congestive heart failure (CHF). The “other cardiac” disease were also allocated as described in Chapter 4 as: other cardiac_IHD, other cardiac_CHF and other cardiac_VHD for the purpose of estimating cardiac mortality. The allocation was performed by a clinician according to disease characteristics.

ICD_10	Description	Group allocated
I200	Unstable angina	IHD
I201	Angina pectoris with documented spasm	IHD
I209	Angina pectoris, unspecified	IHD
I210	ST elevation (STEMI) myocardial infarction of anterior	IHD
I213	ST elevation (STEMI) myocardial infarction of unspecified	IHD
I214	Non-ST elevation (NSTEMI) myocardial infarction	IHD
I219	Non-ST elevation (NSTEMI) myocardial infarction	IHD
I229	Subsequent STEMI of unspecified site	IHD
I248	Other forms of acute ischemic heart disease	IHD
I249	Acute ischemic heart disease, unspecified	IHD
I250	Chronic ischemic heart disease	IHD
I251	Atherosclerotic heart disease of native coronary artery	IHD
I253	Aneurysm of heart	IHD
I254	Coronary artery aneurysm and dissection	IHD
I255	Ischemic cardiomyopathy	IHD
I258	Other forms of chronic ischemic heart disease	IHD
I259	Chronic ischemic heart disease, unspecified	IHD
I050	Rheumatic mitral stenosis	VHD
I051	Rheumatic mitral insufficiency	VHD
I052	Rheumatic mitral stenosis with insufficiency	VHD
I058	Other rheumatic mitral valve diseases	VHD
I059	Rheumatic mitral valve disease, unspecified	VHD
I060	Rheumatic aortic stenosis	VHD
I061	Rheumatic aortic insufficiency	VHD
I069	Rheumatic aortic valve disease, unspecified	VHD
I070	Rheumatic tricuspid stenosis	VHD
I071	Rheumatic tricuspid insufficiency	VHD
I078	Other rheumatic tricuspid valve diseases	VHD

I079	Rheumatic tricuspid valve disease, unspecified	VHD
I080	Rheumatic disorders of both mitral and aortic valves	VHD
I081	Rheumatic disorders of both mitral and tricuspid val	VHD
I082	Rheumatic disorders of both aortic and tricuspid val	VHD
I083	Comb rheumatic disord of mitral, aortic and tricuspi	VHD
I088	Other rheumatic multiple valve diseases	VHD
I089	Rheumatic multiple valve disease, unspecified	VHD
I091	Rheumatic diseases of endocardium, valve unspecified	VHD
I340	Nonrheumatic mitral (valve) insufficiency	VHD
I341	Nonrheumatic mitral (valve) prolapse	VHD
I342	Nonrheumatic mitral (valve) stenosis	VHD
I348	Other nonrheumatic mitral valve disorders	VHD
I350	Nonrheumatic aortic (valve) stenosis	VHD
I351	Nonrheumatic aortic (valve) insufficiency	VHD
I352	Nonrheumatic aortic (valve) stenosis with insufficie	VHD
I358	Other nonrheumatic aortic valve disorders	VHD
I359	Nonrheumatic aortic valve disorder, unspecified	VHD
I361	Nonrheumatic tricuspid (valve) insufficiency	VHD
I371	Nonrheumatic pulmonary valve insufficiency	VHD
I379	Nonrheumatic pulmonary valve disorder, unspecified	VHD
I38	Endocarditis, valve unspecified	VHD
I090	Rheumatic myocarditis	CHF
I10	Essential (primary) hypertension	CHF
I110	Hypertensive heart disease with heart failure	CHF
I130	Hyp hrt & chr kdny dis w hrt fail and stg 1-4/unsp c	CHF
I132	Hyp hrt & chr kdny dis w hrt fail and w stg 5 chr kd	CHF
I400	Infective myocarditis	CHF
I401	Isolated myocarditis	CHF
I408	Other acute myocarditis	CHF
I409	Acute myocarditis, unspecified	CHF
I420	Dilated cardiomyopathy	CHF
I421	Obstructive hypertrophic cardiomyopathy	CHF
I422	Other hypertrophic cardiomyopathy	CHF
I423	Endomyocardial (eosinophilic) disease	CHF
I424	Endocardial fibroelastosis	CHF
I425	Other restrictive cardiomyopathy	CHF
I426	Alcoholic cardiomyopathy	CHF
I427	Cardiomyopathy due to drug and external agent	CHF
I428	Other cardiomyopathies	CHF
I429	Cardiomyopathy, unspecified	CHF
I500	Heart failure	CHF
I514	Myocarditis, unspecified	CHF

