

# RADIATION-RELATED CARDIOVASCULAR DISEASE FOLLOWING CANCER THERAPY

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## **Abstract**

### **Introduction**

Some cancer survivors are known to have an elevated risk of morbidity and mortality from cardiovascular disease. An important cause of this elevated risk is recognised to be irradiation of normal tissues during radiotherapy received as part of cancer therapy. There are substantial difficulties in studying radiation-related cardiovascular disease (RRCD). The reasons for this include the complexities of measuring radiation normal tissue doses retrospectively and the prolonged latencies of many of the cardiovascular endpoints. A variety of complimentary research methodologies can help provide additional knowledge to guide the appropriate management of patients treated in the past and of new patients in the future.

### **Methods**

1) A cohort study of mortality from circulatory disease in the nationwide British Childhood Cancer Survivor Study (BCCSS). 2) A case-control study of valvular heart disease (VHD) in Dutch Hodgkin lymphoma (HL) survivors, including retrospective radiation dosimetry to estimate the radiation dose to heart valves. 3) A dosimetric study of cardiovascular radiation doses in patients entered into the UK NCRI Lymphoma Study Group RAPID trial, including predictions of 15-year cardiac mortality using innovative methods. 4) A modelling study to predict mean whole heart dose (MWHd) from involved field radiotherapy (IFRT) for HL using anatomical measures. 5) A prospective study using cardiovascular magnetic resonance (CMR) imaging to characterise the heart in women receiving radiotherapy for breast cancer.

### **Results**

1) The risks of all types of circulatory mortality are elevated in survivors of childhood cancer. The absolute excess risks continue to increase 40+ years following diagnosis. The risk of death from cardiomyopathy and heart failure increased substantially with the introduction of anthracycline chemotherapy. There is no evidence of a reduction in risk of circulatory mortality in more recent eras of diagnosis. 2) There is a strong relationship between estimated radiation dose to the affected heart valve and the risk of subsequent VHD ( $p < 0.001$ ). This effect was modelled to allow prediction of the risk of VHD. 3) A proportion of patients treated with IFRT received a substantial cardiac radiation dose (MWHd = 8.8 Gy, SD = 5.6) but, on average, the predicted 15-year cardiac mortality following treatment is low (absolute risk 0.2%, range 0.0 to 2.7%). 4) It is possible to estimate the mean whole heart dose from IFRT prior to detailed radiotherapy planning based on pre-treatment diagnostic imaging to an accuracy of 5-6% of the prescribed dose. 5) Although women received low cardiac doses (MWHd = 1.5 Gy, SD = 0.8) and have a low predicted risk of cardiac radiation-related morbidity and mortality, there is some evidence of subclinical effects on strain and strain rate imaging of the anterior portions of the left ventricle that receive the highest radiation dose.

### **Conclusions**

Using a variety of methods these studies have all succeeded in adding to knowledge about the nature, magnitude and timing of RRCD. This knowledge can be used to help the future management of cancer patients. In addition, each of the studies has natural and planned extensions and will continue to contribute further knowledge into the future.

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## **List of Abbreviations**

|                   |                                                    |
|-------------------|----------------------------------------------------|
| AAA               | anisotropic analytic algorithm                     |
| ACE               | angiotensin-converting enzyme                      |
| ACT               | anthracycline chemotherapy                         |
| AER               | absolute excess risk                               |
| ALL               | acute lymphoblastic leukaemia                      |
| AMI               | acute myocardial infarction                        |
| AML               | acute myeloid leukaemia                            |
| Ang II            | angiotensin II                                     |
| ANP               | atrial natriuretic peptide                         |
| AR                | angiotensin receptor                               |
| AT <sub>1</sub> R | angiotensin II subtype 1 receptor                  |
| AT <sub>2</sub> R | angiotensin II subtype 2 receptor                  |
| AVN               | atrioventricular node                              |
| BC                | breast cancer                                      |
| BCCSS             | British Childhood Cancer Survivor Study            |
| bFGF              | basic fibroblast growth factor                     |
| BMP-2             | bone morphogenic protein 2                         |
| BNP               | brain natriuretic peptide                          |
| BSA               | body surface area                                  |
| CABG              | coronary artery bypass grafting                    |
| CAD               | coronary artery disease                            |
| CGRP              | calcitonin gene related peptide                    |
| CHD               | coronary heart disease                             |
| CHF               | congestive heart failure                           |
| ChT               | chemotherapy                                       |
| CI                | confidence interval                                |
| CM/HF             | cardiomyopathy and heart failure                   |
| CMR               | cardiovascular magnetic resonance                  |
| CNS               | central nervous system                             |
| CT                | computed tomography                                |
| CTCAE             | Common Terminology Criteria for Adverse Events     |
| CTGF              | connective tissue growth factor                    |
| DCIS              | ductal carcinoma in-situ                           |
| DICOM             | Digital Imaging and Communications in Medicine     |
| DNA               | deoxyribonucleic acid                              |
| DVH(s)            | dose volume histogram(s)                           |
| EBCTCG            | Early Breast Cancer Trialists' Collaborative Group |
| EBR               | expected background rate                           |
| EC                | endothelial cell                                   |
| ECG               | electrocardiogram                                  |
| EFRT              | extended field radiotherapy                        |
| EOR(s)            | excess odds ratio(s)                               |
| EPCs              | endothelial progenitor cells                       |
| EQD <sub>2</sub>  | equivalent dose in 2 Gy fractions                  |
| ER                | oestrogen receptor                                 |
| ERR               | excess relative risk                               |
| FDG               | fluorodeoxyglucose                                 |
| FU                | follow-up                                          |
| GCT               | germ cell tumour                                   |

|                |                                                      |
|----------------|------------------------------------------------------|
| GPOH           | German Society of Paediatric Oncology                |
| Gy             | Gray                                                 |
| HDL            | high density lipoprotein                             |
| HER2           | human epidermal growth factor receptor 2             |
| HGF            | hepatocyte growth factor                             |
| HL             | Hodgkin lymphoma                                     |
| HR             | hazard ratio                                         |
| ICAM-1         | intracellular adhesion molecule 1                    |
| ICD            | International Classification of Diseases             |
| IFRT           | involved field radiotherapy                          |
| IGF            | insulin-like growth factor                           |
| IHD            | ischaemic heart disease                              |
| IL             | interleukin                                          |
| IMC            | internal mammary chain                               |
| IMRT           | intensity modulated radiotherapy                     |
| INRT           | involved node radiotherapy                           |
| ISRT           | involved site radiotherapy                           |
| LAD            | left anterior descending                             |
| LENT           | late effects of normal tissues                       |
| LGE            | late gadolinium enhancement                          |
| LKB            | Lyman-Kucher-Burman                                  |
| LV             | left ventricle/left ventricular                      |
| LVEF           | left ventricular ejection fraction                   |
| LVEDV          | left ventricular end diastolic volume                |
| LVESV          | left ventricular end systolic volume                 |
| LQ             | linear quadratic                                     |
| MAE            | median absolute error                                |
| MCP-1          | monocyte chemotactic protein 1                       |
| MLCs           | multi-leaf collimators                               |
| MRE            | median relative error                                |
| mRNA           | messenger ribonucleic acid                           |
| MU(s)          | monitoring unit(s)                                   |
| MV             | megavoltage                                          |
| MWHD           | mean whole heart dose                                |
| NB             | neuroblastoma                                        |
| NCNSGTC        | non-central nervous system germ cell tumour          |
| NCRI           | National Cancer Research Institute                   |
| NF- $\kappa$ B | nuclear factor kappa beta                            |
| NHL            | non Hodgkin lymphoma                                 |
| NICE           | National Institute of Health and Clinical Excellence |
| NO             | nitric oxide                                         |
| NOS            | nitrogen oxide species                               |
| NTCP           | normal tissue complication probability               |
| NT-proBNP      | N-terminal pro-B-type natriuretic peptide            |
| O/E            | observed/expected                                    |
| OR(s)          | odds ratio(s)                                        |
| PDGF           | platelet-derived growth factor                       |
| PDI            | phosphodiesterase inhibitor                          |
| PECAM-1        | platelet endothelial cell adhesion molecule 1        |
| PET            | positron emission tomography                         |
| PFS            | progression-free survival                            |



|                  |                                                  |
|------------------|--------------------------------------------------|
| PNET             | primitive neuroectodermal tumour                 |
| PPAR $\gamma$    | peroxisome proliferator-activated receptor gamma |
| PTV              | planning target volume                           |
| PTX              | pentoxifylline                                   |
| PGI <sub>2</sub> | prostacycline                                    |
| PYs FU           | person years follow-up                           |
| RAA              | renin-angiotensin-aldosterone                    |
| RB               | retinoblastoma                                   |
| RMSEP            | root mean square error prediction                |
| RNS              | reactive nitrogen oxide species                  |
| ROCK             | Rho-associated protein kinase                    |
| ROS              | reactive oxygen species                          |
| RR               | relative risk                                    |
| RS               | relative seriality                               |
| RSD              | relative standard deviation                      |
| RRCD             | radiation-related cardiovascular disease         |
| RRPD             | radiation-related pericardial disease            |
| RT               | radiotherapy                                     |
| SAN              | sino-atrial node                                 |
| SBP              | systolic blood pressure                          |
| SCF              | supraclavicular fossa                            |
| SD               | standard deviation                               |
| SE               | standard error                                   |
| SI               | signal intensity                                 |
| SMR              | standardised mortality ratio                     |
| SOD              | superoxide dismutase                             |
| SPECT            | single-photon emission computed tomography       |
| SRI              | strain rate imaging                              |
| STIR             | short-tau inversion recovery                     |
| STS              | soft tissue sarcoma                              |
| SV               | stroke volume                                    |
| TBI              | total body irradiation                           |
| TGF- $\beta$ 1   | transforming growth factor beta one              |
| TIA              | transient ischaemic attack                       |
| TM               | thrombomodulin                                   |
| TNF- $\alpha$    | tumour necrosis factor alpha                     |
| TnI              | troponin I                                       |
| tPA              | tissue plasminogen activator                     |
| TPS              | treatment planning system                        |
| US               | United States                                    |
| USCCS            | United States Childhood Cancer Survivor Study    |
| VCAM-1           | vascular cell adhesion molecule 1                |
| VEGF             | vascular endothelial growth factor               |
| VHD              | valvular heart disease                           |
| WH               | whole heart                                      |
| WT               | Wilms' tumour                                    |
| XO               | xanthine oxidase                                 |
| 3-D              | three-dimensional                                |

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For Mum

## **General Introduction**

### **Radiation-Related Cardiovascular Disease Following Cancer Therapy**

The success of modern multi-modality cancer therapy, combined with a general improvement in life expectancy, has resulted in an increasing number of people surviving more than 5 years from a cancer diagnosis. It has been estimated that by the end of 2008 there were more than 2 million cancer survivors in the UK alone.<sup>1</sup> Whilst improvements in survival rates are obviously to be welcomed, it is increasingly recognised that many cancer survivors are at an elevated risk of morbidity and mortality from a variety of causes. This is partly as a consequence of the treatments that they have received to cure their cancer. Cardiovascular disease is one such consequence, resulting in a substantial proportion of the burden of excess illness and death observed.

There is compelling evidence that ionising radiation can give rise to an increased risk of cardiovascular morbidity and mortality following the successful treatment of various types of cancer.<sup>2</sup> This evidence has come from a number of independent sources including randomised trials and observational studies in breast cancer,<sup>3,4</sup> childhood cancer<sup>5</sup> and Hodgkin lymphoma (HL).<sup>6</sup> Worldwide, an estimated 50 million cancer survivors have been treated with radiotherapy (RT),<sup>7</sup> a substantial proportion of whom will be at increased risk. Whilst it is certain that radiation techniques from previous decades resulted in substantially elevated risks, it is less certain what risk current treatment regimens pose. Due to improvements in RT techniques and, in some cases, reduction in prescribed radiation doses, contemporary treatments generally result in lower radiation doses to cardiovascular structures than those that occurred historically.<sup>8,9</sup> However, uncertainty remains regarding the magnitude of risk from lower radiation doses. There is also substantial uncertainty regarding the cardiovascular damage that may be caused by the combination of RT and systemic therapies and the extent of any interaction between them.<sup>10</sup> It remains likely that a proportion of patients treated today will still

experience an increased cardiovascular risk as a result of incidental radiation exposure of the cardiovascular system. Further research is needed in order to make decisions for these patients regarding the optimal use of RT as part of their treatment and the appropriate follow-up required for survivors.

A practical difficulty in studying radiation-related cardiovascular disease (RRCD) is that the latency between exposure and clinically evident disease is often prolonged. For example an increased risk of cardiac death in left-sided breast cancer patients treated with radiotherapy may not become apparent until more than 10 years from diagnosis.<sup>11</sup> The latency for some individual conditions can be even longer, for example the median time to diagnosis of valvular disease following mediastinal radiotherapy for HL has been reported as 22 years.<sup>12</sup> There are three possible approaches to studying adverse effects with such prolonged latencies. The first is to study previously established cohorts with already prolonged follow-up. A substantial difficulty with this approach is that the radiotherapy in the majority of such cohorts was performed prior to the development of three-dimensional (3-D) computed tomography (CT)-based radiotherapy planning. Assessment of historical radiation exposures received by specific cardiovascular structures requires the development of methods to retrospectively estimate doses received in the past, where individual 3-D anatomical data are not available. The second approach is to investigate the use of early surrogate markers of later cardiovascular disease that could be useful clinically and in the further study of RRCD. A third approach is the recording of contemporary cardiovascular radiation exposures (and other relevant exposures) within cohorts that can be followed prospectively for the future occurrences of late cardiovascular events. The first three chapters of this thesis review what is currently known about RRCD in terms of the clinical manifestations, pathogenesis and the relationships between radiation dose and risk. The following 5 chapters present original studies, utilising elements of the three approaches to the

investigation of RRCD described above, to produce new knowledge relating to RRCD following cancer therapy.

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## **Chapter 1 - Clinical Manifestations, Pathology and Treatment of Radiation-Related Cardiovascular Disease**

### **Introduction**

The study of radiation-related cardiovascular disease (RRCD) is complicated by the wide spectrum of clinical and pathological manifestations that may occur as a consequence of irradiation of the cardiovascular system. It is therefore useful to start off by summarising how RRCD may present to the physician, clinically and pathologically, and how it is currently treated. For this purpose RRCD can be considered in 7 categories; coronary artery disease (CAD), cardiomyopathy, valvular heart disease (VHD), pericardial disease, conduction system abnormalities, cerebrovascular disease and peripheral vascular disease. Vascular damage can indirectly impair the function of all organ systems and tissues by the restriction of blood flow and hypoxia. However this thesis concentrates primarily on the adverse effects of radiation on the cardiovascular system itself and, therefore, the adverse effects of vascular damage on other tissues and organs are not described in this chapter.

### **Coronary Artery Disease**

Irradiation of the coronary arteries is known to increase the risk of CAD.<sup>1</sup> The manifestations of radiation-related CAD are generally similar to those due to age-related atherosclerotic CAD, but there are some notable clinical and pathological differences. Clinically, patients irradiated during childhood or early adulthood may present with CAD at a much younger age than would be expected for CAD due to other causes and they may not have conventional cardiac risk factors.<sup>2</sup> Radiation-related damage to the autonomic system innervating the heart may also result in 'silent' ischaemia, where patients present atypically without chest pain, as has been commonly observed in patients with diabetic neuropathy. In the past, the pathology of radiation-related atherosclerosis has been described as resembling age-related disease. More recently, detailed pathological studies of human arteries have revealed qualitative and

quantitative differences, with variations in intima-media wall thickness and collagen, proteoglycan and inflammatory cell contents.<sup>3</sup> Animals models also suggest that radiation-induced disease may be more prone to rupture and subsequent thrombotic complications.<sup>4</sup> The anatomical distribution of radiation-related CAD differs from age-related disease with a predisposition for sections of the coronary arteries that absorbed the highest dose of radiation. For example isolated coronary ostial narrowing, although rare in spontaneous disease, has been reported following irradiation for Hodgkin lymphoma where the proximal coronary arteries commonly receive the highest dose.<sup>5</sup> Also, the left anterior descending artery is more commonly diseased than would be expected in the general population following tangential irradiation for left breast cancer, where this artery receives the highest dose.<sup>6,7</sup>

Medical treatment for radiation-related CAD does not currently differ from that used for CAD due to other causes. Conventional cardiac risk factors, such as smoking, hypertension and hypercholesterolaemia, are known to increase the risk of CAD above that of radiation-alone,<sup>8-10</sup> and therefore early and aggressive management of these risk factors should be recommended in patients with a history of cardiac irradiation or radiation-related disease.<sup>11</sup> Surgical treatment with coronary artery bypass grafting (CABG) can be successful for radiation-related CAD but may be complicated by associated tissue damage from radiation. Connective tissue fibrosis within the mediastinum makes surgery technically more challenging and myocardial and pulmonary fibrosis may increase the probability of peri-operative morbidity. The internal mammary artery is commonly used as a donor artery for CABG and may lie in the irradiated volume making it also vulnerable to damage, but available evidence suggests that this artery may still be used safely if patent at the time of the procedure.<sup>12</sup> Prior to CABG for radiation-related CAD it is vital that a thorough assessment of all aspects of cardiac function is undertaken, as it is not uncommon for radiation-related CAD to co-exist with other radiation-related cardiac complications such as pericardial or valvular disease. Any synchronous pathology which is likely to require future



intervention with cardiac surgery should be considered at the same time as CABG, as later procedures through the irradiated field will become increasingly difficult due to radiation-induced and surgical scarring.<sup>11</sup> Immediate outcomes following CABG for radiation-related CAD are good, but late survival may be limited by further cardiac morbidity and recurrent or second malignancies.<sup>13</sup>

### **Cardiomyopathy**

Clinically evident radiation-related cardiomyopathy is rare following radiation alone except following irradiation of large volumes of the myocardium to high doses (>30 Gy), which is unusual for most radiotherapy (RT) regimens since the 1970s. It is more common nowadays to see clinically evident cardiomyopathy primarily due to anthracycline chemotherapy and perhaps exacerbated by irradiation. In individual cases the manifestations seen depend on the dose and volume of cardiac irradiation, the presence or absence of anthracycline toxicity, and the age of the patient at irradiation. Irradiation of a large volume of the heart to high dose without anthracycline chemotherapy leads to a restrictive cardiomyopathy due to widespread fibrosis, which may occur in combination with constrictive pericardial disease. The combination of anthracyclines and radiotherapy more commonly produces a progressive dilated cardiomyopathy. Irradiation at a young age however, whilst the heart is still growing and developing, may increase the risk of a restrictive pattern of disease. Subclinical radiation-related myocardial damage is much more common than clinically-evident cardiomyopathy. Asymptomatic diastolic dysfunction, detected by echocardiography, has been linked with an increased risk of later cardiac events<sup>14</sup> which indicates that, whilst not clinically evident, such changes may still be clinically relevant. The microvasculature of the myocardium is known to be damaged by relatively small volumes of cardiac irradiation as demonstrated using nucleotide imaging, but the clinical significance of these findings is currently unknown.<sup>15</sup>

The characteristic pathological change seen in irradiated myocardium is diffuse interstitial fibrosis with bands of collagen separating and replacing myocytes. An increase in the ratio of type I to type III collagen has been reported,<sup>16</sup> which is suggested to reduce myocardial compliance and contribute to diastolic dysfunction.

Treatment for radiation-related cardiomyopathy is as for other causes of heart failure. Systolic dysfunction is treated with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and aldosterone antagonists as normally indicated. For patients with end-stage heart failure, orthotopic heart transplant is technically possible, but is undertaken with caution (especially in adults) due to the high risk of peri-operative complications and second malignancies in these patients.<sup>17</sup> There is no evidence that the treatment of subclinical systolic or diastolic dysfunction due to radiation with, for example, ACE inhibitors improves prognosis. However, given that subclinical abnormalities can be identified, and that a proportion of patients progress to develop clinical heart failure, there is a potential for pharmacological intervention in this condition.

### **Valvular Heart Disease**

Radiation-related VHD is often a very late complication of RT with a median time to clinical diagnosis of 22-23 years.<sup>8,18</sup> Although a larger study has recently reported evidence of an increased risk of VHD just 5-9 years after diagnosis.<sup>19</sup> The incidence is higher for left-sided heart valves (mitral and aortic) than the right-sided valves (tricuspid and pulmonary). It has been suggested that this is due to greater haemodynamic stresses present within the higher pressure left ventricle.<sup>20</sup> Valvular stenosis is more common than regurgitation,<sup>8</sup> although both occur and may often co-exist.<sup>21</sup> Subvalvular stenosis due to fibrosis of the mural endocardium may occur, but is rare.<sup>11</sup>

Valvular lesions described post-irradiation are non-specific with fibrotic thickening and calcification. Such lesions are pathologically indistinguishable from those due to other aetiologies, including rheumatic valvular disease, leading some previous authors to doubt the existence of radiation-induced VHD. The epidemiological evidence is convincing however, and detailed pathological studies are planned to more accurately characterise radiation-related VHD (FA Stewart, personal communication) that may describe differences from other VHD, as recently described for radiation-related CAD.<sup>3</sup>

Where valvular dysfunction is severe enough to warrant surgical treatment, outcomes are often good except in the presence of constrictive pericarditis or cardiomyopathy.<sup>22</sup> Valve replacement should be preferred to repair however, as repairs appear to have limited durability when performed on irradiated structures.<sup>23</sup>

### **Pericardial Disease**

Historically, radiation-related pericardial disease (RRPD) was the first manifestation of RRCD to be documented following mediastinal irradiation for Hodgkin lymphoma (HL). During the 1960s and 1970s, pericarditis was reported in 25-60% of patients treated for HL with mediastinal RT.<sup>24</sup> Due to changes in RT techniques the incidence of RRPD has fallen and it is now relatively rare.<sup>25,26</sup> Radiation of the pericardium can cause acute and/or chronic pericarditis, often with associated pericardial effusion, and may result in late pericardial constriction. Radiation-induced acute pericarditis occurs several weeks following RT. It can occasionally occur earlier, during the course of treatment, in which case it is usually related to the irradiation of a large tumour adjacent to the heart where inflammation and necrosis of the tumour due to RT directly irritates the pericardium. Later-onset radiation-induced chronic pericarditis may occur following an initial episode of acute pericarditis or may occur without prior manifestations. The clinical presentation of radiation-induced pericarditis is similar to that due to other causes, with

pleuritic chest pain, tachycardia, fever, pericardial friction rub and ECG changes. Echocardiography or other imaging may demonstrate an associated pericardial effusion. Alternative aetiologies for any pericardial thickening or effusion such as malignant effusion, infection or hypothyroidism (which may be induced by thyroid irradiation) should be excluded before making a diagnosis of radiation-induced disease. Radiation-related constrictive pericardial disease presents as that due to other aetiologies with symptoms of heart failure.

The characteristic pathological change seen in the pericardium post-irradiation is fibrosis. The visceral and parietal pericardium are both thickened, with the outer parietal layer more severely affected and the external adipose layer also replaced by dense fibrotic tissue. In contrast to other causes of pericarditis it is uncommon to see adhesions between the visceral and parietal pericardium due to radiation-induced disease. Effusion associated with radiation-related pericarditis tends to be protein rich.<sup>27</sup>

The majority of cases of radiation-induced pericarditis resolve spontaneously and are usually managed symptomatically with non-steroidal anti-inflammatory drugs. Colchicine may be beneficial as adjunctive therapy, while glucocorticoids may be associated with recurrent pericarditis and should be reserved for specific aetiologies such as autoimmune or uraemic pericarditis.<sup>28</sup> Occasionally an associated pericardial effusion may accumulate quickly enough to cause cardiac tamponade and necessitate urgent pericardiocentesis to prevent acute compromise of cardiac function and death. Persistent or recurrent effusion large enough to cause symptoms may be managed by pericardiocentesis, pericardial window formation or surgical pericardiectomy. Mild constrictive disease may be managed medically in the first instance, for example with diuretics for oedema, although it has been argued that early subtotal pericardiectomy may prevent the progression to more severe constrictive disease.<sup>29</sup> Severe pericardial constriction may be managed with total pericardiectomy, although the

prognosis is significantly worse for radiation-induced constrictive pericarditis than for non-radiation-induced disease, presumably partially due to concomitant underlying cardiomyopathy.<sup>30,31</sup>

### **Conduction System Abnormalities**

A wide variety of conduction defects have been described following mediastinal irradiation. These include supraventricular arrhythmias, junctional disorders (including all degrees of heart block), prolonged QTc interval and ventricular defects (such as bundle branch blocks and ventricular ectopic beats).<sup>11</sup> Pathologically, the cause of radiation-related conduction defects appears to be fibrotic scarring as a consequence of ischaemia secondary to both micro- and macrovascular damage. The more severe radiation-related conduction defects tend to occur concomitantly with other forms of radiation-related heart disease such as CAD.<sup>32</sup> Persistent invariant tachycardia has also been described and is presumed to be secondary to damage to the autonomic nerves that normally regulate heart rate.<sup>33</sup> Minor ECG abnormalities, such as T-wave changes, have been described acutely post-irradiation, but appear to resolve spontaneously without clinical consequence.<sup>34</sup>

There are no specific recommendations for the treatment of radiation-related conduction abnormalities and they are usually managed as would be otherwise clinically indicated, for example with pacemaker implantation for symptomatic or high-grade atrioventricular block.<sup>11</sup>

### **Cerebrovascular Disease**

Irradiation of the cerebral vasculature, the carotid arteries, the aortic arch and the heart increases the risk of developing cerebrovascular disease.<sup>35,36</sup> The type of cerebrovascular disease varies depending on the vessels irradiated, the radiation dose and the age at irradiation. High dose irradiation of the brain itself can result in cerebral radionecrosis usually presenting

within the first year following RT,<sup>37</sup> the symptoms depending on the extent and location of necrosis. Irradiation of larger vessels of the head and neck increases the risk of transient ischaemic attacks (TIAs) and stroke.<sup>38</sup> The presentation of radiation-related TIAs and strokes mimics those due to naturally occurring atheromatous disease, although patients often present at a younger age than expected for cerebrovascular disease due to other causes and with less concurrent vascular disease at other sites. In a Dutch study, 36% of ischaemic events occurring following irradiation to the neck and chest for Hodgkin lymphoma were observed to be of cardiac origin,<sup>36</sup> suggesting that radiation-related damage to the heart including arrhythmias, myocardial dysfunction, valvular disease and endocardial damage may pre-dispose to intra-cardiac thrombosis and embolism. In contrast to cerebral radionecrosis, TIAs and strokes tends to occur late after RT with a median interval of >15 years,<sup>36,39</sup> but the range is wide occurring from 1 to 22 years after treatment.<sup>40</sup> A syndrome of stroke-like migraine attacks after RT (SMART syndrome) has recently been described,<sup>41</sup> the presumed pathphysiology of which is also vascular damage and dysfunction.<sup>42</sup> Cranial irradiation in childhood may also cause abnormal development of the cerebral vasculature, leading to a vasculopathy with a similar appearance to primary Moyamoya syndrome with netlike vessels and transdural anastomoses.<sup>43</sup> The adverse cognitive effects of cranial irradiation during childhood are also thought to be due, in part, to small vessel damage.<sup>44</sup>

Vessels of all sizes within the cerebrovasculature are sensitive to the effects of radiation. The smallest vessels (arterioles and capillaries) are the most vulnerable with radiation-induced endothelial cell injury leading to thrombotic occlusion and ischaemia, which may result in cerebral radionecrosis.<sup>45</sup> Medium and large-sized vessels exhibit a chronic occlusive vasculopathy with vascular wall thickening, atherosclerosis and stenosis.<sup>46,47</sup>

Management of cerebral radionecrosis may be conservative, with corticosteroid therapy alone, but often requires surgery for the management of raised intracranial pressure or rapid control of symptoms. The management of radiation-related TIA and stroke is generally as for other causes. No adequate trials have been performed to assess the use of standard medical treatment options in this specific circumstance. The roles of anti-platelet agents and statins, for example, remain unclear. Experience has demonstrated that intervention for carotid artery stenosis as for indications in non-radiation-related disease can be successful. Both open endarterectomy<sup>48</sup> and angioplasty with stenting<sup>49</sup> have been used for radiation-related disease. There are particular challenges with an open surgical approach after previous surgery and/or radiotherapy including pre-existing fibrosis, scarring and poor healing of irradiated tissue.<sup>50</sup> Disease may also be situated more proximally within the common carotid.<sup>51</sup> These factors may result in increased operative risk. Carotid artery stenting has been reported to have a higher rate of re-stenosis in radiation-related disease<sup>38</sup> and there remains some uncertainty and debate as to which is the optimum treatment approach. As the number of patients with radiation-related disease is insufficient to conduct a randomised trial of open endarterectomy versus carotid artery stenting, it has been suggested that the appropriate management should be decided by experts on an individual basis.<sup>50</sup>

### **Peripheral Vascular Disease**

The entire arterial tree is sensitive to the late effects of radiation and, although less well studied than cardiac damage and cerebrovascular disease, radiation-related peripheral vascular disease has also been described. Examples include; subclavian and axillary artery stenoses following neck irradiation,<sup>8,52</sup> renal and superior mesenteric artery stenoses following abdominal irradiation,<sup>53,54</sup> iliac and femoral disease following pelvic irradiation<sup>55,56</sup> and femoral and popliteal disease following RT for osteosarcoma.<sup>57</sup> The clinical manifestations depend on the site and severity of disease and include upper and lower extremity ischaemia, renal

hypertension and mesenteric ischaemia. The venous system is generally thought less sensitive to damage from irradiation but may also suffer late adverse effects, most commonly stenosis complicated by thrombosis.<sup>58</sup>

As with radiation-related CAD, the pathological lesions of radiation-related peripheral vascular disease in small and medium arteries are similar to age-related atherosclerosis. Distinguishing features are that they occur in atypical sites, in clear relation with known volumes of irradiation and with a severity of disease in contrast to the rest of the individual's (unirradiated) vasculature.<sup>59</sup> For larger arteries damage to the vasa vasorum, which supplies the arterial wall, becomes a more prominent pathological finding, resulting in ischaemic lesions of the vessel wall itself with characteristic morphological features that distinguish this radiation-related injury from spontaneous atherosclerosis.<sup>60</sup>

When vascular intervention is required, it has been suggested that percutaneous procedures rather than open surgery may be preferred due to the technical difficulties that arise through operating within a surgical field that is scarred and fibrotic due to the late effects to radiotherapy.<sup>61</sup> In the past however, open surgical revascularisation has been performed with good results<sup>59</sup> and the management of individual cases is best decided by a vascular surgeon with some experience of the condition. As for all forms of RRCD, good control of cardiovascular risk factors, such as hypertension, diabetes and hypercholesterolemia should be maintained, and anti-platelet therapy considered based on the severity of disease.<sup>61</sup>



## **Conclusion**

From these brief descriptions of RRCD it can be seen that the clinical and pathological effects of radiation on the cardiovascular system are extremely varied and, although much studied, remain incompletely understood. Of particular importance is whether and how radiation-related disease should be managed differently from similar diseases with alternative aetiologies.

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## **Chapter 2 - Cellular and Molecular Mechanisms of Radiation-Related Cardiovascular Disease**

### **Introduction**

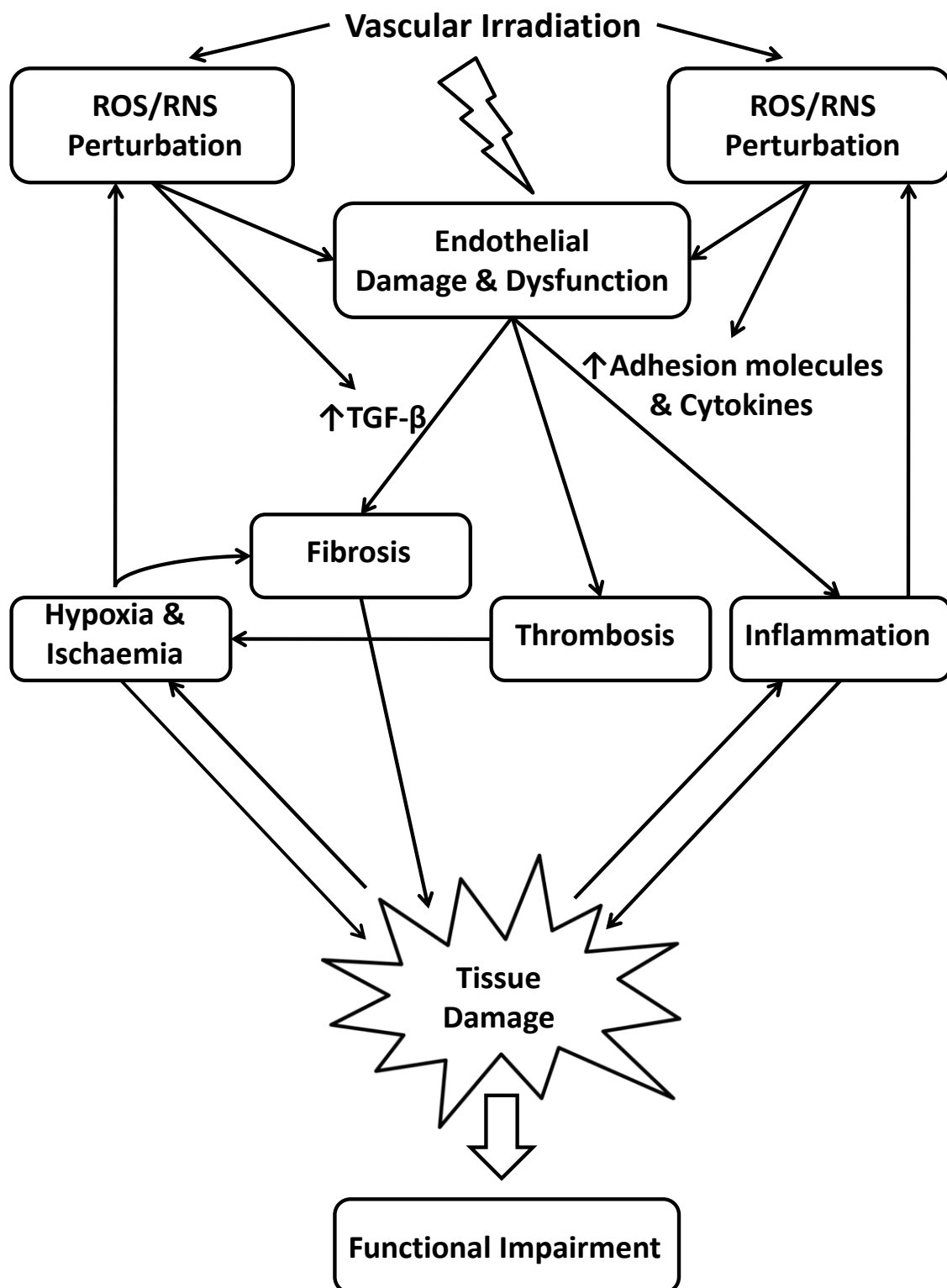
In contrast to the acute adverse effects of irradiation, where depletion of rapidly proliferating cells through cell death is the predominant mechanism of damage, the late adverse effects of irradiation arise through a wider variety of mechanisms.<sup>1</sup> The pathogenesis involves the interaction of various tissue components and multiple cell types including the endothelium, parenchyma, stroma, and immune system. Late adverse effects on the cardiovascular system are no exception and, although it is generally accepted that the main target in radiation-related cardiovascular disease is the endothelial cell (EC), the pathogenesis cannot be simply explained in terms of depletion of this cell type. There is experimental evidence that a range of cellular and molecular regulatory systems and mechanisms contribute to the development of radiation-related cardiovascular disease (RRCD). These mechanisms are summarised in this chapter.

### **Endothelial damage and dysfunction**

The endothelial cells (ECs) that line the vasculature are thought to be the primary target for all forms of microvascular and macrovascular RRCD.<sup>2</sup> Although the heart valve leaflets are avascular, they are also covered in endocardium composed of ECs which represents a target of irradiation<sup>3</sup> and may contribute to the development of fibrosis and calcification seen in radiation-related valve dysfunction. Rather than simply lining the vasculature and acting as a selectively permeable barrier, the vascular endothelium has many functions including the control of vascular tone and blood flow and the regulation of immune, inflammatory, thrombotic and coagulation responses.<sup>4</sup> Therefore the response of ECs to irradiation is central to understanding the mechanisms that underlie RRCD.

Much of the experimental evidence regarding the EC response to irradiation in the context of radiation-related heart disease pertains to microvascular damage within the myocardium. During animal experiments performed in the 1960s, it was observed using light microscopy that radiation damage to the heart muscle was preceded by alteration in capillary ECs.<sup>5,6</sup> These changes were later extensively described at the ultrastructural level using electron microscopy.<sup>7</sup> In response to irradiation, ECs swell and develop blebbing and extrusions. Vascular permeability is increased due to increased pinocytotic transport and widening of gap junctions, with transudation of serum components into the vessel wall causing sub-endothelial oedema. Leukocyte adhesion and extravasation and platelet sequestration are also seen. There is thickening of the basement membrane and foci of EC detachment cause exposure of the subendothelium. There is an increased proliferation of the remaining ECs, but this is inadequate to maintain microvascular function.<sup>8</sup> The end result of these observed changes is functional and physical capillary loss with narrowing, thrombosis, occlusion and a reduction in capillary density. This leads to parenchymal ischaemia initiating and exacerbating tissue injury with myocardial cell death and subsequent fibrosis.

Whilst the pattern of endothelial response to irradiation described above has been recognised for more than 40 years, it is only more recently that the cellular and molecular mechanisms underlying this response are being elucidated through a combination of *in vitro* and animal experiments. The main pathways and processes thought to be involved are illustrated in Figure 2.1. Whilst the details are not yet fully understood an increasing volume of data is beginning to form a coherent picture of the cellular and molecular radiobiology underlying RRCD.



**Figure 2.1** – A cartoon of the major processes thought to be involved in the pathogenesis of radiation-related cardiovascular damage

### **Cytokine activation, inflammation and increased vascular permeability**

Endothelial activation by irradiation is known to result in the up-regulation of cellular adhesion molecules and cytokines, and the disruption of normal vascular permeability. These combine to produce a dysfunctional endothelium where resultant inflammation and oedema contribute to tissue damage.

Studies involving irradiation of ECs up to 20 Gray (Gy), both *in vitro*<sup>9-14</sup> and *in vivo*,<sup>15,16</sup> have reported dose-related elevations in the expression of the adhesion molecules ICAM-1, VCAM-1, PECAM-1, P-selectin and E-selectin. These molecules are known to mediate the rolling, adhesion and transmigration of leukocytes through the endothelium. The precise results vary between different experimental systems, apparently with the origin of the ECs, suggesting that the response may vary between different types of vessels and vascular beds. There is strong evidence that the induction of ICAM-1 by radiation is regulated by nuclear factor kappa-beta (NF- $\kappa$ B).<sup>17</sup> Recently, activation of the NF- $\kappa$ B signalling pathway has been shown to result in sustained inflammation in irradiated human arteries.<sup>18</sup>

The dose-dependent up-regulation of pro-inflammatory cytokines, including IL-6, IL-8, tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and monocyte chemotactic protein-1 (MCP-1) has been observed following endothelial cell irradiation.<sup>19,20</sup> These are chemo-attractant to leukocytes and are also known to induce endothelial activation and proliferation.<sup>21</sup>

Irradiation of the endothelium results in dysregulation of its barrier function resulting in tissue oedema and contributing to local haemoconcentration and stasis of blood flow.<sup>22</sup> *In vitro* irradiation of cultured monolayers of ECs has been shown to affect the structure of the cytoskeleton, the organisation of actin microfilaments and the integrity of intracellular junctions in a dose-dependent manner, with cells originating from the microvasculature being more



severely affected than those from larger vessels.<sup>23,24</sup> A link between radiation-induced activation of the Rho/Rho-associated protein kinase (ROCK) pathway in endothelial cells and cytoskeletal remodelling and increased permeability has been demonstrated *in vitro*.<sup>23</sup> *In vivo*, changes in microvascular permeability have been observed within hours of irradiation in rodent models with leucocyte infiltration and fibrin accumulation in the perivascular tissues.<sup>25</sup>

In contrast to experiments utilising higher doses mentioned above, studies of low dose irradiation of ECs in the range 0.3 to 0.7 Gy have been associated with reductions in leukocyte adhesion molecules<sup>26-28</sup> and varying radiation doses have been shown to have differential effects on cytokine expression.<sup>29</sup> It is therefore possible that the endothelial inflammatory response may vary qualitatively as well as quantitatively depending on radiation dose.

The inflammatory infiltrates produced by the above processes cause tissue injury through the release of proteases and reactive oxygen species (ROS) from activated phagocytes, and also contribute to tissue fibrosis as discussed below.

### **Thrombosis, abnormal coagulation and altered vascular tone**

Endothelial cells are central to the control of platelet adhesion, coagulation, fibrinolysis and vascular tone.<sup>30</sup> Impairment of this control can cause occlusion of the vascular lumen and impaired perfusion leading to hypoxia, oxidative stress and ischaemic tissue damage.

In response to injury, including radiation-induced damage, a number of prothrombotic changes are known to occur. Molecular responses reported following endothelial irradiation include the increased release of von Willebrand factor in both *in vitro*<sup>31,32</sup> and *in vivo*<sup>33,34</sup> experimental systems. Inhibition of the production of prostacycline (PGI<sub>2</sub>), which normally functions as a potent inhibitor of platelet aggregation, has also been observed following 2 Gy irradiation of *in*

*vitro* preparations of human endothelial cells.<sup>35</sup> These changes result in increased platelet recruitment to the vessel wall and the promotion of platelet aggregation and thrombus formation with the consequent release of platelet-derived mediators. EC death and detachment, with exposure of the basement membrane components, also contributes to platelet adhesion activation, and aggregation.

Endothelial cells normally express a number of surface molecules with anti-coagulant properties, including thrombomodulin (TM). In an *in vivo* model, irradiation of rat gut microvasculature resulted in a dose-dependent deficiency in TM due to inhibition of synthesis by mediators released by platelets adherent to the activated endothelium. This leads to the accumulation of thrombin which, as well as being a powerful coagulant also has inflammatory and fibrogenic effects.<sup>36</sup> Activity of tissue factor (also known as factor III), an important initiator of the coagulation cascade, has been shown to be increased following EC irradiation.<sup>37</sup> Apoptotic ECs are also known to be pro-coagulant.<sup>38</sup> The normally pro-fibrinolytic properties of ECs are disrupted following irradiation<sup>39</sup> and the release of tissue plasminogen activator (tPA) is decreased.<sup>40</sup> The sum consequence of these changes is coagulation and fibrin deposition contributing to vascular occlusion.

Endothelial dysfunction is also characterised by the by an imbalance in vascular tone with a reduction in the availability of nitric oxide (NO) and other vasodilators, such as PGI<sub>2</sub>, and an increase in the levels of vasoconstrictors such as endothelin-1, thromboxane A<sub>2</sub> and angiotensin-II.<sup>4</sup> NO-mediated relaxation of arteries has been shown to be impaired following irradiation in animal models<sup>41,42</sup> and in humans.<sup>43,44</sup> Changes in vascular tone may lead to altered blood flow causing reduced perfusion and worsening tissue hypoxia. In addition, NO and PGI<sub>2</sub> not only affect vascular tone but also inhibit platelet aggregation and have tPA-like properties, thus their reduction also contributes to thrombosis and coagulation.

### **Hypoxia and oxidative stress**

There is a growing body of evidence that tissue hypoxia and chronic oxidative stress drive a variety of radiation-induced late effects.<sup>45,46</sup> Oxidative stress is postulated to play a role in the initiation and/or perpetuation of non-radiation induced cardiovascular conditions, including atherosclerosis and cardiac fibrosis,<sup>47</sup> and most classical cardiovascular risk factors contribute to oxidative stress.<sup>48</sup> It is therefore likely that oxidative stress also contributes to radiation-induced cardiovascular late effects.

The molecular mechanisms underlying oxidative stress are beginning to be understood in terms of an imbalance between reactive oxygen and nitrogen oxide species. Reactive oxygen species (ROS), such as superoxide ( $O_2^{\bullet -}$ ), hydrogen peroxide ( $H_2O_2$ ) and hydroxyl radicals ( $^{\bullet}OH$ ) are continuously generated by normal aerobic cell metabolism. These are usually neutralised by anti-oxidant enzymes, such as superoxide dismutase (SOD) and catalase, or dietary anti-oxidants, such as vitamin C and E, to prevent the oxidative damage of proteins, deoxyribonucleic acid (DNA) and lipids. Reactive nitrogen oxide species (RNS) also play a role in physiological and pathophysiological processes. These include the free radical nitrogen oxide ( $^{\bullet}NO$ ) and other RNS formed by the reaction of  $^{\bullet}NO$  with oxygen or  $O_2^{\bullet -}$ .  $^{\bullet}NO$  is synthesised by the enzyme nitrogen oxide synthase (NOS), which is found in a variety of cells and tissues including the vascular endothelial cells.<sup>45</sup> Under normal conditions the production and destruction of ROS and RNS remain in balance. In some pathological circumstances however the mechanisms maintaining this balance are disrupted, creating a cellular state known as oxidative stress.

Irradiation of biological material produces an immediate burst of ROS generation due to the direct ionisation of water and other target molecules. However, the quantity of ROS produced in this fashion is minute compared to that produced by normal cell activity<sup>49</sup> and prolonged cellular production of ROS/RNS has been observed days after irradiation.<sup>45</sup> It seems likely that it

is perturbation of normal cellular functioning, rather than direct production of reactive species by radiation, which causes oxidative stress in these circumstances. There are several postulated mechanisms by which this could occur including radiation-induced inflammation, hypoxia and mitochondrial dysfunction.

The inflammatory processes initiated by irradiation, as described above, result in increased levels of ROS, which are produced by activated phagocytes such as macrophages. Irradiation-induced endothelial damage and dysfunction lead to microvascular thrombosis and reduced capillary density, resulting in reduced tissue perfusion, hypoxia and further ROS production. Both of these processes can be self-perpetuating in the absence of normal physiological controls as ROS can cause tissue damage and further inflammation and decreased levels of NO, due to degradation by superoxide or a reduction in NOS activity, can cause further endothelial dysfunction.

There are several results from animal experiments supporting the involvement of these mechanisms in the context of RRCD. Cardiac irradiation of a rat model resulted in activation of anti-oxidant pathways, with decreased vitamin E and increased SOD and glutathione peroxidase, and an associated decline in cardiac function.<sup>50</sup> Total body irradiation of rats resulted in a reduction in endothelial NOS activity and structural and functional cardiac degeneration.<sup>51</sup> Xanthine oxidase (XO) activation, and increased superoxide production, resulting in endothelial dysfunction and increased vascular stiffness has also been observed in rat aorta following irradiation.<sup>42,52</sup> In addition, a number of animal experiments investigating anti-oxidant strategies to ameliorate endothelial or cardiovascular effects of irradiation have met with some success (see Table 2.1) lending further weight to the concept that oxidative stress is involved in the pathogenesis of RRCD.

Mitochondria are the primary site of ROS and RNS following irradiation,<sup>53</sup> and damage and dysfunction of endothelial mitochondria has been linked to the development of non-radiation-related cardiovascular disease.<sup>54</sup> Recently, proteomic analyses of cardiac mitochondria following in vivo irradiation of mouse hearts with doses of 0.2 and 2 Gy revealed persistent alterations in oxidative function and mitochondrial cytoskeletal proteins 4 weeks following irradiation.<sup>55</sup> There was also evidence of enhanced ROS production in the mitochondria irradiated to 2Gy.

Taken together these findings support the theory that inflammation, hypoxia and mitochondrial dysfunction with resultant free-radical production produce chronic oxidative stress that contributes to late normal tissue damage within the cardiovascular system.

### **Fibrosis**

Radiation-induced fibrosis is a process central to late adverse effects of radiation treatment in many organs, including the skin, lung, gut and liver.<sup>56</sup> The pathogenesis is complex and remains incompletely understood, but has been likened to a 'wound that does not heal' with an abnormal perpetual activation of repair signalling by cytokines thought to be key.<sup>57</sup> Myocardial fibrosis was described decades ago as a component of radiation-induced heart disease both in experimental animal models and in post-mortem studies of humans.<sup>58</sup> An increase in the ratio of type I to type III collagen has been reported in irradiated myocardium from human autopsy studies, which is thought to decrease myocardial compliance and contribute to diastolic dysfunction.<sup>59</sup> As well as interfering with the mechanical function of the heart, fibrosis may also affect electrophysiological function further reducing cardiac efficiency.<sup>60</sup>

Radiation is known to trigger fibroblasts and other progenitors (e.g. vascular smooth muscle cells)<sup>61</sup> to differentiate into post-mitotic functional myofibroblasts resulting in the increased collagen and extracellular matrix deposition that characterises tissue fibrosis.<sup>62</sup> Experiments in

cell culture models suggest that radiation doses as low as 1 Gy may be able to stimulate the fibrogenic process.<sup>63</sup> A greater understanding of the cellular and molecular mechanisms underlying radiation-induced fibrosis has developed over the last decade.

Transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) effects<sup>64</sup> mediated by the SMAD pathway<sup>65</sup> play a pivotal role in radiation-induced fibrosis. TGF- $\beta$ 1 is activated by release from a latent form bound to the extracellular matrix, both directly by irradiation and also indirectly through endothelial cell damage and perturbation of the ROS/RNS balance.<sup>66</sup> TGF- $\beta$ 1 activation has been observed following irradiation by doses as low as 0.1 Gy.<sup>67</sup> Studies of the TGF- $\beta$ 1/SMAD pathway have been performed in a variety of tissues including the skin, gut and lung, and there is good evidence that TGF- $\beta$ 1 is also involved in the fibrotic processes seen in radiation-related heart disease. In rats the expression of TGF- $\beta$ 1 mRNA has been shown to increase within 1 day of cardiac irradiation and remain elevated for at least 3 months subsequently, during which time cardiac fibrosis is seen to develop.<sup>68</sup> Over-expression of TGF- $\beta$ 1 leads to an increase in pro-collagen mRNA, the precursor of collagen production.<sup>68,69</sup> Administration of pentoxifylline (PTX) and vitamin E to suppress this up-regulation reduces the appearance of cardiac fibrosis, both in the myocardium and the walls of coronary arteries.<sup>56,70</sup> Conversely, administration of a TGF- $\beta$ 1-inducing compound worsens radiation-induced cardiac fibrosis.<sup>71</sup> In humans, a recent study of women previously irradiated for breast cancer suggested an association between a TGF- $\beta$ 1 genetic polymorphism (TGF- $\beta$ 1 29C>T) and subsequent cardiovascular disease risk (HR=1.76, 95% CI 0.99-3.26, p=0.06), but it could be that this effect is independent of radiotherapy as there was not sufficient power to test for any interaction.<sup>72</sup>

As well as the involvement of the TGF- $\beta$ /SMAD pathway, the Rho/ROCK pathway has more recently been demonstrated to be activated in fibrotic irradiated tissues.<sup>73</sup> ROCKs, the downstream regulators of Rho GTPases, are involved in the regulation of cell motility and

morphology through action on the cytoskeleton. This is thought to result in fibrogenic changes in cell phenotype. Activation of this pathway been demonstrated to occur following irradiation in both cultured mouse cardiomyocytes *in vitro* and in the heart and lungs of mice *in vivo*, where it was associated with cardiac hypertrophy and a decline in left ventricular (LV) function. Inhibition of the pathway with statins (which inhibit Rho) or the ROCK inhibitor Y-27632, protected against cardiac fibrosis.<sup>74</sup>

The best characterised downstream target of TGF- $\beta$ 1 signalling is connective tissue growth factor (CTGF), a protein which promotes fibroblast proliferation and extracellular matrix production. After the initiation of fibrogenic processes, and despite very low TGF- $\beta$ 1 levels, CTGF induction persists via activation of the Rho/ROCK pathway, independent of SMAD signalling, in an auto-feedback mechanism.<sup>75</sup> It has therefore been suggested that initiation of fibrosis may occur through SMAD pathway signalling but, even following removal of the initial stimulus, it is maintained through the Rho/ROCK/CTGF cascade.