I515	Myocardial degeneration	CHF
I517	Cardiomegaly	CHF
I099	Rheumatic heart disease, unspecified	OTH_IHD
I119	Hypertensive heart disease without heart failure	OTH_IHD
I131	Hypertensive heart and chronic kidney disease w/o hr	OTH_IHD
I139	Hyp hrt & chr kdny dis w hrt fail and w stg 5 chr kd	OTH_IHD
I510	Cardiac septal defect, acquired	OTH_IHD
I511	Rupture of chordae tendineae, not elsewhere classifi	OTH_IHD
I513	Intracardiac thrombosis, not elsewhere classified	OTH_IHD
I516	Myocardial degeneration	OTH_IHD
I518	Other ill-defined heart diseases	OTH_IHD
I519	Heart disease, unspecified	OTH_IHD
I010	Acute rheumatic pericarditis	OTH_VHD
I018	Other acute rheumatic heart disease	OTH_VHD
I019	Acute rheumatic heart disease, unspecified	OTH_VHD
I270	Primary pulmonary hypertension	OTH_VHD
I271	Kyphoscoliotic heart disease	OTH_VHD
I272	Other secondary pulmonary hypertension	OTH_VHD
I278	Other specified pulmonary heart diseases	OTH_VHD
I279	Pulmonary heart disease, unspecified	OTH_VHD
I300	Acute nonspecific idiopathic pericarditis	OTH_VHD
I301	Infective pericarditis	OTH_VHD
I308	Other forms of acute pericarditis	OTH_VHD
I309	Acute pericarditis, unspecified	OTH_VHD
I310	Chronic adhesive pericarditis	OTH_VHD
I311	Chronic constrictive pericarditis	OTH_VHD
I312	Hemopericardium, not elsewhere classified	OTH_VHD
I313	Pericardial effusion (noninflammatory)	OTH_VHD
I319	Disease of pericardium, unspecified	OTH_VHD
I330	Acute and subacute infective endocarditis	OTH_VHD
I339	Acute and subacute endocarditis, unspecified	OTH_VHD
I440	Atrioventricular block, first degree	OTH_CHF
I441	Atrioventricular block, second degree	OTH_CHF
I442	Atrioventricular block, complete	OTH_CHF
I443	Other and unspecified atrioventricular block	OTH_CHF
I447	Left bundle-branch block, unspecified	OTH_CHF
I451	Other and unspecified right bundle-branch block	OTH_CHF
I453	Trifascicular block	OTH_CHF
I454	Nonspecific intraventricular block	OTH_CHF
I455	Other specified heart block	OTH_CHF
I456	Pre-excitation syndrome	OTH_CHF
I458	Other specified conduction disorders	OTH_CHF

I459	Conduction disorder, unspecified	OTH_CHF
I461	Cardiac arrest	OTH_CHF
I469	Cardiac arrest, cause unspecified	OTH_CHF
I470	Re-entry ventricular arrhythmia	OTH_CHF
I471	Supraventricular tachycardia	OTH_CHF
I472	Ventricular tachycardia	OTH_CHF
I489	Unspecified atrial fibrillation and atrial flutter	OTH_CHF
I490	Ventricular fibrillation and flutter	OTH_CHF
I491	Atrial premature depolarization	OTH_CHF
I495	Sick sinus syndrome	OTH_CHF
I498	Other specified cardiac arrhythmias	OTH_CHF
I499	Cardiac arrhythmia, unspecified	OTH_CHF