Experimental rat models have suggested a regulatory role for mast cells in the pathogenesis of myocardial fibrosis. Mast cell deficient rats were observed to suffer more severe post-irradiation collagen deposition and a greater reduction of cardiac function in response to cardiac irradiation when compared to normal controls.<sup>76</sup> Mast cells are known to express a wide range of mediators, including pro- and anti-fibrotic factors which may affect tissue deposition of collagen and collagen cross-linking through effects on cardiac fibroblasts. It has been suggested that mast cells may interact with the cardiac endothelin system during response to irradiation,<sup>77</sup> which has also been implicated in the pathophysiology of non-radiation-related cardiovascular disease.<sup>78</sup> The cardiac sensory nervous system signalling through neuro-peptide mediators including calcitonin gene related peptide (CGRP), substance P and neuropeptide Y may also play a role in these interactions.<sup>71</sup>

In addition to those described above there is a long list of further fibrogenic factors that can activate fibroblasts in response to tissue injury, including IL-4, IL-13, basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF).<sup>79</sup> PDGF inhibitors have been shown to inhibit pulmonary fibrosis secondary to irradiation in mice,<sup>80</sup> but the significance of these other mediators in cardiac radiation fibrosis is currently unknown.

### **Renin-angiotensin-aldosterone system**

The renin-angiotensin-aldosterone (RAA) system is established as a key endocrine and paracrine component in the regulation of blood volume, arterial blood pressure and cardiovascular function.<sup>81</sup> It is known to have an important pathophysiological role in many forms of cardiovascular disease. The significance of this role has been confirmed by a number of clinical trials demonstrating the benefits of down-regulating the RAA system, using angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor (AR) blockers, in hypertension, ischaemic heart disease and heart failure.

More recently additional functions of the RAA system have been recognised, including tissue homeostasis and response to injury,<sup>82</sup> which may be relevant to the pathogenesis of radiation-induced late effects. The involvement of the RAA system has been demonstrated in animal-models of radiation-induced nephropathy, pulmonary fibrosis and late brain injury.<sup>83</sup> ACE inhibitors appear to decrease the risk of radiation damage at doses that do not affect blood pressure and molecular types without a free-radical scavenging thiol group are also effective. Therefore it has been proposed that they may act locally and through non-anti-oxidant mechanisms. What these exact mechanisms may be are currently unknown, but the effects of the RAA system at a molecular and cellular level are wide ranging and there are several routes through which it could be involved. For example, angiotensin II (Ang II) is recognised as having



many non-haemodynamic effects, acting as a pro-inflammatory mediator and growth factor, participating in transcriptional regulation via NF- $\kappa$ B and exerting effects through the endothelin-1 and Rho pathways.<sup>84</sup> Importantly it is known that local Ang II enhances TGF- $\beta$ 1 expression,<sup>85</sup> an important signal in fibrosis following irradiation as described above. Ang II also alters cell function by increasing the generation of ROS<sup>83</sup> which could contribute to chronic oxidative stress. It therefore seems likely that the RAA system is involved in the pathogenesis of radiation-induced heart disease and there is some experimental evidence to support this hypothesis. For example, in rat models the RAA system is activated following local heart irradiation by single doses of 15 Gy, with systemic increases in the levels of Ang II and aldosterone<sup>86</sup> and local increases in the cardiac expression of ACE and AR type 1.<sup>69</sup> Also, the ACE inhibitor captopril reduced myocardial fibrosis and prevented capillary density loss after cardiac irradiation of in rats, although it did not protect function.<sup>87</sup> Interestingly, mast cell chymases are a main converter of Angiotensin I to AngII other than ACE and the RAA system may also interact with the endothelin and cardiac nervous systems, demonstrating again the interrelated nature of the candidate systems thought to be involved in the pathogenesis of RRCD.<sup>71</sup>

### **Endothelial cell death, compensatory proliferation and repair**

As well as endothelial damage and dysfunction, EC death and compensatory EC proliferation are known to play a role in radiation-induced vascular effects. It is thought that EC death occurs mainly through delayed mitotic death. It has been suggested that early radiation-induced apoptosis may also play a role,<sup>88,89</sup> but this mechanism remains controversial.<sup>90</sup> The paradigm-shift away from the target-cell hypothesis towards cytokine networks<sup>91</sup> suggests that that sub-lethal EC damage and dysfunction as discussed above is more important in the pathogenesis of radiation-related cardiovascular disease than EC death.

Radiation dose-dependent loss of alkaline phosphatase activity (an endothelial marker) prior to capillary loss and subsequent myocardial degeneration has been observed in irradiated animal models.<sup>92</sup> Compensatory EC proliferation and subsequent myocardial degeneration was seen only in the areas of focal enzyme loss. The mechanistic significance of loss of alkaline phosphatase activity in this circumstance remains unclear, but it is known to be involved in EC proliferation and regulation of microvascular blood flow by dephosphorylating extracellular nucleoside phosphates.<sup>93</sup>

Irradiation has been demonstrated to inhibit re-endothelialisation and angiogenesis,<sup>94</sup> reducing the regenerative capacity of the vasculature. Concomitant irradiation of bone marrow may also impair the production of endothelial progenitor cells (EPCs)<sup>95</sup> that would normally contribute to repair.<sup>96</sup> Recently reported experiments utilising mouse and human-cultured EPCs have demonstrated that their irradiation results in functional defects, mediated by p53 activation and vascular endothelial growth factor (VEGF) suppression, leading to attenuated vascular regeneration.<sup>97</sup> The importance of damage of these endothelial repair mechanisms to the development of RRCD is yet to be confirmed.

### **Mechanisms of radiation-induced atherosclerosis**

Much of the laboratory investigation into the endothelial mechanisms underlying the vascular effects of irradiation has concentrated on ECs in culture or on the microvasculature, largely because of the technical difficulties of studying larger vessels. There is good experimental evidence, however, that radiation is a risk factor for macrovascular, as well as microvascular, damage. Commonly used laboratory animals tend to be relatively resistant to atherosclerosis and investigators have therefore needed to utilise atherosclerosis prone models. For example irradiation has been shown to cause atherosclerosis in hypercholesterolaemic rabbits<sup>98,99</sup> and apolipoprotein-E negative (ApoE(-/-)) mice.<sup>100-103</sup> The EC is thought to still represent the primary

target, with the initial events being endothelial damage, monocyte adhesion and transmigration into the vessel wall. These are then activated into lipid ingesting macrophages forming foam cells and fatty streaks, the earliest stage of atheroma formation.<sup>104</sup> Sustained inflammation within irradiated human arterial walls has recently been demonstrated<sup>18</sup> analogous to the type of on-going inflammatory process that is thought to underlie spontaneous atherosclerosis.<sup>105</sup> Both microvascular and macrovascular radiation-related damage likely combine to cause clinical disease in the heart.<sup>2</sup>

### **DNA damage**

Irradiation is known to cause damage to DNA both directly and via the production of free radicals. However the extent to which DNA damage is responsible for triggering the observed late effects of radiotherapy, including cardiovascular late effects, is not known. It has been theorised that the risk and severity of adverse normal tissue responses may depend on an underlying genetically determined DNA repair capacity.<sup>106</sup> Against this suggestion in the context of RRCD is that the classical molecular radiobiology of DNA strand breaks leading to cell depletion does not appear to play a predominant role in what is understood of the mechanisms described above. Results from immunohistochemical staining of irradiated human arteries indicate that an important early step in endothelial activation, NF- $\kappa$ B activation, is present in virtually every single cell of the arterial wall,<sup>48</sup> making it unlikely that the cause was DNA-damage in each separate cell. It is much more likely that either an original DNA-damage signal is propagated between cells by a 'bystander effect'<sup>107</sup> or that the initiating signal is some other stressor, such as oxidative stress. These observations bring into question the logic of using classic radiobiological models, such as the linear quadratic model, to describe dose-responses for late effects cardiovascular effects, as this is based on an assumption that DNA-damage is the underlying mechanism.

One cardiovascular disease in which DNA damage, in the form of somatic mutation, has been recognised is atherosclerosis. Proliferating smooth muscle cells in atherosclerotic plaques have been shown to be monoclonal and these clones could, in theory, be initiated or propagated by irradiation.<sup>108</sup> Genetic instability in age-related human atherosclerotic plaques has also been described.<sup>109</sup> Additionally radiation damage to telomeres within ECs may trigger cells into senescence, initiating atherosclerosis.<sup>104</sup> Low doses of radiation are known to induce persistent genetic instability, suggesting a mechanism by which the pathogenic pathways of age-related and radiation-related atherosclerosis may interact.

### **Direct radiation damage to myocytes**

Although the generally held view is that myocyte death and subsequent myocardial fibrosis is secondary to microvascular damage and ischaemia, there are experimental findings that suggest direct death of myocardial cells secondary to high-dose irradiation (>30 Gy) with replacement fibrosis may occur.<sup>110,111</sup> There are however differences in the degree of myocardial degeneration seen between different species and strains of experimental animal, and whether this mechanism is apparent in humans or at the doses and fractionations used in therapeutic radiotherapy is uncertain. Studies of biomarkers of myocardial damage (e.g. troponin) have not revealed any evidence of direct damage during or immediately after radiotherapy<sup>112,113</sup> and it remains most likely that the development of cardiovascular disease occurs through indirect pathways involving other cell types, rather than through a direct effect on cardiomyocytes themselves.

### **Abscopal effects**

It is possible that cardiovascular risk may be elevated by indirect or abscopal effects, i.e. 'off target' effects as a consequence of irradiation of tissues other than those comprising the organ in which the late effects are expressed clinically. There are many theoretical mechanisms by

which this could occur, for example; renal irradiation causing hypertension,<sup>114,115</sup> systemic inflammatory or immune effects,<sup>116-120</sup> effects on lipid metabolism<sup>121,122</sup> and endocrine effects including diabetes,<sup>123,124</sup> hypothyroidism, hyperparathyroidism<sup>125</sup> and growth hormone deficiency.<sup>126,127</sup> There is some experimental evidence in rats demonstrating cardiac abnormalities following total body irradiation that did not occur with localised thoracic irradiation to the same dose<sup>51</sup> and degenerative cardiac changes have been observed in mice following brain irradiation.<sup>128</sup> However it remains uncertain whether and to what extent these possible abscopal effects of irradiation affect cardiovascular risk in humans.

## **Conclusion**

Whilst the pathogenesis of RRCD is clearly complicated and remains incompletely understood, advances in cellular and molecular radiobiology have led to an improved understanding of the mechanisms underlying this important late effect of radiation therapy. It can be anticipated that further technical advances, perhaps utilizing newer techniques such as radiogenomics<sup>48,72</sup> and radioproteomics,<sup>55,129</sup> will continue to improve our knowledge over the coming years. For example, profiling by microarray has recently been used to characterise gene expression in irradiated human arteries versus controls from the same individual and has revealed over-representation of genes associated with angiogenesis, coagulation, and inflammation in the irradiated vessels and suggested a role for the HOXA9 homeobox transcription factor in the regulation of NF- $\kappa$ B activation.<sup>48</sup> The primary clinical motivation for understanding these mechanisms is that it opens potential opportunities to reduce or avoid the adverse effects of radiation on the cardiovascular system by pharmacological intervention. This concept has already resulted in a substantial number of animal experiments and studies using cultured human cells where drugs have been used in an effort to ameliorate radiation damage (see Table 2.1). A small number of clinical trials in patients have also been performed,<sup>130-133</sup> but such agents remain largely experimental and are yet to establish any role in clinical practice.

Radiation remains an important component of curative cancer therapy. It may be hoped that, in the future, the combination of advances in radiotherapy planning and delivery with the development of pharmacological interventions, both based on improved radiobiological understanding, may improve outcomes in cancer survivors by reducing the negative impact of RRCD.

**Table 2.1** – Examples of studies investigating the use of pharmacological agents to ameliorate radiation-induced vascular damage.

| Category             | Agents                                    | Species (organ)                             | Relevant Finding(s)                                                                                                                      | Reference(s)                              |
|----------------------|-------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Anti-oxidant</b>  |                                           |                                             |                                                                                                                                          |                                           |
|                      | Oxypurinol (XO inhibitor)                 | Rat (aorta)                                 | Prevention of XO activation and superoxide elevation following irradiation. Maintenance of NO production and endothelial function.       | Soucy <sup>52</sup>                       |
|                      | Hydrogen-rich water                       | Mice (heart)                                | Reduction in myocardial damage and improved survival following irradiation                                                               | Qian <sup>134</sup>                       |
|                      | Anti-oxidants (various)                   | Rabbit (Iliac arteries)                     | Anti-oxidants (Vitamins E and C, Se, Zn, Cu, Mn, N-acetylcysteine and glutamine) reduced atherosclerotic plaques in irradiated animals   | Leborgne <sup>135</sup>                   |
|                      | Superoxide dismutase (SOD)                | Mice (intestine)                            | Decreased oxidative stress, up-regulation of adhesion molecules and inflammation                                                         | Molla <sup>136</sup>                      |
|                      | Vitamin C                                 | Rat (aorta)                                 | Prevention of oxidative endothelial damage and dysfunction. Maintenance of NO production.                                                | On <sup>137</sup>                         |
|                      | Superoxide dismutase                      | Mice (aorta)                                | Over-expression reduced size of atherosclerotic lesions                                                                                  | Tribble <sup>138</sup>                    |
|                      | Cu/Zn and Mn SOD                          | Pig (skin)                                  | Reversal of radiation-induced skin fibrosis                                                                                              | Lefaix <sup>139</sup>                     |
|                      | Hesperidin                                | Rat (heart)                                 | Reduction in radiation-induced cellular damage and oxidative stress                                                                      | Pradeep <sup>140</sup>                    |
|                      | Caffeic acid phenethyl ester              | Rat (heart)                                 | Restoration of serum lipid profiles and cardiac enzymes                                                                                  | Mansour <sup>141</sup>                    |
| <b>Anti-platelet</b> |                                           |                                             |                                                                                                                                          |                                           |
|                      | Clopidogrel                               | ApoE <sup>-/-</sup> Mice (carotid arteries) | Inhibition of inflammatory markers & increased NOS expression, but did not reduce radiation-induced atherosclerosis                      | Hoving <sup>142</sup>                     |
|                      | Aspirin and NO-Aspirin                    | ApoE <sup>-/-</sup> Mice (carotid arteries) | Did not reduce the development of radiation-induced atherosclerosis (although high dose aspirin increased plaque stability)              | Hoving <sup>143</sup>                     |
|                      | Clopidogrel                               | Rat (intestine)                             | Reduction of vascular sclerosis post-irradiation                                                                                         | Wang <sup>144</sup>                       |
| <b>Anti-fibrotic</b> |                                           |                                             |                                                                                                                                          |                                           |
|                      | Y-27632 (ROCK inhibitor)                  | Mice (heart & lung)                         | Attenuated myocardial and pulmonary fibrosis                                                                                             | Monceau <sup>74</sup>                     |
|                      | PPAR-γ agonists                           | Rabbits (iliac artery)                      | Pioglitazone reduced neo-intimal area following balloon denudation and irradiation                                                       | Pakala <sup>145</sup>                     |
|                      | Pentoxifylline (PDI) and Alpha-tocopherol | Rat (heart)                                 | Prevention of radiation-induced increases in LV diastolic pressure, reduction in deposition of collagen I/III & expression of TGF-β mRNA | Boerma <sup>70</sup><br>Liu <sup>56</sup> |
|                      | 6.3G9 (anti-integrin αvβ6 antibody)       | Mice (lung)                                 | Inhibition of irradiation induced TGF-β activation and prevention of fibrosis                                                            | Puthawala <sup>146</sup>                  |
|                      | SM16 (TGF-β type I receptor inhibitor)    | Rat (lung)                                  | Reduced functional lung damage, fibrotic changes, inflammatory response, and activation of TGF-β following irradiation                   | Anscher <sup>147</sup>                    |

|                      |                                                                              |                                 |                                                                                                                                                |                                                      |
|----------------------|------------------------------------------------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
|                      | 1D11 (anti-TGF- $\beta$ antibody)                                            | Rat (lung)                      | Reduced lung damage caused by irradiation                                                                                                      | Anscher <sup>148</sup>                               |
|                      | Halofuginone (inhibits TGF- $\beta$ signalling)                              | Mice (hind leg)                 | Reduced radiation-induced fibrosis (hind leg contraction)                                                                                      | Xavier <sup>149</sup>                                |
|                      | Soluble TGF- $\beta$ type II receptor                                        | Rat (lung)                      | Reduction of acute radiation-induced lung injury                                                                                               | Rabbani <sup>150</sup>                               |
|                      | Pentoxifylline (PDI) and Alpha-tocopherol                                    | Pig (skin)                      | Reversal of radiation-induced skin fibrosis                                                                                                    | Lefaix <sup>151</sup>                                |
| <b>Statins*</b>      |                                                                              |                                 |                                                                                                                                                |                                                      |
|                      | Atorvastatin                                                                 | ApoE-/- Mice (carotid arteries) | Did not inhibit age-related or radiation-induced atherosclerosis                                                                               | Hoving <sup>142</sup>                                |
|                      | Pravastatin                                                                  | Mice (heart & lung)             | Attenuated myocardial and pulmonary fibrosis                                                                                                   | Monceau <sup>74</sup>                                |
|                      | Lovastatin                                                                   | Human (umbilical vein ECs)      | Protected ECS from irradiation-induced cell death                                                                                              | Nubel <sup>152</sup>                                 |
|                      | Pravastatin                                                                  | Human (lung ECs)                | Multiple anti-inflammatory and anti-thrombotic effects on irradiated ECs                                                                       | Gaugler <sup>153</sup>                               |
| <b>Anti-RAAS**</b>   |                                                                              |                                 |                                                                                                                                                |                                                      |
|                      | L158809 (AT <sub>1</sub> R blocker) and PD123319 (AT <sub>2</sub> R blocker) | Rats (kidney)                   | Reduced incidence of renal failure after TBI                                                                                                   | Cohen <sup>154</sup>                                 |
|                      | ACE inhibitors and L-158809 (AT <sub>1</sub> R blocker)                      | Rat (lung)                      | Reduction in radiation-induced pneumonitis and fibrosis                                                                                        | Molteni <sup>155</sup>                               |
|                      | Captopril (ACE inhibitor)                                                    | Rat (heart)                     | Prevented myocardial fibrosis and capillary density loss                                                                                       | Yarom <sup>87</sup>                                  |
| <b>Cell-based</b>    |                                                                              |                                 |                                                                                                                                                |                                                      |
|                      | Mesenchymal stromal cells                                                    | Rat (aorta)                     | Normalisation of vascular function damaged by irradiation                                                                                      | Soloviev <sup>41</sup>                               |
|                      | Stem/progenitor cell therapy                                                 | Human (peripheral vasculature)  | Mobilised endothelial progenitor cells improved endothelial dysfunction and exercise tolerance. No current data for cardiac stem cells in RRCD | Subramaniyam <sup>156</sup><br>Coppes <sup>157</sup> |
|                      | Adipose-derived stromal cells                                                | Mice (skin)                     | Improved skin perfusion, capillary density and VEGF levels in irradiated animals with skin punch wounds                                        | Ebrahimian <sup>158</sup>                            |
| <b>Miscellaneous</b> |                                                                              |                                 |                                                                                                                                                |                                                      |
|                      | L-Arginine                                                                   | Mice (heart)                    | Mitigated cardiac inflammatory response and normalised ECG changes when administered 2 hours after TBI                                         | Shukla <sup>159</sup>                                |
|                      | Hepatocyte growth factor (HGF)                                               | Rat (heart)                     | Adenovirus-mediated delivery of HGF attenuated cardiac injury following irradiation, maintaining perfusion and reducing fibrosis               | Hu <sup>160</sup>                                    |

Abbreviations: PPAR $\gamma$  = peroxisome proliferator-activated receptor gamma. PDI = phosphodiesterase inhibitor. AT<sub>1</sub>R = Ang II subtype I receptor. AT<sub>2</sub>R = Ang II subtype 2 receptor. TBI = Total body irradiation. HGF = hepatocyte growth factor.

\* - Statins have multiple putative targets and possible mechanisms of action: HMG-CoA inhibitor – Inhibits cholesterol synthesis; Inhibits Rac1 – Reduces oxidative stress; Inhibits protein geranylation and NF- $\kappa$ B gene expression – Anti-inflammatory; Blocks TNF- $\alpha$  and increases TM – Anti-thrombotic; Inhibits smooth muscle cell proliferation and Rho – Anti-fibrotic; Increases availability of NO – Protects ECs.

\*\* - Possible mechanisms of action: Decrease Angiotensin II – Anti-fibrotic; Free-radical scavenger – Reduces oxidative stress

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### **Chapter 3 - Dose, Fractionation and Volume Effects on the Risks of Radiation-Related Cardiovascular Disease following Therapeutic Radiation Exposure**

#### **Introduction**

A fundamental principle underlying the practice of radiation oncology is to maximise the therapeutic radiation dose to the tumour and other target tissues, whilst sparing potentially damaging irradiation of adjacent normal tissues. As exposure of normal tissues is to some extent inevitable during treatment, knowledge regarding the radiation tolerance of these tissues and the risk produced by their irradiation is essential to balance anticipated benefits appropriately with the possible hazards of a particular course of treatment.

Late radiation effects are a function of many variables, the majority of which are generally not under direct control of the treating radiation oncologist (see Figure 3.1). Important exceptions to this (marked in bold in Figure 3.1) are total radiation dose, dose fractionation and the volumes of an organ exposed to a certain dose. These are known to be important determinants of the risk of late radiation effects and are, to a degree, amenable to modification during radiotherapy (RT) planning. This modification is increasingly possible with modern techniques of radiation treatment, such as intensity modulated radiotherapy (IMRT) and proton therapy, which allow a substantially more conformal delivery of the radiation dose than was previously achievable.

Historically, the radiation tolerance of the cardiovascular system was poorly understood and the heart was, for many years, considered to be a relatively radiation-resistant organ. A landmark paper by Emami *et al* published in 1991<sup>1</sup> reviewed contemporary knowledge of normal tissue radiation toxicity but, regarding cardiovascular risks, only reported pericarditis as an end-point. It stated that the 5 year risk of pericarditis was 5% if the entire heart was irradiated to 40 Gray

(Gy), 50% if irradiated to 50 Gy, and suggested higher tolerances for smaller volumes of irradiation.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>Treatment Related</u> <ul style="list-style-type: none"> <li>• <b>Total radiation dose to the organ</b></li> <li>• <b>Radiation dose per fraction</b></li> <li>• <b>Irradiated volume</b></li> <li>• Radiation dose distribution (homogeneity)</li> <li>• Radiation dose rate</li> <li>• Overall treatment time</li> <li>• Time between fractions</li> <li>• Time between treatment courses (in the context of re-irradiation)</li> <li>• Concurrent or sequential chemotherapy (e.g. anthracyclines)</li> <li>• Radiation effect modifiers/protectors</li> </ul> | <u>Patient Related</u> <ul style="list-style-type: none"> <li>• Age</li> <li>• Gender</li> <li>• Co-morbid conditions (e.g. diabetes, connective tissue diseases)</li> <li>• Environmental and Genetic risk factors (e.g. Smoking, hypertension, hypercholesterolaemia, family history)</li> <li>• Individual response to irradiation (genetically determined variability, e.g. ataxia telangiectasia)</li> </ul> |
| <u>Organ Related</u> <ul style="list-style-type: none"> <li>• Pre-existing organ damage or disease (functional reserve)</li> <li>• Structural organisation of the organ (e.g. 'parallel' vs. 'serial' organisation of functional sub-units)</li> <li>• Variable radiosensitivity of tissues or substructures within an organ (e.g. valves and coronary arteries)</li> </ul>                                                                                                                                                                                          | <u>Tumour Related</u> <ul style="list-style-type: none"> <li>• Damage through direct tumour infiltration</li> <li>• Distortion of adjacent normal tissue architecture</li> <li>• Indirect tumour effects (e.g. release of proteolytic enzymes and pro-inflammatory/fibrogenic mediators)</li> </ul>                                                                                                               |

**Figure 3.1** – Factors affecting the risk of late adverse effects of radiation on normal tissues/organs

There was no mention of the other radiation-related cardiovascular diseases that were known to occur. The report from the 1992 Late Effects of Normal Tissues (LENT) Consensus Conference<sup>2</sup> stated evidence from clinical and animal studies of a dose-response for myocardial and pericardial disease, as well as a greater risk with increased dose per fraction, but concluded that there was insufficient data to establish a radiation dose effect for coronary artery disease. Radiation-related valvular heart disease (VHD) was not mentioned in this review. These papers from 20 years ago serve to highlight how little was known about the relationships between radiation dose and late cardiovascular effects at that time. Two more recent reviews have been published<sup>3,4</sup> which, whilst summarising further knowledge obtained over the last 20 years,

emphasize the persistent scarcity of good quality clinical data. Although there has been an accumulation of clinical and epidemiological evidence confirming elevated risks for a variety of radiation-related cardiovascular disease (RRCD) after treatment of a range of cancers,<sup>5</sup> the number of studies that have attempted to derive dose-response relationships is far fewer. The most recent paper to review this topic<sup>4</sup> concludes that a clear quantitative dose and/or volume dependence has not yet been demonstrated for most cardiac end-points. This chapter summarises current evidence regarding radiation dose, fractionation and volume effects on the probability of cardiac late effects following RT, including that published since the last systematic review and, in addition, evidence regarding radiation-related cerebrovascular disease.

### **Cardiac mortality**

The effect of cardiac radiation exposure on death from heart disease (mainly ischaemic heart disease (IHD), but also through other causes) is well established by the analysis of historical patient cohorts who received substantial (>30 Gy) doses to the heart.<sup>6</sup> More recently, data from a number of independent sources including the atomic bomb adult health and life-span studies,<sup>7</sup> breast cancer<sup>8</sup> and childhood cancer<sup>9</sup> survivors and patients treated for peptic ulcer disease,<sup>10</sup> have shown that heart doses <5 Gy increase the risk of cardiac mortality. Importantly none of these studies have confirmed the existence of a threshold dose below which cardiac radiation exposure is without risk. It appears that the relationship between heart radiation dose and cardiac mortality may be linear.<sup>11,12</sup> However, it could be true that there is a threshold effect at cardiac doses <2 Gy or that the relationship may not be linear. The current epidemiological data are insufficient to fully characterise the relationship with any confidence.

The studies that have calculated predictive dose parameters or dose-response relationships for cardiac mortality are summarised in Table 3.1. The earliest study in Hodgkin lymphoma (HL)<sup>13</sup> reported that the introduction of sub-carinal shielding of the heart in 1972 reduced the relative

risk (RR) of cardiac mortality from causes other than acute myocardial infarction (AMI) from 5.3 (95% CI 3.1-7.5) to 1.4 (95% CI 0.6-2.9). But sub-carinal shielding did not significantly reduce the RR of death from AMI, which was 3.7 (95% CI 2.3-5.1) before 1972 and 3.4 (95% CI 2.0-4.8) after. This implies that the particular structures of the heart that are irradiated may be relevant as well as the mean heart dose received, the suggestion being that the proximal coronary arteries are a critical structure and remained exposed even with sub-carinal shielding. This observation is an indication that greater certainty regarding the critical cardiac substructures could aid radiation planning where there may be flexibility with respect to the dose and volume of irradiation that individual structures receive whilst maintaining dose delivery to the target.

| Study Author & Year                       | Diagnosis<br>Number of patients<br>Era of treatment    | Dose Response or NTCP parameters                                                                                                          |
|-------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Hancock <i>et al</i> 1993 <sup>13</sup>   | Hodgkin lymphoma (HL)<br>2,232 patients<br>1960-1990   | Dose to mediastinum:<br>≤30 Gy – RR = 2.6 (95% CI 0.4 to 8.7)*<br>>30Gy – RR = 3.5 (95% CI 2.7 to 4.3)                                    |
| Gagliardi <i>et al</i> 1996 <sup>14</sup> | Breast cancer (BC)<br>809 patients<br>1964-1976        | Relative seriality model†:<br>D50 = 52.3 Gy, $\gamma = 1.28$ , $s = 1$                                                                    |
| Eriksson <i>et al</i> 2000 <sup>15</sup>  | Hodgkin lymphoma<br>157 patients<br>1972-1985          | Relative seriality model†:<br>HL only – D50 = 70.3 Gy, $\gamma = 0.96$ , $s = 1$<br>HL and BC‡ – D50 = 63.0 Gy, $\gamma = 0.94$ , $s = 1$ |
| Carr <i>et al</i> 2005 <sup>10</sup>      | Peptic ulcer<br>1,859 patients<br>1936-1965            | Excess RR of IHD death = 13.1% per 1 Gy mean heart dose (MHD). Significant excess when MHD>2.5 Gy.                                        |
| Darby <i>et al</i> 2007 <sup>8</sup>      | Breast cancer<br>31,161 patients<br>1950s-1990s        | Excess RR of cardiac death per 1 Gy MHD = 4.7%, standard error (SE) 1.0%                                                                  |
| Tukenova <i>et al</i> 2010 <sup>9</sup>   | Solid childhood cancers<br>4,122 patients<br>1942-1986 | Excess RR of cardiac death per 1 Gy MHD = 60.0% (95% CI 40-250%)                                                                          |
| Darby <i>et al</i> 2013 <sup>12</sup>     | Breast cancer<br>1121 patients<br>1958-2001            | Excess RR of IHD death per 1 Gy MHD = 7.2% (95% CI 2.4-14.9%)<br>(based on fatal cases and controls only)                                 |

**Table 3.1** – Dose-response and normal tissue complication probability (NTCP) parameters for cardiac mortality (adapted and expanded from Gagliardi *et al* 2010).<sup>4</sup> \* - Based on 2 heart deaths only. †Defined further in Chapter 6. ‡In combination with Gagliardi *et al* 1996 (based on 966 patients).

The two largest studies of cardiac mortality following fractionated radiotherapy for cancer are in breast cancer<sup>8</sup> and childhood cancer<sup>9</sup> and result in very different estimates of the ERR for cardiac death per Gy of mean heart dose (5% and 60% respectively). Assuming that these differences are real this could be an indication that relative risk may vary substantially with age at irradiation, as the higher risk was calculated from a population of patients treated for childhood cancer (mean age at diagnosis approximately 5.5 years) and the lower risk from a population of patients treated for breast cancer (mean age at diagnosis in the mid-50s).<sup>16</sup> Age at diagnosis and therefore age at radiation exposure is, of course, not something that can be modified by the treating physician. However, greater knowledge of how relative risks vary with age at radiation exposure, and with years from exposure, combined with an accurate assessment of absolute risk for an individual may lead to the identification of cases where the utilisation of specific radiation techniques, e.g. respiratory-adapted therapy or proton therapy, may be desirable to maximise heart protection. Reduction in radiation dose or even the avoidance of irradiation entirely could be considered in cases where the adverse effects are anticipated to exceed the benefits.

### **Ischaemic heart disease**

Perhaps due to the frequency of ischaemic heart disease (IHD) in the general population it proved difficult to demonstrate epidemiologically the increased risk of IHD due to therapeutic radiation. But, by the mid-80s, the theory that radiation increases IHD risk, including coronary artery disease, began to become established.<sup>17</sup>

Many of the cardiac deaths discussed in the previous section are due to IHD. A recent case-control study of breast cancer survivors has investigated the dose-response of both incident and fatal IHD (see Appendix F.4).<sup>12</sup> The estimated rate of IHD events (fatal or non-fatal) increased at 7.4% per Gy mean heart dose. This risk was present in the first 10 years following diagnosis.

The absolute risk was higher in women with a history of previous ischaemic heart disease or other cardiac risk factors.

The only other data suggesting a dose-response including non-fatal IHD is from the United States Childhood Cancer Survivor Study (USCCSS). In this cohort the hazard ratio (HR) for myocardial infarction increases from a baseline of 1 (for no cardiac irradiation), becoming significantly elevated for those receiving 15 to <35 Gy (HR=2.4, 95% CI 1.2 to 4.9) and  $\geq 35$  Gy (HR=3.6, 95% CI 1.9 to 6.9) to the heart.<sup>18</sup> The USCCSS have not yet used their data to calculate formal radiation dose-response relationships (Mulrooney, personal communication). If a linear non-threshold relationship is assumed (as was the best fit for IHD in the RACE study) the risk increases by 7.6% per Gy mean heart dose.

As well as initiating or accelerating coronary artery disease, radiation can also damage the microvasculature of the myocardium. It has been suggested that macrovascular and microvascular damage in the heart may interact to result in an increased risk or severity of IHD events.<sup>6</sup> Radiation-induced microvascular damage has been visualised following radiotherapy as myocardial perfusion defects using single-photon emission computed tomography (SPECT). The largest prospective study of this type was performed in breast cancer patients.<sup>19</sup> In those women where  $\leq 5\%$  of the left ventricle (LV) was in the treatment field the incidence of left ventricular perfusion defects was 25% compared to 55% in those patients where  $>5\%$  of the left ventricle was in the field,<sup>20</sup> suggesting a volume dependence. The presence of left ventricular perfusion defects in this study was analysed in more detail with respect to the dose and volume of irradiation of the left ventricle using two different normal tissue complication probability (NTCP) models – The relative seriality (RS) model (defined in Chapter 6) and the Lyman-Kucher-Burman (LKB) model (defined in Appendix A).<sup>21</sup> A serial behaviour was suggested by the fit with the RS model ( $s=1$ ), consistent with previous use of the RS model to analyse cardiac mortality

data (see Table 3.1). The dose required to obtain a 50% complication probability differed substantially between the two models (RS = 12 Gy, 95% CI 8 to 24 and LKB = 29 Gy, 95% CI 18 to 44). The dose estimated by the RS model to cause a 50% probability of a perfusion defect is less than that predicted to cause a 50% probability of cardiac death (12 Gy vs. 52.3 Gy),<sup>14</sup> suggesting a greater sensitivity to radiation for these subclinical imaging abnormalities as compared to hard clinical endpoints. However, the clinical significance of these perfusion defects in terms of later IHD risk has not been demonstrated.

### **Decreased myocardial function and heart failure**

Early retrospective studies of myocardial function in HL patients revealed that left ventricular ejection fraction (LVEF) decreases with increasing radiation dose to the heart.<sup>17</sup> The average LVEF was reported to decrease with an increasing proportion of the myocardium treated<sup>22</sup> and the distribution of abnormalities in ventricular function has also been described to correspond with areas of the heart that would have received a higher dose per treatment fraction (the right ventricle and left ventricular apex) due to the radiation techniques used.<sup>23</sup> These reports have identified the effects of radiation dose, volume and fractionation on myocardial function but few studies have attempted to quantify risk predictors or dose-response relationships. Individual studies have often been limited by a low variability in cardiac dose within a single cohort, thus reducing the ability to detect radiation effects, let alone quantify them.

A French study of survivors of childhood solid cancers<sup>24</sup> related mean radiation dose to the heart to the risk of cardiac failure and asymptomatic cardiac abnormalities in 229 individuals (who all also received anthracycline chemotherapy) with a median follow-up of 18 years. The cardiac radiation dose range in this cohort was wide with a mean heart dose of 8.1 Gy, a standard deviation of 15.6 Gy, a minimum of 0 Gy and a maximum of 102 Gy. The excess RRs (ERRs) for cardiac failure and asymptomatic abnormalities were 19% (95% CI -2 to 50%) and 35% (95% CI -

0.5 to 120%) per Gy mean heart dose respectively. There was evidence for a greater ERR per Gy with younger age (<8 years) at treatment. The ERR per Gy was also greater with *lower* anthracycline doses, possibly because the anthracycline risk becomes dominant at higher anthracycline doses. The US National Wilms Tumour Study Group published data on the increased risk of congestive heart failure (CHF) with lung or left abdominal irradiation.<sup>25</sup> The ERRs of CHF were 6% (95% CI 0% to 15%) per Gy of lung irradiation and 8% (95% CI 2% to 18%) per Gy of left abdominal irradiation, but dose estimates for cardiac exposure have not been published and how these may relate to cardiac doses is unclear.

The United States Childhood Cancer Survivor Study (USCCSS) published evidence of increasing hazard ratio of CHF with increasing categories of average cardiac radiation dose compared to no irradiation.<sup>18</sup> These data correspond to an increased risk of CHF of approximately 9-11% per Gy mean heart dose, consistent with the results of the French study described above.

There is good evidence of impaired myocardial function in patients irradiated in adulthood for HL. A cohort of 294 intensively investigated HL survivors who had received at least 35 Gy to the mediastinum<sup>26,27</sup> revealed reduced left ventricular fractional shortening, reduced left ventricular mass and a higher incidence of diastolic dysfunction compared to a reference population. However, possibly because the study eligibility included a minimum dose of 35 Gy to the mediastinum, limiting the dose range, no dose-response relationship could be estimated.

Evidence regarding the occurrence of CHF after breast radiotherapy is conflicting, with one study reporting an increased risk following internal mammary chain (IMC) irradiation,<sup>28</sup> but others showing no increased risk of CHF in left-sided versus right-sided irradiation.<sup>29,30</sup> It is possible that this is indirect evidence of volume dependence with only a larger volume of irradiation, as during IMC treatment, sufficient to cause clinical disease. Volume dependence is also suggested



by the previously mentioned prospective study of SPECT imaging following breast radiotherapy,<sup>19</sup> where the risk of perfusion defects was higher when a greater volume of the LV was within the treatment field. The underlying pathophysiology of radiation-induced myocardial damage is thought, from animal models, to be microvascular damage which would correspond with the perfusion defects seen in these studies. The presence of perfusion defects has not yet been associated with wall motion abnormalities or a reduction in ejection fraction.<sup>20</sup> A recent study utilising strain rate imaging by Doppler echocardiography to assess myocardial function<sup>31</sup> demonstrated a reduction in left ventricular systolic strain in patients receiving RT for left-sided breast cancer. These reductions were only observed in myocardial regions receiving >3 Gy and were topographically related to the dose distribution. There was a correlation between the volume of the LV receiving 30Gy and the reduction in strain and a non-significant ( $p=0.06$ ) greater reduction in women who received anthracycline-based chemotherapy. Again the clinical significance of these asymptomatic findings is unknown. Therefore, although myocardial effects are recognised to occur following cardiac irradiation in adults, evidence for a dose-response for clinical endpoints is lacking.

### **Pericardial disease**

In early clinical studies the incidence of pericarditis was reported to increase markedly from  $\leq 10\%$  to  $\geq 50\%$  over a relatively narrow dose range of 40 to 60 Gy of fractionated treatment to the anterior pericardium. This was approximately equal to the steep dose-response reported in experimental animals with a 50% incidence of pericarditis following a single dose of 15 Gy (the equivalent of 54-64 Gy in 2 Gy fractions assuming an alpha-beta ratio of 2-3 Gy).<sup>17</sup> A suggestion of an increased risk of pericardial disease following irradiation with cardiac doses per fraction of  $\geq 3$ Gy was also reported in a study of Hodgkin lymphoma patients.<sup>32</sup> These early clinical studies, all performed in the era prior to 3-D CT-based radiotherapy planning, are summarised in Table 3.2. Two studies of patients irradiated for oesophageal cancer in the 3-D planning era have also

been reported.<sup>33,34</sup> Martel *et al*<sup>33</sup> produced LKB parameters consistent with those estimated from non-CT based historical data,<sup>35</sup> reported other dosimetric parameters associated with risk and confirmed the increased risk with a larger dose per fraction previously noted by Cosset *et al*.<sup>32</sup> Data from the USCCSS<sup>18</sup> also show clear evidence of a dose-response with an increasing HR of pericardial disease for increasing dose categories of cardiac irradiation when compared to no irradiation, with an increased risk of approximately 9.3% per Gy mean heart dose.

| Study Authors/Year                        | Diagnosis<br>Number of patients<br>Era of treatment            | Dose Response or NTCP parameters                                                                                                                                                      |
|-------------------------------------------|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Carmel & Kaplan 1976 <sup>36</sup>        | Hodgkin lymphoma<br>377 patients<br>1964-1972                  | Dose to whole pericardium and % risk of pericarditis (requiring treatment):<br><6 Gy = 7% (1.5%)<br>6 to 15 Gy = 12% (9.5%)<br>>15 to 30 Gy = 19% (6.5%)<br>>30 Gy = 50% (36%)        |
| Mill <i>et al</i> 1984 <sup>37</sup>      | Hodgkin lymphoma<br>193 patients<br>1968-1976                  | Dose at 5cm depth from anterior chest wall and % risk of pericarditis:<br><40 Gy = 0%<br>40 to <45 Gy = 3.4%<br>45 to <50 Gy = 8.6%<br>≥50 Gy = 31.3%                                 |
| Cosset <i>et al</i> 1991 <sup>32</sup>    | Hodgkin lymphoma<br>499 patients<br>1971-1984                  | Relative risks for pericarditis:<br>Mediastinal doses of ≥41 Gy = 3.25 (p=0.006)<br>Dose per fraction ≥3 Gy = 2.00 (p=0.06)                                                           |
| Burman <i>et al</i> 1991 <sup>35</sup>    | (Based on parameters in Emami <i>et al</i> 1991 <sup>1</sup> ) | Risk of pericarditis estimated by the LKB Model:<br>TD <sub>50</sub> = 48 Gy, m = 0.10, n = 0.35                                                                                      |
| Martel <i>et al</i> 1998 <sup>33</sup>    | Oesophageal cancer<br>57 patients<br>1985-1991                 | Parameters related to higher risk:<br>MHD > 27.1 Gy (p=0.014)<br>Maximum heart dose > 47 Gy (p=0.014)<br>3.5 Gy per fraction vs. 1.5 Gy (p=0.0002)                                    |
| Wei <i>et al</i> 2008 <sup>34</sup>       | Oesophageal cancer<br>101 patients<br>2000-2003                | V30 (only DVH parameter significantly associated with higher risk on multivariate analysis)                                                                                           |
| Mulrooney <i>et al</i> 2009 <sup>18</sup> | Childhood cancers<br>14,358 patients<br>1970-1986              | HRs compared to no cardiac irradiation:<br><5 Gy MHD = 0.7 (0.4 to 1.1)<br>5 to <15 Gy MHD = 1.9 (0.9 to 3.9)<br>15 to <35 Gy MHD = 2.2 (1.9 to 3.9)<br>≥35 Gy MHD = 4.8 (2.8 to 8.3) |

**Table 3.2** – Dose-response and normal tissue complication probability (NTCP) parameters for radiation-related pericardial disease. LKB model defined in Appendix A. V30 = Percentage volume of the heart receiving ≥30 Gy.

### Valvular heart disease

Only within the past few years (and since the last systematic review)<sup>4</sup> has some evidence been published of a dose-response relationship for radiation-related valvular heart disease (VHD). These studies are summarised in Table 3.3. The largest numbers of patients studied are survivors of childhood cancer within the USCCSS,<sup>18</sup> where there is evidence, from the increasing hazard ratios with increasing categories of radiation dose to the heart, that there is a dose-response relationship above 15 Gy. These data correspond to an increased risk of 11.9% per Gy of mean heart dose.

| Study Authors/Year                                                                                     | Diagnosis<br>Number of patients<br>Era of treatment | Dose Response or NTCP parameters                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mulrooney <i>et al</i> 2009 <sup>18</sup>                                                              | Childhood cancers<br>14,358 patients<br>1970-1986   | HRs compared to no cardiac irradiation:<br><5 Gy MHD = 0.6 (95% CI 0.4 to 1.0)<br>5 to <15 Gy MHD = 1.4 (95% CI 0.7 to 2.9)<br>15 to <35 Gy MHD = 3.3 (95% CI 2.1 to 5.1)<br>≥35 Gy MHD = 5.5 (95% CI 3.5 to 8.6)                              |
| Cella <i>et al</i> 2011 <sup>38</sup>                                                                  | Hodgkin lymphoma<br>56 patients<br>2002-2008        | Asymptomatic aortic or mitral disease:<br>LA-V <sub>25</sub> >63% vs. ≤63%, OR = 5.7 (p=0.03)<br>LV-V <sub>30</sub> >25% vs. ≤25%, OR = 4.4 (p=0.02)<br>Asymptomatic tricuspid disease:<br>RV-V <sub>30</sub> >65% vs. ≤65%, OR = 7.2 (p=0.02) |
| Maraldo <i>et al</i> 2012 <sup>39</sup><br>(from data in Schellong<br><i>et al</i> 2010) <sup>40</sup> | Hodgkin lymphoma<br>1,132 patients<br>1978-1995     | 25 year absolute excess risk of valvular<br>disease estimated by a logistic dose-<br>response curve:<br>$\gamma_{50} = 4.44$ , $D_{50} = 39.6$ Gy                                                                                              |

**Table 3.3** – Dose-response and normal tissue complication probability (NTCP) parameters for radiation-related valvular heart disease. Definitions: LA-V<sub>25</sub> = Percentage volume of the left atrium receiving ≥25 Gy, LV-V<sub>30</sub> = Percentage volume of the left ventricle receiving ≥30 Gy, RV-V<sub>30</sub> = Percentage volume of the right ventricle receiving ≥30 Gy,  $\gamma_{50}$  = Normalised dose-response gradient at the 50% level,  $D_{50}$  = Dose for a 50% response. The logistic dose response curve is defined in Appendix A.

Two studies of patients treated for HL, one a small study using 3-D CT-based radiation dosimetry<sup>38</sup> and one based on published historical data of children treated for HL<sup>39</sup> suggest a threshold effect at 25-30 Gy. The smaller study suggests that the volumes of the cardiac chambers receiving >25 or 30 Gy may help predict an increased risk of asymptomatic VHD

(although this is not formalised in terms of a dose-response relationship) and the second produces a logistic dose-response curve with an extremely steep gradient between 30 and 40 Gy (see Table 3.3 for details). However, a recent cohort study of radiation-related heart disease in women irradiated for breast cancer<sup>30</sup> gives qualitative evidence that the dose-response for VHD may continue below 15 Gy. In that study the relative risk of VHD following left- versus right-sided irradiation was 1.54 (95% CI 1.11 to 2.13), and the mean heart doses were 6.3 Gy and 2.7 Gy for left- and right-sided irradiation respectively.

### **Cerebrovascular disease**

Although various studies have reported increased risk of incidence of or death from cerebrovascular disease following radiotherapy treatment to the head and/or neck for CNS tumours, head and neck cancers,<sup>41</sup> lymphomas<sup>42,43</sup> and childhood cancers,<sup>44</sup> only one study has calculated a dose-response relationship. That study analysed a joint French-UK cohort of 4,227 5-year survivors of solid tumours diagnosed in childhood from 1942 to 1986, with a median follow-up period of 29 years.<sup>45</sup> Individual treatment data were used to retrospectively estimate the dose to points within the brain using a mathematical phantom.<sup>46</sup> The only risk factor identified was the estimated dose to the pre-pontine cistern, which gave a calculated ERR of 22% per Gy received (95% CI 1-44%). As the pre-pontine cistern is closely related anatomically to the circle of Willis it is plausible that this region may represent a critical area for radiation damage. This conclusion is supported by a more recent publication in 431 survivors of primary brain tumours, where the HR for stroke following circle of Willis irradiation was 9.0 (95% CI 1.2 to 70.0) and following focal non-circle of Willis irradiation was 3.4 (95% CI 0.21 to 55.0).<sup>47</sup> The value of 22% per Gy is consistent with the risk of fatal stroke calculated from the atomic bomb survivor cohort, which was 12% (95% CI 2 to 22%) following whole body irradiation up to dose of 4Gy in a single fraction. A study of scalp irradiation for tinea capitis<sup>48</sup> with very prolonged follow-up has suggested that irradiation to very low doses (perhaps 1-2 Gy to the brain and <0.1

Gy to the neck)<sup>49</sup> may significantly increase the risk of stroke. The effect of such low doses when given as fractionated treatment for malignancy, especially in adults, is however unproven. There also remains a need for a dose-response relationship between radiation to the neck and subsequent risk of carotid disease and stroke over the range 20 to 60 Gy as many patients treated for lymphoma and head and neck cancer receive doses of this magnitude.

### **Peripheral vascular disease**

Radiation-induced peripheral vascular disease is recognised to occur in a variety of peripheral arteries following irradiation at higher doses (>30 Gy).<sup>50</sup> There is no knowledge however regarding the risk of lower doses of irradiation, nor knowledge regarding the shape or steepness of the dose-response relationship.

### **Conclusion**

While it is clear from the above discussion that there are dose and volume effects on the risk of various cardiovascular endpoints, a number of factors preclude the formulation of accurate dose-volume-response relationships. These have included the relative rarity of events, small numbers of patients in individual studies, heterogeneity between the methods used in studies (particularly the measurement of end-points) and a lack of detailed information regarding radiation exposure. There are also uncertainties regarding how radiation risk may interact with other risk factors, such as conventional cardiovascular risk factors and other cardiotoxic treatments (especially anthracyclines).

With the now near-universal availability of 3-D CT-based RT treatment planning and the increasing use of more sophisticated radiation delivery, the technical sophistication of RT has far outstripped the available knowledge regarding the risk of late cardiovascular effects. Simple questions remain unanswered, for example it is still not known whether a relatively high dose to a

small volume of the heart or a lower dose to a larger volume is more important in determining risk.<sup>11</sup> The prevalent concept of appropriate metrics to use when predicting normal tissue complication probabilities tends to be to use the volume of a tissue or structure receiving greater than a given dose (or doses),<sup>3</sup> suggesting that a ‘threshold’ dose is critical. Recent knowledge of radiation-induced cardiovascular effects, however, suggest that this type of measure may not be appropriate as, for example, the dose-response curve for IHD appears not to have a threshold below which there is no increased risk.

Late cardiovascular effects remain an important adverse effect of radiation therapy in certain groups of patients. It is therefore important that radiation oncologists develop a more sophisticated understanding of the appropriate dose-response relationships for cardiovascular disease in order to advise patients correctly, plan optimal courses of treatment and follow-up survivors appropriately.

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## **Chapter 4 - Circulatory Mortality in the British Childhood Cancer Survivor Study**

### **Introduction**

Due to advances in diagnosis, risk-adapted multi-modality therapy and supportive care it is estimated that the 5-year overall survival for childhood cancer now exceeds 80% in developed countries.<sup>1</sup> Despite this excellent cure rate, survivors of childhood cancer exhibit long-term survival that is substantially inferior to the general population.<sup>2</sup> There is also a greater burden of non-fatal illness among survivors than expected when compared to siblings.<sup>3</sup> Cardiovascular disease is the leading cause of non-neoplastic disease in 5-year survivors. Treatments commonly used for childhood cancer, particularly anthracycline chemotherapy (ACT) and radiotherapy (RT), are known to increase the risk of substantial late cardiovascular morbidity<sup>4</sup> and mortality.<sup>2,5</sup> As such, the study of cardiovascular disease in childhood cancer survivors is of great importance.

There are estimated to be 60,000 childhood cancer survivors in the UK. With a growing number of them now entering middle age there is an increasing need to understand the long-term cardiovascular risks of this population, so that they may receive the appropriate follow-up, advice and intervention. Despite this need there is, at present, a lack of information regarding risks in the longest term survivors of childhood cancer.<sup>6,7</sup> The aims of this study were to investigate long-term cardiovascular mortality in a large population-based cohort, with more than 4 times the number of person years and more than 3 times the number of deaths beyond 25 years from original cancer diagnosis than has previously been available.<sup>2</sup>

## **Materials and Methods**

### **Cohort studied**

The nationwide British Childhood Cancer Survivor Study (BCCSS) is the largest population-based study to comprehensively examine a wide spectrum of adverse effects of childhood cancer and its treatment. The cohort for this analysis consists of 17,981 5-year survivors of cancer diagnosed in children aged less than 15 years in Britain between 1<sup>st</sup> January 1940 and 31<sup>st</sup> December 1991.<sup>8</sup>

### **Vital status and cause of death ascertainment**

Death or emigration among the cohort was ascertained by linkage with the National Health Service Registers based at Southport (England and Wales) and Edinburgh (Scotland). For deaths, the death certificate and underlying cause of death, as coded by the Office of National Statistics (for England and Wales) or the General Registrar Office (for Scotland), was sought. Causes of death were coded by the appropriate chronological revisions of the International Classification of Diseases (ICD).<sup>9</sup> Codes signifying a circulatory cause of death were identified and sub-categorised into clinically relevant groups prior to analysis. These are given for ICD revisions 5 to 10 in Appendix B (Table B.1). Follow-up for mortality commenced 5 years after initial diagnosis of childhood cancer and continued until the earliest of death, emigration, other loss to follow-up, or 31<sup>st</sup> December 2009.

### **Statistical analysis**

Standardised mortality ratios (SMRs) and absolute excess risks (AERs) were used to compare the observed mortality within the cohort to that expected. The expected numbers of deaths were calculated by applying death rates for the general population of England, Wales and Scotland to cohort person-years. For this purpose, population cause-specific death counts and head counts by single calendar years (1945-2009), 5-year age groups and gender were obtained from the Office for National Statistics for England and Wales and the General Register Office for Scotland. SMRs<sup>10</sup> (= observed death count/expected death count (O/E)) were analysed using Poisson

regression on observed death counts with expected numbers of deaths as the exposure variable. AERs were analysed using an additive covariate regression model based on a generalised linear model with a user-defined link function.<sup>11</sup> AERs (= (observed death count – expected death count)/follow-up time) are consistently reported per 10,000 person years of follow-up. Confidence intervals for SMRs and AERs were calculated assuming that the number of observed deaths had a Poisson distribution and that the number of expected deaths was not subject to random variation. Hypothesis tests were performed with likelihood-ratios wherever possible. Significance tests are two-sided. Repeat analyses not including the relatively data deficient eras of diagnosis (pre-1955) did not substantially affect the results. Calculations were performed using STATA statistical software , release 12 (Statacorp)<sup>12</sup> under the Windows operating system.

## **Results**

### **Characteristics of cohort**

The cohort comprises 17,981 individuals, who were followed up for a total of 413,681 person years from 5-year survival, with a median follow-up of 27.1 years from original diagnosis (range 5.0 to 69.6) to a median attained age of 34.2 years (range 5.7 to 81.4) at the end of follow-up. There were more than 170,000 person-years of follow-up beyond 20 years from diagnosis and more than 66,000 beyond 30 years. The distribution of person-years of follow-up by era of diagnosis and time since diagnosis can be seen in Appendix B (Table B.2). The characteristics of the cohort regarding the diagnosis and types of initial treatment for the first primary tumour, and vital status at the end of follow-up are summarised in Table 4.1. Further details of individual diagnostic groups are given in Table 4.2.1 and a summary of the initial treatments received in each diagnostic group are given in Table 4.2.2. In a substantial proportion of cases overall (27.8%) the initial treatments given were not recorded, but prior to 1985 they were recorded in >90% of cases, see Appendix B (Table B.3).

| Characteristic        |                                 | Vital status at end of follow-up |              | Total (%)    |
|-----------------------|---------------------------------|----------------------------------|--------------|--------------|
|                       |                                 | Died (%)                         | Alive (%)    |              |
| Total Population      |                                 | 3,300 (100)                      | 14,681 (100) | 17,981 (100) |
| Sex                   | Male                            | 1,955 (59.2)                     | 7,932 (54.0) | 9,887 (55.0) |
|                       | Female                          | 1,345 (40.8)                     | 6,749 (46.0) | 8,094 (45.0) |
| Age at Diagnosis      | 0-4                             | 1,235 (37.4)                     | 7,015 (47.8) | 8250 (45.9)  |
|                       | 5-9                             | 976 (29.6)                       | 3,834 (26.1) | 4810 (26.8)  |
|                       | 10-14                           | 1,089 (33.0)                     | 3,832 (26.1) | 4921 (27.4)  |
| Era of Diagnosis      | 1940-1949                       | 52 (1.6)                         | 51 (0.3)     | 103 (0.6)    |
|                       | 1950-1959                       | 399 (12.1)                       | 616 (4.2)    | 1015 (5.6)   |
|                       | 1960-1969                       | 758 (23.0)                       | 1,870 (12.7) | 2628 (14.6)  |
|                       | 1970-1979                       | 1,125 (34.1)                     | 4,254 (29.0) | 5379 (29.9)  |
|                       | 1980-1991                       | 966 (29.3)                       | 7,890 (53.7) | 8856 (49.3)  |
| Diagnostic Group      | Leukaemia                       | 869 (26.3)                       | 3,982 (27.1) | 4,851 (27.0) |
|                       | Hodgkin lymphoma                | 273 (8.3)                        | 1,053 (7.2)  | 1,326 (7.4)  |
|                       | Non-Hodgkin lymphoma            | 108 (3.3)                        | 873 (5.9)    | 981 (5.5)    |
|                       | Central nervous system (CNS)**  | 1,247 (37.8)                     | 2,962 (20.2) | 4,209 (23.4) |
|                       | Neuroblastoma                   | 101 (3.1)                        | 692 (4.7)    | 793 (4.4)    |
|                       | Retinoblastoma (non-hereditary) | 25 (0.8)                         | 626 (4.3)    | 651 (3.6)    |
|                       | Retinoblastoma (hereditary)     | 113 (3.4)                        | 436 (3.0)    | 549 (3.1)    |
|                       | Wilms' tumour                   | 146 (4.4)                        | 1,332 (9.1)  | 1,478 (8.2)  |
|                       | Bone sarcoma                    | 124 (3.8)                        | 519 (3.5)    | 643 (3.6)    |
|                       | Soft tissue sarcoma (STS)       | 167 (5.1)                        | 1,034 (7.0)  | 1,201 (6.7)  |
|                       | Non-CNS germ cell tumour (GCT)  | 27 (0.8)                         | 694 (4.7)    | 505 (2.8)    |
|                       | Other                           | 100 (3.0)                        | 478 (3.3)    | 794 (4.4)    |
| Years from Diagnosis* | 5-9                             | 1,478 (44.8)                     | 44 (0.3)     | 1,522 (8.5)  |
|                       | 10-19                           | 836 (25.3)                       | 1,660 (11.3) | 2,496 (13.9) |
|                       | 20-29                           | 444 (13.5)                       | 6,315 (43.0) | 6,759 (37.6) |
|                       | 30-39                           | 300 (9.1)                        | 4,197 (28.6) | 4,497 (25.0) |
|                       | 40+                             | 242 (7.3)                        | 2,465 (16.8) | 2,707 (15.1) |
| Attained Age*         | <20                             | 1,634 (49.5)                     | 210 (1.4)    | 1,844 (10.3) |
|                       | 20-29                           | 787 (23.8)                       | 4,030 (27.5) | 4817 (26.8)  |
|                       | 30-39                           | 430 (13.0)                       | 5,235 (35.7) | 5,665 (31.5) |
|                       | 40-49                           | 252 (7.6)                        | 3,462 (23.6) | 3,714 (20.7) |
|                       | 50-59                           | 152 (4.6)                        | 1,335 (9.1)  | 1,487 (8.3)  |
|                       | 60+                             | 45 (1.4)                         | 409 (2.8)    | 454 (2.5)    |
| Initial Surgery       | Yes                             | 1,523 (46.2)                     | 5,771 (39.3) | 7,294 (40.6) |
|                       | No                              | 1,327 (40.2)                     | 4,623 (31.5) | 5,950 (33.1) |
|                       | No Record                       | 450 (13.6)                       | 4,287 (29.2) | 4,737 (26.3) |
| Initial Radiotherapy  | Yes                             | 2,190 (66.4)                     | 7,025 (47.9) | 9,215 (51.2) |
|                       | No                              | 621 (18.8)                       | 3,203 (21.8) | 3,824 (21.3) |
|                       | No Record                       | 489 (14.8)                       | 4,453 (30.3) | 4,942 (27.5) |
| Initial Chemotherapy  | Yes                             | 1,259 (38.2)                     | 5,361 (36.5) | 6,620 (36.8) |
|                       | No                              | 1,453 (44.0)                     | 4,579 (31.2) | 6,032 (33.5) |
|                       | No Record                       | 588 (17.8)                       | 4,741 (32.3) | 5,329 (29.6) |

**Table 4.1** – Characteristics of British Childhood Cancer Survivor Study (BCCSS) cohort, including diagnosis, initial treatment of first primary cancer and vital status at end of follow-up (31/12/09). \* On 31/12/09 (if alive) or at death or emigration (if prior to 31/12/09)

\*\*Including primitive neuroectodermal tumours (PNETs)

| Diagnostic Group                | Mean Age at Diagnosis (SD) | Male:Female  | Person Years of Follow-up (%) |
|---------------------------------|----------------------------|--------------|-------------------------------|
| Leukaemia                       | 5.6 (3.6)                  | 54:46        | 91,864 (22.2)                 |
| Hodgkin lymphoma (HL)           | 10.7 (3.3)                 | 71:29        | 30,351 (7.3)                  |
| Non-Hodgkin lymphoma (NHL)      | 8.7 (3.8)                  | 71:29        | 23,089 (5.6)                  |
| Central nervous system (CNS)*   | 7.9 (4.1)                  | 53:47        | 96,700 (23.4)                 |
| Neuroblastoma                   | 2.2 (3.1)                  | 50:50        | 19,661 (4.8)                  |
| Retinoblastoma (non-hereditary) | 2.4 (1.6)                  | 49:51        | 20,246 (4.9)                  |
| Retinoblastoma (hereditary)     | 1.1 (1.0)                  | 54:46        | 16,468 (4.0)                  |
| Wilms' tumour                   | 3.3 (2.5)                  | 51:49        | 38,247 (9.2)                  |
| Bone sarcoma                    | 10.8 (3.1)                 | 51:49        | 14,453 (3.5)                  |
| Soft tissue sarcoma (STS)       | 6.6 (4.6)                  | 58:42        | 29,741 (7.2)                  |
| Non-CNS germ cell tumour (GCT)  | 5.9 (5.2)                  | 50:50        | 12,622 (3.1)                  |
| Other                           | 9.9 (4.5)                  | 40:60        | 20,238 (4.9)                  |
| <b>Total</b>                    | <b>6.6 (4.5)</b>           | <b>55:45</b> | <b>413,681 (100)</b>          |

**Table 4.2.1** – Further characteristics of individual diagnostic groups in the BCCSS

\*Including primitive neuroectodermal tumours (PNETs)

| Diagnostic Group                   | Initial Surgery<br>(% by row) |                         |                         | Initial Radiotherapy<br>(% by row) |                         |                         | Initial Chemotherapy<br>(% by row) |                         |                         | Total Number<br>(% by column) |
|------------------------------------|-------------------------------|-------------------------|-------------------------|------------------------------------|-------------------------|-------------------------|------------------------------------|-------------------------|-------------------------|-------------------------------|
|                                    | Yes                           | No                      | NR                      | Yes                                | No                      | NR                      | Yes                                | No                      | NR                      |                               |
| Leukaemia                          | 2<br>(0.0)                    | 3,540<br>(73.0)         | 1,309<br>(27.0)         | 3,161<br>(65.2)                    | 352<br>(7.3)            | 1,338<br>(27.6)         | 3,598<br>(74.2)                    | 4<br>(0.1)              | 1,249<br>(25.7)         | 4,851<br>(27.0)               |
| HL                                 | 190<br>(14.3)                 | 830<br>(62.6)           | 306<br>(23.1)           | 830<br>(62.6)                      | 180<br>(13.6)           | 316<br>(23.8)           | 442<br>(33.3)                      | 509<br>(38.4)           | 375<br>(28.3)           | 1,325<br>(7.4)                |
| NHL                                | 209<br>(21.3)                 | 439<br>(44.8)           | 333<br>(33.9)           | 432<br>(44.0)                      | 198<br>(20.2)           | 351<br>(35.8)           | 411<br>(41.9)                      | 204<br>(20.8)           | 366<br>(37.3)           | 981<br>(5.5)                  |
| CNS*                               | 2,898<br>(68.9)               | 551<br>(13.1)           | 760<br>(18.1)           | 2,238<br>(53.2)                    | 1,111<br>(26.4)         | 860<br>(20.4)           | 284<br>(6.7)                       | 2,845<br>(67.6)         | 1,080<br>(25.7)         | 4,209<br>(23.4)               |
| Neuroblastoma                      | 441<br>(55.6)                 | 110<br>(13.9)           | 242<br>(30.5)           | 279<br>(35.2)                      | 266<br>(33.5)           | 248<br>(31.3)           | 233<br>(29.4)                      | 291<br>(36.7)           | 269<br>(33.9)           | 793<br>(4.4)                  |
| Retinoblastoma<br>(non-hereditary) | 392<br>(60.2)                 | 11<br>(1.7)             | 248<br>(38.1)           | 66<br>(10.1)                       | 287<br>(44.1)           | 298<br>(45.8)           | 5<br>(0.8)                         | 321<br>(49.3)           | 325<br>(49.9)           | 651<br>(3.6)                  |
| Retinoblastoma<br>(hereditary)     | 334<br>(60.8)                 | 46<br>(8.4)             | 169<br>(30.8)           | 313<br>(57.0)                      | 65<br>(11.8)            | 171<br>(31.1)           | 61<br>(11.1)                       | 272<br>(49.5)           | 216<br>(39.3)           | 549<br>(3.1)                  |
| Wilms' tumour                      | 919<br>(62.2)                 | 12<br>(0.8)             | 547<br>(37.0)           | 764<br>(51.7)                      | 165<br>(11.2)           | 549<br>(37.1)           | 710<br>(48.0)                      | 203<br>(13.7)           | 565<br>(38.2)           | 1,478<br>(8.2)                |
| Bone sarcoma                       | 325<br>(50.5)                 | 155<br>(24.1)           | 163<br>(25.3)           | 288<br>(44.8)                      | 192<br>(29.9)           | 163<br>(25.3)           | 285<br>(44.3)                      | 182<br>(28.3)           | 176<br>(27.4)           | 643<br>(3.6)                  |
| STS                                | 737<br>(61.4)                 | 168<br>(14.0)           | 296<br>(24.6)           | 523<br>(43.5)                      | 387<br>(32.2)           | 291<br>(24.2)           | 425<br>(35.4)                      | 447<br>(37.2)           | 329<br>(27.4)           | 1,201<br>(6.7)                |
| Non-CNS GCT                        | 307<br>(60.8)                 | 10<br>(2.0)             | 188<br>(37.2)           | 104<br>(20.6)                      | 215<br>(42.6)           | 186<br>(36.8)           | 92<br>(18.2)                       | 221<br>(43.8)           | 192<br>(38.0)           | 505<br>(2.8)                  |
| Other                              | 540<br>(68.0)                 | 78<br>(9.8)             | 176<br>(22.2)           | 217<br>(27.3)                      | 406<br>(51.1)           | 171<br>(21.5)           | 74<br>(9.3)                        | 533<br>(67.1)           | 187<br>(23.6)           | 794<br>(4.4)                  |
| <b>Total</b>                       | <b>7,294<br/>(40.6)</b>       | <b>5,950<br/>(33.1)</b> | <b>4,737<br/>(26.3)</b> | <b>9,215<br/>(51.2)</b>            | <b>3,824<br/>(21.3)</b> | <b>4,942<br/>(27.5)</b> | <b>6,620<br/>(36.8)</b>            | <b>6,032<br/>(33.5)</b> | <b>5,329<br/>(29.6)</b> | <b>17,981<br/>(100)</b>       |

**Table 4.2.2** – Initial treatments recorded as being received by each diagnostic group in the BCCSS. NR = Not recorded. \*Including primitive neuroectodermal tumours (PNETs).

### **All circulatory mortality**

3300 individuals from the cohort (18.4%) had died by 31<sup>st</sup> December 2009 and 274 (1.5%) were lost to follow-up due to emigration. Death certificates were obtained for 3286 of those who had died (99.6%). 220 (6.7%) died from circulatory causes: 129 cardiac, 59 cerebrovascular and 32 'other' circulatory causes. Of the cardiac deaths, 65 (50.4%) were due to ischaemic heart disease (IHD), 42 (32.6%) to cardiomyopathy and heart failure (CM/HF), 7 (5.4%) to valvular heart disease (VHD) and 15 (11.6%) to 'other cardiac' causes, including arrhythmias and pericardial disease. Of the cerebrovascular deaths 25 (42.4%) were specified as haemorrhagic and 11 (18.6%) as ischaemic. The remaining 23 cerebrovascular deaths (40.0%) were not specified on the death certificate as either ischaemic or haemorrhagic. Of the 'other' circulatory deaths, 20 (62.5%) were due to thromboembolic causes. See Appendix B for a more detailed list of the causes of circulatory death in the cohort.

Table 4.3 contains SMRs and AERs for groups of circulatory causes of death and, for comparison, the SMRs and AERs for other non-neoplastic causes, all non-neoplastic causes and all causes combined. The SMR for all circulatory causes combined is 3.89 (95% CI 3.39 to 4.43) with an AER of 3.95 (95% CI 3.27 to 4.70). Circulatory causes represent less than 6% of the excess deaths within the entire cohort, but a third of all excess non-neoplastic deaths. SMRs are significantly elevated for all the categories of circulatory disease except peripheral vascular disease. Cardiac and cerebrovascular causes are responsible for 55% and 29% of the excess circulatory deaths respectively, with other circulatory causes accounting for the remaining 16%. The SMRs for individual causes of cardiac death vary substantially from 2.30 (95% CI 1.77 to 2.93) for IHD to 6.87 (95% CI 5.08 to 9.29) for CM/HF. The AERs for IHD and CM/HF are, however, similar each contributing approximately 40% of the excess mortality due to cardiac causes, the remainder being due to VHD and 'other cardiac' diseases.

| Cause of Death                     | O/E Deaths  | SMR (95% CI)         | AER (95% CI)           |
|------------------------------------|-------------|----------------------|------------------------|
| <b>All circulatory causes</b>      | 220/56.61   | 3.89 (3.39 to 4.43)  | 3.95 (3.27 to 4.70)    |
| • All cardiac disease              | 129/38.52   | 3.35 (2.80 to 3.98)  | 2.19 (1.67 to 2.77)    |
| - Ischaemic heart disease          | 65/28.27    | 2.30 (1.77 to 2.93)  | 0.89 (0.53 to 1.32)    |
| - Cardiomyopathy & heart failure   | 42/6.11     | 6.87 (4.95 to 9.28)  | 0.87 (0.58 to 1.22)    |
| - Valvular heart disease           | 7/1.57      | 4.45 (1.79 to 9.16)  | 0.13 (0.03 to 0.31)    |
| - Other cardiac disease*           | 15/2.56     | 5.86 (3.28 to 9.67)  | 0.30 (0.14 to 0.54)    |
| • Cerebrovascular disease          | 59/11.57    | 5.10 (3.88 to 6.58)  | 1.15 (0.81 to 1.56)    |
| • Thromboembolic disease**         | 20/3.55     | 5.63 (3.44 to 8.69)  | 0.40 (0.21 to 0.66)    |
| • Peripheral vascular disease      | 6/2.32      | 2.59 (0.95 to 5.63)  | 0.09 (0.00 to 0.26)    |
| • Other circulatory disease***     | 6/0.65      | 9.18 (3.37 to 19.97) | 0.13 (0.04 to 0.30)    |
| <b>Other non-neoplastic causes</b> | 540/217.88  | 2.48 (2.27 to 2.70)  | 7.79 (6.71 to 8.94)    |
| <b>All non-neoplastic causes</b>   | 760/274.49  | 2.77 (2.58 to 2.97)  | 11.74 (10.45 to 13.09) |
| <b>Neoplastic causes†</b>          | 2524/85.83  | -                    | -                      |
| <b>All causes‡</b>                 | 3300/360.32 | 9.16 (8.85 to 9.48)  | 71.06 (68.36 to 73.83) |

**Table 4.3** – Standardised mortality ratios (SMRs) and absolute excess risks (AERs) for death from circulatory and other causes.

\*Includes pericardial disease, conduction defects, arrhythmias and miscellaneous cardiac conditions (e.g. kyphoscoliotic heart disease)

\*\*Excluding cerebrovascular thromboembolic causes

\*\*\*Includes pulmonary hypertension

†Includes both death from recurrence of the primary cancer and subsequent malignancies

‡Includes 16 deaths from unknown causes not placed in other categories

### **All cardiac mortality**

The SMR for deaths from all cardiac causes combined for the whole cohort is significantly elevated at 3.35 (95% CI 2.80 to 3.98) with an AER of 2.19 (95% CI 1.67 to 2.77), see Table 4.4.

The SMR for cardiac death is significantly higher for females than males ( $p < 0.0001$ ), however the AERs are not significantly different ( $p = 0.70$ ). SMRs for cardiac death appear to be higher in children who were younger when diagnosed with cancer in a univariable analysis ( $p = 0.004$ ), but this trend is no longer significant after adjustment for attained age ( $p = 0.35$ ). There is no significant trend in the AERs with age at diagnosis ( $p = 0.29$ ).

The SMR for death from all cardiac causes decreases with increasing years from diagnosis and with increasing attained age (both  $p < 0.0001$ ). For AER the trends are, however, both in the opposite direction with greater absolute excess risk with increasing years from diagnosis and with attained age ( $p < 0.0001$  and  $p = 0.0006$  respectively). The significantly increasing SMR with



later era of diagnosis ( $p < 0.0001$ ) is largely due to deaths from CM/HF and is discussed further below.

There is significant heterogeneity in both relative and absolute excess risk between diagnostic groups ( $p < 0.0001$  and  $p = 0.0001$  respectively). This marked heterogeneity is likely to be mainly a consequence of differences in treatment rather than a direct effect of the primary cancer. This conclusion is supported by the significant heterogeneity between the risk for initial treatment categories ( $p = 0.0001$  and  $p = 0.007$ ). All categories involving chemotherapy (ChT) and/or radiotherapy (RT) have elevated risk. Only the category with surgery alone has no significant increase in risk. As a substantial proportion of individuals did not have their initial treatment status recorded, no detailed information was available regarding initial treatment, and no information regarding any subsequent treatment was available, the effects of initial chemotherapy and radiotherapy treatment were further examined by analysing *a priori* combinations of diagnostic groups according to the likelihood that they would have received treatments with known cardiotoxic effects, i.e. anthracyclines and incidental cardiac irradiation (see sections below).

|                      |                        | Deaths<br>O/E | PYs FU  | SMR (95% CI)                                                                          | AER (95% CI)                                                                      |
|----------------------|------------------------|---------------|---------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Gender               | Male                   | 82/30.83      | 224,020 | 2.66 (2.12 to 3.30)                                                                   | 2.28 (1.54 to 3.17)                                                               |
|                      | Female                 | 47/7.69       | 189,661 | 6.11 (4.49 to 8.13)<br><b>Heterogeneity p&lt;0.0001</b>                               | 2.07 (1.42 to 2.89)<br>Heterogeneity p=0.70                                       |
| Age at Diagnosis     | 0-5                    | 51/10.49      | 195,054 | 4.86 (3.62 to 6.39)                                                                   | 2.08 (1.41 to 2.90)                                                               |
|                      | 5-10                   | 27/9.18       | 107,702 | 2.94 (1.94 to 4.28)                                                                   | 1.65 (0.80 to 2.79)                                                               |
|                      | 10-15                  | 51/18.85      | 110,925 | 2.71 (2.01 to 3.56)<br><b>Heterogeneity p=0.01</b><br><b>Trend p=0.004*</b>           | 2.90 (1.72 to 4.35)<br>Heterogeneity p=0.29<br>Trend p=0.39                       |
| Era of Diagnosis     | 1940-49                | 6/2.75        | 4,403   | 2.19 (0.80 to 4.76)                                                                   | 7.39 (-1.23 to 23.42)                                                             |
|                      | 1950-59                | 27/12.76      | 37,587  | 2.12 (1.39 to 3.08)                                                                   | 3.79 (1.34 to 7.06)                                                               |
|                      | 1960-69                | 24/12.44      | 83,942  | 1.93 (1.24 to 2.87)                                                                   | 1.38 (0.35 to 2.77)                                                               |
|                      | 1970-79                | 37/7.25       | 135,340 | 5.10 (3.59 to 7.04)                                                                   | 2.20 (1.39 to 3.23)                                                               |
|                      | 1980-91                | 35/3.33       | 152,408 | 10.52 (7.33 to 14.63)<br><b>Heterogeneity p&lt;0.0001</b><br><b>Trend p&lt;0.0001</b> | 2.08 (1.38 to 2.98)<br>Heterogeneity p=0.36<br>Trend p=0.64                       |
| Diagnostic Group     | Leukaemia (excl. AML)  | 14/2.63       | 85,671  | 5.33 (2.91 to 8.94)                                                                   | 1.33 (0.59 to 2.44)                                                               |
|                      | AML                    | 7/0.25        | 6,194   | 28.02 (11.26 to 57.72)                                                                | 10.90 (4.14 to 22.88)                                                             |
|                      | Hodgkin lymphoma       | 23/4.51       | 30,351  | 5.10 (3.23 to 7.65)                                                                   | 6.09 (3.32 to 9.88)                                                               |
|                      | NHL                    | 16/3.29       | 23,089  | 4.87 (2.78 to 7.91)                                                                   | 5.51 (2.54 to 9.83)                                                               |
|                      | CNS (excl. PNET)       | 21/10.45      | 84,306  | 2.01 (1.24 to 3.07)                                                                   | 1.25 (0.30 to 2.57)                                                               |
|                      | PNET                   | 3/1.13        | 12,394  | 2.65 (0.55 to 7.55)                                                                   | 1.51 (-0.41 to 6.16)                                                              |
|                      | Neuroblastoma          | 4/1.26        | 19,661  | 3.19 (0.87 to 8.16)                                                                   | 1.40 (-0.08 to 4.57)                                                              |
|                      | Retinoblastoma (NH)    | 2/2.08        | 20,246  | 0.96 (0.12 to 3.47)                                                                   | -0.04 (-0.91 to 2.54)                                                             |
|                      | Retinoblastoma (H)     | 3/1.42        | 16,468  | 2.12 (0.44 to 6.19)                                                                   | 0.96 (-0.48 to 4.46)                                                              |
|                      | Wilms' tumour          | 15/2.21       | 38,247  | 6.80 (3.81 to 11.21)                                                                  | 3.35 (1.62 to 5.89)                                                               |
|                      | Bone sarcoma           | 3/2.13        | 14,453  | 1.41 (0.29 to 4.11)                                                                   | 0.60 (-1.05 to 4.59)                                                              |
|                      | Soft tissue sarcoma    | 10/3.70       | 29,741  | 2.71 (1.30 to 4.98)                                                                   | 2.12 (0.37 to 4.94)                                                               |
|                      | Non-CNS GCT            | 2/0.88        | 12,622  | 2.26 (0.27 to 8.17)                                                                   | 0.88 (-0.51 to 5.02)                                                              |
|                      | Other                  | 6/2.59        | 20,238  | 2.32 (0.85 to 5.05)<br><b>Heterogeneity p&lt;0.0001</b>                               | 1.69 (-0.19 to 5.17)<br><b>Heterogeneity p=0.0001</b>                             |
| Initial Treatment    | Surgery + No ChT or RT | 15/9.45       | 70,070  | 1.59 (0.89 to 2.62)                                                                   | 0.79 (-0.15 to 2.18)                                                              |
|                      | Surgery + ChT or RT    | 34/13.45      | 82,454  | 2.53 (1.75 to 3.53)                                                                   | 2.49 (1.22 to 4.13)                                                               |
|                      | Surgery + ChT & RT     | 9/1.53        | 32,044  | 5.89 (2.69 to 11.18)                                                                  | 2.33 (0.81 to 4.85)                                                               |
|                      | ChT or RT (No Surgery) | 29/5.99       | 41,350  | 4.84 (3.24 to 6.96)                                                                   | 5.57 (3.25 to 8.62)                                                               |
|                      | ChT & RT (No Surgery)  | 17/3.16       | 81,437  | 5.38 (3.13 to 8.61)                                                                   | 1.70 (0.83 to 2.95)                                                               |
|                      | Rx not fully recorded  | 25/4.94       | 106,325 | 5.06 (3.27 to 7.46)<br><b>Heterogeneity p=0.0001</b>                                  | 1.89 (1.06 to 3.01)<br><b>Heterogeneity p=0.007</b>                               |
| Years from Diagnosis | 5-9                    | 6/0.81        | 85,200  | 7.37 (2.70 to 16.04)                                                                  | 0.61 (0.16 to 1.44)                                                               |
|                      | 10-19                  | 29/3.14       | 157,813 | 9.24 (6.19 to 13.27)                                                                  | 1.64 (1.03 to 2.44)                                                               |
|                      | 20-29                  | 33/6.95       | 104,385 | 4.75 (3.27 to 6.67)                                                                   | 2.50 (1.51 to 3.77)                                                               |
|                      | 30-39                  | 32/11.58      | 47,239  | 2.76 (1.89 to 3.90)                                                                   | 4.32 (2.18 to 7.11)                                                               |
|                      | 40+                    | 29/16.04      | 19,042  | 1.81 (1.21 to 2.60)<br><b>Heterogeneity p&lt;0.0001</b><br><b>Trend p&lt;0.0001</b>   | 6.81 (1.78 to 13.45)<br><b>Heterogeneity p=0.0004</b><br><b>Trend p&lt;0.0001</b> |
| Attained Age         | 5-19                   | 17/1.32       | 141,477 | 12.86 (7.49 to 20.59)                                                                 | 1.11 (0.61 to 1.83)                                                               |
|                      | 20-29                  | 29/3.20       | 139,138 | 9.06 (6.07 to 13.01)                                                                  | 1.85 (1.17 to 2.76)                                                               |
|                      | 30-39                  | 30/7.17       | 84,994  | 4.18 (2.82 to 5.97)                                                                   | 2.69 (1.54 to 4.20)                                                               |
|                      | 40-49                  | 25/12.07      | 35,342  | 2.07 (1.34 to 3.06)                                                                   | 3.66 (1.16 to 7.03)                                                               |
|                      | 50+                    | 28/14.76      | 12,729  | 1.90 (1.26 to 2.74)<br><b>Heterogeneity p&lt;0.0001</b><br><b>Trend p&lt;0.0001</b>   | 10.40 (3.02 to 20.20)<br><b>Heterogeneity p=0.006</b><br><b>Trend p=0.0006</b>    |
| Total                |                        | 129/38.52     | 413,681 | 3.35 (2.80 to 3.98)<br><b>SMR ≠ 1, p&lt;0.0001</b>                                    | 2.19 (1.67 to 2.77)<br><b>AER ≠ 0, p&lt;0.0001</b>                                |

**Table 4.4** - SMRs and AERs for death from all cardiac causes by individual explanatory variables, with likelihood ratio tests for heterogeneity and trend where appropriate. Where tests indicated a statistically significant heterogeneity or trend they are marked in bold.

\*Not significant on adjustment for attained age (p=0.35). PYs FU = Person years follow-up.

### **Death from cardiomyopathy and heart failure**

There were 42 deaths from CM/HF accounting for 32.6% of the cardiac deaths. For the entire cohort the SMR for CM/HF is 6.87 (95% CI 4.95 to 9.28), with an AER of 0.87 (95% CI 0.58 to 1.22). There is marked heterogeneity in both relative and absolute excess risks of death from CM/HF between diagnostic groups (both  $p < 0.0001$ ), see Table 4.5. The cohort was divided into combinations of diagnostic groups depending on their possible exposure to ACT during initial treatment following the introduction of ACT in the 1970s, see Table 4.6. The risk of CM/HF in the group unlikely to have received ACT is not significantly increased (SMR = 1.52, 95% CI 0.41 to 3.88). In contrast, in the groups possibly exposed to ACT there is an approximately ten-fold increase in the risk of death from CM/HF (SMR = 10.93, 95% CI 7.74 to 15.01) with an AER of 1.40 per 10,000 person years (both  $p < 0.0001$  for difference from the group unlikely to have been exposed to ACT). Amongst those possibly exposed to ACT, the relative and absolute risks are consistently greater in the haematological malignancies group than the non-haematological malignancies group.

The SMR for death from CM/HF in the entire group possibly exposed to ACT, regardless of whether they were recorded as receiving initial ChT, is 10.93 (7.74 to 15.01) compared to 1.52 (0.41 to 3.88) in the group unlikely to have been exposed to ACT ( $p < 0.0001$  for difference, see Table 4.6). Within the group possibly exposed to ACT the SMR for death from CM/HF for those actually recorded as receiving initial ChT is 13.05 (8.08 to 19.95) versus 4.63 (1.70 to 10.07) for those recorded as not receiving initial ChT ( $p = 0.015$  for difference, see Table 4.6).

The combination of diagnostic groups possibly exposed to ACT contained >90% (38/42) of the deaths from CM/HF in the entire cohort, despite representing <60% of the person-years of follow-up. In this combination of groups the SMR is significantly higher for females at 24.03 compared with 7.08 for males ( $p = 0.0003$ ), but the AER does not differ significantly by gender

( $p=0.30$ ), see Table 4.7. There is a non-significant trend for an increased relative risk with younger age at diagnosis ( $p=0.15$ ) which remains non-significant after adjustment for attained age ( $p=0.94$ ). There is no evidence of an effect of age at diagnosis on absolute excess risk ( $p=0.89$ ). There is a significant trend for increasing relative and absolute excess risk with more recent era of diagnosis ( $p<0.0001$ ). During the late 1970s there was an approximately 10-fold increase in risk, during the early 1980s an almost 20-fold increase risk and during the late 1980s and into the 1990s a greater than 30-fold increase in risk with an AER of 2.65 deaths per 10,000 person years. The trend for increasing SMR with more recent era of diagnosis remains highly significant after adjustment for either years from diagnosis ( $p<0.0001$ ) or attained age ( $p=0.0001$ ). The decreasing SMR with increasing years from diagnosis is, however, no longer significant after adjustment for era of diagnosis ( $p=0.86$ ). Similarly the decreasing SMR with increasing attained age is no longer significant after adjustment for era of diagnosis ( $p=0.23$ ).

| Diagnostic Group      | Deaths (O/E) | PYs FU  | SMR (95% CI)*           | AER (95% CI)*        |
|-----------------------|--------------|---------|-------------------------|----------------------|
| Leukaemia (excl. AML) | 10/0.87      | 85,671  | 11.49 (5.51 to 21.13)   | 1.07 (0.46 to 2.05)  |
| AML                   | 6/0.07       | 6,194   | 87.96 (32.28 to 191.45) | 9.58 (3.44 to 20.98) |
| Hodgkin lymphoma      | 4/0.63       | 30,351  | 6.34 (1.73 to 16.24)    | 1.11 (0.15 to 3.17)  |
| NHL                   | 7/0.45       | 23,089  | 15.73 (6.32 to 32.40)   | 2.84 (1.03 to 6.05)  |
| CNS                   | 3/1.62       | 96,700  | 1.86 (0.38 to 5.43)     | 0.14 (-0.10 to 0.74) |
| Neuroblastoma         | 1/0.23       | 19,661  | 4.41 (0.11 to 24.59)    | 0.39 (-0.10 to 2.72) |
| Wilms' tumour         | 5/0.45       | 38,247  | 11.00 (3.57 to 25.67)   | 1.19 (0.31 to 2.93)  |
| Bone sarcoma          | 1/0.27       | 14,453  | 3.65 (0.09 to 20.35)    | 0.50 (-0.17 to 3.67) |
| Soft tissue sarcoma   | 4/0.51       | 29,741  | 7.91 (2.15 to 20.25)    | 1.17 (0.20 to 3.27)  |
| All others**          | 1/1.02       | 69,574  | 0.98 (0.02 to 5.44)     | 0.00 (-0.14 to 0.65) |
| Total                 | 42/6.1       | 413,681 | 6.87 (4.95 to 9.28)     | 0.87 (0.58 to 1.22)  |

**Table 4.5** – SMRs and AERs for CM/HF death by individual diagnostic groups.

\*Heterogeneity between diagnostic groups,  $p < 0.0001$  for both SMRs and AERs

\*\*All others = 'Others', retinoblastoma (hereditary and non-hereditary) and non-CNS GCT

| Possible anthracycline exposure | SMRs (95% CI)                    |                                 |                                  |                                  | PYs FU (All) |
|---------------------------------|----------------------------------|---------------------------------|----------------------------------|----------------------------------|--------------|
|                                 | Initial ChT Yes                  | Initial ChT No                  | Initial ChT NR                   | All                              |              |
| <b>Yes (All):</b>               | <b>13.05*</b><br>(8.08 to 19.95) | <b>4.63*</b><br>(1.70 to 10.07) | <b>19.31</b><br>(9.64 to 34.55)  | <b>10.93†</b><br>(7.74 to 15.01) | 247,407      |
| - Haematological                | <b>13.29</b><br>(7.44 to 21.92)  | <b>7.35</b><br>(2.00 to 18.81)  | <b>23.44</b><br>(10.12 to 46.19) | <b>13.40</b><br>(8.83 to 19.50)  | 145,304      |
| - Non-haematological            | <b>12.49</b><br>(4.58 to 27.19)  | <b>2.66</b><br>(0.32 to 9.61)   | <b>13.13</b><br>(2.71 to 38.38)  | <b>7.53</b><br>(3.76 to 13.47)   | 102,103      |
| <b>Unlikely:</b>                | <b>0.00**</b><br>(0.00 to 26.17) | <b>1.98</b><br>(0.54 to 5.07)   | <b>0.00**</b><br>(0.00 to 7.71)  | <b>1.52†</b><br>(0.41 to 3.88)   | 166,274      |

| Possible anthracycline exposure | AERs (95% CI)                     |                                |                                   |                                 | PYs FU (All) |
|---------------------------------|-----------------------------------|--------------------------------|-----------------------------------|---------------------------------|--------------|
|                                 | Initial ChT Yes                   | Initial ChT No                 | Initial ChT NR                    | All                             |              |
| <b>Yes (All):</b>               | <b>1.46</b><br>(0.85 to 2.29)     | <b>0.82</b><br>(0.16 to 2.05)  | <b>1.84</b><br>(0.87 to 3.37)     | <b>1.40‡</b><br>(0.95 to 1.97)  | 247,407      |
| - Haematological:               | <b>1.49</b><br>(0.78 to 2.54)     | <b>1.69</b><br>(0.27 to 4.74)  | <b>2.41</b><br>(0.98 to 4.85)     | <b>1.72</b><br>(1.09 to 2.56)   | 145,304      |
| - Non-haematological:           | <b>1.37</b><br>(0.43 to 3.13)     | <b>0.34</b><br>(-0.14 to 1.75) | <b>1.11</b><br>(0.16 to 3.42)     | <b>0.93</b><br>(0.39 to 1.78)   | 102,103      |
| <b>Unlikely:</b>                | <b>-0.12**</b><br>(-0.12 to 3.10) | <b>0.17</b><br>(-0.08 to 0.70) | <b>-0.12**</b><br>(-0.12 to 0.77) | <b>0.08‡</b><br>(-0.09 to 0.46) | 166,274      |

**Table 4.6** – SMRs and AERs for death from CM/HF by combined diagnostic groups, based on likely exposure to anthracyclines (following their introduction in the 1970s) and by initial ChT treatment group. Yes (Haematological) = Leukaemia, Hodgkin lymphoma and non-Hodgkin lymphoma. Yes (Non-haematological) = Wilms, Neuroblastoma, Bone and soft-tissue sarcomas. Unlikely = CNS tumours, retinoblastoma, germ cell tumours and others.

\*Test for difference  $p = 0.015$ . †Test for difference  $p < 0.0001$ . ‡Test for difference  $p = 0.0001$

\*\*No deaths from CM/HF in these groups

|                             |                        | Deaths<br>(O/E) | PYs FU  | SMR (95% CI)                                                                             | AER (95% CI)                                                                 |
|-----------------------------|------------------------|-----------------|---------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>Gender</b>               | Male                   | 19/2.68         | 139,612 | 7.08 (4.26 to 11.05)                                                                     | 1.17 (0.63 to 1.93)                                                          |
|                             | Female                 | 19/0.79         | 107,795 | 24.03 (14.47 to 37.53)<br><b>Heterogeneity p=0.0003</b>                                  | 1.69 (0.99 to 2.68)<br>Heterogeneity p=0.30                                  |
| <b>Age at Diagnosis</b>     | 0-5                    | 18/1.24         | 121,303 | 14.52 (8.61 to 22.95)                                                                    | 1.38 (0.78 to 2.24)                                                          |
|                             | 5-10                   | 9/0.94          | 64,883  | 9.56 (4.37 to 18.14)                                                                     | 1.24 (0.49 to 2.49)                                                          |
|                             | 10-15                  | 11/1.29         | 61,221  | 8.50 (4.24 to 15.21)<br>Heterogeneity p=0.32<br>Trend p=0.15*                            | 1.59 (0.69 to 3.00)<br>Heterogeneity p=0.89<br>Trend p=0.81                  |
| <b>Era of Diagnosis</b>     | 1940-74                | 6/1.88          | 94,413  | 3.20 (1.17 to 6.96)                                                                      | 0.44 (0.03 to 1.18)                                                          |
|                             | 1975-79                | 6/0.62          | 46,890  | 9.75 (3.58 to 21.22)                                                                     | 1.15 (0.34 to 2.65)                                                          |
|                             | 1980-84                | 10/0.51         | 47,455  | 19.67 (9.43 to 36.18)                                                                    | 2.00 (0.90 to 3.77)                                                          |
|                             | 1985-91                | 16/0.48         | 58,649  | 33.61 (19.21 to 54.58)<br><b>Heterogeneity p&lt;0.0001</b><br><b>Trend p&lt;0.0001**</b> | 2.65 (1.48 to 4.35)<br><b>Heterogeneity p=0.004</b><br><b>Trend p=0.0003</b> |
| <b>Initial Treatment</b>    | Surgery + No ChT or RT | 1/0.34          | 16,564  | 2.96 (0.07 to 16.50)                                                                     | 0.40 (-0.19 to 3.16)                                                         |
|                             | Surgery + ChT or RT    | 6/0.65          | 33,694  | 9.18 (3.37 to 19.98)                                                                     | 1.59 (0.46 to 3.68)                                                          |
|                             | Surgery + ChT & RT     | 3/0.32          | 25,175  | 9.52 (1.96 to 27.82)                                                                     | 1.07 (0.12 to 3.36)                                                          |
|                             | ChT or RT (No Surgery) | 6/0.61          | 30,399  | 9.83 (3.61 to 21.40)                                                                     | 1.77 (0.52 to 4.10)                                                          |
|                             | ChT & RT (No Surgery)  | 9/0.92          | 79,669  | 9.82 (4.49 to 18.65)                                                                     | 1.01 (0.40 to 2.03)                                                          |
|                             | Rx not fully recorded  | 13/0.64         | 61,906  | 20.24 (10.78 to 34.62)<br>Heterogeneity p=0.20                                           | 2.00 (1.01 to 3.49)<br>Heterogeneity p=0.54                                  |
| <b>Years from Diagnosis</b> | 5-9                    | 4/0.28          | 53,143  | 14.19 (3.87 to 36.33)                                                                    | 0.70 (0.15 to 1.87)                                                          |
|                             | 10-19                  | 17/0.89         | 98,762  | 19.04 (11.09 to 30.48)                                                                   | 1.63 (0.91 to 2.67)                                                          |
|                             | 20-29                  | 13/0.96         | 62,517  | 13.61 (7.25 to 23.27)                                                                    | 1.93 (0.95 to 3.40)                                                          |
|                             | 30+                    | 4/1.35          | 32,984  | 2.97 (0.81 to 7.61)<br><b>Heterogeneity p=0.001</b><br><b>Trend p=0.0015†</b>            | 0.80 (-0.08 to 2.70)<br>Heterogeneity p=0.23<br>Trend p=0.43                 |
| <b>Attained Age</b>         | 5-19                   | 12/0.52         | 90,498  | 23.10 (11.93 to 40.34)                                                                   | 1.27 (0.63 to 2.26)                                                          |
|                             | 20-29                  | 14/0.89         | 85,592  | 15.73 (8.60 to 26.40)                                                                    | 1.53 (0.79 to 2.64)                                                          |
|                             | 30-39                  | 9/0.89          | 48,381  | 10.16 (4.65 to 19.29)                                                                    | 1.68 (0.67 to 3.35)                                                          |
|                             | 40+                    | 3/1.18          | 22,936  | 2.54 (0.52 to 7.43)<br><b>Heterogeneity p=0.0004</b><br><b>Trend p=0.0001‡</b>           | 0.79 (-0.24 to 3.31)<br>Heterogeneity p=0.82<br>Trend p=0.95                 |
| <b>Total</b>                |                        | 38/3.48         | 247,407 | 10.93 (7.74 to 15.01)<br><b>SMR ≠ 1, p&lt;0.0001</b>                                     | 1.40 (0.95 to 1.97)<br><b>AER ≠ 0, p&lt;0.0001</b>                           |

**Table 4.7** – Univariable analysis of death from CM/HF in diagnostic groups potentially exposed to anthracycline chemotherapy (from the mid-1970s onwards).

\*Remains non-significant after adjustment for attained age (p=0.94)

\*\*Remains highly significant after adjustment for either years from diagnosis (p<0.0001) or attained age (p=0.0001)

†No longer statistically significant after adjustment for era of diagnosis (p=0.86)

‡No longer statistically significant after adjustment for era of diagnosis (p=0.23)

### **Deaths from ischaemic heart disease and other cardiac causes**

There were 87 deaths from cardiac causes other than CM/HF. The majority of these were from IHD (65 deaths, 50.4% of cardiac deaths overall). The results for IHD alone were qualitatively similar to those for the entire group (see Appendix B, Table B.5). The results for IHD were therefore not analysed further separately.

The SMR for cardiac causes of death other than CM/HF is 2.68 (95% CI 2.15 to 3.31), with an AER of 1.32 (95% CI 0.90 to 1.81), see Table 4.8. The relative risk is significantly higher for females than males (SMR = 4.24 versus 2.32,  $p=0.01$ ) but there is no significant difference in the absolute risk (AER = 1.05 versus 1.55,  $p=0.25$ ). There is a suggestion of a higher relative risk with younger age at diagnosis ( $p=0.04$ ), but this is no longer significant when adjusted for attained age ( $p=0.30$ ). There is also a suggestion of higher relative risk with a more recent era of diagnosis ( $p=0.03$ ), but this is no longer significant when adjusted for years from diagnosis ( $p=0.95$ ). In contrast, the highly significant trends of a higher relative risk with fewer years from diagnosis and a lesser attained age ( $p=0.0005$  and  $p<0.0001$  respectively) remained significant following adjustment for era of diagnosis ( $p=0.006$ ) and age at diagnosis ( $p<0.0001$ ) respectively.

There is significant heterogeneity in the AERs between different diagnostic groups ( $p=0.02$ ), but not between the SMRs ( $p=0.15$ ). Again, any heterogeneity is likely due to differences in the initial treatment received, which is supported by significant heterogeneity in SMRs and AERs between the initial treatment groups (Table 4.8).

The cohort was divided into combinations of diagnostic groups depending on the likely incidental exposure of the heart to radiation during initial treatments (Table 4.9). The group with an increased likelihood of incidental cardiac irradiation had a significantly greater relative and absolute risk of death from cardiac causes other than CM/HF when compared to the group less

likely to have received cardiac irradiation ( $p=0.005$  and  $p=0.0007$ ). This higher risk group was examined separately. The results were qualitatively similar to those for the whole cohort (Table 4.8), but noticeable differences are a more marked difference between males and females in terms of relative risk (SMR = 8.64 versus 2.87,  $p=0.0009$ ) and a more substantial increase in the absolute risks with attained age and years from diagnosis (Table 4.11). The absolute excess risks of death from cardiac causes other than CM/HF among the group more likely to have received cardiac irradiation are presented by years from diagnosis and initial radiotherapy treatment in Table 4.10. There is a significant and substantial continued increase the AER following RT up to 19 excess deaths per 10,000 person years at 40 years or more after diagnosis (Table 4.10.1,  $p<0.0001$ ), approximately equivalent to a 2 in 1000 chance of death from this cause over the next 10 years, whereas there is no evidence of excess risk in those who were recorded as not receiving initial RT (Table 4.10.2,  $p=0.39$ ).



|                              |                        | Deaths<br>(O/E) | PYs FU  | SMR (95% CI)                  | AER (95% CI)                  |
|------------------------------|------------------------|-----------------|---------|-------------------------------|-------------------------------|
| <b>Gender</b>                | Male                   | 61/26.26        | 224,020 | 2.32 (1.78 to 2.98)           | 1.55 (0.91 to 2.33)           |
|                              | Female                 | 26/6.14         | 189,661 | 4.24 (2.77 to 6.21)           | 1.05 (0.57 to 1.68)           |
|                              |                        |                 |         | <b>Heterogeneity p=0.01</b>   | Heterogeneity p=0.25          |
| <b>Age at Diagnosis</b>      | 0-5                    | 32/8.31         | 195,054 | 3.85 (2.63 to 5.44)           | 1.21 (0.70 to 1.89)           |
|                              | 5-10                   | 17/7.57         | 107,702 | 2.25 (1.31 to 3.60)           | 0.88 (0.22 to 1.82)           |
|                              | 10-15                  | 38/16.53        | 110,925 | 2.30 (1.63 to 3.16)           | 1.94 (0.93 to 3.21)           |
|                              |                        |                 |         | Heterogeneity p=0.07          | Heterogeneity p=0.27          |
|                              |                        |                 |         | <b>Trend p=0.04*</b>          | Trend p=0.38                  |
| <b>Era of Diagnosis</b>      | 1940-49                | 6/2.58          | 4,403   | 2.33 (0.85 to 5.07)           | 7.77 (-0.85 to 23.80)         |
|                              | 1950-59                | 27/11.69        | 37,587  | 2.31 (1.52 to 3.36)           | 4.07 (1.62 to 7.34)           |
|                              | 1960-69                | 23/10.81        | 83,942  | 2.13 (1.35 to 3.19)           | 1.45 (0.45 to 2.82)           |
|                              | 1970-79                | 23/5.41         | 135,340 | 4.25 (2.69 to 6.37)           | 1.30 (0.68 to 2.15)           |
|                              | 1980-91                | 8/1.91          | 152,408 | 4.19 (1.81 to 8.25)           | 0.40 (0.10 to 0.91)           |
|                              |                        |                 |         | Heterogeneity p=0.10          | <b>Heterogeneity p=0.002</b>  |
|                              |                        |                 |         | <b>Trend p=0.03**</b>         | <b>Trend p=0.0001</b>         |
| <b>Diagnostic Group</b>      | Leukaemia (excl. AML)  | 4/1.76          | 85,671  | 2.28 (0.62 to 5.83)           | 0.26 (-0.08 to 0.99)          |
|                              | AML                    | 1/0.18          | 6,194   | 5.51 (0.14 to 30.67)          | 1.32 (-0.25 to 8.70)          |
|                              | Hodgkin lymphoma       | 19/3.88         | 30,351  | 4.89 (2.95 to 7.64)           | 4.98 (2.49 to 8.50)           |
|                              | NHL                    | 9/2.84          | 23,089  | 3.17 (1.45 to 6.01)           | 2.67 (0.55 to 6.17)           |
|                              | CNS (excl. PNET)       | 18/9.02         | 84,306  | 2.00 (1.18 to 3.15)           | 1.07 (0.20 to 2.30)           |
|                              | PNET                   | 3/0.94          | 12,394  | 3.19 (0.66 to 9.31)           | 1.66 (-0.26 to 6.31)          |
|                              | Neuroblastoma          | 3/1.03          | 19,661  | 2.92 (0.60 to 8.53)           | 1.00 (-0.21 to 3.94)          |
|                              | Retinoblastoma (NH)    | 2/1.79          | 20,246  | 1.12 (0.14 to 4.04)           | 0.10 (-0.76 to 2.69)          |
|                              | Retinoblastoma (H)     | 3/1.20          | 16,468  | 2.51 (0.52 to 7.34)           | 1.10 (-0.35 to 4.60)          |
|                              | Wilms' tumour          | 10/1.75         | 38,247  | 5.71 (2.74 to 10.50)          | 2.16 (0.80 to 4.35)           |
|                              | Bone sarcoma           | 2/1.86          | 14,453  | 1.08 (0.13 to 3.89)           | 0.10 (-1.12 to 3.71)          |
|                              | Soft tissue sarcoma    | 6/3.19          | 29,741  | 1.88 (0.69 to 4.09)           | 0.94 (-0.33 to 3.32)          |
|                              | Non-CNS GCT            | 2/0.72          | 12,622  | 2.78 (0.34 to 10.03)          | 1.01 (-0.38 to 5.15)          |
|                              | Other                  | 5/2.24          | 20,238  | 2.23 (0.72 to 5.20)           | 1.36 (-0.31 to 4.66)          |
|                              |                        |                 |         | Heterogeneity p=0.15          | <b>Heterogeneity p=0.02</b>   |
| <b>Initial Other Therapy</b> | Surgery + No ChT or RT | 11/8.21         | 70,070  | 1.34 (0.67 to 2.40)           | 0.40 (-0.39 to 1.64)          |
|                              | Surgery + ChT or RT    | 28/11.87        | 82,454  | 2.36 (1.57 to 3.41)           | 1.96 (0.82 to 3.47)           |
|                              | Surgery + ChT & RT     | 6/1.12          | 32,044  | 5.33 (1.96 to 11.61)          | 1.52 (0.34 to 3.72)           |
|                              | ChT or RT (No Surgery) | 22/5.2          | 41,350  | 4.23 (2.65 to 6.41)           | 4.06 (2.08 to 6.80)           |
|                              | ChT & RT (No Surgery)  | 8/2.22          | 81,437  | 3.61 (1.56 to 7.10)           | 0.71 (0.15 to 1.66)           |
|                              | Any Treatment N/R      | 12/3.78         | 106,325 | 3.18 (1.64 to 5.55)           | 0.77 (0.23 to 1.62)           |
|                              |                        |                 |         | <b>Heterogeneity p=0.01</b>   | <b>Heterogeneity p=0.004</b>  |
| <b>Years from Diagnosis</b>  | 5-9                    | 2/0.37          | 85,200  | 5.44 (0.66 to 19.63)          | 0.19 (-0.01 to 0.80)          |
|                              | 10-19                  | 11/1.74         | 157,813 | 6.31 (3.15 to 11.28)          | 0.59 (0.24 to 1.14)           |
|                              | 20-29                  | 20/5.39         | 104,385 | 3.71 (2.27 to 5.73)           | 1.40 (0.65 to 2.44)           |
|                              | 30-39                  | 26/10.21        | 47,239  | 2.55 (1.66 to 3.73)           | 3.34 (1.43 to 5.90)           |
|                              | 40+                    | 28/14.70        | 19,042  | 1.91 (1.27 to 2.75)           | 6.99 (2.05 to 13.53)          |
|                              |                        |                 |         | <b>Heterogeneity p=0.01</b>   | <b>Heterogeneity p=0.0001</b> |
|                              |                        |                 |         | <b>Trend p=0.0005†</b>        | <b>Trend p&lt;0.0001</b>      |
| <b>Attained Age</b>          | 5-19                   | 5/0.52          | 141,477 | 9.55 (3.10 to 22.29)          | 0.32 (0.08 to 0.79)           |
|                              | 20-29                  | 14/1.80         | 139,138 | 7.78 (4.26 to 13.06)          | 0.88 (0.42 to 1.56)           |
|                              | 30-39                  | 20/5.67         | 84,994  | 3.53 (2.15 to 5.45)           | 1.69 (0.77 to 2.97)           |
|                              | 40-49                  | 22/10.79        | 35,342  | 2.04 (1.28 to 3.09)           | 3.17 (0.85 to 6.37)           |
|                              | 50+                    | 26/13.62        | 12,729  | 1.91 (1.25 to 2.80)           | 9.73 (2.65 to 19.23)          |
|                              |                        |                 |         | <b>Heterogeneity p=0.0001</b> | <b>Heterogeneity p=0.0004</b> |
|                              |                        |                 |         | <b>Trend p&lt;0.0001‡</b>     | <b>Trend p&lt;0.0001</b>      |
| <b>Total</b>                 |                        | 87/32.40        | 413,681 | 2.68 (2.15 to 3.31)           | 1.32 (0.90 to 1.81)           |
|                              |                        |                 |         | <b>SMR ≠ 1, p&lt;0.0001</b>   | <b>AER ≠ 0, p&lt;0.0001</b>   |

**Table 4.8** - SMRs and AERs for death from cardiac causes except cardiomyopathy and heart failure, by individual explanatory variables, with likelihood ratio tests. Where tests indicated a statistically significant heterogeneity or trend they are marked in bold.

\*No longer statistically significant after adjustment for attained age (p=0.30)

\*\*No longer statistically significant after adjustment for years from diagnosis (p=0.95)

†Remains highly statistically significant after adjustment for era of diagnosis (p=0.006)

‡Remains highly statistically significant after adjustment for age at diagnosis (p<0.0001)

| Possible cardiac irradiation | SMRs (95% CI)                 |                               |                               |                                | PYs FU (All) |
|------------------------------|-------------------------------|-------------------------------|-------------------------------|--------------------------------|--------------|
|                              | Initial RT Yes                | Initial RT No                 | Initial RT NR                 | All                            |              |
| More likely                  | <b>3.92</b><br>(2.79 to 5.36) | <b>3.17</b><br>(1.16 to 6.91) | <b>2.10</b><br>(0.05 to 6.91) | <b>3.74†</b><br>(2.74 to 4.99) | 138,195      |
| Less likely                  | <b>2.35</b><br>(1.54 to 3.45) | <b>1.31</b><br>(0.63 to 2.40) | <b>3.59</b><br>(1.17 to 8.38) | <b>2.04†</b><br>(1.46 to 2.77) | 275,485      |

| Possible cardiac irradiation | AERs (95% CI)                 |                                |                                |                                | PYs FU (All) |
|------------------------------|-------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------|
|                              | Initial RT Yes                | Initial RT No                  | Initial RT NR                  | All                            |              |
| More likely                  | <b>3.47</b><br>(2.13 to 5.18) | <b>1.67</b><br>(0.13 to 4.55)  | <b>0.18</b><br>(-0.15 to 1.70) | <b>2.44‡</b><br>(1.55 to 3.55) | 138,195      |
| Less likely                  | <b>1.04</b><br>(0.41 to 1.87) | <b>0.31</b><br>(-0.37 to 1.41) | <b>0.66</b><br>(0.04 to 1.88)  | <b>0.76‡</b><br>(0.34 to 1.29) | 275,485      |

**Table 4.9** – SMRs and AERs for death from cardiac causes other than CM/HF grouped by possible cardiac radiation exposure and by initial radiotherapy treatment group.

More likely = HL, NHL, Neuroblastoma, Wilms', bone sarcoma and PNET. Less likely = All others.

†Test for difference, p=0.005. ‡Test for difference, p=0.0007.

| Years from Diagnosis | AER (95% CI), given initial RT* | O/E     | PYs    |
|----------------------|---------------------------------|---------|--------|
| 5-29                 | 1.07 (0.32 to 2.31)             | 9/2.07  | 64,954 |
| 30-39                | 8.76 (3.79 to 16.08)            | 15/3.36 | 13,293 |
| 40+                  | 19.16 (7.10 to 36.96)           | 15/4.51 | 5,473  |
| All                  | 3.47 (2.13 to 5.18)             | 39/9.94 | 83,719 |

**Table 4.10.1** – AERs (with 95% CIs) for death from cardiac causes other than CM/CHF by years from diagnosis for diagnostic groups more likely to have received cardiac irradiation, recorded as *being initially treated with radiotherapy*. \*Test for trend with years from diagnosis, p<0.0001

| Years from Diagnosis | AER (95% CI), not given initial RT* | O/E    | PYs    |
|----------------------|-------------------------------------|--------|--------|
| 5-29                 | 1.17 (0.04 to 3.92)                 | 3/0.54 | 21,009 |
| 30-39                | 5.43 (-1.42 to 25.79)               | 2/0.61 | 2,566  |
| 40+                  | 2.65 (-7.44 to 50.01)               | 1/0.74 | 965    |
| All                  | 1.67 (0.13 to 4.55)                 | 6/1.89 | 24,541 |

**Table 4.10.2** – AERs (with 95% CIs) for death from cardiac causes other than CM/CHF by years from diagnosis for diagnostic groups more likely to have received cardiac irradiation, recorded as *not being initially treated with radiotherapy*. \*Test for trend with years from diagnosis, p=0.39

|                                |                        | Deaths<br>(O/E) | PYs FU  | SMR (95% CI)                  | AER (95% CI)                      |
|--------------------------------|------------------------|-----------------|---------|-------------------------------|-----------------------------------|
| <b>Gender</b>                  | Male                   | 30/10.45        | 82,327  | 2.87 (1.94 to 4.10)           | 2.37 (1.19 to 3.93)               |
|                                | Female                 | 16/1.85         | 55,868  | 8.64 (4.94 to 14.03)          | 2.53 (1.31 to 4.32)               |
|                                |                        |                 |         | <b>Heterogeneity p=0.0009</b> | Heterogeneity p=0.87              |
| <b>Age at Diagnosis</b>        | 0-5                    | 15/2.64         | 60,543  | 5.68 (3.18 to 9.37)           | 2.04 (0.95 to 3.65)               |
|                                | 5-10                   | 10/2.71         | 35,287  | 3.69 (1.77 to 6.78)           | 2.07 (0.59 to 4.44)               |
|                                | 10-15                  | 21/6.95         | 42,366  | 3.02 (1.87 to 4.62)           | 3.32 (1.43 to 5.94)               |
|                                |                        |                 |         | Heterogeneity p=0.19          | Heterogeneity p=0.54              |
|                                |                        |                 |         | Trend p=0.07                  | Trend p=0.33                      |
| <b>Era of Diagnosis</b>        | 1940-59                | 20/5.27         | 14,872  | 3.80 (2.32 to 5.86)           | 9.91 (4.67 to 17.23)              |
|                                | 1960-69                | 13/4.18         | 30,135  | 3.11 (1.65 to 5.31)           | 2.93 (0.91 to 5.99)               |
|                                | 1970-79                | 11/2.11         | 43,617  | 5.21 (2.60 to 9.32)           | 2.04 (0.77 to 4.03)               |
|                                | 1980-91                | 2/0.74          | 49,572  | 2.70 (0.33 to 9.76)           | 0.25 (-0.10 to 1.31)              |
|                                |                        |                 |         | Heterogeneity p=0.62          | <b>Heterogeneity p&lt;0.0001*</b> |
|                                |                        |                 |         | Trend p=0.84                  | <b>Trend p&lt;0.0001*</b>         |
| <b>Initial Other Treatment</b> | Surgery + No ChT or RT | 8,645           | 1/1.30  | 0.77 (0.02 to 4.28)           | -0.35 (-1.48 to 4.94)             |
|                                | Surgery + ChT or RT    | 32,826          | 15/4.26 | 3.52 (1.97 to 5.81)           | 3.27 (1.26 to 6.24)               |
|                                | Surgery + ChT & RT     | 23,853          | 5/0.84  | 5.95 (1.93 to 13.88)          | 1.74 (0.33 to 4.54)               |
|                                | ChT or RT (No Surgery) | 22,972          | 19/3.81 | 4.99 (3.00 to 7.79)           | 6.61 (3.32 to 11.26)              |
|                                | ChT & RT (No Surgery)  | 12,253          | 2/0.79  | 2.54 (0.31 to 9.18)           | 0.99 (-0.44 to 5.25)              |
|                                | Rx not fully recorded  | 37,646          | 4/1.31  | 3.06 (0.83 to 7.84)           | 0.72 (-0.06 to 2.37)              |
|                                |                        |                 |         | Heterogeneity p=0.1857        | <b>Heterogeneity p=0.005</b>      |
| <b>Years from Diagnosis</b>    | 5-9                    | 1/0.13          | 27,837  | 7.41 (0.19 to 41.30)          | 0.31 (-0.04 to 1.95)              |
|                                | 10-19                  | 3/0.66          | 52,185  | 4.53 (0.93 to 13.25)          | 0.45 (-0.01 to 1.55)              |
|                                | 20-29                  | 9/2.14          | 35,229  | 4.20 (1.92 to 7.97)           | 1.95 (0.56 to 4.24)               |
|                                | 30-39                  | 17/4.03         | 16,348  | 4.22 (2.46 to 6.75)           | 7.93 (3.59 to 14.18)              |
|                                | 40+                    | 16/5.33         | 6,597   | 3.00 (1.71 to 4.87)           | 16.17 (5.78 to 31.30)             |
|                                |                        |                 |         | Heterogeneity p=0.80          | <b>Heterogeneity p&lt;0.0001</b>  |
|                                |                        |                 |         | Trend p=0.26                  | <b>Trend p&lt;0.0001</b>          |
| <b>Attained Age</b>            | 5-19                   | 1/0.17          | 44,553  | 5.79 (0.15 to 32.25)          | 0.19 (-0.03 to 1.21)              |
|                                | 20-29                  | 6/0.64          | 46,730  | 9.31 (3.42 to 20.26)          | 1.15 (0.33 to 2.66)               |
|                                | 30-39                  | 12/2.16         | 29,785  | 5.56 (2.87 to 9.71)           | 3.30 (1.36 to 6.31)               |
|                                | 40-49                  | 12/4.21         | 12,662  | 2.85 (1.47 to 4.98)           | 6.15 (1.57 to 13.23)              |
|                                | 50+                    | 15/5.12         | 4,464   | 2.93 (1.64 to 4.84)           | 22.14 (7.35 to 43.96)             |
|                                |                        |                 |         | Heterogeneity p=0.11          | <b>Heterogeneity p&lt;0.0001</b>  |
|                                |                        |                 |         | <b>Trend p=0.02</b>           | <b>Trend p&lt;0.0001</b>          |
| <b>Total</b>                   |                        | 46/12.30        | 138,195 | 3.74 (2.74 to 4.99)           | 2.44 (1.55 to 3.55)               |
|                                |                        |                 |         | <b>SMR ≠ 1, p&lt;0.0001</b>   | <b>AER ≠ 0, p&lt;0.0001</b>       |

**Table 4.11** – Death from cardiac causes except CM/HF in diagnostic groups more likely exposed to cardiac irradiation by individual explanatory variables.

\*Not statistically significant after adjustment for years from diagnosis (Heterogeneity p=0.43, trend p=0.20).

### **Cerebrovascular mortality**

There were a total of 59 deaths due to cerebrovascular disease, with a median time from diagnosis of childhood cancer to death of 28.5 years and a median age at death of 40 years. For the entire cohort, the SMR for cerebrovascular death is 5.10 (95% CI 3.88 to 6.58) with an AER of 1.15 (95% CI 0.81 to 1.56). However, these vary significantly ( $p < 0.0001$ ) between the diagnostic groups (Table 4.12). When the individual diagnostic groups were combined into larger groups based on how likely it is that the individuals within the diagnostic groups received high-dose radiotherapy to the brain (CNS, including PNETs), lower dose radiotherapy to the brain (leukaemia), radiotherapy to the neck (lymphomas), no radiotherapy to the brain or neck (neuroblastoma, retinoblastoma, Wilms' tumour, sarcomas and non-CNS GCTs) or unknown (others), the resulting SMRs and AERs are as in table 4.13. The SMR for cerebrovascular death is significantly elevated only for the CNS, lymphoma and 'other' groups. There was only 1 death from cerebrovascular disease in the leukaemia group, despite more than 90,000 person years of follow-up and no significant excess in the combination group judged unlikely to have received RT to the brain or neck, despite more than 150,000 person years of follow-up. The SMR and AER are significantly higher for individuals in the CNS group recorded as receiving initial RT versus those recorded as not receiving initial RT ( $p = 0.0001$  and  $p = 0.0002$  respectively).

More than two thirds of the deaths from cerebrovascular disease within the cohort were among those originally diagnosed with a CNS tumour. Therefore this group was analysed in further detail (Table 4.14). Overall the SMR for death from cerebrovascular disease after diagnosis of a CNS tumour is 11.81 (95% 8.43 to 16.08) and the AER is 3.79 (95% CI 2.60 to 5.28). These increased risks do not vary significantly between males and females ( $p = 0.97$  and  $p = 0.61$ ). The increased SMR is significantly greater in those recorded as initially receiving RT versus those who were recorded as not receiving RT ( $p = 0.0001$ ) and the AER was more than 6-fold higher in those recorded as receiving RT ( $p = 0.0002$ ). In contrast, there was no evidence of a difference in risk

for those registered as having initial treatment with chemotherapy ( $p=0.42$  and  $p=0.84$ ) or surgery ( $p=0.80$  and  $p=0.44$ ) versus those who were registered as not. The other variables significantly associated with an increased AER of cerebrovascular death are increasing years from diagnosis ( $p<0.0001$ ) and greater attained age ( $p<0.0001$ ). On univariable analysis there is a significant trend for a decrease in the AER of cerebrovascular death with era of diagnosis, but when this trend was adjusted for years from diagnosis it is no longer significant. Similarly there is a borderline-significant trend for an increasing AER with age at diagnosis ( $p=0.06$ ), but this disappears after adjustment for attained age ( $p=0.27$ ). In contrast, the significant trends for an increasing AER of stroke with years from diagnosis and attained age remain highly significant after adjustment for either era of diagnosis or age at diagnosis (both  $p<0.0001$ ). The AERs for deaths from cerebrovascular disease amongst those originally treated with and without RT and by years from diagnosis are given in table 4.15. There is a significant trend for increasing AER with years from diagnosis for those initially treated with RT (Table 4.15.1,  $p<0.0001$ ) reaching 37.15 at 40 years or more after diagnosis, approximately equivalent to a 4 in 1000 chance of death from this cause over the next 10 years. There were insufficient events to test for a trend or heterogeneity among those not originally treated with RT (Table 4.15.2).

| Diagnostic Group      | Deaths (O/E) | PYs FU  | SMR (95% CI)*         | AER (95% CI)*         |
|-----------------------|--------------|---------|-----------------------|-----------------------|
| Leukaemia (minus AML) | 0/1.04       | 85,671  | 0.00 (0.00 to 3.55)   | -0.12 (-0.12 to 0.31) |
| AML                   | 1/0.09       | 6,194   | 11.68 (0.30 to 65.06) | 1.48 (-0.10 to 8.86)  |
| Hodgkin lymphoma      | 3/1.14       | 30,351  | 2.63 (0.54 to 7.67)   | 0.61 (-0.17 to 2.51)  |
| Non-Hodgkin lymphoma  | 5/0.85       | 23,089  | 5.91 (1.92 to 13.79)  | 1.80 (0.34 to 4.69)   |
| CNS (minus PNET)      | 34/3.06      | 84,306  | 11.11 (7.69 to 15.52) | 3.67 (2.43 to 5.27)   |
| PNET                  | 6/0.33       | 12,394  | 18.37 (6.74 to 39.97) | 4.58 (1.51 to 10.27)  |
| Neuroblastoma         | 1/0.40       | 19,661  | 2.53 (0.06 to 14.08)  | 0.31 (-0.19 to 2.63)  |
| Retinoblastoma (NH)   | 0/0.62       | 20,246  | 0.00 (0.00 to 5.98)   | -0.30 (-0.30 to 1.52) |
| Retinoblastoma (H)    | 0/0.44       | 16,468  | 0.00 (0.00 to 8.30)   | -0.27 (-0.27 to 1.97) |
| Wilms' tumour         | 1/0.75       | 38,247  | 1.34 (0.03 to 7.44)   | 0.07 (-0.19 to 1.26)  |
| Bone sarcoma          | 1/0.62       | 14,453  | 1.62 (0.04 to 9.00)   | 0.26 (-0.41 to 3.43)  |
| Soft tissue sarcoma   | 1/1.02       | 29,741  | 0.98 (0.02 to 5.44)   | -0.01 (-0.34 to 1.53) |
| Non-CNS GCT           | 1/0.33       | 12,622  | 3.04 (0.08 to 16.91)  | 0.53 (-0.24 to 4.15)  |
| Other                 | 5/0.89       | 20,238  | 5.62 (1.83 to 13.12)  | 2.03 (0.36 to 5.33)   |
| Total                 | 59/11.57     | 413,681 | 5.10 (3.88 to 6.58)   | 1.15 (0.81 to 1.56)   |

**Table 4.12** – SMRs and AERs for cerebrovascular death by diagnostic groups.

\*Heterogeneity between diagnostic groups,  $p < 0.0001$  for both SMRs and AERs

| Combined Diagnostic Groups    | SMR (95% CI)                      |                                  |                                 | PYs FU (All) |
|-------------------------------|-----------------------------------|----------------------------------|---------------------------------|--------------|
|                               | Initial RT Yes                    | Initial RT No                    | All*                            |              |
| CNS (including PNET)          | <b>18.09†</b><br>(12.67 to 25.04) | <b>3.44†</b><br>(0.94 to 8.80)   | <b>11.81</b><br>(8.43 to 16.08) | 96,700       |
| Leukaemias                    | <b>1.24</b><br>(0.03 to 6.92)     | <b>0.00**</b><br>(0.00 to 20.39) | <b>0.89</b><br>(0.02 to 4.95)   | 91,864       |
| NHL & HL                      | <b>3.83</b><br>(1.41 to 8.34)     | <b>3.57</b><br>(0.09 to 19.90)   | <b>4.02</b><br>(1.74 to 7.93)   | 53,440       |
| NB, RB, WT, Sarcoma & NCNSGTC | <b>2.06</b><br>(0.67 to 4.81)     | <b>0.00**</b><br>(0.00 to 2.63)  | <b>1.20</b><br>(0.39 to 2.79)   | 151, 438     |
| Other                         | <b>5.03</b><br>(0.61 to 18.16)    | <b>5.33</b><br>(0.65 to 19.27)   | <b>5.62</b><br>(1.83 to 13.12)  | 20,238       |

| Combined Diagnostic Groups    | AER (95% CI)                    |                                   |                                 | PYs FU (All) |
|-------------------------------|---------------------------------|-----------------------------------|---------------------------------|--------------|
|                               | Initial RT Yes                  | Initial RT No                     | All*                            |              |
| CNS (including PNET)          | <b>6.43‡</b><br>(4.39 to 9.05)  | <b>0.97‡</b><br>(-0.03 to 3.10)   | <b>3.79</b><br>(2.60 to 5.28)   | 96,700       |
| Leukaemias                    | <b>0.03</b><br>(-0.12 to 0.73)  | <b>-0.25**</b><br>(-0.25 to 4.85) | <b>-0.01</b><br>(-0.12 to 0.48) | 91,864       |
| NHL & HL                      | <b>1.34</b><br>(0.19 to 3.48)   | <b>0.80</b><br>(-0.28 to 5.88)    | <b>1.12</b><br>(0.27 to 2.58)   | 53,440       |
| NB, RB, WT, Sarcoma & NCNSGTC | <b>0.36</b><br>(-0.11 to 1.31)  | <b>-0.31**</b><br>(-0.31 to 0.51) | <b>0.05</b><br>(-0.17 to 0.49)  | 151, 438     |
| Other                         | <b>2.62</b><br>(-0.25 to 11.16) | <b>1.55</b><br>(-0.13 to 6.55)    | <b>2.03</b><br>(0.36 to 5.33)   | 20,238       |

**Table 4.13** – SMRs and AERs for cerebrovascular death by combined diagnostic groups, with and without initial RT treatment. \*Includes 27.5% with initial RT status not recorded. \*\*No deaths from cerebrovascular disease in these groups.

†Test for difference,  $p = 0.0001$ . ‡Test for difference,  $p = 0.0002$ .

|                             |         | Deaths<br>O/E | PYs FU | SMR (95% CI)                                         | AER (95% CI)                                                   |
|-----------------------------|---------|---------------|--------|------------------------------------------------------|----------------------------------------------------------------|
| <b>Gender</b>               | Male    | 23/1.94       | 51,364 | 11.86 (7.52 to 17.80)                                | 4.10 (2.46 to 6.34)                                            |
|                             | Female  | 17/1.45       | 45,336 | 11.73 (6.83 to 18.78)                                | 3.43 (1.86 to 5.68)                                            |
|                             |         |               |        | Heterogeneity p=0.97                                 | Heterogeneity p=0.61                                           |
| <b>Age at Diagnosis</b>     | 0-5     | 7/0.52        | 27,537 | 13.43 (5.40 to 27.67)                                | 2.35 (0.83 to 5.05)                                            |
|                             | 5-10    | 13/1.10       | 35,737 | 11.79 (6.28 to 20.16)                                | 3.33 (1.63 to 5.91)                                            |
|                             | 10-15   | 20/1.76       | 33,425 | 11.34 (6.92 to 17.51)                                | 5.46 (3.13 to 8.71)                                            |
|                             |         |               |        | Heterogeneity p=0.93<br>Trend p=0.72                 | Heterogeneity p=0.15<br>Trend p=0.06                           |
| <b>Era of Diagnosis</b>     | 1940-59 | 11/1.16       | 11,964 | 9.45 (4.72 to 16.91)                                 | 8.22 (3.62 to 15.48)                                           |
|                             | 1960-69 | 15/1.23       | 25,032 | 12.23 (6.84 to 20.16)                                | 5.50 (2.86 to 9.39)                                            |
|                             | 1970-79 | 8/0.71        | 31,107 | 11.32 (4.89 to 22.31)                                | 2.34 (0.88 to 4.84)                                            |
|                             | 1980-91 | 6/0.29        | 28,596 | 20.63 (7.57 to 44.91)                                | 2.00 (0.67 to 4.47)                                            |
|                             |         |               |        | Heterogeneity p=0.53<br>Trend p=0.21                 | <b>Heterogeneity p=0.02</b><br><b>Trend p=0.004*</b>           |
| <b>Initial Surgery</b>      | Yes     | 36/2.90       | 72,847 | 12.42 (8.70 to 17.19)                                | 4.54 (3.06 to 6.44)                                            |
|                             | No      | 4/0.37        | 12,150 | 10.90 (2.97 to 27.91)                                | 2.99 (0.60 to 8.13)                                            |
|                             | N/R     | 0/0.12        | 11,703 | (data omitted)                                       | (data omitted)                                                 |
|                             |         |               |        | Heterogeneity p=0.80                                 | Heterogeneity p=0.44                                           |
| <b>Initial Radiotherapy</b> | Yes     | 36/1.99       | 52,895 | 18.09 (12.67 to 25.04)                               | 6.43 (4.39 to 9.05)                                            |
|                             | No      | 4/1.16        | 29,302 | 3.44 (0.94 to 8.80)                                  | 0.97 (-0.03 to 3.10)                                           |
|                             | N/R     | 0/0.23        | 14,502 | (data omitted)                                       | (data omitted)                                                 |
|                             |         |               |        | <b>Heterogeneity p=0.0001</b>                        | <b>Heterogeneity p=0.0002</b>                                  |
| <b>Initial Chemotherapy</b> | Yes     | 2/0.10        | 5,541  | 20.55 (2.49 to 74.24)                                | 3.43 (0.26 to 12.86)                                           |
|                             | No      | 31/2.86       | 70,734 | 10.86 (7.38 to 15.41)                                | 3.98 (2.57 to 5.82)                                            |
|                             | N/R     | 7/0.44        | 20,425 | (data omitted)                                       | (data omitted)                                                 |
|                             |         |               |        | Heterogeneity p=0.42                                 | Heterogeneity p=0.84                                           |
| <b>Years from Diagnosis</b> | 5-9     | 2/0.13        | 19,723 | 15.53 (1.88 to 56.12)                                | 0.95 (0.06 to 3.60)                                            |
|                             | 10-19   | 6/0.44        | 35,292 | 13.77 (5.05 to 29.97)                                | 1.58 (0.50 to 3.58)                                            |
|                             | 20-29   | 13/0.74       | 24,351 | 17.63 (9.39 to 30.15)                                | 5.04 (2.54 to 8.83)                                            |
|                             | 30-39   | 7/0.98        | 12,282 | 7.16 (2.88 to 14.76)                                 | 4.90 (1.50 to 10.95)                                           |
|                             | 40+     | 12/1.11       | 5,052  | 10.82 (5.59 to 18.90)                                | 21.56 (10.08 to 39.29)                                         |
|                             |         |               |        | Heterogeneity p=0.37<br>Trend p=0.25                 | <b>Heterogeneity p&lt;0.0001</b><br><b>Trend p&lt;0.0001**</b> |
| <b>Attained Age</b>         | 5-19    | 2/0.15        | 27,081 | 13.43 (1.63 to 48.51)                                | 0.68 (0.03 to 2.61)                                            |
|                             | 20-29   | 11/0.45       | 32,721 | 24.70 (12.33 to 44.19)                               | 3.23 (1.54 to 5.88)                                            |
|                             | 30-39   | 7/0.73        | 22,066 | 9.60 (3.86 to 19.77)                                 | 2.84 (0.94 to 6.21)                                            |
|                             | 40-49   | 9/0.98        | 10,699 | 9.15 (4.18 to 17.36)                                 | 7.49 (2.93 to 15.05)                                           |
|                             | 50+     | 11/1.8        | 4,133  | 10.18 (5.08 to 18.22)                                | 24.00 (10.67 to 45.00)                                         |
|                             |         |               |        | Heterogeneity p=0.20<br>Trend p=0.10                 | <b>Heterogeneity p&lt;0.0001</b><br><b>Trend p&lt;0.0001**</b> |
| <b>Total</b>                |         | 40/3.39       | 96,700 | 11.81 (8.43 to 16.08)<br><b>SMR ≠ 1, p&lt;0.0001</b> | 3.79 (2.60 to 5.28)<br><b>AER ≠ 0, p&lt;0.0001</b>             |

**Table 4.14** - SMRs and AERs for cerebrovascular deaths within the CNS tumour group by individual explanatory variables with likelihood ratio tests for heterogeneity and trend (where appropriate). Where tests indicated a statistically significant heterogeneity or trend they are marked in bold. \*Trend no longer significant when adjusted for years from diagnosis. \*\*Trends remain significant after adjustment for either age at diagnosis or era of diagnosis.

| Years from Diagnosis | AER (95% CI), given initial RT* | O/E     | PYs    |
|----------------------|---------------------------------|---------|--------|
| 5-9                  | 1.87 (0.17 to 6.95)             | 2/0.07  | 10,297 |
| 10-19                | 3.19 (1.09 to 7.10)             | 6/0.24  | 18,055 |
| 20-29                | 6.66 (3.03 to 12.51)            | 10/0.44 | 14,341 |
| 30-39                | 8.64 (3.00 to 18.66)            | 7/0.59  | 7,413  |
| 40+                  | 37.15 (17.40 to 69.28)          | 11/0.64 | 2,789  |

|     |                     |         |        |
|-----|---------------------|---------|--------|
| All | 6.43 (4.39 to 9.05) | 36/1.99 | 52,895 |
|-----|---------------------|---------|--------|

**Table 4.15.1** – AERs (with 95% CIs) by years from diagnosis for CNS tumours recorded as being initially treated with radiotherapy. \*Test for trend with years from diagnosis,  $p < 0.0001$

| Years from Diagnosis | AER (95% CI), not given initial RT* | O/E    | PYs   |
|----------------------|-------------------------------------|--------|-------|
| 5-9                  | -0.07 (-0.07 to 6.88)               | 0/0.04 | 5,308 |
| 10-19                | -0.13 (-0.13 to 3.60)               | 0/0.13 | 9,893 |
| 20-29                | 3.44 (0.47 to 10.65)                | 3/0.25 | 8,005 |
| 30-39                | -0.80 (-0.80 to 8.20)               | 0/0.33 | 4,098 |
| 40+                  | 2.88 (-2.00 to 25.76)               | 1/0.42 | 1,998 |

|     |                      |        |        |
|-----|----------------------|--------|--------|
| All | 0.97 (-0.03 to 3.10) | 4/1.16 | 29,302 |
|-----|----------------------|--------|--------|

**Table 4.15.2** – AERs (with 95% CIs) by years from diagnosis for CNS tumours recorded as not being initially treated with radiotherapy. \*There are insufficient events to test for a trend or heterogeneity.

### **Thromboembolic mortality**

The majority (20) of the remaining 32 deaths from other circulatory causes were due to non-cerebrovascular thromboembolic disease with an SMR of 5.63 (95% CI 3.63 to 8.72) and an AER of 0.40 (95% CI 0.19 to 0.61). Both the SMR and AER for death from thromboembolic disease are significantly higher following initial treatment with radiotherapy ( $p=0.02$  and  $p=0.03$ ) and in females compared to males ( $p=0.04$  and  $p=0.03$ ). There were statistically significant trends for an increase in the AER for death from thromboembolic disease with both years from diagnosis and attained age ( $p=0.01$  and  $p=0.002$ ) (Table 4.16).

### **Other circulatory mortality**

The remainder of the cardiovascular deaths were due to peripheral vascular disease and ‘other’ circulatory disease with elevated SMRs of 2.59 (95% CI 0.95 to 5.63) and 9.17 (95 CI 3.37 to 19.97) respectively. The numbers of deaths in these categories (6 in each) were not high enough to allow any meaningful analysis by explanatory variables.



|                        |                       | Deaths<br>(O/E) | PYs FU  | SMR (95% CI)                         | AER (95% CI)                                          |
|------------------------|-----------------------|-----------------|---------|--------------------------------------|-------------------------------------------------------|
| Gender                 | Male                  | 6/1.86          | 224,020 | 3.22 (1.18 to 7.01)                  | 0.18 (0.02 to 0.50)                                   |
|                        | Female                | 14/1.69         | 189,661 | 8.28 (4.53 to 13.0)                  | 0.65 (0.31 to 1.15)                                   |
|                        |                       |                 |         | <b>Heterogeneity p=0.04</b>          | <b>Heterogeneity p=0.03</b>                           |
| Age at Diagnosis       | 0-5                   | 5/1.11          | 195,054 | 4.51 (1.47 to 10.53)                 | 0.20 (0.03 to 0.54)                                   |
|                        | 5-10                  | 8/0.90          | 107,702 | 8.91 (3.85 to 17.55)                 | 0.66 (0.24 to 1.38)                                   |
|                        | 10-15                 | 7/1.55          | 110,925 | 4.52 (1.82 to 9.32)                  | 0.49 (0.11 to 1.16)                                   |
|                        |                       |                 |         | Heterogeneity p=0.35<br>Trend p=0.90 | Heterogeneity p=0.18<br>Trend p=0.14                  |
| Era of Diagnosis       | 1940-49               | 1/0.14          | 4,403   | 7.04 (0.18 to 39.22)                 | 1.95 (-0.27 to 12.33)                                 |
|                        | 1950-59               | 3/0.79          | 37,587  | 3.80 (0.78 to 11.11)                 | 0.59 (-0.05 to 2.12)                                  |
|                        | 1960-69               | 3/1.08          | 83,942  | 2.78 (0.57 to 8.13)                  | 0.23 (-0.05 to 0.92)                                  |
|                        | 1970-79               | 10/0.97         | 135,340 | 10.26 (4.92 to 18.87)                | 0.67 (0.28 to 1.29)                                   |
|                        | 1980-91               | 3/0.57          | 152,408 | 5.27 (1.09 to 15.41)                 | 0.16 (0.00 to 0.54)                                   |
|                        |                       |                 |         | Heterogeneity p=0.24<br>Trend p=0.29 | Heterogeneity p=0.21<br>Trend p=0.19                  |
| Diagnostic Group       | Leukaemia (excl. AML) | 2/0.41          | 85,671  | 4.92 (0.60 to 17.79)                 | 0.19 (-0.02 to 0.80)                                  |
|                        | AML                   | 0/0.03          | 6,194   | 0.00 (0.00 to 114.51)                | -0.05 (-0.05 to 5.90)                                 |
|                        | Hodgkin lymphoma      | 3/0.34          | 30,351  | 8.88 (1.83 to 25.96)                 | 0.88 (0.09 to 2.78)                                   |
|                        | NHL                   | 0/0.25          | 23,089  | 0.00 (0.00 to 14.98)                 | -0.11 (-0.11 to 1.49)                                 |
|                        | CNS (excl. PNET)      | 9/0.90          | 84,306  | 10.04 (4.59 to 19.06)                | 0.96 (0.38 to 1.92)                                   |
|                        | PNET                  | 2/0.10          | 12,394  | 20.16 (2.44 to 72.83)                | 1.53 (0.12 to 5.75)                                   |
|                        | Neuroblastoma         | 1/0.12          | 19,661  | 8.10 (0.21 to 45.13)                 | 0.45 (-0.05 to 2.77)                                  |
|                        | Retinoblastoma (NH)   | 0/0.18          | 20,246  | 0.00 (0.00 to 20.20)                 | -0.09 (-0.09 to 1.73)                                 |
|                        | Retinoblastoma (H)    | 1/0.13          | 16,468  | 7.65 (0.19 to 42.62)                 | 0.53 (-0.06 to 3.30)                                  |
|                        | Wilms' tumour         | 1/0.24          | 38,247  | 4.09 (0.10 to 22.76)                 | 0.20 (-0.06 to 1.39)                                  |
|                        | Bone sarcoma          | 1/0.18          | 14,453  | 5.43 (0.14 to 30.28)                 | 0.56 (-0.11 to 3.73)                                  |
|                        | Soft tissue sarcoma   | 0/0.30          | 29,741  | 0.00 (0.00 to 12.22)                 | -0.10 (-0.10 to 1.14)                                 |
|                        | Non-CNS GCT           | 0/0.11          | 12,622  | 0.00 (0.00 to 34.99)                 | -0.08 (-0.08 to 2.84)                                 |
|                        | Other                 | 0/0.26          | 20,238  | 0.00 (0.00 to 14.08)                 | -0.13 (-0.13 to 1.69)                                 |
|                        |                       |                 |         | Heterogeneity p=0.14                 | Heterogeneity p=0.10*                                 |
| Initial Surgery**      | Yes                   | 11/2.26         | 204,335 | 4.86 (2.43 to 8.70)                  | 0.43 (0.16 to 0.85)                                   |
|                        | No                    | 8/1.01          | 131,661 | 7.96 (3.44 to 15.68)                 | 0.53 (0.19 to 1.12)                                   |
|                        |                       |                 |         | Heterogeneity p=0.30                 | Heterogeneity p=0.70                                  |
| Initial Radiotherapy** | Yes                   | 17/2.16         | 228,085 | 7.88 (4.59 to 12.62)                 | 0.65 (0.34 to 1.10)                                   |
|                        | No                    | 2/1.04          | 100,879 | 1.93 (0.23 to 6.97)                  | 0.10 (-0.08 to 0.61)                                  |
|                        |                       |                 |         | <b>Heterogeneity p=0.02</b>          | <b>Heterogeneity p=0.03</b>                           |
| Initial Chemotherapy** | Yes                   | 4/0.86          | 144,681 | 4.67 (1.27 to 11.97)                 | 0.22 (0.02 to 0.65)                                   |
|                        | No                    | 15/4            | 170,770 | 6.85 (3.84 to 11.30)                 | 0.75 (0.36 to 1.32)                                   |
|                        |                       |                 |         | Heterogeneity p=0.48                 | <b>Heterogeneity p=0.04</b>                           |
| Years from Diagnosis   | 5-19                  | 5/0.53          | 85,200  | 9.42 (3.06 to 21.98)                 | 0.18 (0.04 to 0.46)                                   |
|                        | 19-29                 | 5/0.88          | 157,813 | 5.68 (1.84 to 13.24)                 | 0.39 (0.07 to 1.03)                                   |
|                        | 30-39                 | 4/1.01          | 104,385 | 3.97 (1.08 to 10.18)                 | 0.63 (0.02 to 1.95)                                   |
|                        | 40+                   | 6/1.13          | 47,239  | 5.29 (1.94 to 11.51)                 | 2.55 (0.56 to 6.26)                                   |
|                        |                       |                 |         | Heterogeneity p=0.64<br>Trend p=0.35 | <b>Heterogeneity p=0.03</b><br><b>Trend p=0.01</b>    |
| Attained Age           | 5-29                  | 4/0.65          | 141,477 | 6.12 (1.67 to 15.67)                 | 0.12 (0.02 to 0.34)                                   |
|                        | 30-39                 | 5/0.93          | 139,138 | 5.36 (1.74 to 12.52)                 | 0.99 (0.08 to 1.26)                                   |
|                        | 40-49                 | 6/0.98          | 84,994  | 6.10 (2.24 to 13.28)                 | 2.78 (0.34 to 3.42)                                   |
|                        | 50+                   | 5/0.98          | 35,342  | 5.08 (1.65 to 11.86)                 | 6.60 (0.50 to 8.39)                                   |
|                        |                       |                 |         | Heterogeneity p=0.99<br>Trend p=0.85 | <b>Heterogeneity p=0.002</b><br><b>Trend p=0.0002</b> |
| Total                  |                       | 20/3.55         | 413,681 | 5.63 (3.44 to 8.69)                  | 0.40 (0.21 to 0.66)                                   |
|                        |                       |                 |         | <b>SMR not 1, p&lt;0.0001</b>        | <b>AER not 0, p=0.0002</b>                            |

**Table 4.16** - SMRs and AERs for death from non-CNS thromboembolic causes by individual explanatory variables, with likelihood ratio tests for heterogeneity and trend where appropriate. Where tests indicated a statistically significant heterogeneity or trend they are marked in bold.  
\*Test of deviance. \*\*Excluding N/R groups.

## **Discussion**

### **Overall findings**

Compared to the general population the relative risk of death from circulatory causes is significantly elevated for 5-year survivors of childhood cancer treated within the United Kingdom between 1940 and 1991 (SMR = 3.89, 95% 3.39 to 4.43). The risk is significantly elevated for all sub-categories of circulatory disease analysed except for death from peripheral vascular disease, where the risk is non-significantly elevated (see Table 4.3). Previous studies have reported that overall mortality rates in 5-year survivors have been decreasing with more recent eras of diagnosis.<sup>13-18</sup> However, the majority of this improvement is known to be due to a reduction in the mortality from progression/recurrence of the primary disease.<sup>16</sup> Only one study<sup>15</sup> has demonstrated a reduction in deaths from non-cancer causes with more recent era of diagnosis and in that study it is note-worthy that the decrease in mortality occurred in the interval 5 to 9 years following cancer diagnosis whilst the mortality after 10+ years remained largely unchanged between diagnostic eras. This study of the BCCSS cohort demonstrates no evidence of a decrease in the risk of death from cardiac or cerebrovascular causes for 5-year survivors treated in the more recent eras between 1940 and 1991. Indeed, the risk of death from CM/HF increased dramatically over this time period. These observations highlight the importance of studying cohorts large enough to allow the analysis of subdivisions of causes of death into clinically relevant categories and also the need for continued follow-up for late cardiovascular events amongst patients treated more recently.

The absolute risk of death from circulatory causes was also significantly elevated (AER = 7.79, 95% CI 6.71 to 8.94). As consistently reported across many studies, the SMRs for cardiac causes are higher for females than males, reflecting the lower background mortality in the female population. Importantly, however, this study reinforces findings from the previous BCCSS report<sup>2</sup> that there is no difference between males and females in the absolute excess rate of

death from cardiac causes, either from CM/HF or other cardiac causes. The one exception to this pattern was thromboembolic disease, where female survivors had both an increased relative and absolute excess increase in the death rate from this cause compared to males. Additionally this study demonstrates that the absolute excess risk of death from cardiac causes other than CM/HF and of death from cerebrovascular causes continues to increase substantially with prolonged follow-up. The AER for cardiac death other than CM/HF reached 19.2 (95% CI 7.1 to 37.0) at 40+ years following diagnosis amongst those more likely to have received initial incidental cardiac irradiation and the AER for cerebrovascular death reached 37.2 (95% CI 17.4 to 69.3) amongst those treated for CNS tumours with initial RT. These findings highlight the need to examine absolute excess as well as relative risks in these studies, and also the importance of studying cohorts which have follow-up that is suitably prolonged in order to properly assess the life-long impact of diagnosis and treatment-related excess mortality.

#### **All cardiac mortality**

Several studies, including the large US and Nordic cohorts have previously reported increased cardiovascular mortality in 5-year survivors of childhood cancer (see Table 4.17). Previously reported SMRs for cardiac death vary from 3.2 to 7.0, consistent with the SMR of 3.4 reported in the current study. The variation in the SMRs observed between studies presumably reflects differences between the cohorts in terms of age range at diagnosis, era of diagnosis and length of follow-up, which can all affect the SMR for death from cardiac causes (see Table 4.4). For example, in the reports from the USCCSS the era of diagnosis is more recent and the length of follow-up shorter, both of which may contribute to the higher observed relative risk of cardiac death. Some variation may also be due to the composition of the different cohorts in terms of the types of childhood cancer included and the specific treatment protocols used in different countries. There are also some differences in the definition of 'cardiac' death in different

cohorts, with differences in the specific ICD editions and codes used to define the categories, which may affect results.

Long-term cause-specific mortality from all cardiac causes has previously been reported in the BCCSS.<sup>2</sup> This analysis is the first to attempt to look in greater detail at individual causes of cardiac death in long term survivors of childhood cancer, taking advantage of the greater number of deaths and person years of follow-up when compared to other cohorts.

#### **Deaths from cardiomyopathy and heart failure**

The increased risk of cardiac death observed in the more recent eras of diagnosis in the BCCSS (see Table 4.4) is predominantly due to an increased risk of death from CM/HF (see Table 4.7). This increased risk is observed in the tumour types that are likely to have received ACT. When compared to previous eras, the relative risk of death from CM/HF increases markedly in the late 1970s, which is the period when ACT came into use. This risk increases further in the 1980s when ACT use became more widespread. An increase in the number of heart transplants performed for childhood cancer survivors has previously been reported in a population-based UK study over the same period.<sup>19</sup>

| Study location (reference)     | Number of 5 year survivors | Years of diagnosis | Age at diagnosis | Mean FU, years (total PYs†)          | Cardiovascular SMR (95% CI)                | Cardiac SMR (95% CI)                       | Cerebrovascular SMR (95% CI)               |
|--------------------------------|----------------------------|--------------------|------------------|--------------------------------------|--------------------------------------------|--------------------------------------------|--------------------------------------------|
| UK, BCCSS (this study)         | 17,981                     | 1940-1991          | 0-14             | 23.0<br>(413,681)                    | 3.9 (3.4 to 4.4)<br>AER = 4.0 (3.3 to 4.7) | 3.4 (2.8 to 4.0)<br>AER = 2.2 (1.7 to 2.8) | 5.1 (3.9 to 6.6)<br>AER = 1.2 (0.8 to 1.6) |
| USA, USCCSS <sup>5,20</sup>    | 20,483                     | 1970-1986          | 0-20             | 16.5<br>(337,334)                    | Not reported                               | 7.0 (5.9-8.2)**                            | Not reported                               |
| Scandinavia <sup>13</sup>      | 13,711                     | 1960-1989          | 0-19             | 11.4<br>(156,046)                    | Not reported                               | 5.8 (4.2 to 7.6)***                        | 4.6 (3.3 to 6.2)****                       |
| Scotland <sup>14</sup>         | 5,229                      | 1981-2003          | 0-24             | 11.2<br>(58,358)                     | 2.4 (1.4 to 3.9)<br>AER = 0.8 (0.1 to 2.1) | Not reported                               | Not reported                               |
| France & UK <sup>21</sup>      | 4,122                      | 1942-1986          | 0-16             | 21.0<br>(86,453)                     | 5.0 (3.3 to 6.7)                           | 5.8 (3.9 to 9.0)                           | 3.2 (1.4 to 6.3)                           |
| Finland <sup>22</sup>          | 2,948                      | 1966-1999          | 0-14             | 15.7<br>(46,412)                     | 2.7 (1.1 to 5.5)                           | Not reported                               | Not reported                               |
| Canada <sup>17</sup>           | 2,354                      | 1970-1995          | 0-19             | 10.4<br>(24,491)                     | 9.69 (4.19-19.1)<br>AER = 3.00             | Not reported                               | Not reported                               |
| US, St Jude <sup>18</sup>      | 2,053                      | 1962-1983          | Not reported     | 24.7*, 1963-1970<br>14.2*, 1971-1983 | Not reported                               | 6.0 (1.7-15.0)                             | 4.2 (1.1 to 10.8)                          |
| US, Roswell Park <sup>23</sup> | 1,441                      | 1960-1989          | 0-19             | Not reported                         | Not reported                               | 3.2                                        | Not reported                               |
| Netherlands <sup>24</sup>      | 1,378                      | 1966-1996          | 0-17             | 16.1*                                | 5.64 (1.16-16.5)<br>AER = 1.5              | Not reported                               | Not reported                               |

**Table 4.17** – Studies which have reported circulatory SMRs. †PYs = Person years follow-up. †Plus AERs if reported. \*Median FU. \*\*Cardiac SMR was 8.2 (6.4 to 10.4) with 208,947 PYs FU (mean of 10.3 years). \*\*\*Includes other circulatory diseases except stroke. \*\*\*\*Includes other CNS diseases.

This undoubted increase in the relative risk of death from CM/HF must be placed in the context of two facts; 1) the 5-year overall survival rates for cancer in which there is the most substantially increased risk (ALL, AML, NHL, Wilms' tumour and soft tissue sarcoma) have all improved dramatically over the same period as evidenced by data from the UK Childhood Cancer Research Group<sup>25</sup> (see Table 4.18), and 2) the absolute number of deaths from CM/HF (42 in 17,891 5-years survivors) and heart transplants (46 between 1986 and 2006)<sup>19</sup> is relatively small when compared to the number of children who, without receiving potentially cardiotoxic treatment, may not have achieved 5-year survivorship. Additionally the number of deaths from cardiac causes is still substantially smaller than those caused by cancer (primary, recurrent, and second malignancies).

| 5-year survival in UK by diagnostic era (%) |           |           |           |           |           |           |           |
|---------------------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Diagnostic group                            | 1971-75   | 1976-80   | 1981-85   | 1986-90   | 1991-95   | 1996-00   | 2001-05   |
| Leukaemia (excl. AML)                       | 41        | 53        | 69        | 74        | 81        | 83        | 88        |
| AML                                         | 6         | 14        | 26        | 44        | 51        | 65        | 64        |
| Hodgkin lymphoma                            | 80        | 87        | 90        | 91        | 97        | 94        | 95        |
| NHL                                         | 24        | 41        | 65        | 74        | 77        | 81        | 83        |
| CNS (excl. PNET)                            | 47        | 50        | 58        | 58        | 67        | 71        | 71        |
| PNET                                        | 25        | 35        | 42        | 42        | 46        | 55        | 56        |
| Neuroblastoma                               | 17        | 28        | 42        | 40        | 52        | 60        | 64        |
| Retinoblastoma                              | 88        | 88        | 89        | 95        | 95        | 97        | 99        |
| Wilms' tumour                               | 59        | 76        | 78        | 84        | 78        | 88        | 85        |
| Bone sarcoma                                | 28        | 32        | 41        | 57        | 61        | 64        | 61        |
| Soft tissue sarcoma                         | 37        | 49        | 58        | 62        | 64        | 65        | 67        |
| Non-CNS GCT                                 | 45        | 59        | 73        | 81        | 85        | 86        | 92        |
| <b>All childhood cancers</b>                | <b>40</b> | <b>50</b> | <b>61</b> | <b>66</b> | <b>73</b> | <b>76</b> | <b>78</b> |

**Table 4.18** – 5-year survival for childhood cancers diagnosed in the UK, by era of diagnosis and by diagnostic group

More than 50% of childhood cancer survivors treated recently will have received ACT.<sup>26</sup> The potential for cardiotoxicity from ACT has been understood since anthracyclines were first used clinically almost half a century ago.<sup>27</sup> The primary pathology seen is dilated cardiomyopathy, with systolic dysfunction leading to heart failure. In children a restrictive cardiomyopathy may also be seen as cardiac damage occurs whilst the heart is still developing.<sup>28</sup> The risk is well known to be related to the dose of ACT received but importantly there is no dose of ACT for

which there is no risk of late-onset and progressive toxicity.<sup>29</sup> It is now recognised that exposure to ACT may initiate a process of injury that can be followed by a period of years to decades of subclinical compensatory response to that injury, that is eventually followed by overt symptomatic HF, when contractility and adequate cardiac function can no longer be adequately maintained.<sup>30</sup> It has been previously reported that, as well as dose, younger age at treatment and female sex are associated with a higher risk of cardiac abnormalities and congestive heart failure following anthracycline treatment.<sup>4,31</sup> The results from this study for deaths from CM/HF in the group potentially exposed to anthracyclines (see Table 4.7) demonstrate the relative SMR for females is significantly higher than for males (24.0 vs. 7.1,  $p=0.0003$ ), but this is largely reflective of the lower background population rate for females rather than a higher ACT-related risk for females versus males per se. The AER of death from CM/HF for females is not significantly different to that for males (1.69 vs. 1.17,  $p=0.3$ ). The absolute death rate ratio for females versus males is 1.3, however, which is consistent with the hazard ratio of 1.4 (95% CI 1.1 to 1.9) for females versus males reported for non-fatal congestive heart failure in the USCCSS.<sup>4</sup> There was no evidence of any significant difference in the SMR, or the AER, for CM/HF by age at diagnosis.

Due to a lack of population-based data on long-term follow-up for detection of anthracycline toxicity, the true prevalence of subclinical cardiomyopathy in survivors who received ACT is difficult to establish with any certainty, but may be up to 56%.<sup>32</sup> A substantial population of adult survivors who previously received ACT are no longer in routine follow-up and yet are at risk of developing late-onset clinical cardiac toxicity. Various national guidelines<sup>33,34</sup> state that survivors who have received anthracyclines should be monitored so that any evidence of cardiac dysfunction can be detected and, if it becomes clinically necessary, treated. Although subclinical cardiac toxicity has been demonstrated to be linked to self-reported health scores in the absence of clinically apparent cardiac disease,<sup>35</sup> it is important to recognise that there is no

current treatment identified that can prevent the progression of cardiotoxicity detected at a preclinical stage.<sup>36</sup> Whilst there is a recognised need for evidence-based guidelines to monitor cardiac function in childhood cancer survivors, unfortunately there is a lack of good evidence to determine the best type and frequency of testing to achieve this.<sup>37</sup> A promising approach seems to be a combination of blood biomarkers, such as cardiac troponin t and N-terminal pro-brain natriuretic peptide, taken at the time of treatment, in combination with appropriate cardiac imaging, to identify those at greatest risk.<sup>38</sup> Genetic polymorphisms may also be able to identify which individuals may be predisposed to developing cardiomyopathy,<sup>39,40</sup> but such approaches remain investigational.

#### **Death from ischaemic heart disease and other cardiac causes**

The relative and absolute excess risks of death from IHD and other cardiac causes are also elevated in this study (see Table 4.3). This is consistent with an elevated risk of non-fatal IHD and VHD identified in the USCCSS.<sup>4</sup> The risk of non-fatal pericardial disease was also elevated in the USCCSS, but as there was only 1 death from pericardial disease reported in the BCCSS this could not be analysed separately. The commonest cause of cardiac death was IHD, with an SMR of 2.30 (95% CI 1.77 to 2.93) and, in combination with CM/HF, these two categories contain the majority (80%) of excess cardiac deaths observed in the cohort. As for CM/HF the relative risk of death from the other cardiac causes of death is higher in females than in males, again reflecting the lower background rate for females. The apparent trend for an increased relative risk of death for an earlier age at diagnosis was no longer significant after adjustment for attained age. Similarly, the trend for a higher relative risk of death in more recent eras of diagnosis was no longer significant after adjustment (see Table 4.8). The relative risk of death from cardiac causes other than CM/HF decreases with years from diagnosis, but importantly still remains elevated compared to the general population at 40+ years, SMR=1.91 (95% CI 1.27 to 2.75). Despite the trend for a reduction in relative risk with years from diagnosis, the trend in terms of absolute



risk is in the opposite direction, with the absolute excess risk increasing to 7 extra deaths per 10,000 person years at 40+ years after diagnosis. This absolute risk is highest amongst those survivors within diagnostic groups more likely to have received incidental cardiac irradiation and recorded as have received initial RT, reaching 19 extra deaths per 10,000 person years at 40+ years after diagnosis (see Table 4.10.1). These observations serve to highlight 2 important risk factors that determine the absolute risk of cardiac death from causes other than CM/HF amongst childhood cancer survivors; years from diagnosis (or attained age) and the receipt of cardiac irradiation, reinforcing the need for life-long health promotion amongst these individuals.

The majority of cardiac deaths in this cohort are from IHD. Unlike anthracycline-induced cardiomyopathy discussed above, for IHD there are evidence-based interventions in the form of control of conventional cardiovascular risk factors (smoking, hypertension, hypercholesterolaemia) that can be employed to reduce the future risk. Given the equivalence of the AERs for CM/HF and IHD within this cohort, and the absence of effective interventions to prevent the progression of cardiomyopathy even when identified at an early, subclinical stage, it can be argued that the healthcare resources available for the care of childhood cancer survivors may be better used in the prevention, detection and treatment of conventional cardiovascular risk factors to reduce the risk of IHD, rather than on regular cardiac imaging such as echocardiography to detect, but not to treat, anthracycline-induced cardiomyopathy.

### **Cerebrovascular disease and cranial irradiation**

Cases of cerebrovascular disease after the treatment of paediatric CNS tumours have long been recognised.<sup>41</sup> The first large cohort study to examine the incidence of non-fatal stroke in childhood cancer survivors was the USCCSS, who reported dose-dependent risks following neck and cranial radiotherapy for Hodgkin lymphoma,<sup>42</sup> leukaemia and brain tumours.<sup>43</sup> The results

from this study have recently been updated<sup>44</sup> demonstrating an elevation in the relative risk of stroke, compared to sibling controls, for a wider range of tumour types varying from 2.6 (95% CI 1.2-5.9) for NHL to 30.1 (95% CI 17.9– 50.8) for CNS tumours.

Death from cerebrovascular disease following treatment for childhood cancer has been less well studied than the risk of non-fatal cerebrovascular events. The calculated SMR for cerebrovascular deaths within the whole BCCSS cohort was 5.1 (95% CI 3.88 to 6.58) which is similar to SMRs that have been previously reported (see Table 4.17).<sup>13,18</sup> This study is the first to look in more detail at deaths from stroke in childhood cancer survivors. Unsurprisingly, the majority of cerebrovascular deaths (68%) occurred in survivors of CNS tumours, with an SMR of 11.8 (95% CI 8.4 to 16.1). The only other study that has previously reported an SMR for cerebrovascular death following treatment for CNS tumours diagnosed within this age group found a comparable increase (SMR = 8.9, 95% CI 1.1 to 32.2).<sup>22</sup> Within the BCCSS cohort the only tumour groups, other than CNS tumours, where the risk of stroke death was significantly elevated were NHL and 'Others' (see Table 4.12). It is important to note that, despite the association recognised between treatment for leukaemia and non-fatal stroke in the USCCSS,<sup>44</sup> there was only 1 death from stroke amongst the patients treated for leukaemia within the BCCSS, despite more than 90,000 person years of follow-up. This strongly suggests that the lower dose of cranial irradiation that has been used in the treatment of leukaemia does not result in a substantially increased risk of fatal stroke over the follow-up period studied. In contrast, the risk of non-fatal stroke observed following higher dose irradiation of the cerebral or cervical vasculature, as used in the treatment of CNS tumours and lymphomas, is reflected in a subsequently increased risk of death from cerebrovascular disease.

The only significant risk factors for death from stroke following treatment for CNS tumours within this cohort were the initial use of RT and years from diagnosis (or attained age). The

absolute risk of death from stroke continues to increase more than 40 years from diagnosis with no evidence of any plateau. There is no evidence from this analysis that the risk of stroke following treatment for CNS tumours has decreased for patients treated in recent eras. These observations highlight the importance of life-style advice (especially with regards to smoking) and life-long surveillance for potentially modifiable cerebrovascular risk factors (such as hypertension, hypercholesterolaemia and diabetes) amongst these patients.

### **Strengths of the study**

The main strengths of this study are the size of the cohort and the fact that it is population-based and nationwide. It can be seen from Table 4.17 that it is the second largest in terms of the number of 5-year childhood cancer survivors included and has the highest number of person years of follow-up of any study world-wide. The median length of follow-up also exceeds that of any other study and the cohort has the highest number of individuals with >20 years follow-up. As stated above, this allows individual causes of cardiac death to begin to be examined, 3 decades and more following diagnosis with childhood cancer. The fact that the cohort is population-based, utilising data from the National Registry of Childhood Tumours based at the Childhood Cancer Research Group,<sup>25</sup> has ensured that the cohort is representative of children diagnosed and treated within the UK. Vital status and cause of death ascertainment from national registries, in combination with cause-specific population-based death rates, allows the confident calculation of the relative and absolute excess risks observed.

### **Limitations of the study**

The main limitation of the study is the absence of detailed treatment data, such as radiotherapy details and anthracycline doses, for individuals within the cohort. A record of whether individuals received initial treatment with surgery, chemotherapy or radiotherapy is available for a substantial proportion of the cohort which, in combination with the known tumour type,

allows the production of useful results based on reliable assumptions regarding the probability that groups would have received certain treatments. But the lack of individual treatment data prevents any more detailed analysis regarding the effects of treatment with anthracyclines and radiotherapy within the cohort. Additionally there is no record of any treatment for cancer recurrence (or second cancer). This is important as such additional therapy may also be cardiotoxic and has been linked to a higher risk of subsequent death from non-cancer causes.<sup>24</sup>

The causes of death used within the study are obtained from national registries and, whilst this allows the near complete ascertainment of cause of death within the cohort (99.6%), these are the causes of death that are recorded on death certificates and have not been validated. Lack of validation is unlikely to affect the results however as causes of death from cardiovascular disease occurring at a young age, such as in this population, are likely to be reliable in the majority of cases. In addition, the calendar year, age and gender-matched reference population rates are also based on non-validated causes of death, so that estimates of risk would be unbiased in this respect.

## **Conclusions**

This study highlights that the absolute excess risk of death from heart disease and stroke continues to increase in the decades following the achievement of cure of childhood cancer, with no evidence of a plateau at more than 40 years after diagnosis. Although a substantial issue, cardiovascular toxicity in adult survivors of childhood cancer probably remains under-recognised. There are several possible reasons for this. It may be difficult to diagnose partly because the interval between cancer therapy and onset of late cardiovascular effects can be several decades. Moreover, a treatment history of prior cancer therapies may not be routinely obtained in adult patients presenting with symptoms, potentially leading to misattribution of aetiology. Even when a prior history of childhood cancer treatment is known, the general

appreciation of late risks for treatment-related cardiovascular problems may remain underestimated. Also there tends to be an emphasis on monitoring for CM/HF whereas, in the longer term, it appears that IHD may cause the largest proportion of late excess cardiac disease. These data underlines the importance of the work currently being undertaken by the National Cancer Survivorship Initiative<sup>45</sup> to promote the development of life-long pathways of care for survivors of childhood cancer including the appropriate education, support and surveillance as decided on an individualised basis. Although an analysis of children treated more than 20 years ago, these data remain relevant for patients being treated today who are still exposed to anthracyclines and radiotherapy as part of their curative treatment. Such analyses are likely to become increasingly important in the future with the introduction of newer treatments, such as tyrosine kinase inhibitors, that may cause additional cardiovascular toxicity.<sup>46</sup> It is appropriate therefore that the BCCSS is being prolonged and expanded by the addition of more than 16,000 5-year survivors diagnosed with cancer aged under 15 years within the UK between the years 1992 to 2005 and will continue to be updated with those diagnosed in subsequent years. In order to get the most clinically useful information from this cohort in the future, studies will need to be designed that incorporate individual treatment data. Although not collated routinely in the past there is hope that, with formal end-of-treatment summaries becoming routine practice on a national basis, such treatment data will be more easily available in the future.

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## **Chapter 5 - Risk Factors for Valvular Heart Disease following Hodgkin Lymphoma**

### **Introduction**

Hodgkin lymphoma (HL) is an archetype type of curable malignancy. Treatment for HL has developed over the last 40-50 years, and survival rates have improved, such that >80% of patients are now expected to survive for 10 years or more following diagnosis. However, it is well documented that radiotherapy (RT) given in the past for HL is an important cause of increased mortality and morbidity from cardiovascular disease in long-term survivors.<sup>1-8</sup> Increasing recognition of the potential for adverse late effects of RT, along with the successful use of combined modality involving both RT and chemotherapy, has led to a reduction in the doses and volumes of RT used for HL treatment. Despite this, involved-field RT to 20 or 30 Gy may still result in substantial incidental radiation exposure of the heart if the disease affects the mediastinum (see Chapter 6). Even the reduced target volumes used for involved-node RT will result in a substantial cardiac dose in a proportion of patients.<sup>9</sup> Whilst it is predicted that the risk of radiation-induced heart disease will be less for patients treated today, who will receive lower doses and volumes of radiotherapy on average than in the past, it is not known what this risk will be. Dose-response relationships for cardiac mortality (see Chapter 6) and ischaemic heart disease following breast cancer (see Appendix F)<sup>10</sup> are now available. Cardiac irradiation is also known to increase the risk of valvular heart disease (VHD).<sup>2,8,11-13</sup> But, despite the frequency of asymptomatic valvular defects being reported as 36% by 6 years following treatment<sup>14</sup> and haemodynamically significant valvular dysfunction being as high as 42% in 20 year survivors,<sup>15</sup> very little is known regarding the radiation dose-response for VHD or other risk factors for the development of VHD in HL survivors. The aims of this study were to characterise the risk factors and to develop a dose-response for radiation-induced VHD that will assist estimation of VHD risk for patients whose treatment involves incidental irradiation of the heart.

## **Methods and Materials**

### **Overview and cohort**

A case-control study of VHD was conducted, nested within a cohort of long-term HL survivors. The cohort consisted of 1,851 5-year survivors of HL, diagnosed between the ages of 15 and 41, treated in the Netherlands between 1965 and 1995. They were identified through hospital-based cancer registries at The Netherlands Cancer Institute, Amsterdam (NKI-AvL), The Erasmus MC-Daniel den Hoed Cancer Center, Rotterdam (DdHK) and Leiden University Medical Center, Leiden (LUMC). This cohort is long-established and detailed descriptions of patient selection and methods of the original data collection have been published in previous reports from The Netherlands Cancer Institute.<sup>1,2,16,17</sup> The study protocol was approved by the ethics review board of Netherlands Cancer Institute. The requirement for informed consent was waived as the study only required review of medical information that had already been collected.

### **Cases and controls**

Patients were eligible for the study if: a) they had survived for 5 years after a histologically confirmed diagnosis of HL, b) they were between 15 and 41 years of age at HL diagnosis, c) they had no other malignancy (apart from non-melanomatous skin cancer or carcinoma in-situ of the breast or cervix) prior to HL. Patients who developed VHD (CTCAEv.4.0, grade  $\geq 2$ )<sup>18</sup> as their first diagnosis of significant heart disease were included as cases provided that RT for HL was the only RT given towards the head, neck or trunk at the time of their diagnosis of VHD. For each case 3 controls were initially sought from within the cohort, matched on gender, age at HL diagnosis (<1 year) and date of HL diagnosis (<3 years). If <2 controls were found for a case, matching criteria were relaxed until 2 were found, up to maximum difference of 4 years for age at HL diagnosis and 5 years for date of diagnosis. Additionally, controls had to be free of VHD prior to a cut-off date. This was defined as the date of HL diagnosis plus a time interval equal to

the date of HL diagnosis to the date of VHD diagnosis for the corresponding case. Controls were selected with replacement, so some individuals served as a control for more than one case.

For all VHD patients detailed information on their VHD diagnosis was requested from their general practitioner and/or cardiologist. Cardiology reports were requested and reviewed when available. Patients with grade 1 VHD were followed-up in order to identify possible subsequent case-defining events, therefore patients with grade 1 VHD were eligible as controls until a first diagnosis of VHD, but not thereafter.

### **Data collection**

Details of medical history, HL treatment at diagnosis (and any relapse), cumulative doses and dates of administration of all cytotoxic chemotherapy drugs, second malignancies, cardiovascular diseases and cardiovascular risk factors (including smoking, body mass index, hypertension, hypercholesterolaemia and diabetes) both at diagnosis of HL and at diagnosis of VHD (index date for controls) were abstracted from medical records for cases and 2 controls. Where data was already available for a third matched control this was also used.

Copies of original RT prescription sheets and simulation and/or verification x-rays were obtained from the three radiotherapy centres in the study. Where original prescriptions were not available, information regarding RT including dates, anatomical areas, dose, fractionation and treatment energy were abstracted from clinical notes.

### **Retrospective radiation dosimetry methods**

A technique utilising virtual simulation of historic treatment fields on substitute CT data sets within a CT-based treatment planning system was used to reconstruct the RT regimens used for the treatment of HL over the study period.

#### **Choice of substitute CT data sets**

Two CT data sets, one for male patients and one for females, were chosen as typical representative substitute sets on which to recreate the RT treatments, as individual CT data from the actual patients were not available. These were chosen from a library of 50 CT data sets (25 male and 25 female) of patients treated more recently for HL, on the basis of having typical anatomy (defined in terms of body surface area, mediastinal separation and heart volume) and typical dosimetry (defined in terms of mean heart dose from a standardised 8MV mantle field plan).

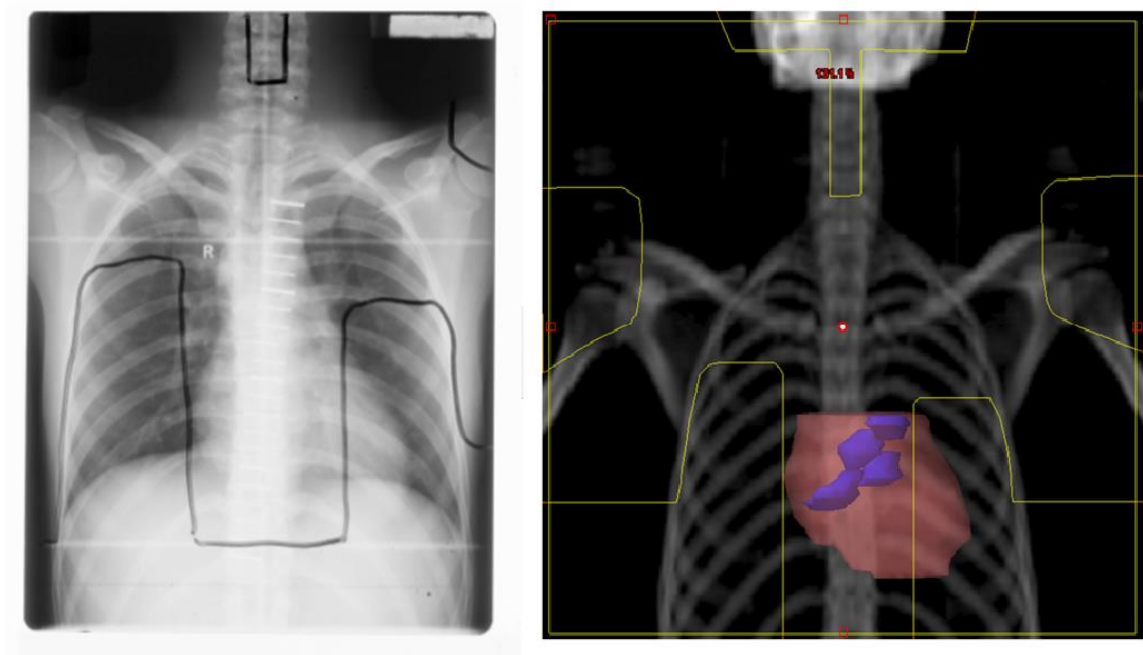
#### **Cardiovascular outlining**

The heart and individual cardiac structures were outlined on the substitute data sets as per a heart atlas specifically developed to study cardiac exposure during radiotherapy.<sup>19</sup> This process is described in greater detail in Chapter 6 (page 138).

#### **Field reconstruction**

Treatment field size and position were reconstructed with virtual simulation using the patient's original simulation and verification films as a guide. Shielding was recreated with reference to the original films. Both bony and mediastinal anatomy were used as landmarks for the positioning of the field and shielding. If there was an obvious discrepancy between the proportions of the heart shielded in the reconstructed field versus the original films when using

bony anatomy as a guide, a pragmatic approach was taken to favour matching the proportion of heart in the field, as this was the organ for which the radiation dose was to be estimated. During reconstruction it was not known whether the patient was case or control. See Figure 5.1 for an example of an original simulation field and the reconstructed field overlaid upon a digitally reconstructed radiograph.



**Figure 5.1** – An example of an original simulation film (left) with field borders marked in black and the same field reconstructed on a substitute CT data set with the field overlain upon a digitally reconstructed radiograph (right), with the field borders in yellow. The heart (pink) and the heart valves (blue) are outlined to demonstrate their position.

Original simulation or verification films were not available for a proportion of the patients reconstructed. In these cases reconstructions were produced based on hand-drawn diagrams from prescription sheets and with reference to x-ray films from patients who had received the same type of treatment during the same era and at the same radiotherapy centre.

Many of the fields reconstructed were large and were treated at an extended focus skin distance (FSD). This distance was generally available from the prescription sheets and replicated in the reconstruction.

A proportion of patients received either total nodal irradiation or sub-total nodal irradiation. The junction between the mediastinal and para-aortic fields was often shifted up and/or down by a thoracic level during treatment to try and reduce the impact of dosimetric uncertainty at the match of adjoining fields. These shifting junctions, or 'slip zones', were reproduced within the reconstructions as they often included the apex of the heart.

Laryngeal and spinal shielding was included in the reconstructions where indicated based on the original treatment information. Some treatments had anterior laryngeal shielding throughout and others incorporated laryngeal shielded at a certain dose. Some treatments had no spinal shielding, some had posterior shielding of the cervical cord only and others had posterior shielding of the entire length of the spinal cord within the field. Again, some treatments shielded the spinal cord throughout the full course and others incorporated spinal cord shielding at a certain dose. No specific sub-carinal shielding of the heart was recorded as being used. For practical reasons, some fields known to have been administered were not recreated where the cardiac radiation dose from that field would have been negligible (e.g. submental or groin electron fields).

#### Dose prescription

For mantle and modified-mantle treatments during the majority of the study period, the dose delivered was manually calculated for several points in a superior-inferior direction (for example the neck, jugular notch, axillae and mediastinum) along the mid-plane of the patient taking the variation in separation at different levels into account. As the organ of interest in this study was the heart the prescription point of most relevance was the mid-mediastinum. Therefore the precise dose and fractionation recorded in the treatment sheets as being delivered to this point

was used as the basis for the prescription of the reconstructed fields. Many other treatments, including those inferior to the diaphragm, were prescribed to the midline in a similar fashion. A minority of fields (for example individual anterior fields to the supraclavicular fossae) were prescribed at depth as indicated in the original treatment records.

#### Dose calculation

Dose distributions were calculated using the Eclipse RT treatment planning system (Version 10.0.28, Varian Medical Systems, Palo Alto, CA). The anisotropic analytical algorithm (AAA) photon-beam dose calculation algorithm was used to calculate linear accelerator-based megavoltage (MV) treatments and the pencil beam model was used to calculate cobalt-60 treatments.

Dose depth calculations, when originally performed for treatment, were not done with any correction for tissue homogeneity. Therefore the dose distributions for the reconstructions were first calculated with homogeneity correction in the dose calculation algorithm turned off. The monitoring units (MUs) that gave the prescribed dose to the midline prescription point were noted down. The homogeneity correction was then turned back on, the dose distribution recalculated and the MUs as noted following the first calculation re-entered to produce the most accurate reflection of the dose distribution that would have been received from the historical techniques. This process was not possible for the cobalt treatment calculations (where a number of MUs is not given).

#### Dosimetric adjustment for variation in fraction size

Many of the radiotherapy treatments did not administer fractions of equal dose throughout the entire course. A common practice at the Netherlands Cancer Institute during the time period covered by the study was to start with a smaller fraction size (e.g. 0.75 Gy) on the first day of treatment and increase the dose to a conventional fraction size (e.g. 2 Gy) over several treatments. In order to take account for the possible biological effect of this alteration in fraction size the equivalent dose in 2 Gy fractions (EQD2 – see Appendix C) was calculated separately for each fraction size and the results summed to gain an EQD2 for the entire course.

#### Dosimetric adjustment for alternation of supine and prone treatment positions

The majority of mantle field treatments during the study period were administered by irradiating anterior and posterior fields on separate days with the patient position alternating from supine to prone. Due to the limited availability of prone CT data sets (HL patients are now treated in a supine position throughout), it was not possible to use a substitute data set with the patient in a prone position to reconstruct the posterior fields and therefore not possible to account for any movement in the heart or cardiac substructures that may occur with alteration in patient position. Both anterior and posterior fields were reconstructed on a substitute CT data set acquired with the patient in a supine position. In order to account for the possible biological effect of the difference in the dose distribution to the heart and cardiac sub-structures that would occur from day-to-day with anterior and posterior fields being administered on separate days, the organ and structure at risk DVHs for anterior and posterior fields were calculated separately and EQD2 calculations were performed using separate DVHs and the results subsequently summed, rather than a summed DVH of the anterior and posterior fields being used to perform EQD2 calculations.



### **Statistical analysis**

Odds ratios (ORs) were estimated using multivariable conditional logistic regression analyses. For analyses in which the explanatory variable was categorical, the confidence intervals for every category, including the reference category, were estimated from the amount of information in that category.<sup>20</sup> For the evaluation of the proportional increase in the frequency of valvular heart disease with increasing radiation dose (d) to the affected valve in EQD2, various models were fitted and compared. These were a standard exponential model where the ORs are exponential in dose (model 1):  $OR(d)=\exp^{\beta d}$  and a simple Excess Odds Ratio (EOR) model where the ORs are linear in dose (model 2):  $OR(d)=1+\beta d$ . Departure from linearity was evaluated by extending the linear model to include an exponential factor (model 3):  $OR(d)=1+\beta d*\exp^{\delta d}$ , where  $\delta$  measures the concavity ( $\delta < 0$ ) or convexity ( $\delta > 0$ ) in the EORs for dose. A test of the null hypothesis  $\delta=0$  is a test of no departure from linearity. In order to ease estimation of confidence intervals, models 2 and 3 were re-parameterised, such that estimates were exponential in dose; model 2a:  $OR(d)=1+\exp^{\beta}d$  and model 3a:  $OR(d)=1+\exp^{\beta}*d*\exp^{\delta d}$ . Confidence intervals for the parameters derived from these models were based on the parameter profile likelihood. We estimated point-wise confidence intervals for the resulting dose-response curves based on Wald tests. The adequacy of these models for summarizing the dose-response relationship was assessed by comparing the resulting estimated ORs with dose to ORs derived from analysis on categories of radiation dose. Multivariable analyses were used to control for confounding and to assess interactions between radiation dose and other factors. All significance tests were two-sided and, for all analyses, a p-value of  $\leq 0.05$  was taken to indicate statistical significance. Analyses were performed using STATA statistical software version 11.0 (STATAcorp 2009)<sup>21</sup> and Epicure, version 1.8 (Hirosoft International).

## **Results**

### **Cases and controls**

89 cases were identified and 200 controls were included in the study. The matching criteria are compared in Table 5.1, demonstrating that cases and controls were well matched. A flow chart of case and control selection is included in Appendix C (Table C.1).

| <b>Characteristics used for matching</b> | <b>Cases (%)</b>  | <b>Controls (%)</b> |
|------------------------------------------|-------------------|---------------------|
| <b>Sex</b>                               |                   |                     |
| Male                                     | 30 (33.7)         | 64 (32.0)           |
| Female                                   | 59 (66.3)         | 136 (68.0)          |
| <b>Age at Diagnosis</b>                  |                   |                     |
| <20 years                                | 21 (23.6)         | 49 (24.5)           |
| 20-29 years                              | 42 (47.2)         | 93 (46.5)           |
| 30-41 years                              | 26 (29.2)         | 58 (29.0)           |
| <b>Treatment Period</b>                  |                   |                     |
| 1965-1972                                | 32 (36.0)         | 79 (39.5)           |
| 1973-1979                                | 28 (31.5)         | 55 (27.5)           |
| 1980-1987                                | 20 (22.5)         | 47 (23.5)           |
| 1988-1995                                | 9 (10.1)          | 19 (9.5)            |
| <b>Follow-up Period</b>                  |                   |                     |
| 0-9 years                                | 7 (7.9)           | 14 (7.0)            |
| 10-19 years                              | 24 (27.0)         | 53 (26.5)           |
| 20-29 years                              | 42 (47.2)         | 99 (49.5)           |
| ≥30 years                                | 16 (18.0)         | 34 (17.0)           |
| <b>Totals</b>                            | <b>89 (100.0)</b> | <b>200 (100.0)</b>  |

**Table 5.1** – Characteristics used for matching cases and controls

Of the 89 cases, 45 first presented with grade 2 aortic valve defects, 22 with grade 2 mitral valve defects, 12 with combined aortic and mitral valve defects, while the remaining 10 patients presented with combined valve defects including the tricuspid valve and 1 unknown. No cases were recorded with a pulmonary valve defect. The characteristics of the valve defects diagnosed and the treatments received for them are described more fully in Table 5.2.

|                                                           | All, N (%) | Male, N (%) | Female, N (%) |
|-----------------------------------------------------------|------------|-------------|---------------|
| <b>First valvular defect</b>                              |            |             |               |
| Aortic                                                    | 45 (50.6)  | 22 (73.3)   | 23 (39.0)     |
| Mitral                                                    | 22 (24.7)  | 3 (10.0)    | 19 (32.2)     |
| Aortic + Mitral                                           | 12 (13.5)  | 2 (6.7)     | 10 (17.0)     |
| Aortic + Tricuspid                                        | 1 (1.1)    | 1 (3.3)     | 0 (0.0)       |
| Mitral + Tricuspid                                        | 3 (3.4)    | 0 (0.0)     | 3 (5.1)       |
| Aortic + Mitral + Tricuspid                               | 5 (5.6)    | 1 (3.3)     | 4 (6.8)       |
| Unknown                                                   | 1 (1.1)    | 1 (3.3)     | 0 (0.0)       |
| <b>Progression of valve defect</b>                        |            |             |               |
| No                                                        | 39 (43.8)  | 13 (43.4)   | 26 (44.1)     |
| Yes                                                       | 50 (56.2)  | 17 (56.7)   | 33 (55.9)     |
| <b>Highest CTCAE grade of VHD</b>                         |            |             |               |
| Grade II                                                  | 23 (25.8)  | 7 (23.3)    | 16 (27.1)     |
| Grade III                                                 | 18 (20.2)  | 3 (10.0)    | 15 (25.4)     |
| Grade IV                                                  | 48 (53.9)  | 20 (66.7)   | 28 (47.5)     |
| <b>Basis for Diagnosis of VHD</b>                         |            |             |               |
| Echocardiography                                          | 55 (61.8)  | 13 (43.3)   | 42 (71.2)     |
| Heart Catheterisation                                     | 5 (5.6)    | 4 (13.3)    | 1 (1.7)       |
| Both of above                                             | 7 (7.9)    | 5 (16.7)    | 2 (3.4)       |
| Unknown                                                   | 22 (24.7)  | 8 (26.7)    | 14 (23.7)     |
| <b>Treatment for VHD</b>                                  |            |             |               |
| None                                                      | 37 (41.6)  | 7 (23.3)    | 30 (50.9)     |
| Drug Therapy                                              | 17 (19.1)  | 3 (10.0)    | 14 (23.7)     |
| Valve replacement or repair                               | 25 (28.1)  | 15 (50.0)   | 10 (17.0)     |
| Both of above                                             | 5 (5.6)    | 3 (10.0)    | 2 (3.4)       |
| Unknown                                                   | 5 (5.6)    | 2 (6.7)     | 3 (5.1)       |
| <b>Treatment for VHD</b><br>(basis for diagnosis unknown) |            |             |               |
| None                                                      | 5 (22.7)   | 1 (12.5)    | 4 (28.6)      |
| Drug Therapy                                              | 5 (22.7)   | 0 (0.0)     | 5 (35.7)      |
| Valve replacement or repair                               | 10 (45.5)  | 5 (62.5)    | 5 (35.7)      |
| Unknown                                                   | 2 (9.1)    | 2 (25.0)    | 0 (0.0)       |
| <b>Totals</b>                                             | 89 (100.0) | 30 (100.0)  | 59 (100.0)    |

**Table 5.2** – Characteristics of the valvular heart disease diagnosed in cases

## **Radiation dosimetry**

### **Reconstructions performed and data available**

Individualised cardiac dose reconstruction was completed for 222 individuals who received RT for Hodgkin lymphoma between 1966 and 1995. These were based on both original prescription sheets and simulator films in 75% of cases and on either the prescription sheet alone or a combination of simulator films and a dose from clinical notes in a further 18%. In 7% of cases the reconstruction was based on a dose and simple description of the field type as detailed in the clinical notes. For 8 individuals who were known to have received RT there were insufficient data available to attempt any dose reconstruction. 15 individuals did not receive RT and did not therefore require dose reconstruction.

### **Treatment descriptors**

The mediastinal prescribed dose and the EQD2 administered to the midline of the mediastinum are given in Table 5.3. The modality and energies used to deliver the treatments are given in Table 5.4.

|                      | <b>Mediastinal prescribed dose (Gy)</b><br>Mean $\pm$ SD, Range (number) | <b>Mediastinal EQD2 delivered (Gy)</b><br>Mean $\pm$ SD, Range (number) |
|----------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------|
| <b>Gender</b>        |                                                                          |                                                                         |
| Male (81)            | 31.89 $\pm$ 11.79, 0.00 to 42.00 (77)                                    | 29.93 $\pm$ 14.52, 0.00 to 45.00 (67)                                   |
| Female(164)          | 34.24 $\pm$ 14.05, 0.00 to 42.00 (160)                                   | 33.26 $\pm$ 11.83, 0.00 to 48.13 (150)                                  |
| <b>Treatment Era</b> |                                                                          |                                                                         |
| 1965-72 (77)         | 34.87 $\pm$ 11.08, 0.00 to 42.00 (71)                                    | 33.30 $\pm$ 11.39, 0.00 to 48.13 (63)                                   |
| 1973-79 (76)         | 31.74 $\pm$ 14.92, 0.00 to 40.00 (75)                                    | 30.48 $\pm$ 15.33, 0.00 to 46.67 (68)                                   |
| 1980-87 (65)         | 32.42 $\pm$ 13.07, 0.00 to 41.40 (65)                                    | 31.29 $\pm$ 13.13, 0.00 to 45.00 (61)                                   |
| 1988-95 (27)         | 37.30 $\pm$ 4.85, 20.00 40.00 (26)                                       | 36.57 $\pm$ 3.79, 23.94 to 41.05 (25)                                   |
| <b>All (245)</b>     | 33.48 $\pm$ 12.59, 0.00 to 42.00 (237)*                                  | 32.23 $\pm$ 12.78, 0.00 to 48.13 (217)**                                |

**Table 5.3** – Mediastinal prescribed dose and the EQD2 delivered to the mediastinum for all patients in the study (cases and controls), by gender and treatment era. \*For 8 patients the individual mediastinal prescribed dose was unavailable. \*\*For 28 patients the individual fractionation was unavailable to calculate an EQD2.

| Era of Treatment   | Treatment Energy, n (%) |     |     |     |          |         | n/a**   |
|--------------------|-------------------------|-----|-----|-----|----------|---------|---------|
|                    | Cobalt-60               | 4MV | 6MV | 8MV | Any MV   | Unknown |         |
| 1965-72 (n=77)     | 20 (26)                 | 10  | 20  | 13  | 43 (56)  | 8 (10)  | 6 (8)   |
| 1973-79 (n=76)     | 4 (5)                   | 12  | 7   | 34  | 53 (70)  | 6 (8)   | 13 (17) |
| 1980-87 (n=65)     | 0 (0)                   | 15  | 4   | 34  | 53 (82)  | 4 (6)   | 8 (12)  |
| 1988-95 (n=27)     | 0 (0)                   | 7   | 5   | 11* | 23 (85)  | 4 (15)  | 0 (0)   |
| <b>All (n=245)</b> | 24 (10)                 | 44  | 36  | 92  | 172 (70) | 22 (9)  | 27 (11) |

**Table 5.4** – RT treatment energies used to treat patients in the study, by treatment era.

\*Includes one treated with 10MV. \*\*Did not receive RT or no RT data available.

#### Sub-diaphragmatic radiotherapy treatment

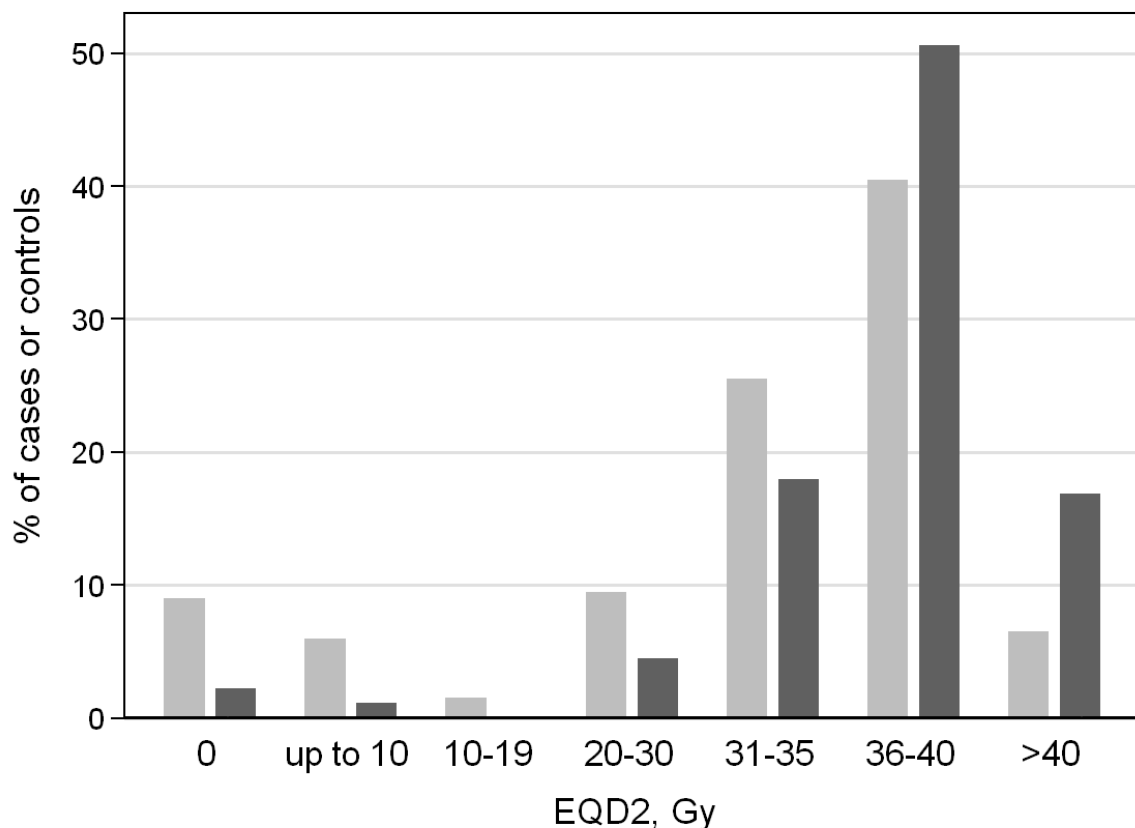
One hundred and eighteen of the patients treated with radiotherapy (51%) received treatment with a para-aortic or ‘inverted-Y’ RT field, either without any supra-diaphragmatic treatment (9 individuals) or, more usually, matched onto the caudal extent of a mediastinal field. 78 of these (66%) also received treatment to the spleen or splenic hilum. The median prescribed sub-diaphragmatic dose was 36 Gy (SD = 4.7, Range = 19.5 to 42.3 Gy), given in a median of 20 fractions (SD = 3.9, Range = 12 to 36), resulting in an average EQD2 of 35.8 Gy (SD = 5.3, Range = 17.1 to 45.0). Of those that received sub-diaphragmatic treatment 77% were treated with a shifting junction, most commonly with the borders shifting from below the vertebral body of T10 to below T11 or below the vertebral body of T11 to below T12.

#### Estimated radiation exposure for heart and cardiac substructures

The estimated radiation exposure to the heart and cardiac substructures from the individualised radiotherapy treatment reconstructions for all cases and controls combined is given in Table 5.5. The dose distribution to the affected heart valve in the cases and the corresponding heart valve in the controls is given in Figure 5.2.

| Cardiac Structure      | Estimated mean dose to structure (Gy) – Average $\pm$ SD (Range) | Estimated mean EDQ2 to structure (Gy) – Average $\pm$ SD (Range) |
|------------------------|------------------------------------------------------------------|------------------------------------------------------------------|
| Whole heart            | 28.70 $\pm$ 11.60 (0 to 62.10)                                   | 27.08 $\pm$ 11.03 (0 to 57.40)                                   |
| Aortic valve           | 33.34 $\pm$ 13.09 (0 to 78.95)                                   | 32.34 $\pm$ 13.15 (0 to 74.84)                                   |
| Mitral valve           | 33.42 $\pm$ 12.93 (0 to 58.99)                                   | 31.91 $\pm$ 12.55 (0 to 54.33)                                   |
| Pulmonary valve        | 34.93 $\pm$ 13.28 (0 to 62.13)                                   | 34.63 $\pm$ 13.62 (0 to 57.62)                                   |
| Tricuspid valve        | 32.73 $\pm$ 13.23 (0 to 84.90)                                   | 31.84 $\pm$ 13.36 (0 to 83.35)                                   |
| Left ventricle         | 22.89 $\pm$ 11.01 (0 to 48.21)                                   | 20.46 $\pm$ 10.13 (0 to 42.05)                                   |
| Right ventricle        | 31.75 $\pm$ 12.72 (0 to 75.83)                                   | 30.62 $\pm$ 12.56 (0 to 73.06)                                   |
| Left atrium            | 33.19 $\pm$ 12.73 (0 to 59.18)                                   | 31.81 $\pm$ 12.56 (0 to 52.96)                                   |
| Right atrium           | 33.67 $\pm$ 13.41 (0 to 85.02)                                   | 32.74 $\pm$ 13.32 (0 to 82.55)                                   |
| Left coronary          | 24.47 $\pm$ 11.56 (0 to 56.02)                                   | 22.44 $\pm$ 10.89 (0 to 50.38)                                   |
| Right coronary         | 32.71 $\pm$ 13.30 (0 to 85.14)                                   | 31.69 $\pm$ 13.14 (0 to 82.80)                                   |
| Circumflex coronary    | 33.54 $\pm$ 12.95 (0 to 51.79)                                   | 32.15 $\pm$ 12.64 (0 to 49.95)                                   |
| Sino-atrial node       | 35.03 $\pm$ 13.58 (0 to 81.29)                                   | 34.62 $\pm$ 13.84 (0 to 78.05)                                   |
| Atrio-ventricular node | 31.81 $\pm$ 12.88 (0 to 78.75)                                   | 30.34 $\pm$ 12.82 (0 to 74.14)                                   |

**Table 5.5** – Estimated doses and equivalent dose in 2 Gy fractions (EQD2) to the whole heart and cardiac substructures for the 237 individuals for whom individual dose reconstruction was performed (n=222) including those who were known not to have received RT (n=15)



**Figure 5.2** – Dose distribution (EQD2) to the affected heart valve in cases (dark grey) and the corresponding heart valves in controls (light grey).

## **Analysis of risk factors**

### **Univariable analysis**

A univariable analysis of patient-related factors is presented in Table 5.6 and of treatment-related factors in Table 5.7. Obesity at diagnosis ( $p=0.02$ ), hypertension at end of follow-up ( $p=0.02$ ), hypercholesterolaemia at end of the follow-up ( $<0.001$ ) and the total number of cardiovascular risk factors recorded ( $p=0.02$ ) were associated with an increased OR for developing VHD. Hodgkin lymphoma stage at diagnosis was associated ( $p=0.05$ ), with the highest OR being for stage II disease. Treatment with vincristine and procarbazine was associated with a *reduced* OR of VHD ( $p=0.003$  and  $p=0.01$  respectively) and splenectomy after HL diagnosis was associated with an increased OR. Radiation dose was associated with an increased OR for VHD whether expressed as prescribed mediastinal dose, estimated whole heart dose or estimated dose to the affected heart valve. The strongest association was for the dose to the affected heart valve ( $p<0.001$ ). The estimated mean dose to the affected heart valves in cases was 37.0 Gy, whereas the estimated mean dose to the corresponding valves in the matched controls was 30.5 Gy ( $p=0.001$  for difference).

| Cardiovascular Risk Factor                | Case (%)  | Control (%) | OR  | 95% CI      | p-value          |
|-------------------------------------------|-----------|-------------|-----|-------------|------------------|
| <b>Obesity at HL Diagnosis</b>            |           |             |     |             | <b>0.02</b>      |
| No                                        | 60 (67.4) | 160 (80.0)  | 1   |             |                  |
| Yes                                       | 27 (30.3) | 36 (18.0)   | 2.1 | 1.1 to 3.8  |                  |
| Unknown                                   | 2 (2.3)   | 4 (2.0)     |     |             |                  |
| <b>Obesity at end of FU</b>               |           |             |     |             | >0.5             |
| No                                        | 55 (61.8) | 124 (62.0)  | 1   |             |                  |
| Yes                                       | 31 (34.8) | 58 (29.0)   | 1.2 | 0.7 to 2.1  |                  |
| Unknown                                   | 3 (3.4)   | 18 (9.0)    |     |             |                  |
| <b>Smoker at Diagnosis</b>                |           |             |     |             | 0.40             |
| No                                        | 44 (49.4) | 96 (48.0)   | 1   |             |                  |
| Yes                                       | 40 (44.9) | 101 (50.5)  | 0.8 | 0.5 to 1.4  |                  |
| Unknown                                   | 5 (5.6)   | 3 (1.5)     |     |             |                  |
| <b>Smoker at end of FU</b>                |           |             |     |             | 0.39             |
| No                                        | 73 (82.0) | 146 (73.0)  | 1   |             |                  |
| Yes                                       | 12 (13.5) | 33 (16.5)   | 0.7 | 0.3 to 1.5  |                  |
| Unknown                                   | 4 (4.5)   | 21 (10.5)   |     |             |                  |
| <b>Diabetes at end of FU</b>              |           |             |     |             | >0.5             |
| No                                        | 78 (87.6) | 170 (85.0)  | 1   |             |                  |
| Yes                                       | 11 (12.4) | 23 (11.5)   | 1.1 | 0.5 to 2.5  |                  |
| Unknown                                   | 0         | 7 (3.5)     |     |             |                  |
| <b>Hypertension at end of FU</b>          |           |             |     |             | <b>0.02</b>      |
| No                                        | 58 (65.2) | 152 (76.0)  | 1   |             |                  |
| Yes                                       | 31 (34.8) | 43 (21.5)   | 2.0 | 1.1 to 3.5  |                  |
| Unknown                                   | 0         | 5 (2.5)     |     |             |                  |
| <b>Hypercholesterolaemia of end of FU</b> |           |             |     |             | <b>&lt;0.001</b> |
| No                                        | 49 (55.1) | 168 (84.0)  | 1   |             |                  |
| Yes                                       | 40 (44.9) | 26 (13.0)   | 4.9 | 2.6 to 9.1  |                  |
| Unknown                                   | 0         | 6 (3.0)     |     |             |                  |
| <b>Risk Factor</b>                        |           |             |     |             | 0.24             |
| No                                        | 12 (13.5) | 38 (19.0)   | 1   |             |                  |
| Yes                                       | 77 (86.5) | 162 (81.0)  | 1.5 | 0.8 to 3.1  |                  |
| <b>Number of Risk Factors</b>             |           |             |     |             | <b>0.02</b>      |
| 0                                         | 12 (13.5) | 38 (19.0)   | 1   | 0.5 to 1.9  |                  |
| 1                                         | 28 (31.5) | 86 (43.0)   | 1.0 | 0.7 to 1.6  |                  |
| 2                                         | 25 (28.1) | 52 (26.0)   | 1.5 | 0.9 to 2.4  |                  |
| 3                                         | 17 (19.1) | 19 (9.5)    | 3.1 | 1.5 to 6.3  |                  |
| 4/5                                       | 7 (7.9)   | 5 (2.5)     | 3.7 | 1.2 to 11.5 |                  |

**Table 5.6** – Patient-related cardiovascular risk factors with univariable odds ratios (ORs)



| Treatment Characteristic                       | Case (%)   | Control (%) | Odds Ratio | 95% CI       | p-value*         |
|------------------------------------------------|------------|-------------|------------|--------------|------------------|
| <b>Treatment Centre</b>                        |            |             |            |              | >0.5             |
| NKI-AvL                                        | 35 (39.3)  | 85 (42.5)   | 1          | 0.7 to 1.5   |                  |
| DdHK                                           | 37 (41.6)  | 81 (40.5)   | 1.2        | 0.8 to 1.8   |                  |
| LUMC                                           | 17 (19.1)  | 34 (17.0)   | 1.2        | 0.7 to 2.2   |                  |
| <b>Stage at HL Diagnosis</b>                   |            |             |            |              | <b>0.047</b>     |
| I                                              | 18 (20.2)  | 49 (24.5)   | 1          | 0.6 to 1.8   |                  |
| II                                             | 55 (61.8)  | 100 (50.0)  | 1.6        | 1.1 to 2.3   |                  |
| III                                            | 14 (15.7)  | 33 (16.5)   | 1.1        | 0.6 to 2.2   |                  |
| IV                                             | 1 (1.1)    | 14 (7.0)    | 0.2        | 0.0 to 1.5   |                  |
| Unknown                                        | 1 (1.1)    | 4 (2.0)     | -          | -            |                  |
| <b>Prescribed mediastinal dose (EQD2)</b>      |            |             |            |              |                  |
| Mean (SD)                                      | 37.0 (7.9) | 32.2 (13.7) | 1.04       | 1.01 to 1.08 | <b>0.009</b>     |
| No mediastinal RT                              | 3 (3.4)    | 28 (14.0)   | 1          | 0.3 to 3.3   | <b>0.025</b>     |
| ≤30 Gy                                         | 2 (2.3)    | 11 (5.5)    | 0.7        | 0.1 to 5.6   |                  |
| 31-35 Gy                                       | 17 (19.1)  | 41 (20.5)   | 3.4        | 2.0 to 6.1   |                  |
| 36-40 Gy                                       | 58 (65.2)  | 109 (54.5)  | 4.5        | 3.2 to 6.2   |                  |
| >40 Gy                                         | 3 (3.4)    | 8 (4.0)     | 3.9        | 1.0 to 14.7  |                  |
| Unknown                                        | 6 (6.7)    | 3 (1.5)     | -          | -            |                  |
| <b>Estimated average heart dose (EQD2)</b>     |            |             |            |              |                  |
| Mean (SD)                                      | 30.6 (7.8) | 25.9 (11.7) | 1.06       | 1.02 to 1.10 | <b>0.002</b>     |
| No mediastinal RT                              | 2 (2.3)    | 17 (8.5)    | 1          | 0.2 to 4.5   | <b>0.024</b>     |
| ≤30 Gy                                         | 34 (38.2)  | 90 (45.0)   | 3.4        | 2.1 to 5.5   |                  |
| 31-35 Gy                                       | 35 (39.3)  | 75 (37.5)   | 4.4        | 3.0 to 6.5   |                  |
| >35 Gy                                         | 12 (13.5)  | 15 (7.5)    | 9.8        | 4.5 to 21.3  |                  |
| Unknown                                        | 6 (6.7)    | 3 (1.5)     | -          | --           |                  |
| <b>Estimated dose to affected valve (EQD2)</b> |            |             |            |              |                  |
| Mean (SD)                                      | 37.0 (9.2) | 30.5 (13.8) | 1.06       | 1.02 to 1.09 | <b>0.001</b>     |
| No mediastinal RT                              | 2 (2.3)    | 18 (9.0)    | 1          | 0.2 to 4.9   | <b>&lt;0.001</b> |
| ≤30 Gy                                         | 5 (5.6)    | 34 (17.0)   | 1.4        | 0.5 to 3.8   |                  |
| 31-35 Gy                                       | 16 (18.0)  | 51 (25.5)   | 3.4        | 1.9 to 6.0   |                  |
| 36-40 Gy                                       | 45 (50.6)  | 81 (40.5)   | 5.6        | 4.0 to 7.7   |                  |
| >40 Gy                                         | 15 (16.9)  | 13 (6.5)    | 12.2       | 5.1 to 29.0  |                  |
| Unknown                                        | 6 (6.7)    | 3 (1.5)     | -          | -            |                  |
| <b>Anthracycline</b>                           |            |             |            |              | >0.5             |
| No                                             | 74 (83.2)  | 173 (86.5)  | 1          |              |                  |
| Yes                                            | 15 (16.9)  | 27 (13.5)   | 1.4        | 0.5 to 3.7   |                  |
| <b>Vincristine</b>                             |            |             |            |              | <b>0.003</b>     |
| No                                             | 62 (69.7)  | 105 (52.5)  | 1          |              |                  |
| Yes                                            | 27 (30.3)  | 95 (47.5)   | 0.4        | 0.2 to 0.7   |                  |
| <b>Procarbazine</b>                            |            |             |            |              | <b>0.012</b>     |
| No                                             | 59 (66.3)  | 104 (52.0)  | 1          |              |                  |
| Yes                                            | 30 (33.7)  | 96 (48.0)   | 0.5        | 0.3 to 0.9   |                  |
| <b>Salvage treatment</b>                       |            |             |            |              | >0.5             |
| No                                             | 69 (77.5)  | 152 (76.0)  | 1          |              |                  |
| Yes                                            | 20 (22.5)  | 47 (23.5)   | 0.9        | 0.5 to 1.6   |                  |
| Unknown                                        | 0          | 1 (0.5)     | -          | -            |                  |
| <b>Staging splenectomy</b>                     |            |             |            |              | <b>&lt;0.001</b> |
| No                                             | 50 (56.2)  | 146 (73.1)  | 1          |              |                  |
| Yes                                            | 39 (43.8)  | 54 (27.0)   | 3.0        | 1.5 to 5.9   |                  |
| <b>Any splenectomy after HL diagnosis</b>      |            |             |            |              | <b>0.004</b>     |
| No                                             | 45 (50.6)  | 133 (66.5)  | 1          |              |                  |
| Yes                                            | 44 (49.4)  | 67 (33.5)   | 2.4        | 1.3 to 4.3   |                  |
| <b>Any invasive second cancer</b>              |            |             |            |              | 0.21             |
| No                                             | 53 (59.6)  | 132 (66.0)  | 1          |              |                  |
| Yes                                            | 36 (40.5)  | 68 (34.0)   | 1.4        | 0.8 to 2.4   |                  |

**Table 5.7** – Treatment factors with univariable odds ratios (ORs). \*p-values based on likelihood ratio test (versus null model).

### Modelling the effect of radiotherapy

The linear model gave an EOR/Gy (EQD2) of 0.116 (95% CI 0.018 to 0.761). However, a linear model with an exponential curvature term fitted the data significantly better ( $p=0.02$ , parameter estimates 0.0066 and 0.07612 for the linear and exponential term respectively). An exponential model, which is convex by definition and requires only one parameter, resulted in an OR/Gy (EQD2) of 1.056 (95% CI 1.022 to 1.091) and fitted the data similarly well based on the Akaike information criterion. Graphically, the linear with curvature model appears to fit the data better for lower radiation doses but, as these models are not nested, they cannot be directly compared. The ORs derived from these three models are compared with the categorical ORs in Table 5.8.

|                          | <u>Dose Categories</u> |                    |                    |                    |
|--------------------------|------------------------|--------------------|--------------------|--------------------|
|                          | <u>≤30 Gy</u>          | <u>31 to 35 Gy</u> | <u>36 to 40Gy</u>  | <u>&gt;40 Gy</u>   |
| <b>Models:</b>           | <b>OR (95% CI)</b>     | <b>OR (95% CI)</b> | <b>OR (95% CI)</b> | <b>OR (95% CI)</b> |
| 1. Exponential           | 2.6 (1.5-4.6)          | 6.3 (2.1-19.1)     | 8.1 (2.3-28.6)     | 11.4 (2.6-48.8)    |
| 2. Linear                | 3.0 (1.4-11.7)         | 5.0 (1.8-21.8)     | 5.5 (1.9-24.6)     | 6.2 (2.0-28.4)     |
| 3. Linear with curvature | 1.4 (1.0-8.2)          | 4.0 (1.5-18.3)     | 5.9 (2.0-24.4)     | 10.0 (3.0-40.8)    |
| <b>Categorical*:</b>     | 1.4 (0.2-8.6)          | 3.4 (0.6-18.3)     | 5.6 (1.1-28.4)     | 12.2 (2.0-73.2)    |
| <b>Dose:**</b>           | 17.5 Gy                | 34.0 Gy            | 38.7 Gy            | 44.8 Gy            |

**Table 5.8** – Comparison of odds ratios derived from three models with categorical ORs. Patients without RT were used as reference. \* These CIs are not based on floating absolute risks. \*\*Mean doses for categories, but exact doses used for models.

### Multivariable modelling

Due to the narrow and somewhat bimodal distribution of the estimates of radiation dose to the affected valves (see Figure 5.2) it was not possible to evaluate effect modification in the linear with curvature model using likelihood ratio-based goodness of fit tests. Therefore effect modification was evaluated using dichotomous categories of dose (see Table 5.9). There was no statistically significant evidence of any interactions.

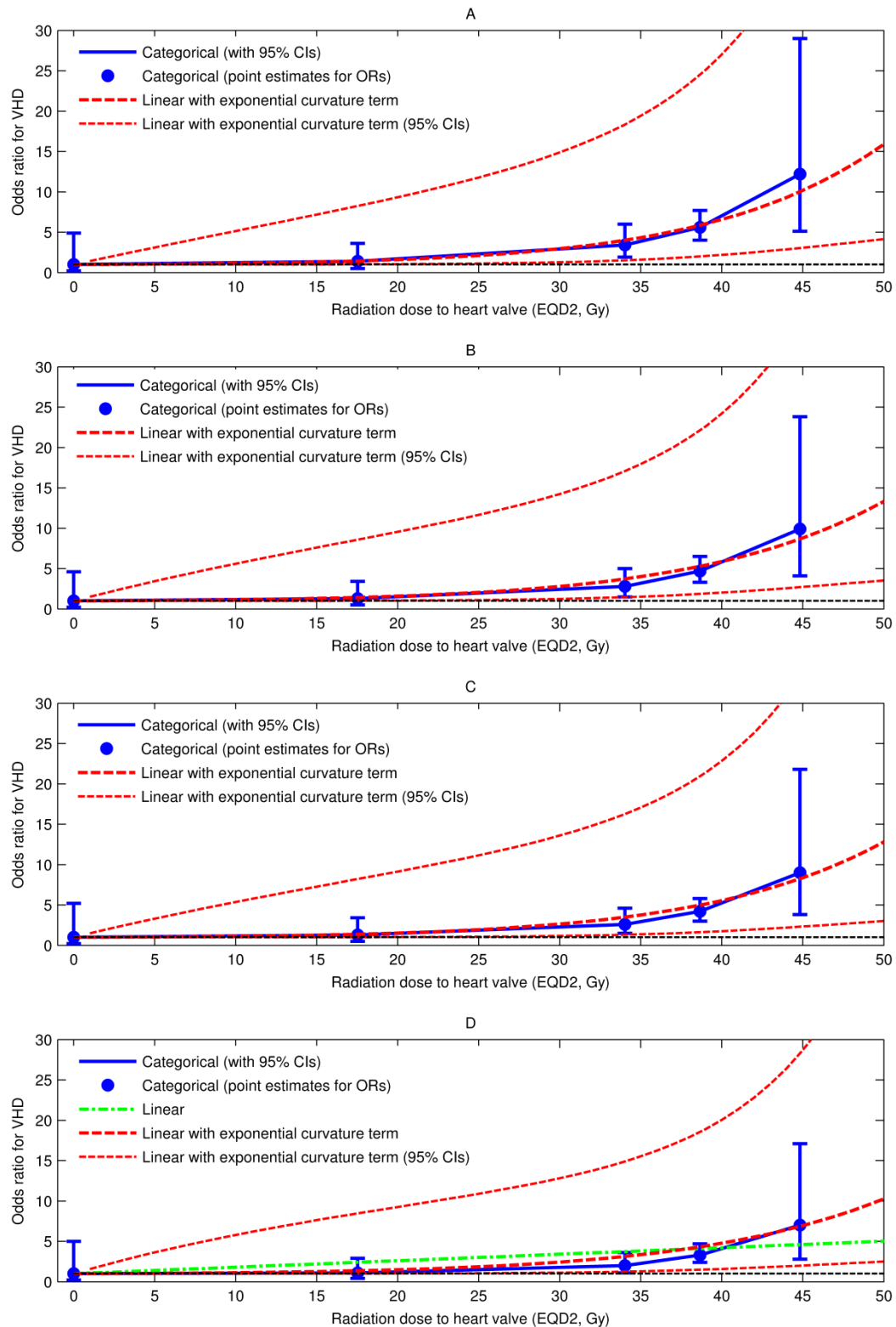
|                                           | Proportion without RT | Dose to affected valve*<br>EQD2, Mean (SD) | Odds ratio<br>(≥35 vs <35 Gy) | P-value** |
|-------------------------------------------|-----------------------|--------------------------------------------|-------------------------------|-----------|
| <b>Gender</b>                             |                       |                                            |                               | >0.5      |
| Male                                      | 6.4%                  | 34.3 (13.0)                                | 2.7 (0.9-7.8)                 |           |
| Female                                    | 5.1%                  | 34.5 (9.1)                                 | 2.7 (1.3-5.4)                 |           |
| <b>Age at diagnosis</b>                   |                       |                                            |                               | >0.5      |
| <20 years                                 | 2.9%                  | 34.1 (11.1)                                | 3.0 (1.0-9.2)                 |           |
| 20-29 years                               | 4.4%                  | 35.6 (8.7)                                 | 2.0 (1.0-4.3)                 |           |
| 30-41 years                               | 9.5%                  | 32.6 (12.2)                                | 4.4 (1.3-14.1)                |           |
| <b>Treatment period</b>                   |                       |                                            |                               | 0.03      |
| 1965-1974                                 | 6.3%                  | 35.6 (9.5)                                 | 1.3 (0.6-2.9)                 |           |
| 1975-1984                                 | 6.4%                  | 33.1 (12.5)                                | 6.0 (1.9-19.0)                |           |
| 1985-1995                                 | 1.9%                  | 33.6 (8.5)                                 | 5.7 (1.5-22.2)                |           |
| <b>Follow-up interval</b>                 |                       |                                            |                               | >0.5      |
| 0-9y                                      | 0.0%                  | 37.2 (4.2)                                 | 2.7 (0.3-28.4)                |           |
| 10-19y                                    | 3.9%                  | 33.1 (10.3)                                | 3.2 (1.1-9.2)                 |           |
| 20-29y                                    | 7.1%                  | 34.7 (10.8)                                | 2.7 (1.2-6.3)                 |           |
| ≥30y                                      | 6.0%                  | 34.4 (11.5)                                | 2.0 (0.5-7.6)                 |           |
| <b>Treatment centre</b>                   |                       |                                            |                               | >0.5      |
| NKI-AvL                                   | 3.3%                  | 33.2 (10.2)                                | 2.3 (1.1-4.7)                 |           |
| DdHK                                      | 8.5%                  | 33.9 (11.1)                                | 3.3 (1.6-6.8)                 |           |
| LUMC                                      | 3.9%                  | 38.9 (8.1)                                 | 2.5 (1.1-6.0)                 |           |
| <b>Anthracycline</b>                      |                       |                                            |                               | 0.26      |
| No                                        | 6.5%                  | 34.3 (10.4)                                | 2.3 (1.2-4.4)                 |           |
| Yes                                       | 0.0%                  | 34.9 (10.7)                                | 6.0 (1.2-30.9)                |           |
| <b>Vincristine</b>                        |                       |                                            |                               | >0.5      |
| No                                        | 0.0%                  | 36.1 (8.3)                                 | 2.1 (0.9-4.7)                 |           |
| Yes                                       | 13.1%                 | 31.8 (12.7)                                | 2.7 (1.0-7.1)                 |           |
| <b>Procarbazine</b>                       |                       |                                            |                               | >0.5      |
| No                                        | 0.6%                  | 36.2 (8.4)                                 | 2.9 (1.2-7.0)                 |           |
| Yes                                       | 11.9%                 | 31.9 (12.5)                                | 2.0 (0.8-5.0)                 |           |
| <b>Any splenectomy after HL</b>           |                       |                                            |                               | 0.09      |
| No                                        | 6.2%                  | 33.0 (10.8)                                | 3.9 (1.7-8.8)                 |           |
| Yes                                       | 4.5%                  | 36.6 (9.5)                                 | 1.4 (0.6-3.4)                 |           |
| <b>Obesity at diagnosis</b>               |                       |                                            |                               | 0.32      |
| No                                        | 6.8%                  | 34.6 (10.0)                                | 3.4 (1.6-7.2)                 |           |
| Yes                                       | 1.6%                  | 34.6 (10.5)                                | 1.7 (0.6-5.1)                 |           |
| <b>Smoker at diagnosis</b>                |                       |                                            |                               | >0.5      |
| No                                        | 5.7%                  | 34.0 (11.3)                                | 2.8 (1.1-6.8)                 |           |
| Yes                                       | 5.0%                  | 35.1 (9.1)                                 | 3.1 (1.3-7.4)                 |           |
| <b>Hypertension at end of FU</b>          |                       |                                            |                               | >0.5      |
| No                                        | 3.8%                  | 34.4 (10.5)                                | 2.7 (1.3-5.5)                 |           |
| Yes                                       | 9.5%                  | 35.6 (9.2)                                 | 2.0 (0.7-5.6)                 |           |
| <b>Hypercholesterolaemia at end of FU</b> |                       |                                            |                               | >0.5      |
| No                                        | 5.5%                  | 33.9 (10.4)                                | 1.7 (0.8-3.8)                 |           |
| Yes                                       | 4.6%                  | 37.2 (9.2)                                 | 2.3 (0.7-7.5)                 |           |

**Table 5.9** – Variation in OR for categories of dose to the affected valve by patient and treatment characteristics. \*If given RT. \*\*For interaction, only interaction term with selected variables included in the model (matching variables).

Logistic regression models were used to examine the effect of multiple treatment variables on the increase OR/Gy for dose to the affected heart valve and by categories of dose to the affected heart valve (Table 5.10). The models examined were; radiation dose to valve only (Model A), radiation dose plus splenectomy (Model B), radiation dose plus vincristine (Model C) and radiation dose plus splenectomy and vincristine (Model D). The only treatment variable that remained statistically significant as an independent predictor for increased risk of VHD when combined with radiation dose to the affected valve was splenectomy (OR 2.2, 95% CI 1.1 to 4.3,  $p=0.03$ ). The addition of treatment with anthracyclines and procarbazine were also examined, but were not significant (see Appendix C, Table C.2). For the crude model A and adjusted models B and C there was evidence that the increase in OR/Gy to the affected heart valve was better modelled by a linear with curvature relationship ( $p$ -values all  $<0.05$ ). However, when both vincristine and splenectomy were added to the model a linear with curvature relationship only retained a borderline statistically superior fit to the data compare to the linear relationship ( $p=0.06$ ). Figure 5.3 shows dose response curves for the unadjusted and adjusted models with the associated 95% confidence intervals for the dose categories and fitted curves.

| Treatment Characteristic                            | Model A   |                |          | Model B   |                |          | Model C   |                |          | Model D   |                |          |
|-----------------------------------------------------|-----------|----------------|----------|-----------|----------------|----------|-----------|----------------|----------|-----------|----------------|----------|
|                                                     | Coeff     | 95% CI         | p        | Coeff     | 95% CI         | p        | Coeff     | 95% CI         | p        | Coeff     | 95% CI         | p        |
| <b>Dose (EQD2) to affected valve (per Gy):</b>      |           |                |          |           |                |          |           |                |          |           |                |          |
| Linear term                                         | -5.02     | -9.19 to -0.84 | 0.02     | -4.93     | -9.21 to -0.66 | 0.024    | -5.25     | -9.80 to -0.71 | 0.023    | -5.24     | -9.95 to -0.54 | 0.029    |
| Curvature term                                      | 0.08      | -0.01 to -0.16 | 0.09     | 0.07      | -0.02 to 0.16  | 0.12     | 0.07      | -0.02 to 0.17  | 0.12     | 0.07      | -0.03 to 0.17  | 0.13     |
| Model 2* vs. Model 3**                              |           |                | 0.02     |           |                | 0.041    |           |                | 0.038    |           |                | 0.06     |
| <b>Any splenectomy after HL diagnosis:</b>          | <b>OR</b> | <b>95% CI</b>  | <b>P</b> | <b>OR</b> | <b>95% CI</b>  | <b>P</b> | <b>OR</b> | <b>95% CI</b>  | <b>P</b> | <b>OR</b> | <b>95% CI</b>  | <b>P</b> |
| No                                                  | -         | -              | -        | 1         |                | 0.03     |           |                | -        |           |                | 0.026    |
| Yes                                                 | -         | -              |          | 2.1       | 1.1 to 4.1     |          |           |                |          | 1         | -              |          |
| <b>Vincristine:</b>                                 |           |                | -        |           |                | -        |           |                | 0.16     |           |                | 0.13     |
| No                                                  | -         | -              |          | -         | -              |          | 1         | -              |          | 1         | -              |          |
| Yes                                                 | -         | -              |          | -         | -              |          | 0.6       | 0.3 to 1.2     |          | 0.6       | 0.3 to 1.2     |          |
| <b>Dose (EQD2) to affected valve (categorical):</b> |           |                | <0.001   |           |                | 0.002    |           |                | 0.006    |           |                | 0.018    |
| No RT                                               | 1         | 0.2 to 4.9     |          | 1         | 0.2 to 4.6     |          | 1         | 0.2 to 5.2     |          | 1         | 0.2 to 5.0     |          |
| ≤30 Gy                                              | 1.4       | 0.5 to 3.8     |          | 1.3       | 0.5 to 3.4     |          | 1.3       | 0.5 to 3.4     |          | 1.1       | 0.4 to 2.9     |          |
| 31-35 Gy                                            | 3.4       | 1.9 to 6.0     |          | 2.8       | 1.5 to 5.0     |          | 2.6       | 1.5 to 4.6     |          | 2.0       | 1.1 to 3.6     |          |
| 36-40 Gy                                            | 5.6       | 4.0 to 7.7     |          | 4.7       | 3.3 to 6.5     |          | 4.2       | 3.0 to 5.8     |          | 3.3       | 2.4 to 4.7     |          |
| >40 Gy                                              | 12.2      | 5.1 to 29.0    |          | 9.9       | 4.1 to 23.8    |          | 9.0       | 3.8 to 21.8    |          | 7.0       | 2.8 to 17.1    |          |
| Unknown                                             | -         | -              |          | -         | -              |          | -         | -              |          | -         | -              |          |
| <b>Any splenectomy after HL diagnosis:</b>          |           |                | -        |           |                | 0.025    |           |                | -        |           |                | 0.021    |
| No                                                  | -         | -              |          | 1         | -              |          | -         | -              |          | 1         | -              |          |
| Yes                                                 | -         | -              |          | 2.2       | 1.1 to 4.3     |          | -         | -              |          | 2.2       | 1.1 to 4.5     |          |
| <b>Vincristine:</b>                                 |           |                | -        |           |                | -        |           |                | 0.22     |           |                | 0.18     |
| No                                                  | -         | -              |          | -         | -              |          | 1         | -              |          | 1         | -              |          |
| Yes                                                 | -         | -              |          | -         | -              |          | 0.7       | 0.3 to 1.3     |          | 0.6       | 0.3 to 1.2     |          |

**Table 5.10** – Crude (A) and adjusted (B, C and D) logistic regression models of OR for VHD by radiation dose to affected valve, both per Gy (top) and by dose category (bottom). \*Linear model. \*\*Linear model with curvature.



**Figure 5.3** – Odds ratio (OR) of valvular heart disease (VHD) according to the estimated radiation dose (EQD2, Gy) to the affected heart valve in cases and to the corresponding heart valve in controls. A: Unadjusted. B: Adjusted for splenectomy. C: Adjusted for vincristine. D: Adjusted for splenectomy and vincristine. The categories of radiation dose were  $\leq 30$  Gy, 31 to 35 Gy, 36 to 40 Gy and  $>40$  Gy. The mean doses to the valves in these categories were 17.5, 34.0, 38.7 and 44.8 Gy.

## **Discussion**

### **Main finding**

This study has confirmed evidence of a dose-response relationship between radiation dose to the heart valves and the risk of subsequent clinically-significant VHD. There is evidence of curvature in the relationship with little apparent increase in risk below 20 Gy and a more steeply increasing risk above doses of 30 Gy. However, due to the distribution of the radiation doses seen within the cohort (Figure 5.2) and the relatively small numbers of cases analysed, the confidence limits for the dose-response remain somewhat broad (Figure 5.3). Both the degree of curvature and gradient of the relationship would be refined by the inclusion of a larger number of cases and controls who have received a wider range of radiation doses.

### **Comparison to previous studies**

Previously there have been few data to clearly define a dose-response relationship between radiation dose to the heart and VHD. A study from the German Society of Paediatric Oncology and Haematology (GPOH) reported late cardiac disease in more than 1,100 patients who received treatment for HL diagnosed before 18 years of age.<sup>11</sup> These patients were treated in consecutive clinical trials between 1978 and 1995 and all received the same dose of anthracyclines (160mg/m<sup>2</sup> doxorubicin). Radiation dose to the whole or part of the mediastinum varied from 0 to 40 Gy, according to whether the mediastinum was involved (or adjacent to an involved site), the trial protocol and the response to induction chemotherapy. At a median follow-up of 19.5 years (and 32.2 years of age) cardiac disease has been diagnosed in 4.4% patients, with VHD being the most frequent diagnosis (33 cases). Multivariate analysis revealed that mediastinal radiation dose was the only available factor that was significantly associated with cardiac event and VHD-free survival. Due to the limited number of cases however, significant differences were only seen between the cumulative incidence in the

highest dose group (median prescribed dose of 36 Gy) and lower dose groups combined, and the group that received no radiotherapy compared to the groups that received radiotherapy. Therefore no dose-response was calculated. Maraldo *et al*<sup>9</sup> subsequently used this data set to calculate a logistic dose-response curve (see Chapter 2 and Appendix A), but the resultant curve is extremely steep and, in essence, defines a threshold around a dose of 36 Gy above which the risk increases dramatically.

A study of 56 patients treated more recently for Hodgkin lymphoma, with anthracycline-based chemotherapy and involved-field radiotherapy, investigated dosimetric predictors of subsequent asymptomatic valvular dysfunction.<sup>22</sup> All patients had echocardiography before chemotherapy, after chemotherapy and before RT, and at intervals after RT. The presence of mild, moderate or severe valvular abnormalities was noted (i.e.  $\geq$ CTCAE grade 1). Individualised CT-based radiation dosimetry was available for all patients. Using estimated doses to the whole heart and cardiac chambers the authors utilised Receiver Operator Curve analysis to produce dichotomised cut-offs for various dose metrics, above which the OR of a valvular defect was significantly elevated. For example, the OR for a left-sided valvular defect in patients where  $>25\%$  of the left ventricle received  $>30$  Gy versus patients where  $\leq 25\%$  of the left ventricle received  $>30$  Gy was 4.4 ( $p=0.02$ ). However, due to the limited number of cases ( $n=18$ ), they were unable to define a dose-response relationship for the risk of valvular dysfunction. The analysis included predominately mild (CTCAE grade 1) valvular heart disease and no severe disease (CTCAE grade  $\geq 3$ ) with a relatively short median follow-up of 70.5 months. A follow-up study with further follow-up<sup>14</sup> proposed logistic NTCP models where risk was shown to increase with maximum heart dose (for all valvular defects) and with the volume of the left cardiac chambers receiving 30 Gy or more (for left-sided valvular defects), and to decrease with increasing lung volumes.



This current study suggests that although there is evidence for curvature in the relationship between radiation dose and VHD there is no good evidence for a strong threshold effect, and no evidence that the risk of VHD does not increase substantially (i.e. perhaps doubling the OR) at doses less than 36 Gy. In support of this, data from the USCCSS reports a hazard ratio for VHD of 3.3 (95% CI 2.1 to 5.1) for individuals who received 15 to <35 Gy MHD.<sup>23</sup> Also evidence of an increased risk of VHD following irradiation for breast cancer has been reported when comparing left-sided versus right-sided patients (1.54, 95% CI 1.11 to 2.13) where the mean heart doses received were 6.3 Gy and 2.7 Gy respectively.<sup>24</sup> Taken together, these studies suggest that although there is evidence for some curvature in the dose-response with a greater effect at higher doses, doses below 35 Gy still increase the risk of VHD. Further research to clarify the magnitude of risks below 35 Gy and the shape of the dose-response relationship in this range is therefore warranted.

### **Effect of splenectomy**

Except for the radiation dose, the only other treatment factor which remained significantly associated with an increased risk of developing of VHD after inclusion in the multi-variable models, was splenectomy. It is not possible from our study to definitively explain the mechanism behind this effect, however there are theoretical possibilities. The first is that there may be a dosimetric effect, i.e. patients that had staging splenectomy may have received a higher cardiac dose from subsequent radiotherapy due to anatomical changes in the position of the heart relative to the irradiated fields. This is feasible as the apex of the heart and the spleen are anatomically related, but there has been no study of alteration in cardiac position following splenectomy to support this hypothesis. The dosimetry for our study was performed on surrogate CT data from patients who had not had splenectomy and so would be unable to account for any dosimetric difference that splenectomy may cause. A second possibility is that

there may be infectious, immune-related or inflammatory effects resulting from splenectomy that may result in an increased risk of developing VHD. The pathology and aetiology of VHD is incompletely understood but it is now recognised that, like atherosclerosis, inflammation may play a role.<sup>25</sup> The third possibility is that splenectomy may have led to an acquisition bias due to asplenic patient being more likely to have echocardiography, perhaps due to a higher level of clinical suspicion of systemic infection and endocarditis in these patients. However, although there may be an increased incidence of endocarditis due to unusual causative organisms following splenectomy,<sup>26</sup> a generally increased risk of endocarditis in asplenic patients per se is not recognised and, as such, this possible explanation seems unlikely.

Splenectomy is no longer routinely used for the staging and treatment of HL, however the effect, if real, could be of relevance to HL survivors who had a splenectomy in the past and are still under clinical follow-up, as they may be at an increased risk of developing VHD. No association between splenectomy and subsequent VHD was seen in the previously mentioned GPOH study.<sup>11</sup> It would be relevant to see whether or not this finding was reproduced in other cohorts.

### **Effect of chemotherapy**

#### **The effect of vincristine (and procarbazine) chemotherapy**

In the univariable analysis there was a significant association between treatment including vincristine ( $p=0.003$ ) or procarbazine ( $p=0.012$ ) chemotherapy and a reduced risk of subsequent VHD. However, it appears likely that these associations are due in part to a greater proportion of patients who received vincristine and procarbazine not receiving radiotherapy and, when they did receive radiotherapy, having a lower estimated radiation dose to the heart valves (see Table 5.9). When combined with radiation dose to the affected valve in adjusted logistic regression

models the associations become non-significant (see Table 5.10 and Appendix C, Table C.2). Exposure to vincristine has previously been associated, along with supra-diaphragmatic RT and anthracyclines, with an increased risk of death from myocardial infarction following treatment for HL,<sup>7</sup> but vincristine treatment has never been associated with the development of valvular heart disease or other radiation-related cardiac disease.

#### The effect of anthracycline chemotherapy on subsequent VHD

Anthracyclines are well recognised to cause cardiomyopathy and congestive cardiac failure in a dose-dependent manner.<sup>27</sup> The effect of anthracyclines on the risk of VHD and the possibility of an interaction between anthracyclines and radiotherapy to increase the risk of radiation-related risk VHD has not been extensively investigated. A previous analysis of the cohort in which the current study is based revealed that anthracycline chemotherapy significantly and independently added to the elevated risk of VHD from mediastinal radiotherapy (HR = 2.1, 95% CI 1.3 to 3.5).<sup>2</sup> A separate study showed an increased risk of hospitalisation following combined treatment with doxorubicin-containing chemotherapy and radiotherapy versus chemotherapy alone, a proportion of which may have been due to valvular heart disease.<sup>6</sup> But other data relating the effect of anthracyclines and the risk of radiation-related VHD are not available. In the current study there was no suggestion of an increased risk from anthracyclines on univariate analysis ( $p > 0.5$ , see Table 5.7) or multi-variable analysis (see Appendix C). The number of individuals included in the study who had received anthracyclines was small however (33, 11.4%), and it may be that the study is underpowered to detect any effect. A further possibility is that the proportion of those individuals treated with anthracyclines who went on to develop a cardiac disease of a different type (for example cardiomyopathy) prior to the development of VHD may be higher than in those not given anthracyclines, especially given the recognised prolonged latency of radiation-related VHD. As this analysis was of cases whose first significant

heart disease was VHD, this may have masked an association with anthracycline treatment and VHD as a second or subsequent cardiac diagnosis that may have led to the result seen in the cohort study. If so, an extended study that does not require cases to have VHD as their first significant heart disease may be revealing.

### **Effect of patient characteristics**

Hypertension and hypercholesterolaemia at the end of follow-up were both associated with an increased risk of VHD following treatment for HL, as were an increasing number of cardiac risk factors in total (see Table 5.6). This is not unexpected as the risk factors for the development of degenerative VHD are recognised to be similar to those for atherosclerosis.<sup>28</sup> However, it is not possible to draw the conclusion that this is a causative association from the data as those patients with a known VHD are presumably much more likely to be monitored for and treated for cardiac risk factors, i.e. there may be an element of inverse causation. In any case, these findings help reinforce the need to monitor and treat patients for conventional cardiovascular risk factors as it is also known that such patients are also at increased risk of coronary artery disease.<sup>2</sup> Obesity at diagnosis, but not at end of follow-up, was also associated with risk for VHD. There are two possible explanations for this finding. The first is that metabolic cardiovascular risk factors associated with obesity may have a role in increasing the subsequent risk of VHD when present at the time of irradiation, but are not as important thereafter. The second possibility is that it is an effect of thoracic size and mediastinal separation which, being greater in obese patients, may have led to increased inhomogeneity in radiation dose in the anterior-posterior direction through the chest, and possibly to areas of increased total dose and dose per fraction to the heart or heart valves. These dosimetric effects would not have been accounted for using the retrospective dose reconstruction methods used (as discussed further below).

## **Limitations**

### **Limitations of retrospective radiation dosimetry**

There are several technical limitations to the technique of using substitute CT data sets to produce retrospective estimates of cardiac radiation dosimetry, as done in this study. These limitations may reduce the accuracy by which this most important exposure variable was quantified. Most important is that inter-patient variability in anatomy, particularly in terms of cardiac size, shape and position, is not fully accounted for. It can be seen from Chapter 7 that for a standardised mantle field reproduced on CT scans from multiple patients, the mean whole heart dose (MWHd) may vary by up to 40% of the prescribed dose due to anatomical differences alone. Limiting this inaccuracy are the facts that the dose to the heart valves would be expected to vary less than MWHd as they are within the centre of the field and generally not close to the shielding (with the exception of the mitral valve and left lung shielding) and that the substitute CT data sets for reconstruction were chosen on the basis of being dosimetrically and anatomically typical such that the estimates would be expected to fall near the average for the expected variability. Further dosimetric uncertainties include the effect of alternate-day prone positioning of the patient would have had on cardiac position and dose, the fact that all treatments were reproduced on 2 CT scans from patients who had not had splenectomy, lack of data regarding day-to-day set-up variability, lack of original planning and/or verification films for a proportion of patients and uncertainty over the accuracy of the reproduction of moving junctions. These uncertainties imply that a substantial proportion of the inter-patient variability of heart and valve dose is lost in this method of dose reconstruction and this presumably reduces the accuracy and reliability of the dose-response relationships produced. It is reassuring that the observed association between dose of the affected heart valve and the OR for subsequent VHD was strong, suggesting that the estimated doses produced were at least adequate for the purpose of the study, but the accuracy of the relationship can be questioned.

### Other limitations

There was incomplete availability of data on conventional cardiovascular risk factors at diagnosis and between diagnosis and last follow-up. This limits the ability of the study to draw conclusions regarding whether the associations seen between hypertension and hypercholesterolaemia are causative.

The study only included cases where VHD was the first significant heart disease diagnosed. This could potentially limit the power of the study and perhaps obscure effects, such as the association between anthracyclines and VHD observed in the cohort, which could be relevant.

There were incomplete data available regarding treatment for relapse and second or subsequent cancers (see Appendix C, tables C.3 and C.4) and these data were not included in the analysis. On univariate analysis however (Table 5.7) there was no apparent effect for either salvage treatment ( $p>0.5$ ) nor diagnosis of a second cancer ( $p=0.21$ ), so the non-inclusion of this data seems unlikely to have affected the observed results.

### Pathogenesis of radiation-related valvular heart disease

The pathogenic mechanisms of radiation-related VHD are currently uncertain. Recent experimental evidence utilising cultured human aortic valve interstitial cells, the predominant cell type in human valves, demonstrated that irradiation with a single dose of 10 Gy (equivalent to a conventionally fractionated dose of approximately 30 Gy for radiobiologically classical late effects, with a low alpha-beta ratio) induces a change in phenotype from a myofibroblast to an osteoblast-like cell, with increases in bone morphogenetic protein 2 (BMP-2), osteopontin, alkaline phosphatase and Runx2.<sup>29</sup> It had been shown in separate experiments that a variety of pro-inflammatory stimuli, other than irradiation, can induce similar changes in phenotype in

valvular interstitial cells<sup>30</sup> and these inflammatory pathways have been linked to the development of calcific aortic valve disease.<sup>31</sup> In support of this, examination of valves from explanted hearts of a patient with a history of mediastinal radiation but no overt valvular disease, and a patient with no history of irradiation but clinical aortic valve stenosis both revealed increased BMP-2 expression, whereas there was no evidence of BMP-2 expression in normal valve leaflets from a patient with no history of irradiation.<sup>29</sup> These findings offer a first possible mechanistic insight into radiation-induced valvular disease which is worthy of further investigation.

## **Conclusions**

This study gives strong evidence that radiation dose to the heart or heart valves is a dominant risk factor leading to the development of VHD following treatment for HL. It is the first time that a dose-response relationship had been explicitly defined in terms that can be easily translated into clinical practice. This study will help clinicians assess the risk of VHD for patients treated in the past and in the future and will assist in guiding the appropriate levels of follow-up for HL survivors. There are plans to extend this study with the extension of the cohort and the addition of further cases so that the results can be refined. With greater understanding of the risk factors and mechanisms underlying radiation-related VHD it may also be possible to offer primary or second forms of pharmacological prevention in patients where incidental cardiac irradiation is unavoidable.

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## **Chapter 6 - Cardiovascular Radiation Dosimetry and Predicted Excess Cardiac Mortality due to Involved Field Radiotherapy within the UK RAPID Trial in Low-Risk Early-Stage Hodgkin Lymphoma**

### **Introduction**

Current standard treatment of early-stage Hodgkin Lymphoma (HL) is the combination of multi-agent chemotherapy and localised radiotherapy (RT). This is very successful with  $\geq 90\%$  of patients becoming long term survivors.<sup>1</sup> Unfortunately, historical forms of this multimodality strategy are known to result in substantial late adverse effects, particularly second malignancy and cardiovascular disease.<sup>2</sup> During the past two decades, and today, clinical trials in early-stage disease have focussed on identifying patients in whom initial treatment can be less intensive in the hope that long-term toxicity will be reduced without compromising the excellent cure rates.<sup>3</sup>

The UK NCRI Lymphoma Study Group RAPID trial was a phase III trial in low-risk early-stage HL designed to test if RT can be withheld following a favourable response to chemotherapy without reducing freedom from disease progression. Patients who were negative on positron emission tomography (PET) scanning using 2-fluorine-[18F]-fluoro-2-deoxy-6-glucose (FDG) following three cycles of standard ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy were randomised to receive either involved field radiotherapy (IFRT) or no further treatment. The trial closed in August 2010 and provisional results were reported in December 2012.<sup>4</sup> Progression-free survival (PFS), the primary end-point of the RAPID trial, is appropriate for assessing the oncologic efficacy of a treatment strategy over the medium term. However in order to assess the overall effect of withholding IFRT on all causes of morbidity and mortality it is important to attempt to predict the longer term hazards of this form of RT, as well as its benefits, particularly as many of the most serious toxicities of HL treatment occur late, after most deaths due to HL have occurred.<sup>2</sup>

The primary cause of increased mortality in HL patients, other than HL, is second malignancy.<sup>2</sup> This risk is known to be reduced with lower radiation doses and volumes of treatment.<sup>5,6</sup> The risks of lung and breast cancer due to radiation exposure have been mathematically modelled and the excess risk from the doses received during contemporary IFRT to the mediastinum has been estimated.<sup>7</sup> Death from cardiac disease however is the leading cause of mortality due to exposure of a single organ.<sup>2,8</sup> Whilst cardiac radiation doses are known to be less with IFRT compared to historical cohorts,<sup>7</sup> no detailed description of the doses received by the heart and individual cardiac sub-structures from IFRT, nor any attempt to predict the resulting excess cardiac mortality, has been published.

The aim of this study is to describe the cardiovascular radiation doses received by a cohort of early-stage HL patients treated with IFRT within the context of a recent clinical trial. The doses are then used to estimate the risk of cardiac mortality that may be expected from IFRT and, hence, the risk that could be potentially eliminated by the avoidance of IFRT as part of the experimental treatment strategy.

## **Materials and Methods**

### **Patients and planned treatment**

602 patients with early-stage, low-risk HL were registered into the RAPID study from 3/10/2003 to 2/8/2010. All patients were scheduled to receive 3 cycles of ABVD chemotherapy followed by FDG-PET imaging (n=571). Individuals who were FDG-PET positive (n=145) went on to receive a further cycle of ABVD followed by IFRT. Those who were FDG-PET negative (n=426) were randomised to IFRT (n=209) or no further treatment (n=211). According to the trial protocol a total of 354 patients should have received IFRT, either as they were FDG-PET positive or were randomised to IFRT.

### **Involved field radiotherapy techniques**

Involved field radiotherapy was defined in the RAPID trial protocol as treating the anatomical extent of detectable masses of HL as determined by computed tomography (CT) imaging prior to the commencement of chemotherapy. There was no intention to treat contiguous nodal areas systematically, nor the whole of any nodal region (especially the mediastinum). Recommended field-edge margins were 5 cm up and down involved nodal chains with 1.5-2 cm lateral margins around the post-chemotherapy volume of disease within the mediastinum. The dose and techniques specified by the protocol were 30 Gy in 1.8-2 Gy fractions delivered in the supine position by opposed anterior and posterior 5-8 MV beams, with both beams treated daily. RT was to be given within 6 weeks of the final dose of chemotherapy.

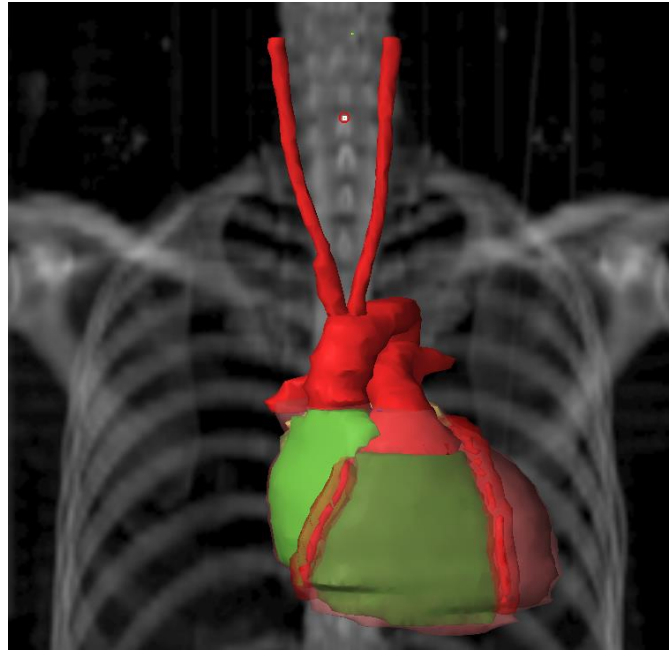
### **Collection of radiotherapy data**

Radiotherapy departments who treated patients in the trial were contacted by a central RT quality assurance office. They were asked to supply details of the RT treatment courses administered. If treatments were planned using a three-dimensional (3-D) CT-based treatment planning system (TPS) copies of the original CT data set, plans and dose cubes were requested,

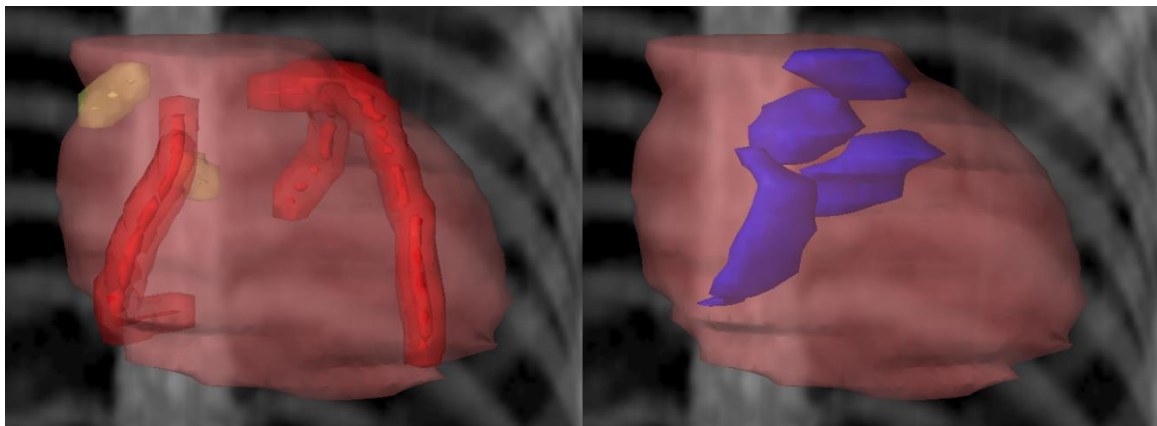
preferably in standard DICOM format. If the planning used virtual simulation, then the CT data set and plan were requested. If the planning used orthogonal x-ray films, then copies of simulation films were requested. The collection of individual radiotherapy treatment data and the assessment of radiation doses to cardiovascular structures were part of the RAPID trial protocol that was approved by the appropriate Research Ethics Committee.

### **Cardiovascular outlining**

Cardiac structures including the whole heart, heart chambers, coronary arteries and heart valves were outlined on CT data sets using the Eclipse TPS (Varian Medical Systems, Palo Alto, CA). This was performed with reference to a validated RT heart atlas,<sup>9</sup> a detailed digital atlas of cardiac anatomy,<sup>10</sup> and to previous work within the University of Oxford Clinical Trial Service Unit.<sup>11</sup> The whole heart included the pericardium and, for simplification and consistency, the inferior parts great vessels superiorly. The left main and left anterior descending (LAD) coronary arteries were outlined as a single structure. The coronary arteries are not easily visible on CT, especially without contrast, therefore the position of a coronary artery was often inferred by surrounding cardiac structures. For example, the position of the LAD was outlined within the intraventricular groove between the left and right ventricles. There is also substantial cardiac movement during the cardio-respiratory cycle.<sup>12,13</sup> For these reasons a 5 mm circumferential margin was added to the coronary arteries and the resulting structure was used for dosimetric analysis. The heart valves were outlined using published guidelines.<sup>9</sup> The internal carotid arteries were outlined, from their origin at the aortic arch to the level of bifurcation superiorly. The sino-atrial node (SAN) and atrio-ventricular node (AVN) of the conduction system were outlined based on their described anatomical positions as they are not visible on CT. For this reason (and due to their small volume) a 5 mm margin was also added to these structures for dosimetric analysis. See Figure 6.1 for an example of the 3-D structures produced.



**Figure 6.1.1** – All cardiovascular structures outlined, demonstrated in 3-D, including the whole heart, cardiac chambers and common carotid arteries.



**Figure 6.1.2** – Further individual cardiac structures outlined, demonstrated in 3-D, including the coronary arteries (red), atrio-ventricular and sino-atrial nodes (yellow) and heart valves (blue)

### **Radiation dosimetry**

#### **Dosimetry for those patients with 3-D CT-based plans**

Where DICOM RT data sets were easily compatible with the Eclipse TPS they were imported and, following cardiovascular outlining as described above, dose volume histograms (DVHs) were exported for analysis. If the plan and dose data sets were not easily compatible with the available Eclipse TPS (e.g. due to the orientation of multi-leaf collimators, availability of appropriate wedges within the software etc.) then the CT data set alone was imported into

Eclipse for cardiovascular outlining. The completed structure set was exported from Eclipse and then imported into VODCA (a software package specifically developed for the visualisation, organisation and analysis of radiotherapy data)<sup>14</sup> with the appropriate CT data set and dose cube(s) to produce DVHs for export and analysis. CT data supplied in non-DICOM format (e.g. RTOG) was first converted to DICOM using VODCA and then imported into Eclipse for outlining.

#### Dosimetry for those patients planned using CT-based virtual simulation

The CT data set and plan were imported into the Eclipse TPS and, following cardiovascular outlining, the dose was calculated with the same beam energy and prescription point as the original treatment using the anisotropic analytical algorithm (AAA) photon-beam dose calculation algorithm (Version 8.1.17) within Eclipse. The results were taken as a good approximation for what would have been calculated by the original RT department if a full 3-D CT-based dose calculation had been produced at the time of treatment.

#### Dosimetry for those patients without CT data

A proportion of patients given radiotherapy were planned using orthogonal x-ray simulation, and for some patients originally planned using a CT data set the original CT data was not available. In these instances the treatment fields were reconstructed based on simulation and/or verification radiographs, using the appropriate beam energy, prescription point, dose and fractionation, upon a substitute CT data set from another individual within the trial. Two CT substitute data sets were chosen, one for males and one for females, from the first 50 complete CT data sets available. The chosen data sets were the most typical both in terms of whole heart dosimetry (assessed using a series of standard IFRT plans, see Chapter 7) and cardiac anatomy (assessed by the size of the heart and the component substructures).

#### Dosimetry for those patients where the heart was not completely covered by the CT data set

A proportion of patients planned using CT-based techniques had a CT data set that included only the superior portion of the heart. Therefore mean doses to the heart or to incomplete or absent cardiac substructures could not be directly calculated. In order to estimate the mean whole heart dose (MWHD) in these circumstances a multiple linear regression model was produced to estimate the volume of heart missing from the CT scan. This model was produced from a library of 123 patients treated with RT for HL, based on the patient's body surface area (BSA), which is known to be strongly correlated to heart volume.<sup>15</sup> The addition of two further anatomical measures (the area of the most superior slice of the heart outlined on the scan and the maximal transverse diameter of the rib cage at the level of the carina) were found to be most predictive of heart volume, with an adjusted  $R^2=0.71$  (See Appendix D for a full description of the model). This model was used to produce estimated heart volumes for cases without a complete heart on their CT scan (n=45). The estimated missing volume was added to the partial heart DVH to produce an estimate of the MWHD.

Among those for whom doses to all cardiac structures were available based on their own CT scan (n=104), the MWHD was strongly linearly correlated with mean dose to all other cardiac structures outlined, with an average  $R^2$  of 0.83 (range 0.68 to 0.92) (See Appendix D, Figure D.1, for a full correlation matrix). Therefore linear regression equations were fitted relating doses to each of the other cardiac structures to the MWHD to allow interpolation of the dose for incomplete or absent cardiac substructures using the MWHD.

A minority of individuals (n=29) had CT scans that did not cover inferiorly enough to include any outlined heart at all. The MWHD for these individuals was estimated by the average MWHD for the same IFRT field type where full data was available. For example, an individual who received IFRT to the unilateral neck and supraclavicular fossa was allocated the average MWHD for that



category of treatment. Doses to other cardiac structures for these individuals were interpolated as described above for those with hearts partially included on the scan.

#### Analysis of dose volume histograms

Dose volume histograms were analysed using programmes written at the Oxford Cancer Centre in GNU Octave version 3.2.4<sup>16</sup> to produce summary dose statistics for individual cardiovascular structures.

#### Prediction of cardiac mortality using the relative seriality model

A radiobiological model that has previously been used to predict cardiac normal tissue complication probability (NTCP) is the relative seriality (RS) model.<sup>17</sup> This model uses Poisson statistics to describe cell survival and incorporates a component that accounts for the functional architecture of the organ at risk, i.e. to what extent the functional sub-units are organised in a parallel or serial arrangement.

For a heterogeneous dose distribution the RS NTCP is given by:

$$NTCP[V_i, D_i] = \left\{ 1 - \prod_{i=1}^n [1 - P(D_i)^s]^{\Delta V_i} \right\}^{1/s}$$

$$P(D_i) = 2^{-\exp[\gamma(1 - D_i/D_{50})]}$$

Where n is the number of dose bins within the DVH,  $V_i$  is the volume within each bin, V is the total volume of the organ,  $\Delta V_i = V_i/V$ ,  $\gamma$  is the maximal relative slope of the dose-response curve,  $D_{50}$  is the dose giving a 50% complication probability and s is the relative seriality of the organ.  $D_i$  is the dose step in the DVH which is normalised to the equivalent dose in 2 Gy per fraction ( $EQD_2$ ) using the equation:

$$EQD_2 = D[(d + \alpha/\beta)/(2 + \alpha/\beta)]$$

The parameters used for this analysis were from a combined analysis of cardiac mortality after irradiation for breast cancer and HL:  $D_{50}=63.3$ ,  $\gamma=0.93$  and  $s=1$ .<sup>18</sup> The NTCP for these parameters represents the absolute excess risk (AER) of cardiac mortality at 15 years following irradiation. The parameters for the HL data alone were not used due to the limited number of deaths in the population modelled. As  $s=1$  in this case (i.e. the model had maximal seriality), the RS NTCP simplifies to:

$$NTCP[V_i, D_i] = 1 - \prod_{i=1}^n [1 - P(D_i)]^{\Delta V_i}$$

For those patients where a heart DVH was not available direct calculations using the relative seriality model were not possible. These patients all had very low mean heart doses ( $\leq 0.63$  Gy) and were allocated a NTCP of 0.01% as, for the cases where a heart DVH was available, all who had a MWHD  $< 1$  Gy had a calculated RS NTCP of 0.01%.

#### **Prediction of cardiac mortality using relative risk per Gy MWHD**

Dose response analyses of radiation-related cardiac mortality, performed more recently than that done using the RS model described above, have demonstrated a linear relationship between the MWHD and the excess relative risk (ERR) of cardiac mortality:

$$OR = ER[1 + (ERR \times MWHD)]$$

Where; OR = Observed risk with RT and ER = Expected risk without RT. The ERR has been calculated as 3.1% per Gy MWHD following treatment for breast cancer (mean age at RT c.55)<sup>19,20</sup> and 60.0% per Gy MWHD following treatment for childhood cancers (mean age at RT 5.5).<sup>21</sup> Additionally the observed relative risk of cardiac death in a large Dutch HL cohort compared to the reference population (Standardised mortality ratio (SMR) = 6.25),<sup>2</sup> combined with an estimation of the average MWHD received (30 Gy, see Chapter 5), enables the calculation of a third ERR per Gy MWHD of 17.5% for a cohort treated at a mean age of 26 years. These findings suggest that the relative risk of cardiac irradiation varies with age at irradiation,

being substantially higher at younger ages. This pattern has also been observed in other studies of HL patients.<sup>22-24</sup> It is also known that the expected absolute risk of cardiac death varies with both attained age and gender (see Appendix C, Figure C.4). Therefore, in order to make an alternative prediction of the absolute excess of cardiac deaths following incidental cardiac irradiation which (unlike the RS model described above) took these factors into account, a model combining estimates of ERR per Gy MWHD that varies with age at irradiation and contemporary National mortality statistics was created. Three data points for the studies described above,<sup>2,20,21</sup> where an estimate of ERR per Gy MWHD was available, were used to produce a model of how ERR may vary with age at irradiation (see Appendix C, Figure C.5). The expected background risk (EBR) of cardiac death 15 years following irradiation for the individuals on whom cardiac dosimetry was completed were calculated from age- and sex-specific cardiac death rates available from the Office of National Statistics (England and Wales) and the General Register Office for Scotland. Cardiac death was defined by the ICD codes I00-99, excluding I26 (pulmonary embolism), I60-69 (cerebrovascular disease), I80 (phlebitis and thrombophlebitis) and I82 (other venous thrombosis and embolism), plus R00-02, R57 and R96. As the national mortality data were only available until 2009, rates from 2004 (the first year of treatment within the trial) to 2009 were used. For subsequent years (2010 to 2025) rates were assumed to remain the same as 2009. The estimated absolute excess risk of death from cardiac causes at 15 years following irradiation was then calculated as:

$$NTCP = [EBR \times (MWHD \times ERR)] - EBR$$

Where; NTCP = AER of cardiac death at 15 years, EBR = Expected background rate of cardiac death at 15 years, MWHD = Mean whole heart dose received in Gy and ERR = Excess relative risk per Gy MWHD.

## **Results**

### **Patients treated within the trial and those included in the analysis**

Of the 354 patients that should have received RT within the trial, 42 did not have RT due to patient and/or clinician choice (n=36), death before the start of RT (n=5) or ineligibility (n=1).

Of those who had IFRT, RT information sufficient to complete cardiovascular dosimetry was received on 247 of 312 (79.2%) patients from 42 of 48 (87.5%) radiotherapy centres treating within the trial. Individual CT data were available for 178 (72.1%) patients on whom cardiovascular dosimetry was completed. Substitute CT data sets were used to estimate doses for the remaining 69 (27.9%). The baseline characteristics of the patients are given in Table 6.1.

|                            | Entire Cohort | RT not planned* | RT dosimetry completed | Insufficient data for dosimetry | RT planned but not given |
|----------------------------|---------------|-----------------|------------------------|---------------------------------|--------------------------|
| Number                     | 602           | 248             | 247                    | 65                              | 42                       |
| Male:Female                | 53:47         | 49:51           | 56:44                  | 55:45                           | 55:45                    |
| Mean Age (years)           | 38.6          | 38.5            | 38.3                   | 37.4                            | 42.9                     |
| Mean Weight (Kg)           | 79.2          | 77.4            | 80.2                   | 80.0                            | 79.8                     |
| Mean BSA (m <sup>2</sup> ) | 1.9           | 1.9             | 1.9                    | 1.9                             | 1.9                      |
| PET+ (%)                   | 25.4          | 0               | 41.7**                 | 38.5**                          | 40.5**                   |
| Mediastinum+ (%)           | 47.8          | 47.7            | 49.2                   | 52.3                            | 33.3                     |

**Table 6.1** – Baseline characteristics of the entire RAPID cohort and relevant sub-groups.

PET+ = A PET score of 3-5 after 3 cycles of ABVD chemotherapy.

Mediastinum+ = Mediastinal involvement at presentation.

\*Randomised to no RT (n=211), withdrawn before randomisation (n=35) or died before randomisation (n=2)

\*\*% expected from the trial design = 40.5%.

### **Involved field radiotherapy treatments received**

Of the 247 patients for whom cardiovascular dosimetry was completed, 170 were originally planned using 3-D CT-based planning (68.8%), 34 using CT-based virtual simulation (13.8%) and 43 using conventional simulation with orthogonal x-rays (17.4%). Although the trial protocol specified opposed anterior-posterior fields, in a minority of cases (n=39, 15.8%) multi-field and field-in-field techniques were utilised to improve dose distributions. The regions treated were

the mediastinum in 45.7%, bilateral neck and/or supraclavicular fossa (SCF) in 47.4%, unilateral neck and/or SCF in 48.2% and axillae in 16.2%, in various combinations.

The most frequently administered dose and fractionation used was 30 Gy in 15 fractions (n=176, 71.3%), as specified in the RAPID trial protocol. A wide variety of alternate fractionations were administered, but 88.3% of prescriptions delivered an EQD<sub>2</sub> of 27-33 Gy (assuming an  $\alpha/\beta$  of 10 for lymphoma). 10.1% of prescriptions delivered an EQD<sub>2</sub> of greater than 33 Gy, with a mean EQD<sub>2</sub> of 35.1 Gy. A higher proportion of this group were PET positive (60.0%) compared to those prescribed an EQD<sub>2</sub> of <33 Gy (39.6%). Only 1.6% received an EQD<sub>2</sub> of <27 Gy, in 2 cases because the courses were stopped early (at 20 and 26 Gy in 2 Gy fractions) and in 2 cases due to the use of moderate hypofractionation for practical reasons (25 Gy in 10 fractions).

#### **Doses received by the heart and cardiac sub-structures**

The average mean doses to the heart and cardiac sub-structures for all cases (n=247) are given in Table 6.2. The average mean doses to the heart and cardiac sub-structures for those cases where the mediastinum was treated (n=113) are given in Table 6.3.

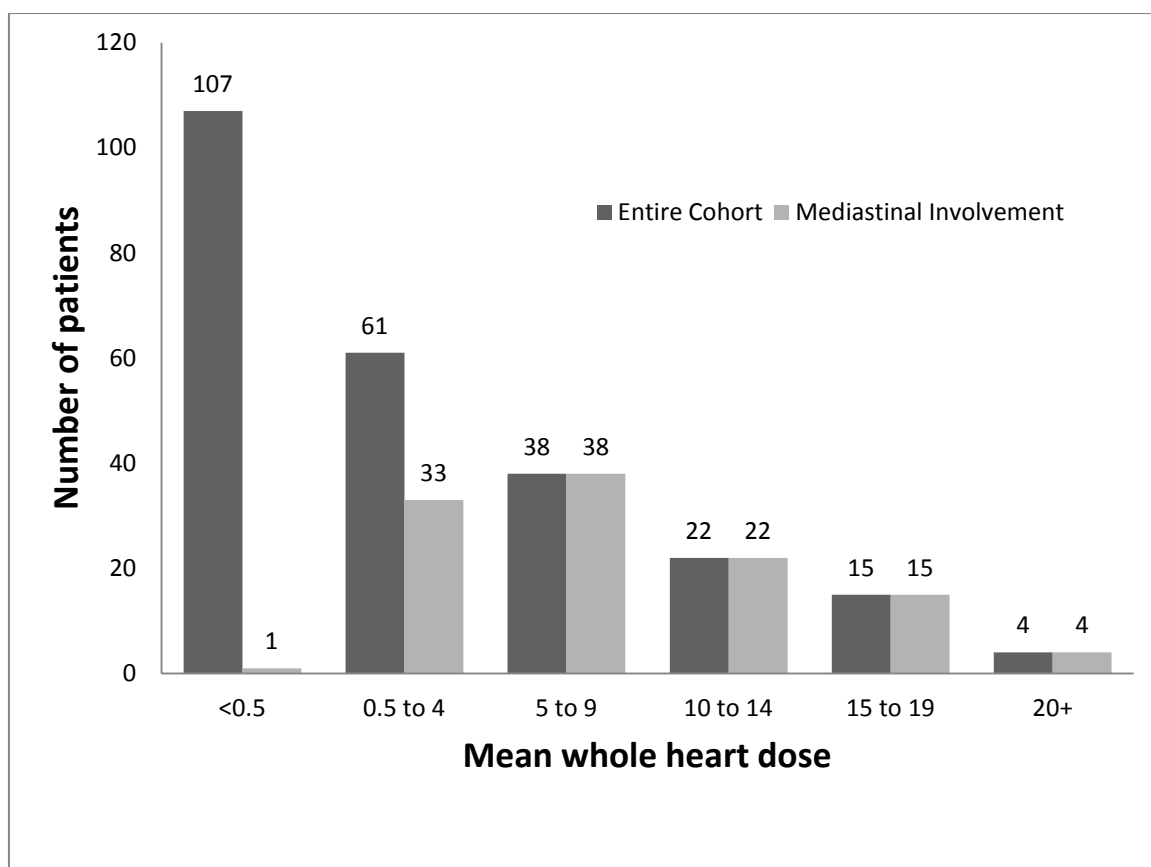
Figure 6.2 shows the distribution of mean heart dose for all cases and those where the mediastinum was treated. Of note the distribution for all cases was positively skewed, with a substantial proportion of the cohort (43.3%) receiving estimated mean heart doses of <0.5 Gy.

| Structure                   | Average mean dose, Gy (range) | Standard deviation |
|-----------------------------|-------------------------------|--------------------|
| Whole heart                 | 4.21 (0.01 to 24.00)          | 5.66               |
| Left coronary artery        | 4.54 (0.01 to 23.91)          | 5.99               |
| Right coronary artery       | 4.19 (0.01 to 31.45)          | 6.75               |
| Circumflex coronary artery  | 6.53 (0.01 to 32.51)          | 8.85               |
| Aortic valve                | 8.63 (0.02 to 34.19)          | 11.49              |
| Mitral valve                | 4.85 (0.01 to 32.65)          | 8.08               |
| Tricuspid valve             | 3.71 (0.00 to 32.45)          | 7.29               |
| Pulmonary valve             | 11.19 (0.05 to 37.74)         | 12.83              |
| Left ventricle              | 1.90 (0.01 to 20.47)          | 3.22               |
| Right ventricle             | 2.88 (0.01 to 26.89)          | 5.18               |
| Left atrium                 | 8.21 (0.02 to 32.79)          | 10.23              |
| Right atrium                | 5.44 (0.01 to 33.77)          | 8.11               |
| Sino-atrial node            | 10.80 (0.05 to 37.71)         | 12.79              |
| Atrio-ventricular node      | 5.03 (0.00 to 32.06)          | 8.93               |
| Left common carotid artery  | 21.68 (0.09 to 39.74)         | 11.55              |
| Right common carotid artery | 20.67 (0.18 to 39.60)         | 11.47              |

**Table 6.2** – Average mean doses to all cardiovascular structures for entire cohort (n=247)

| Structure                   | Average mean dose, Gy (range) | Standard deviation |
|-----------------------------|-------------------------------|--------------------|
| Whole heart                 | 8.77 (0.47 to 24.00)          | 5.61               |
| Left coronary artery        | 9.38 (0.54 to 23.91)          | 5.91               |
| Right coronary artery       | 8.82 (0.35 to 31.45)          | 7.74               |
| Circumflex coronary artery  | 13.60 (0.69 to 32.51)         | 8.85               |
| Aortic valve                | 18.18 (0.79 to 34.19)         | 10.94              |
| Mitral valve                | 10.09 (0.50 to 32.65)         | 9.59               |
| Tricuspid valve             | 7.76 (0.31 to 32.45)          | 9.28               |
| Pulmonary valve             | 23.44 (1.05 to 37.74)         | 8.98               |
| Left ventricle              | 3.84 (0.29 to 20.47)          | 3.96               |
| Right ventricle             | 6.04 (0.26 to 26.89)          | 6.35               |
| Left atrium                 | 17.30 (0.88 to 32.79)         | 8.70               |
| Right atrium                | 11.43 (0.45 to 33.77)         | 8.80               |
| Sino-atrial node            | 22.75 (1.04 to 37.71)         | 9.56               |
| Atrio-ventricular node      | 10.53 (0.54 to 32.06)         | 10.89              |
| Left common carotid artery  | 28.57 (8.71 to 39.74)         | 5.54               |
| Right common carotid artery | 28.72 (12.25 to 39.60)        | 5.01               |

**Table 6.3** – Average mean doses to all cardiovascular structures for those receiving IFRT to the mediastinum (n=113)



**Figure 6.2** – Distribution of mean whole heart dose (Gy) for the entire cohort (n=247) and for those with mediastinal involvement (n=113).

#### Doses received by the carotid arteries

The average mean doses to the carotid arteries when different regions of the neck were treated are given in Table 6.4.

| Region(s) treated                 | Average mean dose, Gy (range), standard deviation |                              |
|-----------------------------------|---------------------------------------------------|------------------------------|
|                                   | Right common carotid                              | Left common carotid          |
| Bilateral neck and/or SCF (n=117) | 29.55 (17.89 to 39.60), 3.75                      | 29.59 (13.86 to 39.74), 3.97 |
| Right neck and/or SCF (n=54)      | 20.95 (4.64 to 30.68), 7.40                       | 4.49 (0.37 to 25.00), 6.39   |
| Left neck and/or SCF (n=65)       | 5.98 (0.66 to 25.62), 6.72                        | 23.75 (1.99 to 34.59), 6.79  |
| No neck or SCF (n=11)             | 11.76 (0.18 to 25.86), 9.08                       | 9.55 (0.09 to 23.83), 8.34   |

**Table 6.4** – Average mean doses to the common carotid arteries.

### **Predicted absolute excess 15-year cardiac mortality**

#### **Relative Seriality Model**

The relative seriality model estimated a 15-year absolute excess cardiac mortality for the entire cohort of 0.60% with a range of 0.01% to 5.08%. The estimate for those that received mediastinal irradiation (n=113) was 1.29% with the same range. The estimate for those that did not receive mediastinal irradiation (n=134) was 0.01% with a range of 0.01% to 0.06%. The number of cases within each of five arbitrary risk groups and the average mean heart dose and NTCP in those groups are given in Table 6.5.

| <b>Estimated NTCP</b> | <b>Patients (%)</b> | <b>Average MWHD, Gy</b> | <b>Average NTCP</b> |
|-----------------------|---------------------|-------------------------|---------------------|
| <0.1%                 | 144 (58.3%)         | 0.40                    | 0.01%               |
| 0.1-1%                | 44 (17.8%)          | 4.93                    | 0.48%               |
| >1-2%                 | 28 (11.3%)          | 9.39                    | 1.35%               |
| >2-3%                 | 24 (9.7%)           | 14.88                   | 2.44%               |
| >3%                   | 7 (2.8%)            | 20.49                   | 4.02%               |

**Table 6.5** – The distribution of NTCPs estimated by the relative seriality model.

#### **Relative risk per Gy MWHD model**

The relative risk per Gy MWHD model estimated a 15-year absolute excess cardiac mortality for the entire cohort of 0.21% with a range of 0.00% to 2.69%. The estimate for those that received mediastinal irradiation (n=113) was 0.42% with a range of 0.01% to 3.87%. The estimate for those that did not receive mediastinal irradiation (n=134) was 0.04% with a range of 0.00% to 0.33%. The number of cases within each of five arbitrary risk groups and the average mean heart dose and NTCP in that level is given in Table 6.6.

| <b>Estimated NTCP</b> | <b>Patients (%)</b> | <b>Average MWHD, Gy</b> | <b>Average NTCP</b> |
|-----------------------|---------------------|-------------------------|---------------------|
| <0.1%                 | 152 (61.5%)         | 0.84                    | 0.03%               |
| 0.1-1%                | 82 (33.2%)          | 8.76                    | 0.28%               |
| >1-2%                 | 9 (3.6%)            | 14.35                   | 1.53%               |
| >2-3%                 | 3 (1.2%)            | 13.90                   | 2.56%               |
| >3%                   | 1 (0.4%)            | 22.83                   | 3.87%               |

**Table 6.6** – The distribution of NTCPs estimated by the ERR per Gy MWHD model.

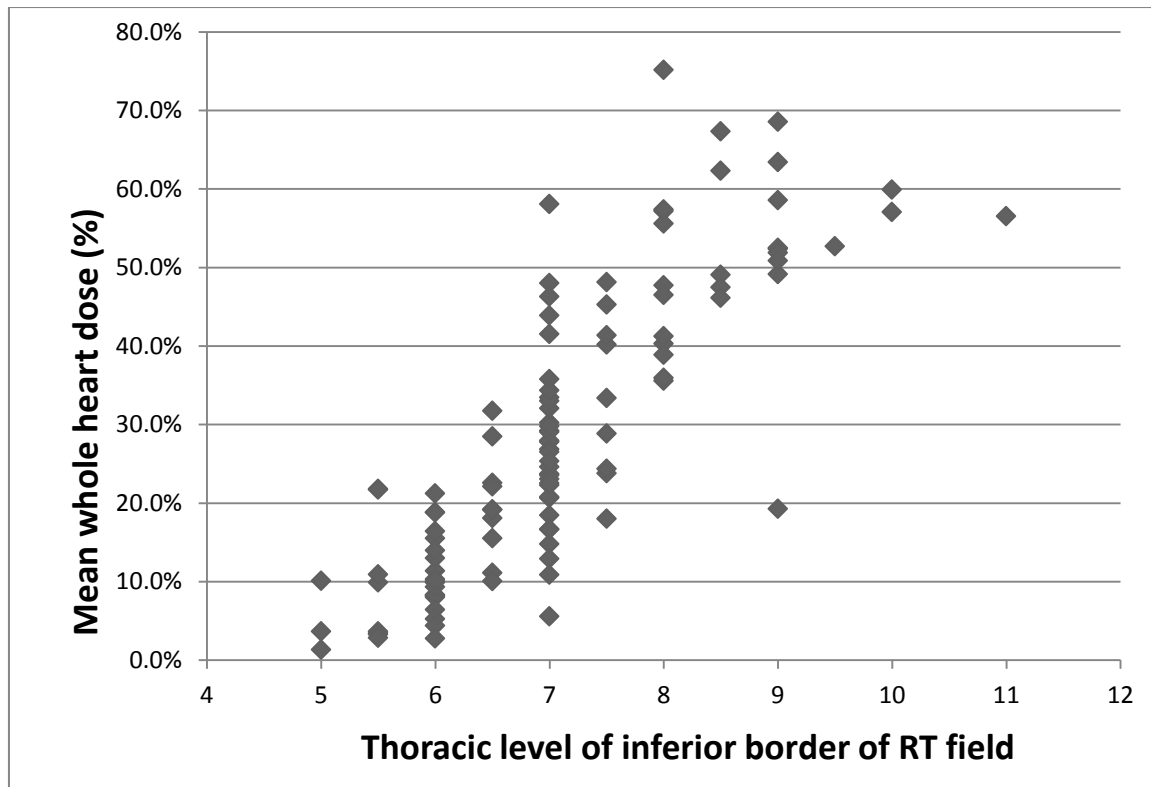


### **Variation with mediastinal involvement, PET status and gender**

The estimated MWHDs and predicted cardiac NTCPs varied with gender, mediastinal involvement, and PET status after initial chemotherapy (see Table 6.7). The MWHDs and the predicted NTCPs from both models were higher for those with mediastinal involvement and for disease which remained PET positive. The main determinant of mean heart dose for involved fields including the mediastinum was the level of the inferior border of the radiotherapy field (Figure 6.3). The MWHD for female patients in the cohort was higher than for male patients, because the proportion with mediastinal involvement was higher for females (44.9% vs. 26.1%). Also in those patients with mediastinal involvement the inferior border of the radiation field was, on average, lower among the females than the males (median thoracic level of inferior border = 7 vs. 6.5) and the vertical proportion of the heart within the field was higher (39.3% vs. 31.1%). Despite the lower average MWHD, the RR/Gy model gave consistently higher absolute risk predictions for male patients compared to females (see Table 6.7), due to the higher baseline cardiovascular risk for males, which is not accounted for in the RS model.

|        |         | MWHD, Gy   |      |       | NTCP - Predicted 15 Year Cardiac AER, % |      |      |                 |      |      |
|--------|---------|------------|------|-------|-----------------------------------------|------|------|-----------------|------|------|
|        |         |            |      |       | Relative Seriality Model                |      |      | RR/Gy MHD Model |      |      |
|        |         | PET Status |      |       | PET Status                              |      |      | PET Status      |      |      |
| Gender | Med Inv | +          | -    | +/-   | +                                       | -    | +/-  | +               | -    | +/-  |
| Male   | +       | 8.55       | 6.23 | 7.13  | 1.28                                    | 0.76 | 0.96 | 0.91            | 0.44 | 0.62 |
|        | -       | 0.44       | 0.29 | 0.37  | 0.01                                    | 0.01 | 0.01 | 0.05            | 0.03 | 0.04 |
|        | +/-     | 2.81       | 2.70 | 2.75  | 0.38                                    | 0.32 | 0.35 | 0.30            | 0.20 | 0.25 |
| Female | +       | 11.91      | 8.98 | 10.03 | 1.79                                    | 1.40 | 1.54 | 0.40            | 0.20 | 0.27 |
|        | -       | 0.42       | 0.29 | 0.33  | 0.01                                    | 0.01 | 0.01 | 0.03            | 0.02 | 0.02 |
|        | +/-     | 7.37       | 5.38 | 6.08  | 1.09                                    | 0.82 | 0.92 | 0.25            | 0.12 | 0.17 |
| Both   | +       | 10.39      | 7.82 | 8.77  | 1.56                                    | 1.13 | 1.29 | 0.63            | 0.30 | 0.42 |
|        | -       | 0.43       | 0.29 | 0.35  | 0.01                                    | 0.01 | 0.01 | 0.05            | 0.03 | 0.04 |
|        | +/-     | 4.49       | 4.00 | 4.21  | 0.64                                    | 0.56 | 0.60 | 0.29            | 0.16 | 0.21 |

**Table 6.7** – Mean whole heart dose (MWHD) and the predicted normal tissue complication probabilities (NTCP) for 15 year absolute excess risk (AER) of cardiac mortality, divided by categories of gender, mediastinal involvement (Med Inv) and PET status following initial chemotherapy (+ = positive, - = negative, +/- = both together).



**Figure 6.3** – Variation in MWHD (%) by the level of the inferior border of the RT field.

## **Discussion**

This study demonstrates that the majority of patients who received IFRT for early low-risk supra-diaphragmatic HL in the UK RAPID trial between 2003 and 2010 received a low MWHD (<5 Gy) and therefore have a low predicted AER of cardiac mortality as a result of their RT. However the range of MWHDs received was wide (0.01 to 24.00 Gy) mainly due to differences in the anatomical distribution of disease. Due to the range of MWHD received the range of predicted absolute excess cardiac risk at 15 years is considerable. The inferior level of mediastinal involvement, and hence the extent of cardiac shielding that can be utilised, is a critical determinant of cardiac dose largely independent of the specific radiation techniques that are employed, as has previously been recognised.<sup>25,26</sup> The majority of patients (76.1% or 94.7%, by the RS and ERR per Gy MWHD models respectively) are estimated as having a predicted cardiac NTCP of <1%. A proportion (23.9% or 5.3%) have a predicted NTCP of >1% and a minority (12.5% or 1.6%) have a predicted NTCP of >2%. Although these risks may seem modest, when

put in the context of an expected 10 year overall survival of >90% for favourable early stage HL<sup>1</sup> they may have a clinically meaningful impact on long term overall survival outcomes, particularly among individuals who are predicted, through cardiac dose and/or high baseline cardiac risk, to have a higher cardiac NTCP.

### **Comparison of estimated cardiac doses with previous studies**

The cardiac doses estimated for IFRT in this study are consistent with those estimated in the only paper to have previously reported cardiac doses for IFRT by Koh *et al.*<sup>7</sup> The reported median of the mean heart dose was higher in this paper than the current study after taking prescribed dose into account (15.0 Gy vs. 7.8 Gy), as the IFRT techniques described placed the inferior border either 50 mm below the carina (which is approximately equivalent to the level of the thoracic interspace T7-8) or 20 mm below the pre-chemotherapy disease if the extent of disease was lower than this. In the current study the level of the inferior border was more variable, ranging from below T5 to below T11 in those that received mediastinal irradiation (see figure 6.3), and a majority did not receive mediastinal irradiation at all. The RAPID trial also excluded patients with bulky mediastinal disease, whereas the study by Koh *et al.*<sup>7</sup> did not. These individuals would be expected to receive a higher cardiac dose.

The doses reported are also consistent with a recent report of cardiac doses from involved node radiotherapy (INRT) for HL.<sup>26</sup> In that study the cardiac doses reported are actually higher than those reported here for IFRT, which may appear unexpected for a treatment designed to deliver treatment to a smaller volume. There are two reasons for this apparent discrepancy; The first is that due to the selected age-range (15-40 years) the cohort in that paper contained a higher proportion of patients with nodular sclerosing HL, which has a propensity for mediastinal involvement, the second is that a proportion of patients were excluded on the basis of not having a CT scan that covered the entire heart and these are likely to have been patients who

would have received a lower cardiac dose. Comparison with both these studies therefore serves to emphasise that the primary determinate of cardiac radiation from RT for HL is the degree of mediastinal involvement, particularly the lower extent of the disease and hence the position of the lower border of the radiation fields.

### **Comparison of predicted cardiac mortality with previous studies**

Previous cohort studies have reported SMRs of death from cardiac causes in the range of 3.1 to 6.3.<sup>2,8,23</sup> The average of the individual ERRs calculated for the RAPID cohort is 60% (14.3% per Gy), equivalent to an SMR of 1.60, which compares favourably with that seen in the aforementioned historical cohorts, as would be anticipated with lower cardiac doses reported in this study. The mediastinal doses administered in these previous cohorts were typically 35-45 Gy using mantle fields. The MWHF for a mantle field would be expected to be 70-80% of the prescribed dose (see Chapter 5),<sup>7,26</sup> i.e. 25-36 Gy. This would equate to an ERR of approximately 6-21% per Gy mean heart dose, consistent with the estimates used in the current study. Notably, however, only a proportion of patients in these cohorts (16-44%) received anthracycline-based chemotherapy, whereas all the patients in the RAPID cohort received such chemotherapy.

### **Additional risk from anthracycline chemotherapy**

Anthracycline chemotherapy is known to further increase the risk of cardiac disease following mediastinal irradiation, even in the presence of a reduced cardiac radiation dose.<sup>22,27,28</sup> There is also evidence of an increased risk of cardiac mortality from anthracyclines (and other agents) following treatment for HL in the absence of radiation.<sup>24</sup> Neither model used in this study was based on data from patients who all received anthracycline chemotherapy. As such it should be taken as an estimation of the cardiac risk from the radiation exposure alone. As the RAPID cohort all received at least 3 cycles of anthracycline-based chemotherapy, it is possible that the

predictions given are an underestimation of the total absolute excess risk of cardiac death within the cohort. It is possible that anthracyclines may approximately double the relative risk from radiation alone.<sup>22,27</sup> With this simple assumption (and assuming no interaction between radiation and anthracycline exposure) the cardiac NTCP as predicted by the ERR per Gy MWH model would increase to an average of 0.62% (range 0.00 to 12.49%).

### **Carotid artery dose and stroke risk**

The averages of the mean radiation doses received by the common carotid arteries of patients who had IFRT to the neck and/or SCF are in the range 20-30 Gy (see table 6.4). As the cervical lymph nodes run adjacent to the carotid arteries, the majority of these arteries are within the planning target volume (PTV) and these doses are therefore to be expected, as the mean dose to the arteries will approach the prescribed dose. It is well recognised that doses of radiation to the neck higher than this for the treatment of head and neck cancer increase the subsequent risk of stroke.<sup>29</sup> It is also known that patients treated in the past for HL to doses higher than currently used (typically 40 Gy) have an increased risk of stroke.<sup>30-32</sup> In one study the median low cervical radiation dose was 38 Gy (range 30 to 57 Gy) in those patients who developed carotid artery disease and 36 Gy (range 12 to 76 Gy) in those who did not ( $p=0.05$  for difference), but a radiation dose greater than the cohort median was not predictive of the occurrence of carotid and subclavian disease in Cox multiple regression analyses.<sup>33</sup> It is unproven whether lower doses to the neck, as received in the RAPID cohort, result in any increased risk but, given the 2-3 fold increased risk for stroke and transient ischaemic attack (TIA) observed after 40 Gy,<sup>32</sup> it seems unlikely that there will be no increased risk from 20-30 Gy. However as there are, as yet, no clinical data available to produce a dose-response for stroke or TIA below 40 Gy it is not possible to quantify this risk. A recently published study<sup>34</sup> has used the limited available published data in adults<sup>32</sup> to estimate the excess risk of stroke following radiotherapy for HL. Using the same method gives point estimates of the 15 year excess risk of

stroke for the RAPID cohort of 0.55% for bilateral neck irradiation, 0.28% for left neck irradiation and 0.24% for right neck irradiation. However, given the uncertainties regarding the dose-responses for unilateral neck irradiation and for neck irradiation when the heart is not irradiated these estimated are best treated with caution.

### **Strengths of the study**

A major strength of this study is the large number of individuals for whom dosimetry was completed (n=247), which is 6 times greater than the next largest study to investigate cardiac doses from IFRT (n=41).<sup>7</sup> Cardiovascular dosimetry was completed on a high proportion of patients receiving RT within the trial (79%) and the baseline characteristics of this group suggest that this sample should be representative of the entire cohort (see Table 6.1). In addition, the study includes patients from 42 radiotherapy centres from across the UK, representing 87.5% of centres who treated patients in the RAPID trial and more than two thirds of all UK RT centres. It can therefore be considered a representative sample of national UK IFRT practice.

This study included all patients with low-risk early-stage supra-diaphragmatic HL recruited to the trial, whether the disease involved the mediastinum or not, whereas other studies have had a greater proportion with mediastinal involvement<sup>7,35,36</sup> perhaps resulting in an overestimation of cardiac dose from IFRT for HL overall. Therefore this study gives a more accurate picture of the cardiac radiation dose from IFRT for all patients with low-risk early-stage HL; the group of patients who arguably have least to gain and most to lose from radiotherapy.

Other recent studies have concentrated on INRT<sup>26,35,37,38</sup> which, while undoubtedly 'state-of-the-art', remains an experimental therapy in the current generation of trials<sup>36,39</sup> where IFRT remains the standard technique. Even if trial evidence supporting the use of INRT is produced there will remain technical challenges, such as the desirability of pre-treatment PET imaging and specialist

knowledge for nodal outlining, that may limit the widespread use of INRT for some time to come. Therefore the doses received by IFRT remain relevant to the practicing Radiation Oncologist. Whilst the radiotherapy technique described in the RAPID protocol was nominally IFRT, there was no imperative to treat entire nodal regions as IFRT has been classically described.<sup>40,41</sup> Many radiotherapy treatment plans in the RAPID study used less generous margins, particularly the inferior mediastinal margin and were, in practice, approaching what has been described as involved 'site' radiotherapy (ISRT)<sup>42</sup> a pragmatic alternative between the established IFRT and the more technically challenging INRT.

### **Limitations**

There are two limitations to this study; the accuracy of the radiation dosimetry and the accuracy of the models used to predict excess cardiac mortality.

#### **Accuracy of radiation dosimetry**

As some patients were not originally planned using a CT scan or the original CT was not available, substitute CT data sets had to be used for a minority of individuals (27.9%). There is some dosimetric variability with the same RT technique due to inter-individual variability in thoracic and cardiac size and shape (see Chapter 7) that is not easy to account for on a case-by-case basis. However, as anatomically and dosimetrically average CT data sets were used as a substitute, this should not substantially affect the overall results and conclusions.

Interpolation of missing data points was necessary for individuals where cardiac structures were not completely covered by the CT scan. This was only necessary for a minority of individuals (30%) and not for all data points in these cases (19% of mean dose data points interpolated overall). This should also not affect the overall results or conclusions.

Original dose cubes calculated from a number of different planning systems and using a variety of different dose calculation algorithms were used in the analysis which could, theoretically, affect the dose distributions produced. However, all outlining of cardiovascular structures was performed using the same TPS (Eclipse) and it has been reported that the use of different algorithms does not significantly affect the calculation of cardiac NTCPs using the relative seriality model.<sup>43</sup> Therefore the small differences in doses that may be produced by the use of more than one algorithm should not affect the overall result or conclusions.

It has been recognised that there is substantial inter-observer variability in the outlining of the of the heart and cardiac substructures<sup>9,44</sup> which would affect the doses calculated for these structures. It has been demonstrated that this variation can be reduced by following the atlas used as a reference for this study.<sup>9</sup> Additionally, all structures were outlined by the author alone to improve consistency.

#### Relative seriality model

There are two main limitations to the use of the RS model in this context. The first is that the parameters used in the model were derived from a limited number of deaths (47 total; 34 breast cancer and 13 HL). The second is the estimations of AER it produces are bound to the absolute risks of the reference populations used when the patients were treated in the 1960s and 70s. The background risk of cardiac death has fallen substantially since then<sup>45</sup> and so the parameters used may lead to an overestimation of risk. Additionally, the relative risk of cardiac death from irradiation varies substantially with the age at irradiation and the absolute risk of cardiac death varies substantially with both gender and attained age. The importance of these factors has been recently illustrated by study utilising population-based data from Sweden which reported an increased excess mortality rate ratio in males and with advancing age.<sup>46</sup> The RS model is not able to take these factors into account when predicting the future risk.



Theoretical advantages of the RS model are that it takes into consideration the functional organisation of the organ at risk and also utilises the linear quadratic (LQ) model which accounts, to some extent, for the effects of inhomogeneous irradiation and fraction sensitivity. However, given that the applicability of the LQ model to late radiation-induced cardiovascular effects can be questioned and that there remains uncertainty regarding the appropriate alpha-beta ratio to use for these clinical endpoints in humans,<sup>47</sup> the extent to which these theoretical advantages apply is not clear in practice.

#### Excess relative risk per Gy model

There are also limitations to the use of the ERR per Gy MWHD model. Unlike the RS model the risk estimate is based on a simple summary dose metric (MWHD) and does not make any attempt to account for effects of inhomogeneous irradiation or fractionation. The model assumes that cardiac death rates will remain constant from 2009 to 2025, whereas they have fallen substantially over the last 15 years and are likely to continue to do so,<sup>45</sup> such that the predicted excess number of cardiac deaths may be overestimated. The model also assumes that the ERR per Gy MWHD does not vary with time from irradiation, whereas there is insufficient data available to confirm whether or not this is the case. If the ERR per Gy MWHD decreases with time for irradiation then again this may lead the model to overestimate the cardiac NTCP.

The main advantage of the ERR per Gy MWHD model is that it is derived from a larger body of clinical data than the RS model (1012 vs. 47 cardiac deaths among irradiated patients) and therefore has a stronger empirical basis. Additionally the ERR per Gy model allows the age at irradiation and gender to be taken into account on an individual basis when predicting cardiac NTCP; two factors which have been recognised in multiple studies to affect cardiac risk.

### Limitations common to both models

Neither of the two models takes individual account of important conventional cardiac risk factors, such as smoking and diabetes, which may individually affect the risk of cardiac death by as much as 2- or 3-fold. Both models effectively assume that prevalence of these other cardiac risk factors in the RAPID cohort will be similar to the reference populations used. This is more likely for the ERR per Gy MWHD model which uses an individually age and sex-matched matched contemporary background rates, but is highly unlikely for the RS model where the demographics of the data set from which the parameters were derived are substantially different and the background absolute rates are non-contemporary. A model that utilised individual data regarding cardiac risk factors (such as described in Chapter 8) would be preferable, but as such information was not available for the RAPID cohort this was not possible.

Neither model estimates the risk of cardiac mortality beyond the next 15 years, whereas it is known that the absolute excess risk of death from cardiovascular disease continues to increase beyond 15 years.<sup>2</sup> This is very relevant to a cohort treated for HL, where the average age of diagnosis and treatment is young. The average age of the RAPID cohort at RT was just 38.6 years and 15 years post-RT the cohort will only just be approaching an average age where the background absolute risk of cardiac death begins to increase sharply (see Appendix C, Figure C.4). An advantage of the ERR per Gy MWHD model is that the age- and sex-matched EBRs could be estimated for the cohort to later time points (20, 25 years etc.). The drawback of this approach is that the assumptions on which the model is based (that the background rates remain constant from 2009 into the future and that the ERR per Gy MWHD does not vary with time from irradiation) become more uncertain with time from treatment.

Both models use the whole heart as the organ at risk, whereas there is on-going uncertainty over the true critical structure or structures and the dose metric which may best help predict cardiac risk following irradiation.<sup>48</sup> The best epidemiological evidence currently available uses mean whole heart dose (or mediastinal dose) as the measure of exposure and this is therefore what was used and what will need to be used in the future until adequately sized studies utilising individual 3D dosimetry with accurate estimations of dose to individual cardiac substructures and sufficient follow-up (and numbers of events) can be completed.

Neither model takes into account the cardiac risk of the anthracyclines included in the ABVD regimen received by all patients in the RAPID cohort. The principal aim of the study was to estimate the excess cardiac risk from IFRT as randomisation to receive IFRT or not was the main question of the RAPID trial. Although the anthracycline exposure is the same in both arms of the randomisation there remains a possibility that the combination of RT and anthracyclines may produce a more than additive risk, in which case it becomes important to include anthracycline in any model used to estimate radiation risk in this circumstance. The data are not currently available to incorporate the risk anthracycline dose into any model appropriately.

Both models predict only the AER of cardiac mortality whereas it is known that HL survivors treated in the past have suffered from a substantial incidence of non-fatal, but still clinically relevant, cardiac illness including ischaemic heart disease, valvular heart disease and cardiac failure.<sup>22,49</sup> Although recent attempts have been made to produce dose-response relationships for valvular heart disease and all cardiac disease using data from survivors of HL treated in childhood,<sup>26</sup> given the limited number of events in the data set and the recognised effect of age at irradiation on the risk of radiation-induced heart disease it is uncertain that the predictions made to date are reliable for survivors treated in adulthood.

### **Clinical relevance**

The primary aim of the RAPID trial was to ask whether RT could be withheld in early low risk HL patients who had a negative PET scan after initial ABVD chemotherapy. The primary endpoint of the trial is progression-free survival (PFS). It is unlikely that HL-specific survival will differ significantly between the two arms due to the success of salvage therapy for relapsed disease as it is known that, whilst patients who receive a single modality therapy seem to have a higher rate of relapse, there is no difference in 5-year survival.<sup>1</sup> If the omission of RT from primary therapy does lead to an increase in HL relapse rate, then the relevant clinical question becomes one of balancing the risk of late adverse effects from a strategy that delivers a combination of both CT and RT to all up front versus this risk in the minority of individuals who will relapse and go on to receive more intensive and toxic salvage therapy in a strategy that selectively withholds initial RT. Preliminary results from the RAPID trial reported a non-significant reduction in 3-year PFS (3.5%, 90.8% versus 94.5%) in the arm that did not receive IFRT (HR = 1.51, 95% CI 0.77 to 2.94,  $p=0.23$ ).<sup>4</sup> However, a substantial number of the patients within the trial randomised to receive RT were not treated with RT ( $n=26$ ), largely due to patient and/or clinician choice. A 'per protocol' analysis of the randomised patients, excluding these 26 individuals and also 2 patients who received RT in the no RT arm, reveals a statistically significant reduction in 3 year PFS (6.3%, 90.7% versus 97.0%) in the arm that did not receive IFRT (HR = 2.39, 95% CI 1.09 to 5.26,  $p=0.03$ ). If one makes the assumption that this difference in 3-year PFS is real and that 4.0% more patients will relapse without IFRT following a negative PET scan then, in order to outweigh the predicted cardiac mortality benefit of omitting IFRT (0.16% for all PET negative patients in the study), the absolute excess non-HL mortality of salvage therapy would need to be in the region of 2.5%. However, if one makes the assumption that the difference is at the lower limit of the confidence interval (i.e. -11.8%), then the absolute excess non-HL mortality of salvage therapy would only need to be in the region of 1.3% to outweigh the predicted benefit. Of course, cardiac mortality is not the only radiotherapy-related cause of death that may be

reduced by the omission of IFRT from initial treatment. It is generally recognised that second cancer risks have been lower following treatment with chemotherapy alone compared to combined modality therapy.<sup>50</sup> However this effect was not seen to be significant following treatment for early stage disease in a meta-analysis focusing on second cancer risks.<sup>51</sup> Also it has been observed that treatment with salvage therapy also increases mortality from second malignancy.<sup>2</sup> Furthermore it is predicted that the shift from extended field RT (EFRT) to IFRT and the reduction in prescribed dose to 20 or 30 Gy in favourable risk patients should reduce the excess risk of second cancers from that which is observed in historical cohorts.<sup>7</sup> Indeed, this has been already demonstrated in the German Hodgkin Study Group HD8 trial of EFRT vs. IFRT, where the incidence of second malignancy at 10 years was 10.9% vs. 8.5% ( $p=0.2$ ) and the risk of death from second malignancy at 10 years was 5.3% vs. 3.4%.<sup>52</sup> Much has been discussed regarding a recent paper which reported long term follow-up of the North American HD6 trial, comparing ABVD only versus ABVD plus sub-total nodal irradiation to 35 Gy as treatment for limited stage HL.<sup>53</sup> This reported superior PFS in the patients receiving radiotherapy (87% vs. 92%, HR=1.91, 95% CI 0.99 to 3.69,  $p=0.05$ ) but inferior overall survival at 12 years (94% vs. 87%, HR=0.50, 95% CI 0.25 to 0.99,  $p=0.04$ ) due to an increased number of deaths from causes other than HL (24 vs. 12). However, the only substantial difference in cause specific death is from second malignancy (10 vs. 4) and the dose and volumes of radiation used in this study are far higher than would be used for modern RT. Given the small numbers of deaths and outdated RT, these results alone cannot be used as a convincing argument for the exclusion of radiotherapy from standard HL treatment in the context of modern radiotherapy. In summary, it is not known with any confidence that the volumes and doses of RT in use today will produce an increase in second cancer risk that, in combination with small predicted radiation-related cardiac mortality risk, will definitely outweigh the possible increased risks of more frequent use of salvage therapy. Further data on the long-term risks of the modern of HL treatments, both chemotherapy and

radiotherapy are required to perform this assessment accurately. The predictions of excess cardiac mortality from IFRT in the current study are a useful contribution to this challenge.

## **Conclusion**

The majority of patients treated with IFRT for low risk early stage HL within the RAPID trial received a low cardiac radiation dose. Consequently it is predicted that they will have a low number of excess cardiac deaths due to their radiotherapy at 15 years following treatment. The low predicted excess risk of cardiac death in the RAPID cohort is in agreement with recent predictions of low excess mortality from diseases of the circulatory system for HL survivors treated since 2000, produced from models created using population-based data in Sweden.<sup>46</sup> Continued follow-up for cause-specific mortality within the RAPID trial will be able to exclude any large difference in non-HL mortality between the treatment arms, but cannot exclude lower risks of the size predicted by this study. The confirmation of the predicted magnitude of excess cardiac deaths (<1%) within a randomised data set (with a power of 90% at a 5% significance level) would require the prolonged observation of >5000 similar patients randomised between RT and no RT, which is clearly impractical in a condition as relatively rare as HL. Given the likely continued absence of randomised evidence pertaining to this issue, a pragmatic empirical approach utilising the largest and best available data sets, as used in this study, has much to recommend it.

Although the average predicted absolute excess risk of cardiac death at 15 years for the cohort is low (<1%), and the majority have a very low predicted risk, the range is wide with a minority of individuals predicted to have substantial risk (>2%). The factors that are most important in determining these estimated risks are the MWHD, which is determined primarily by the mediastinal level of disease, and (for the ERR per Gy MWHD model) the baseline cardiac risk, which is determined by the individual's gender and age. There are two important clinical

conclusions from these observations: 1) as the mediastinal level of disease is known at diagnosis, the cardiac radiation dose and hence the risk of late cardiac death as a result of irradiation can be estimated at diagnosis (see Chapter 7); 2) an individualised assessment of baseline cardiac risk including not only age and gender but also conventional risk factors such as smoking, hypercholesterolaemia, hypertension and diabetes is as important a component of assessing absolute cardiac risk as an individual's radiation dosimetry.

The relative seriality model is the only accepted model that has estimated the excess risk of cardiac mortality following thoracic radiotherapy<sup>54</sup> and it remains in use in recent publications.<sup>55-</sup>

<sup>57</sup> The results of this study suggest that the relative seriality model may overestimate the cardiac NTCP following thoracic irradiation in contemporary populations with age and sex profiles different to that used to originally derive the model parameters.<sup>18</sup> This study suggests an alternative model, with a stronger empirical basis, which may be used to make more reliable predictions of excess cardiac mortality risk.

This study strongly suggests that the majority of patients can, from the point of view of predicted excess cardiac mortality, safely receive primary treatment including IFRT. Potentially, however, it also identifies a minority of patients who, based on current knowledge, should perhaps either not receive primary RT due to a cardiac risk that would be expected to exceed the risks of relapse and subsequent salvage therapy, or who should be considered for treatment using techniques that minimise cardiac radiation exposure, such as deep breath-hold techniques<sup>58</sup> or proton therapy.<sup>37</sup> It is likely that the continued accumulation of data regarding the adverse effects of both chemotherapy and radiotherapy will, in the future, allow individualised decisions regarding whether initial single- or combined-modality therapy is most appropriate for a particular HL patient based on their disease and co-morbid risk factors.

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## **Chapter 7 - A Clinical Tool for Estimating the Mean Whole Heart Radiation Dose from Involved Field Radiotherapy Including the Mediastinum**

### **Introduction**

Mantle irradiation for Hodgkin lymphoma (HL), as given in the past, is well recognised to have resulted in increased risks of cardiac morbidity and mortality.<sup>1,2</sup> It is certain that prescribed mediastinal radiation doses of >30 Gy result in an increased risk of cardiac disease and death, and that shielding to limit cardiac dose can reduce these risks.<sup>3</sup> However, it has also been demonstrated that modern mantle radiotherapy administered during the 1990s, which restricted cardiac doses to  $\leq 30$  Gy, still increased the subsequent risk of cardiac morbidity, particularly in combination with anthracycline-based chemotherapy.<sup>4</sup> More recently data from a number of independent sources, including breast cancer<sup>5</sup> (see Appendix F) and childhood cancer,<sup>6</sup> suggest that the dose-response for late cardiovascular effects may not have a lower threshold and that risk increases over the range 0-30 Gy as well as occurring at higher doses.

Currently, and for the past decade, the standard radiotherapy technique used as treatment for HL has been involved field radiotherapy (IFRT) in combination with anthracycline-based chemotherapy.<sup>7</sup> Unlike mantle treatment, IFRT does not routinely irradiate the entire mediastinum. But an involved field that includes the mediastinum may still result in the incidental exposure of the heart to a substantial radiation dose. The extent of the mediastinum involved by HL, the inferior border of the radiation field, and hence the volume of heart irradiated and the cardiac radiation dose received, varies markedly from individual to individual (see Chapter 6). The level of the inferior border for an involved field may range from superiorly within the mediastinum, above the heart, to the level of the T10-11 interspace, below the apex of the heart with the resulting mean cardiac dose ranging from <1 Gy to >20 Gy (from a prescribed dose of 30 Gy). It is therefore likely that some patients receiving IFRT will have

clinically significant risks of late cardiovascular effects as a consequence of their radiotherapy, but these risks will vary substantially from case to case.

With CT-based 3-D RT planning systems it is possible to accurately estimate cardiac doses prior to treatment on an individual basis. However, this detailed information is not available at the point of diagnosis and at the time of consent for radiotherapy, when the risk of late cardiovascular effects should be considered by the treating physicians and discussed with the patient. Therefore a simple clinical tool that could predict the likely cardiac dose from IFRT (and hence the cardiac risk) using the diagnostic imaging that is available prior to formal RT planning would be practically useful. I investigated the relationship between simple radiological measurements that would be available at the diagnosis of HL and the cardiac radiation dose that would result from subsequent IFRT in order to develop such a tool.

## **Materials and Methods**

### **Study subjects**

Post-chemotherapy RT planning CT data sets from a total of 25 male and 25 female consecutive patients treated with IFRT for HL in the RAPID trial, from 24 different radiotherapy centres around the UK, were selected. Only data sets covering the entire heart were used. 2 data sets (one male and one female) were discarded during selection on the basis of atypical thoracic anatomy (marked kyphosis). According to the trial entry criteria all participants had clinical stage I/IIA disease above the diaphragm, with no bulky mediastinal disease (defined as the ratio of the maximum transverse diameter of mediastinal mass to the internal thoracic diameter at the T5/6 interspace  $\geq 0.33$ ).

### **Involved field radiotherapy planning**

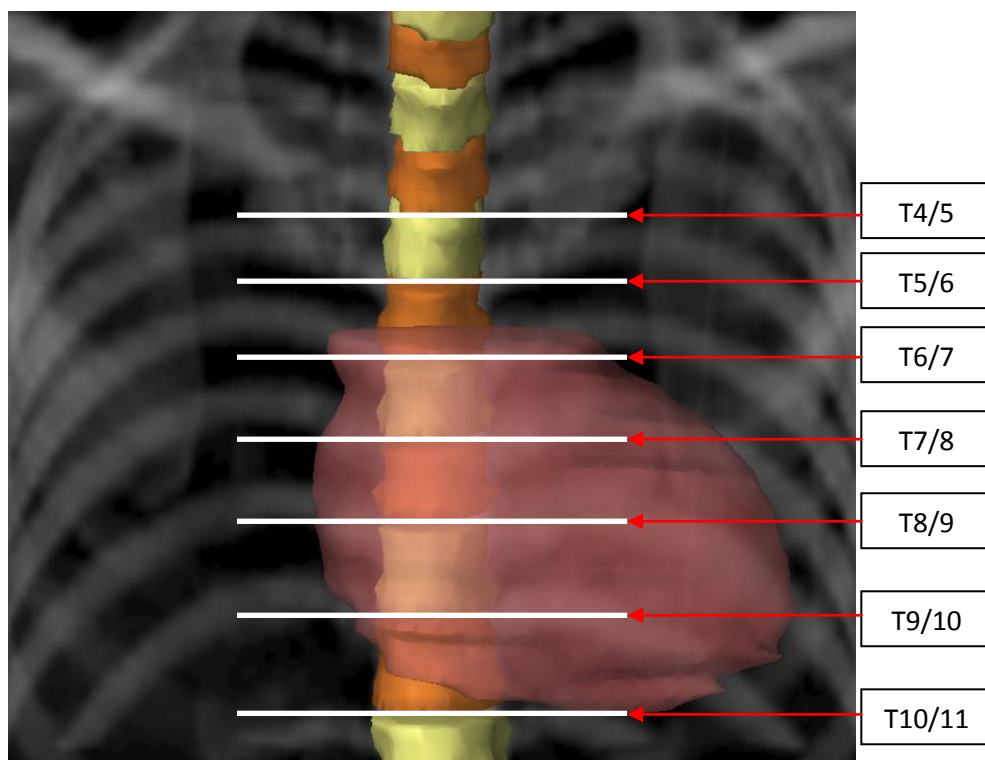
CT data sets were imported into the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). Series of 8 involved field radiotherapy plans were then created using each data set, based on guidelines from the RAPID trial protocol and papers describing the IFRT technique,<sup>8,9</sup> each treating the supraclavicular fossae bilaterally and a varying extent of the mediastinum. The superior border of the field remained constant at the C5-6 interspace and the inferior border was varied in 8 steps from the T4-5 interspace to the T11-12 interspace, thus covering the full extent of the mediastinum that would conceivably be treated with an involved field technique (see Figure 7.1). For a number of CT data sets the lowest slice did not extend below the T10-11 interspace, in these cases only 7 plans were produced. The mediastinal lymph nodes were outlined with reference to a published atlas<sup>10</sup> and a margin of 1.5 cm applied around these to determine lateral mediastinal field borders. The clavicles were outlined and a margin of 1.5 cm applied inferiorly to standardise coverage of the infraclavicular fossae. Lateral borders were placed to cover the medial two thirds of the clavicles. Opposed anterior and posterior 6MV fields of equal size and SSD were used with a prescription point in the mid-plane at the field centre, except if this point was in air when the point was moved laterally in the mid-plane to avoid dosimetric inaccuracy. Multi-leaf collimators were used for shielding of the lung (with borders as described above). No dose compensation was used. Dose calculations were performed using the anisotropic analytic algorithm (Version 8.1.17).

### **Cardiac dosimetry and anatomical measures**

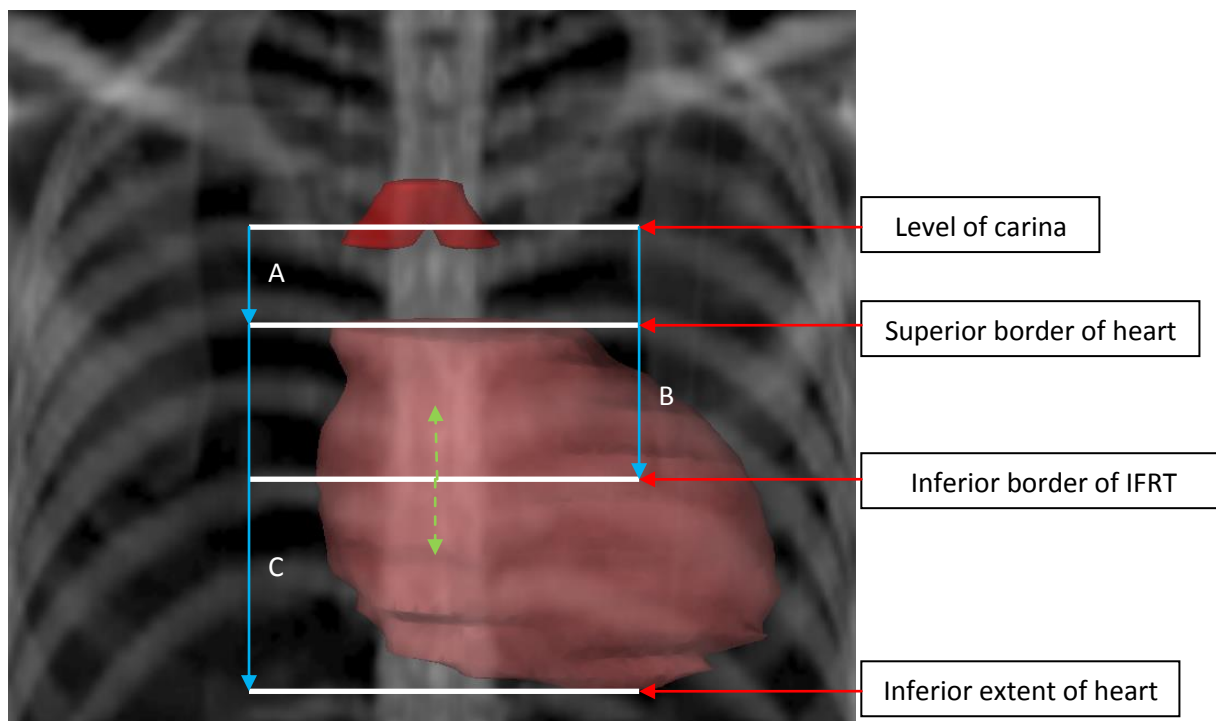
The heart and cardiac substructures were outlined as described in Chapter 6 (see page 138). DVHs were created in Eclipse for the whole heart and the mean whole heart doses (MWHs) calculated. The distance (in mm) between the CT slice showing the top of the carina and the superior border of the heart (defined as per Feng *et al*)<sup>11</sup> was recorded as the 'carina to heart distance' (see Figure 7.2 – A). The distances (in mm) between the carina and the inferior border of each radiotherapy plan (at the point of maximum divergence) were measured and recorded as the 'carina to inferior border distance' (see figure 7.2 – B). If the inferior border of the field was above the carina this distance was recorded as a negative value. The distance (in mm) between the CT slice showing the superior border of the heart and the most inferior part of the heart was also recorded as the 'heart height' (see figure 7.2 – C). From these measurements the vertical extent of the whole heart present within the radiation field was calculated  $((B-A)/C)$ . The 'extent of the heart in the field' in the figures below ranges from -0.5, which should be interpreted as the inferior border of the field being situated 50% of the heart height *above* the superior edge of the heart, to 1.5 which should be interpreted as the inferior border of the field being situated 50% of the heart height *below* the inferior edge of the heart.

### **Statistical analysis**

Four types of sigmoid-shaped curves (logistic, Gompertz, Richards and Weibull) were fitted to the relationships between three anatomical measurements (x) and the MWH (y). The three anatomical measures were; thoracic level of the inferior field border (integers 4 to 12), the distances (in mm) between the carina and the inferior border, and the vertical extent of the whole heart within the radiation field (as defined above). The 4-parameter Gompertz curve provided a good fit.



**Figure 7.1** – 3-D reconstruction of the thoracic vertebral bodies (yellow and orange) and the whole heart (pink), demonstrating the levels where the inferior borders of the IFRT fields were positioned (white lines).



**Figure 7.2** – 3-D reconstruction of the carina (red) and whole heart (pink), demonstrating the anatomical levels used to measure the carina to inferior field border distance (B) and the vertical extent of the whole heart within the IFRT field  $((B-A)/C)$ .



The formula for a Gompertz curve is:

$$y(x) = a + be^{-e^{-c(x-d)}}$$

Where 'a' is the lower asymptote, 'a+b' is the upper asymptote, 'd' is the point of inflection of the curve and  $bce^{-1}$  is the slope at this point. e = Euler's number (2.71828...).

A Gompertz curve was fitted for each individual patient giving 50 sets of parameter estimates for the relationship between each anatomical measurement and MWHD. The average parameters were used to produce average MWHD curves for the relationships. The sample mean and variance of the parameters were used to estimate multivariate normal distributions between patients. In order to demonstrate the variability of doses that may be received due to inter-patient anatomical variability, curves for 100,000 hypothetical patients were generated from these distributions, enabling estimations of the 95% confidence limits for the MWHD curves for individuals. The mean parameters for male and female patients were compared using t-tests.

Of the 50 patients used to fit the Gompertz curves, actual plans and corresponding doses were available for 36. In order to estimate the extra error involved in predicting doses for real plans, the individual fitted curves were used to predict the doses for the actual plans and the predictions compared with the actual doses. The prediction errors were modelled as normally distributed with constant relative standard deviation, and this standard deviation was estimated from the observed prediction errors.

The simulation of 100,000 hypothetical patients was repeated with this extra noise added in, to produce confidence intervals appropriate for the prediction of dose from actual plans. The ability of these models to predict doses for actual plans was then assessed using data from the original 36 patients in the variance estimation, plus 35 additional patients who were treated within the RAPID trial. For the original 36 patients this was done by fitting the model to all the patients but one and then using the fitted model to predict the heart dose on the omitted patient and repeating this process for all 36 patients. The average absolute prediction error was calculated as the square root of the mean values of the squares of the absolute prediction errors (root mean square error prediction, RMSEP). The average relative prediction error was also calculated as the square root of the mean values of the squares of the relative prediction errors (relative standard deviation, RSD). The median absolute error (MAE) and median relative error (MRE) were also calculated as robust estimates of the corresponding standard deviation.

## **Results**

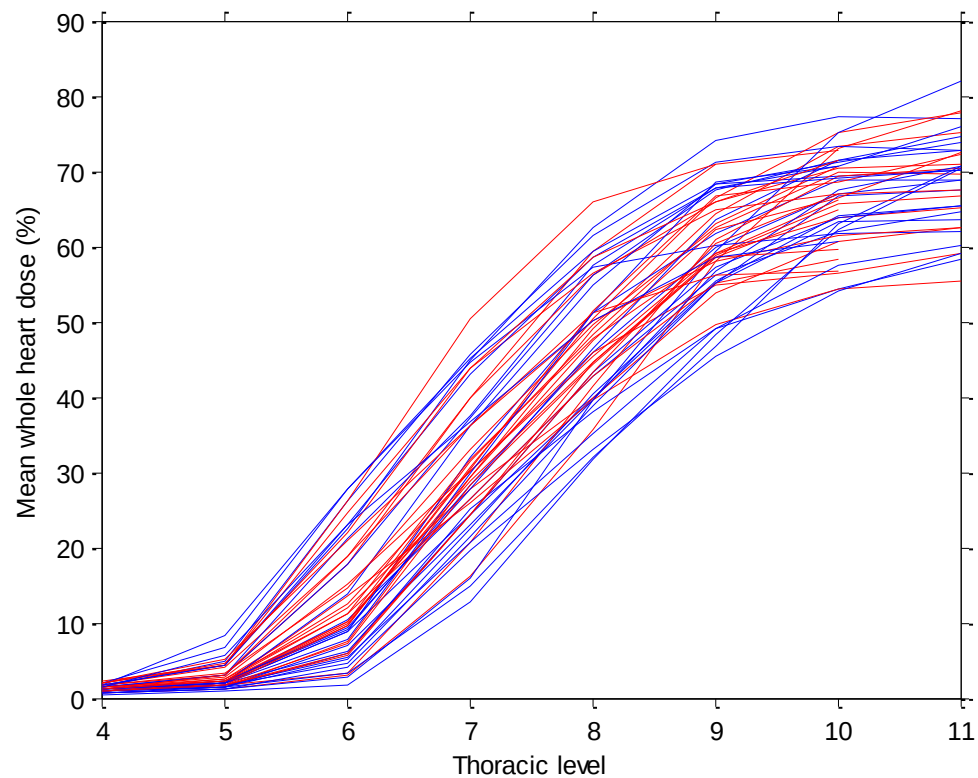
Relevant clinical and anatomical characteristics of the 50 study subjects whose CT data sets were used to produce the curves are described in Table 7.1.

| <b>Characteristic</b>                   | <b>Male</b>   | <b>Female</b> | <b>Both</b>   |
|-----------------------------------------|---------------|---------------|---------------|
| Mean age at CT scan, years (range)      | 40 (22 to 72) | 33 (20 to 69) | 37 (20 to 72) |
| PET+ after initial CT, %                | 40            | 44            | 42            |
| Mean BSA, m <sup>2</sup> (SD)           | 2.0 (0.2)     | 1.7 (0.1)     | 1.9 (0.2)     |
| Mean heart volume, cm <sup>3</sup> (SD) | 850.4 (128.9) | 606.9 (61.7)  | 728.7 (159.8) |
| Mean distance 'A', mm (SD)              | 22.6 (6.9)    | 22.6 (7.2)    | 22.6 (7.1)    |
| Mean distance 'C', mm (SD)              | 102.5 (11.5)  | 104.2 (10.5)  | 103.4 (11.1)  |
| Mean AP separation at carina, cm (SD)   | 21.1 (3)      | 17.2 (1.5)    | 19.2 (3.1)    |

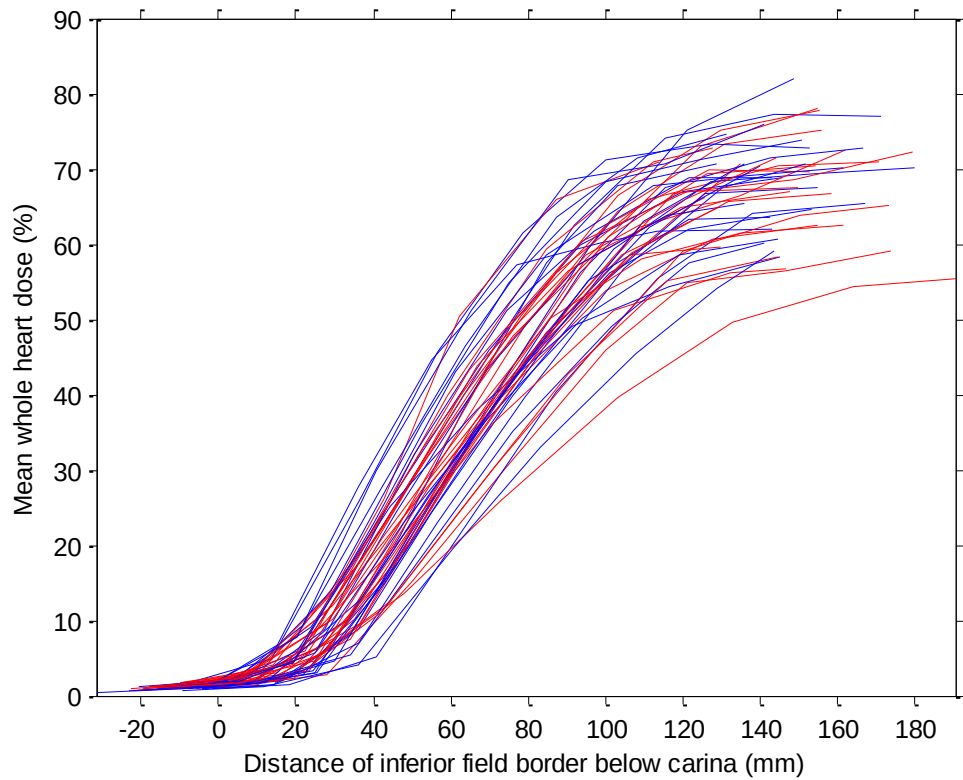
**Table 7.1** – Characteristics of the patients whose CT data sets were used to generate the data

Plots of the MWHDs received from all plans for all 50 individuals with relation to the position of the inferior border as defined by; a) thoracic level, b) distance below the carina and c) the vertical extent of the heart within the field, are given in Figures 7.3(a-c).

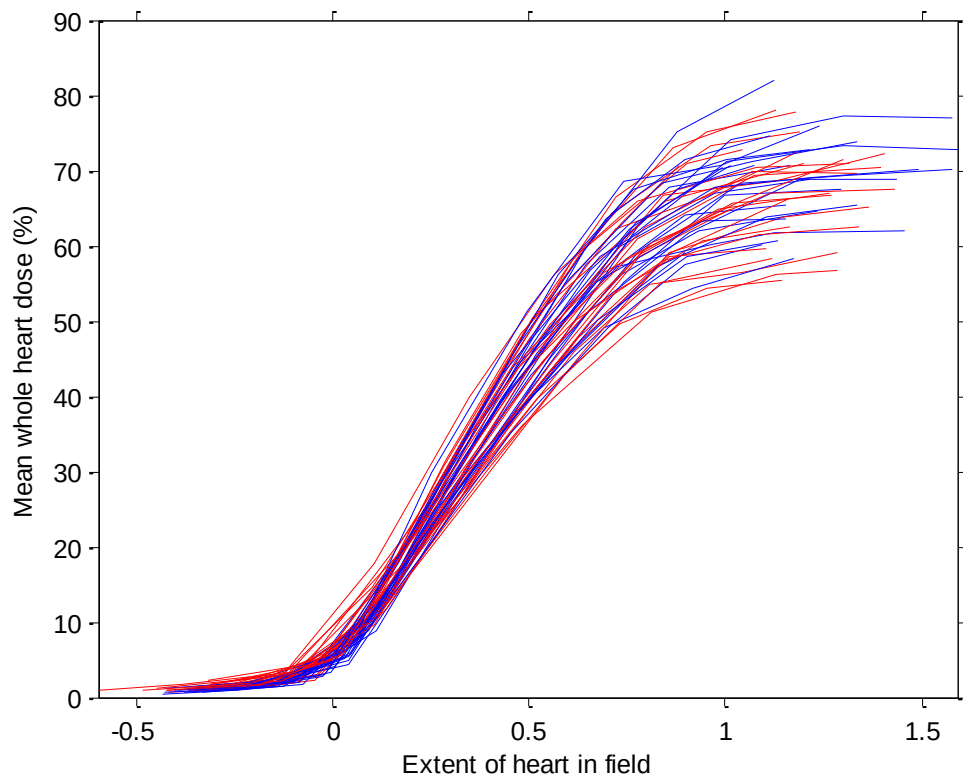
**Figure 7.3a**



**Figure 7.3b**



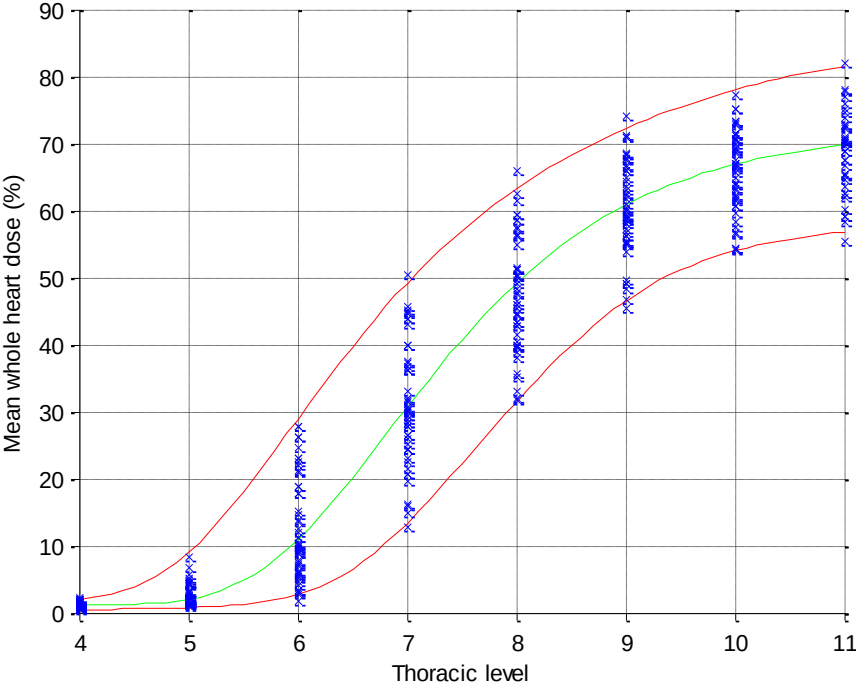
**Figure 7.3c**



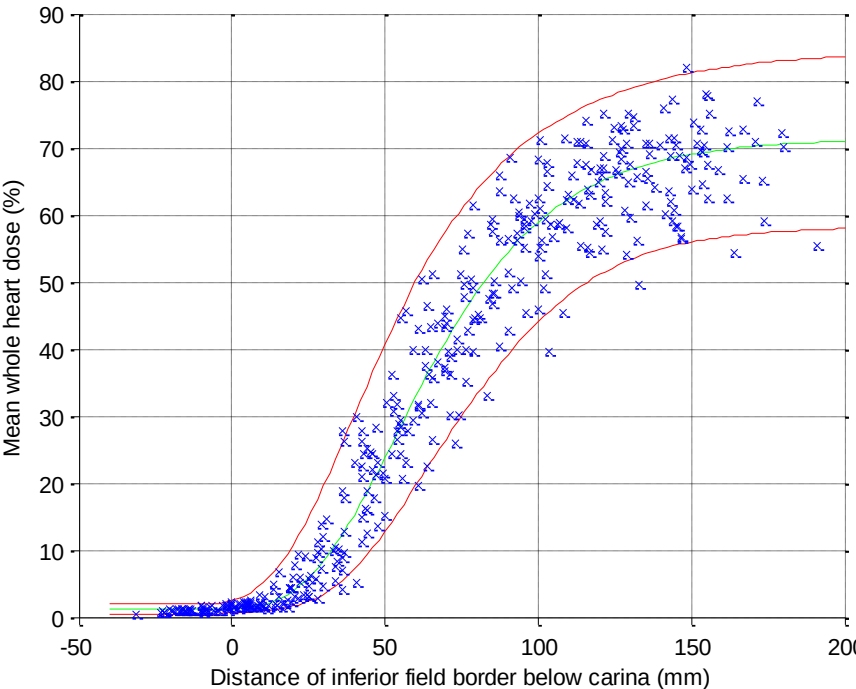
**Figure 7.3(a-c)** – Mean heart doses for the IFRT plans plotted by; thoracic level (a), distance (in mm) below the carina (b), and vertical extent of heart in the field (c). Red=Male. Blue=Female.

Plots of the average MWHHD curves produced by fitting Gompertz curves to the MWHDs and the estimated 95% confidence limits for individual curves are given in Figures 7.4(a-c).

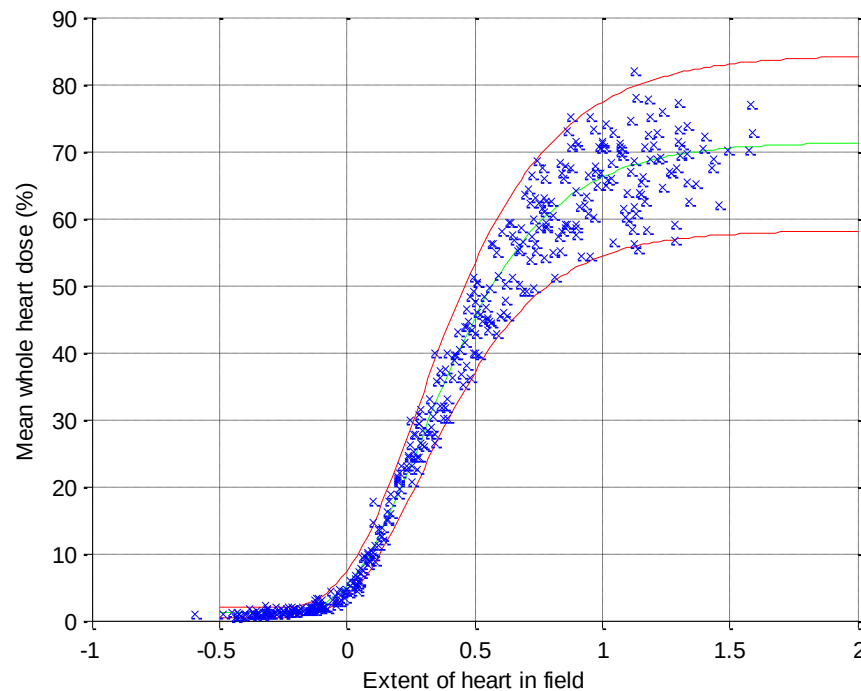
**Figure 7.4a**



**Figure 7.4b**



**Figure 7.4c**



**Figures 7.4(a-c)** – Plots of the average dose curves (green) produced by fitting Gompertz curves to MWHs from the RT plans, with estimated 95% CIs (red) for the individual curves plotted by; thoracic level (a), distance (in mm) below the carina (b), and vertical extent of heart within the field (c). The blue crosses are the data from the standard IFRT plans produced on the 50 different CT data sets.

Table 7.2 gives the Gompertz parameters and the standard deviations of the parameter estimates for the three anatomical measures. The standard deviation is of the 50 parameter estimates and measures the variability of the parameters between patients.

| Gompertz parameters (SD) | Thoracic level | Distance below carina | Extent of heart in field |
|--------------------------|----------------|-----------------------|--------------------------|
| a                        | 1.17 (0.37)    | 1.09 (0.39)           | 1.09 (0.39)              |
| b                        | 71.03 (7.06)   | 70.27 (6.68)          | 70.27 (6.68)             |
| c                        | 0.81 (0.10)    | 0.04 (0.01)           | 3.60 (0.30)              |
| d                        | 6.85 (0.50)    | 53.41 (8.17)          | 0.29 (0.03)              |

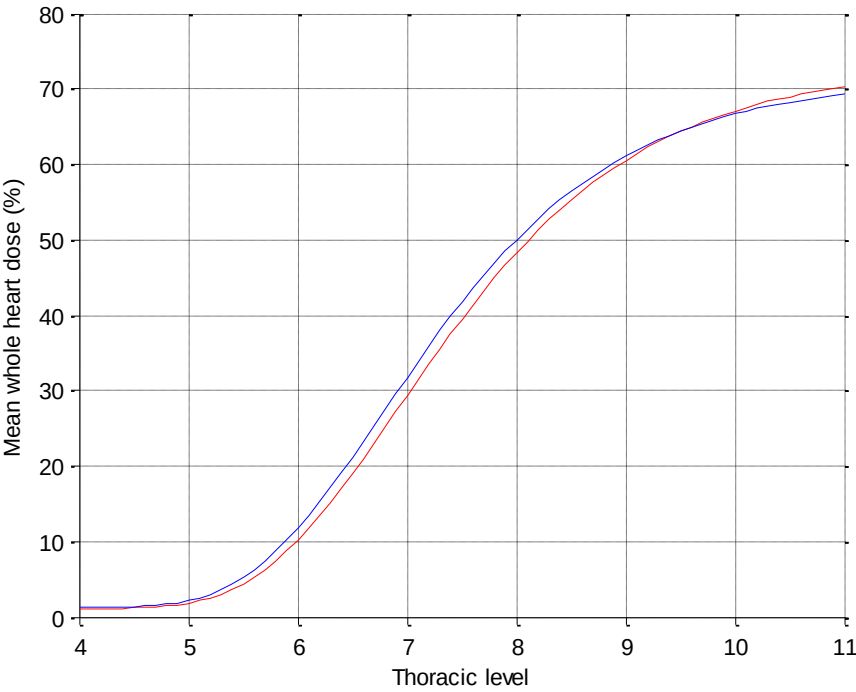
**Table 7.2** – Gompertz parameters and their standard deviations for the three anatomical measures.

With thoracic level as the predictor, there were no significant differences between the parameters of the mean curves for male and female patients. For the other two predictors there were some statistically significant differences between the lower asymptotes for males

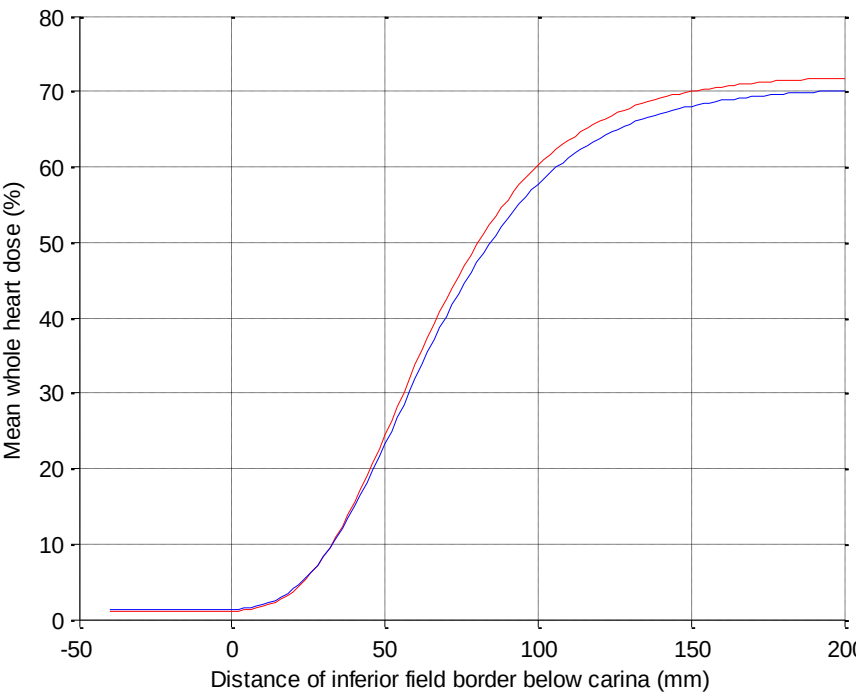
and females, but these differences are so small (0.2%) that they have no practical importance.

The mean curves for the three predictors are illustrated in Figure 7.5(a-c).

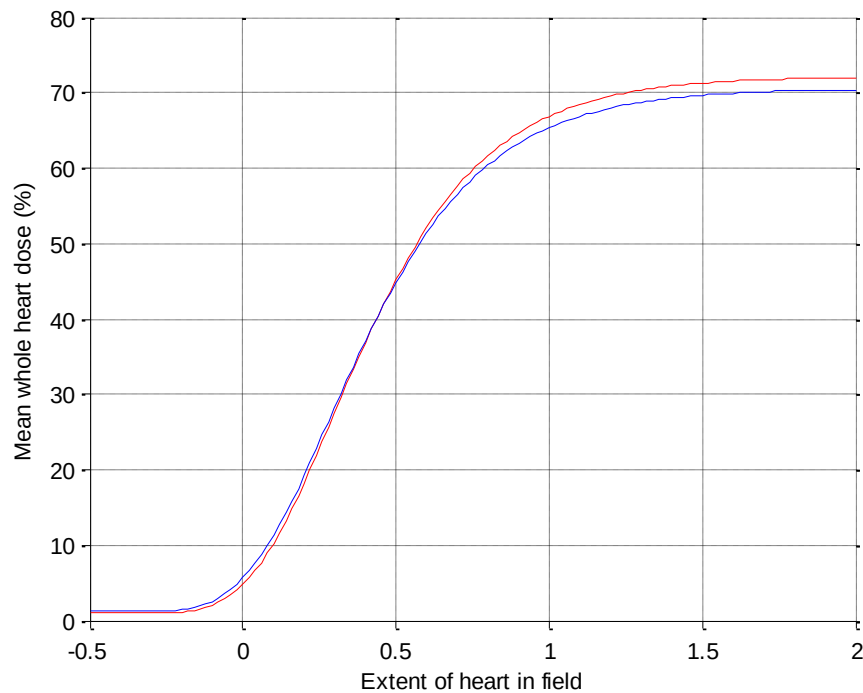
**Figure 7.5a**



**Figure 7.5b**



**Figure 7.5c**



**Figure 7.5(a-c)** – Mean curves for the three anatomical measures: thoracic level (a), distance below carina (b) and extent of heart in field (c). Red = Male. Blue = Female.

Tables 7.3(a-c) give the estimated average MWHD (% of prescribed dose) for the three anatomical measures studied as predictors and the 95% confidence limits for individual curves.

| Thoracic Level | Average (%) | Lower 95% CI | Upper 95% CI |
|----------------|-------------|--------------|--------------|
| T4-5           | 1.2         | 0.5          | 2.2          |
| T5-6           | 2.0         | 0.7          | 9.0          |
| T6-7           | 10.9        | 2.6          | 29.5         |
| T7-8           | 30.6        | 12.8         | 51.6         |
| T8-9           | 49.2        | 29.4         | 68.3         |
| T9-10          | 60.9        | 41.5         | 79.4         |
| T10-11         | 66.9        | 47.4         | 86.6         |
| T11-12         | 69.8        | 49.8         | 90.5         |

**Table 7.3a** - Figures for average MWHD curves (and 95% CIs) to estimate MWHD for actual plans from the thoracic level of the inferior border of the IFRT field.



| Distance below carina | Average (%) | Lower 95% CI | Upper 95% CI |
|-----------------------|-------------|--------------|--------------|
| -40 mm                | 1.1         | 0.3          | 1.9          |
| -20 mm                | 1.1         | 0.3          | 1.9          |
| 0 mm                  | 1.2         | 0.6          | 2.5          |
| 20 mm                 | 3.9         | 1.5          | 11.0         |
| 40 mm                 | 15.3        | 6.8          | 31.1         |
| 60 mm                 | 32.9        | 18.3         | 53.0         |
| 80 mm                 | 48.5        | 30.5         | 69.0         |
| 100 mm                | 58.9        | 39.7         | 79.1         |
| 120 mm                | 64.9        | 45.2         | 85.3         |
| 140 mm                | 68.1        | 48.1         | 88.8         |
| 160 mm                | 69.7        | 49.7         | 90.9         |
| 180 mm                | 70.5        | 50.3         | 91.9         |
| 200 mm                | 71.0        | 50.8         | 93.0         |

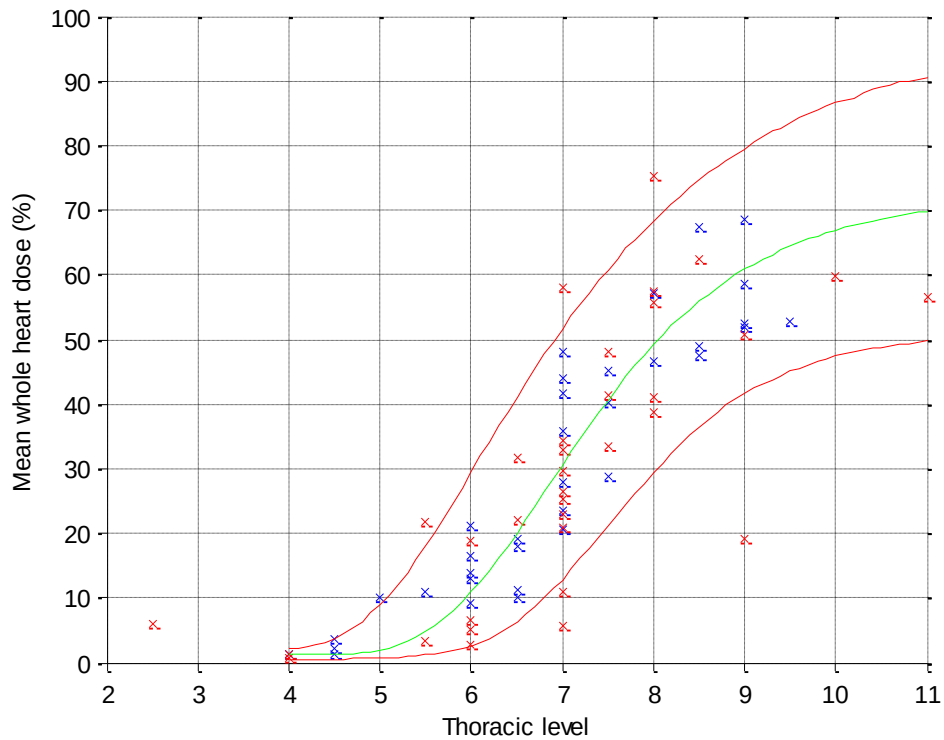
**Table 7.3b** - Figures for average MWHd curves (and 95% CIs) to estimate MWHd for actual plans from the distance of the inferior border of the IFRT field below the carina (mm).

| Extent of heart in field | Average (%) | Lower 95% CI | Upper 95% CI |
|--------------------------|-------------|--------------|--------------|
| -0.5                     | 1.1         | 0.3          | 1.9          |
| -0.4                     | 1.1         | 0.3          | 1.9          |
| -0.3                     | 1.1         | 0.4          | 2.0          |
| -0.2                     | 1.3         | 0.6          | 2.2          |
| -0.1                     | 2.3         | 1.3          | 3.7          |
| 0.0                      | 5.2         | 3.3          | 7.9          |
| 0.1                      | 10.8        | 7.3          | 15.2         |
| 0.2                      | 18.8        | 13.2         | 25.6         |
| 0.3                      | 27.9        | 19.8         | 37.2         |
| 0.4                      | 37.0        | 26.5         | 48.8         |
| 0.5                      | 45.1        | 32.3         | 59.0         |
| 0.6                      | 51.8        | 37.2         | 67.6         |
| 0.7                      | 57.0        | 41.1         | 74.2         |
| 0.8                      | 61.0        | 44.0         | 79.4         |
| 0.9                      | 64.0        | 46.0         | 83.3         |
| 1.0                      | 66.1        | 47.7         | 86.2         |
| 1.1                      | 67.7        | 48.6         | 88.3         |
| 1.2                      | 68.8        | 49.5         | 89.7         |
| 1.3                      | 69.5        | 50.0         | 90.7         |
| 1.4                      | 70.1        | 50.4         | 91.8         |
| 1.5                      | 70.5        | 50.6         | 92.4         |

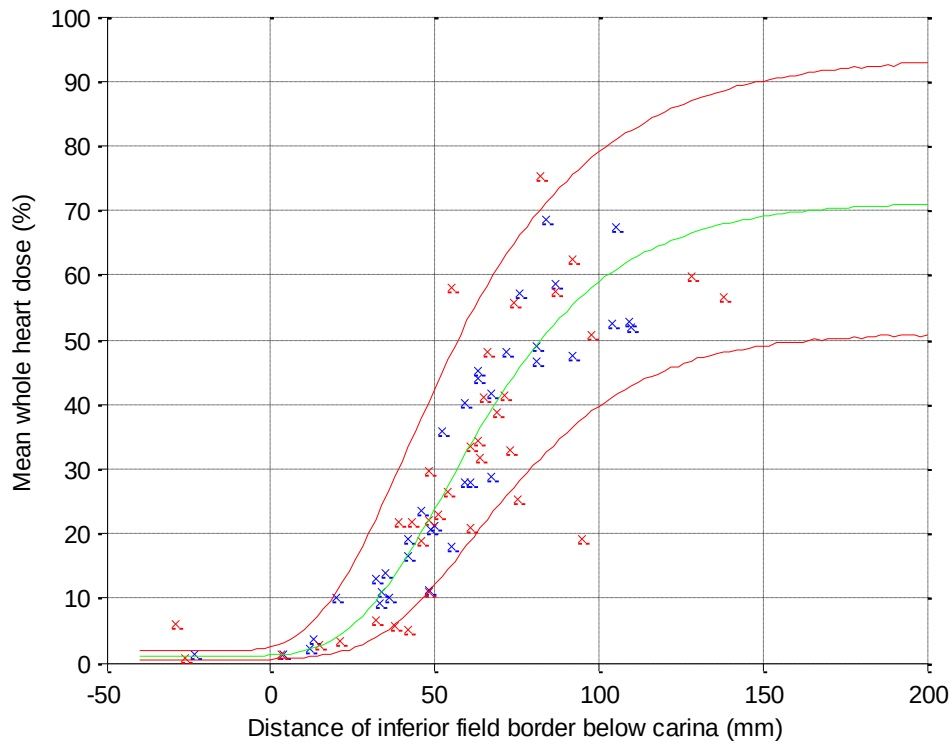
**Table 7.3c** - Figures for average MWHd curves (and 95% CIs) to estimate MWHd for actual plans from the vertical extent of heart within the radiation field.

Figures 7.6(a-c) illustrate the actual MWHDs from 71 RAPID patients plotted against the mean curves produced by the model, together with 95% confidence intervals. These intervals are wider than those in Figures 7.4(a-c), because of the addition of Gaussian noise of relative standard deviation 0.12 in the simulations that produced the limits. There are two notable, but explainable, outliers in Figure 7.6c amongst those patients not used in fitting: 1 plan only treated one side of hilum, i.e. was not technically IFRT and 1 treated both axillae but not the mediastinum, i.e. was highly atypical.

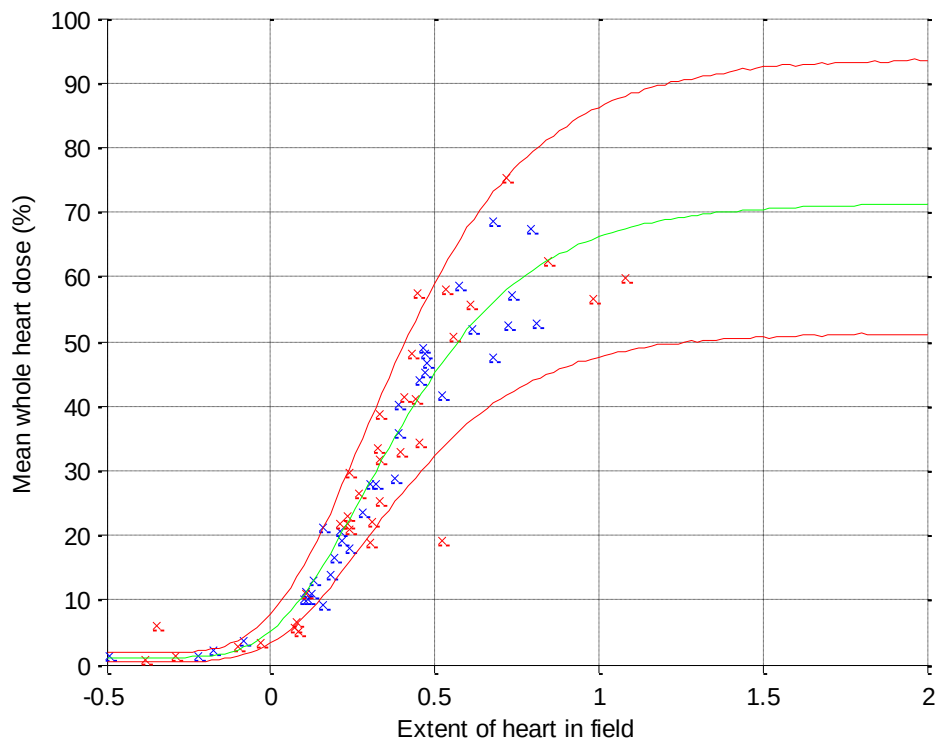
**Figure 7.6a**



**Figure 7.6b**



**Figure 7.6c**



**Figure 7.6(a-c)** – RAPID MWHHD data points plotted by the three anatomical predictors with the curves from the modelled IFRT plans. The blue points are those patients using in fitting (n=36), the red points are those not used in fitting (n=35). The associated mean curve (green) and 95% CIs (red) are also illustrated.

The accuracy of using the mean curves described in Table 7.2, Table 7.3 and Figure 7.6 to predict the dose for the actual plans was assessed by calculating prediction errors for all patients together and for the patients used for fitting and the additional patients separately. These calculations were performed with and without the two outliers identified above. The prediction errors are given in Tables 7.4(a-c) and plotted, by predicted heart dose, in Figures 7.7(a-c), with the two outliers identified in Figure 7.6 excluded. It is apparent that using ‘the vertical extent of the heart within the field’ as a predictor results in the smallest prediction errors and that using ‘thoracic level’ results in the largest prediction errors. When using both ‘the distance below the carina’ and ‘the vertical extent of heart within the field’ as predictors, the absolute prediction error increases with the predicted whole heart dose and the relative prediction error varies less (Figure 7.7(b&c), bottom panels). In summary therefore a typical relative prediction error when using ‘the distance below the carina’ as a predictor is around 30-40% of the predicted whole heart dose and a typical relative prediction error when using ‘the extent of the heart within the field’ as a predictor is 20%. In contrast, when using thoracic level as a predictor the absolute prediction error varies less than the relative prediction error with predicted whole heart dose. Therefore a summary would be that a typical absolute prediction error when using the thoracic level as a predictor is 10%.

**Table 7.4a (thoracic level)**

|                | Including Outliers |        |            | Excluding Outliers* |        |            |
|----------------|--------------------|--------|------------|---------------------|--------|------------|
|                | All                | Fitted | Not fitted | All                 | Fitted | Not fitted |
| <b>RMSEP</b>   | 11.6               | 9.2    | 13.7       | 10.6                | 9.2    | 12.3       |
| <b>1.5xMAE</b> | 9.6                | 8.9    | 11.4       | 9.6                 | 8.9    | 11.4       |
| <b>RSD</b>     | 2.0                | 1.6    | 2.4        | 2.0                 | 1.6    | 2.4        |
| <b>1.5xMRE</b> | 0.39               | 0.38   | 0.40       | 0.36                | 0.37   | 0.36       |

**Table 7.4b (distance below carina)**

|                | Including Outliers |        |            | Excluding Outliers* |        |            |
|----------------|--------------------|--------|------------|---------------------|--------|------------|
|                | All                | Fitted | Not fitted | All                 | Fitted | Not fitted |
| <b>RMSEP</b>   | 9.7                | 7.5    | 11.6       | 8.8                 | 7.5    | 10.3       |
| <b>1.5xMAE</b> | 7.7                | 7.1    | 9.0        | 7.3                 | 7.1    | 9.0        |
| <b>RSD</b>     | 0.75               | 0.43   | 0.97       | 0.40                | 0.43   | 0.38       |
| <b>1.5xMRE</b> | 0.28               | 0.26   | 0.28       | 0.27                | 0.26   | 0.27       |

**Table 7.4c (extent of heart in field)**

|                | Including Outliers |        |            | Excluding Outliers* |        |            |
|----------------|--------------------|--------|------------|---------------------|--------|------------|
|                | All                | Fitted | Not fitted | All                 | Fitted | Not fitted |
| <b>RMSEP</b>   | 6.5                | 4.8    | 7.8        | 5.7                 | 4.8    | 6.7        |
| <b>1.5xMAE</b> | 5.0                | 3.4    | 6.0        | 4.9                 | 3.4    | 5.3        |
| <b>RSD</b>     | 0.66               | 0.20   | 0.92       | 0.21                | 0.20   | 0.22       |
| <b>1.5xMRE</b> | 0.21               | 0.16   | 0.23       | 0.20                | 0.16   | 0.21       |

**Table 7.4(a-c)** – Prediction errors for the models produced using three anatomical measures, including the root mean square error prediction (RMSEP), relative standard deviation (RSD) and 1.5 times the median absolute error (MAE) and median relative error (MRE). \*Excluding the two explained outliers from the additional 35 patients identified in Figure 7.6.

Figure 7.7a

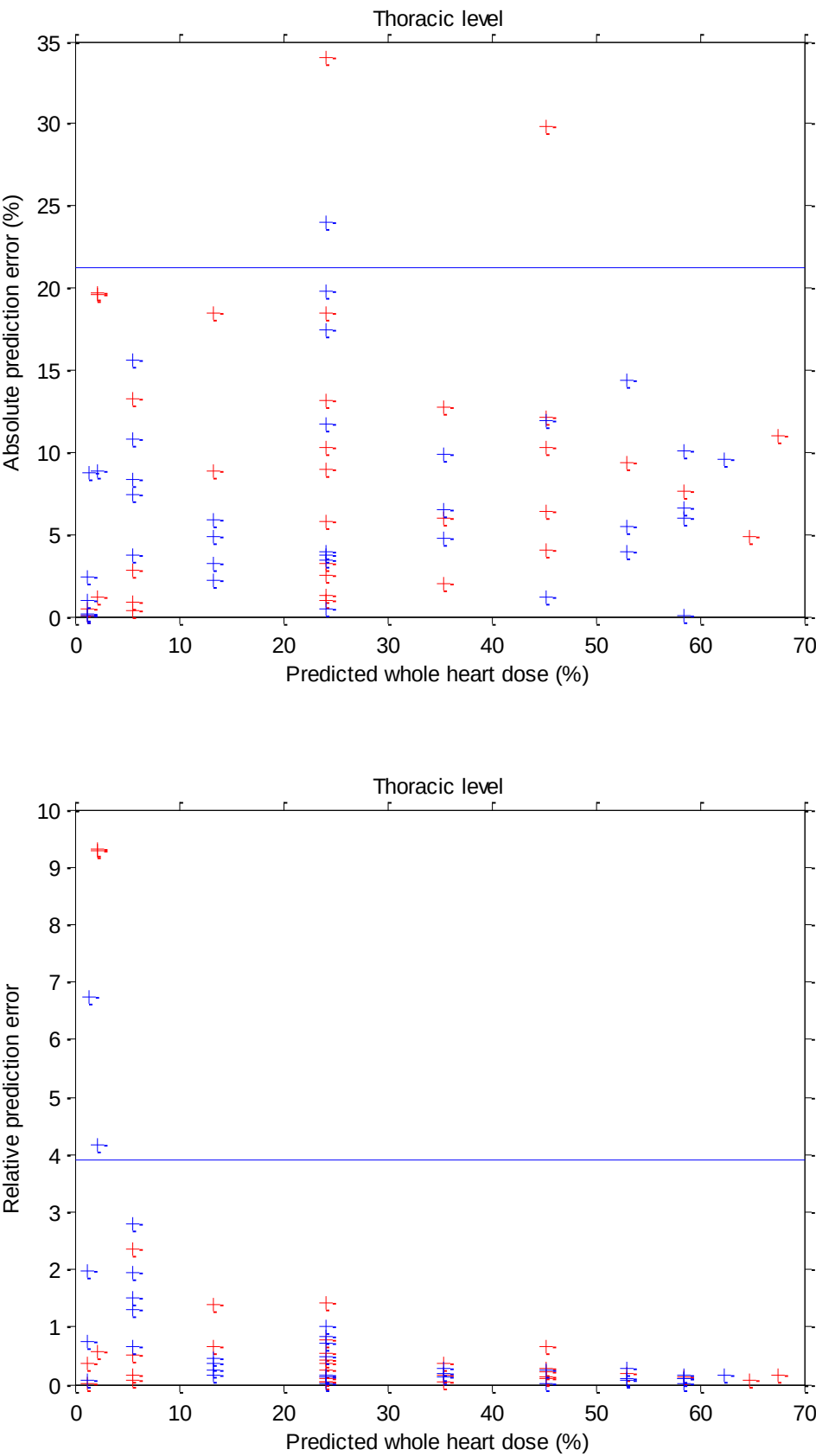
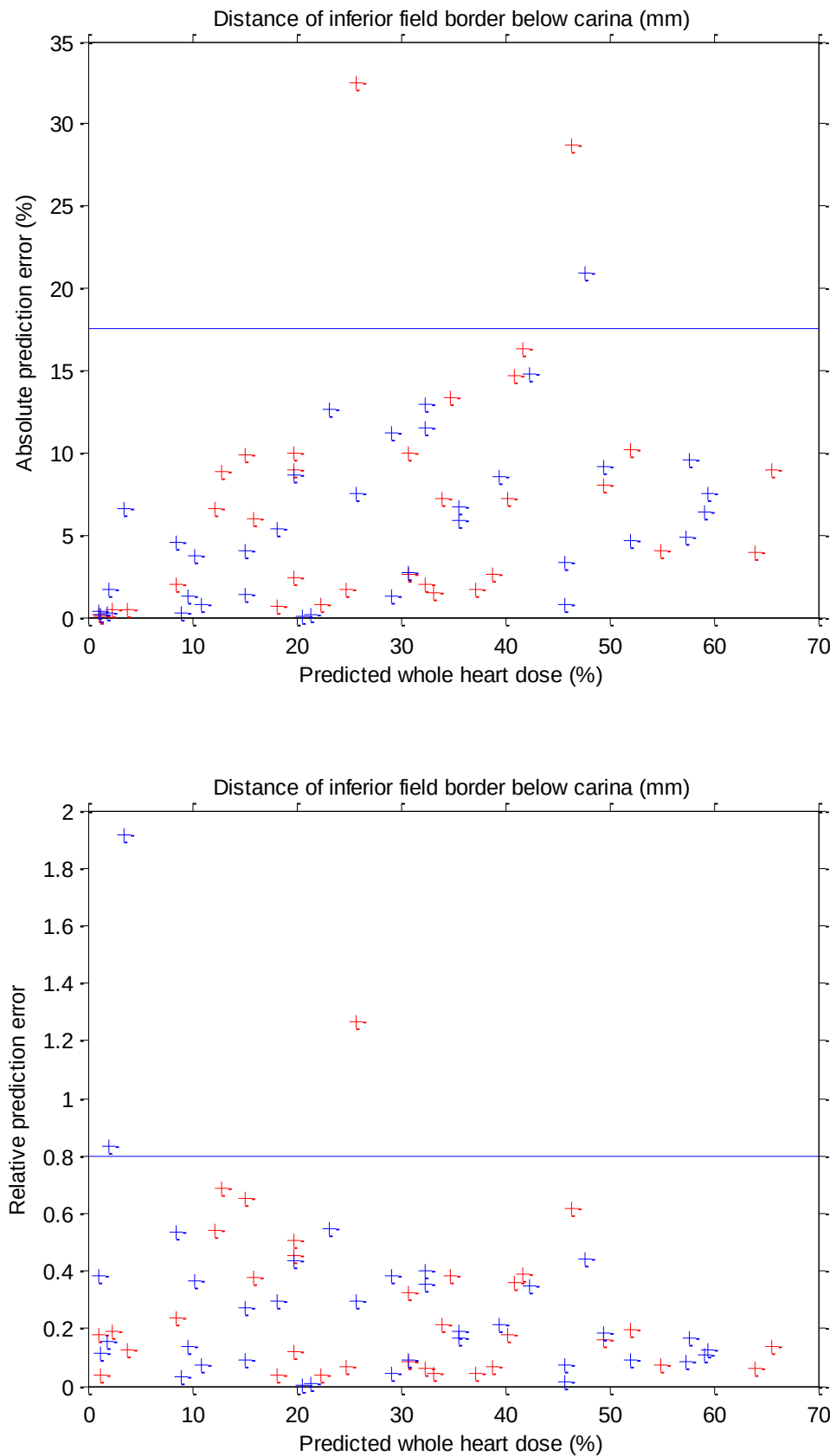
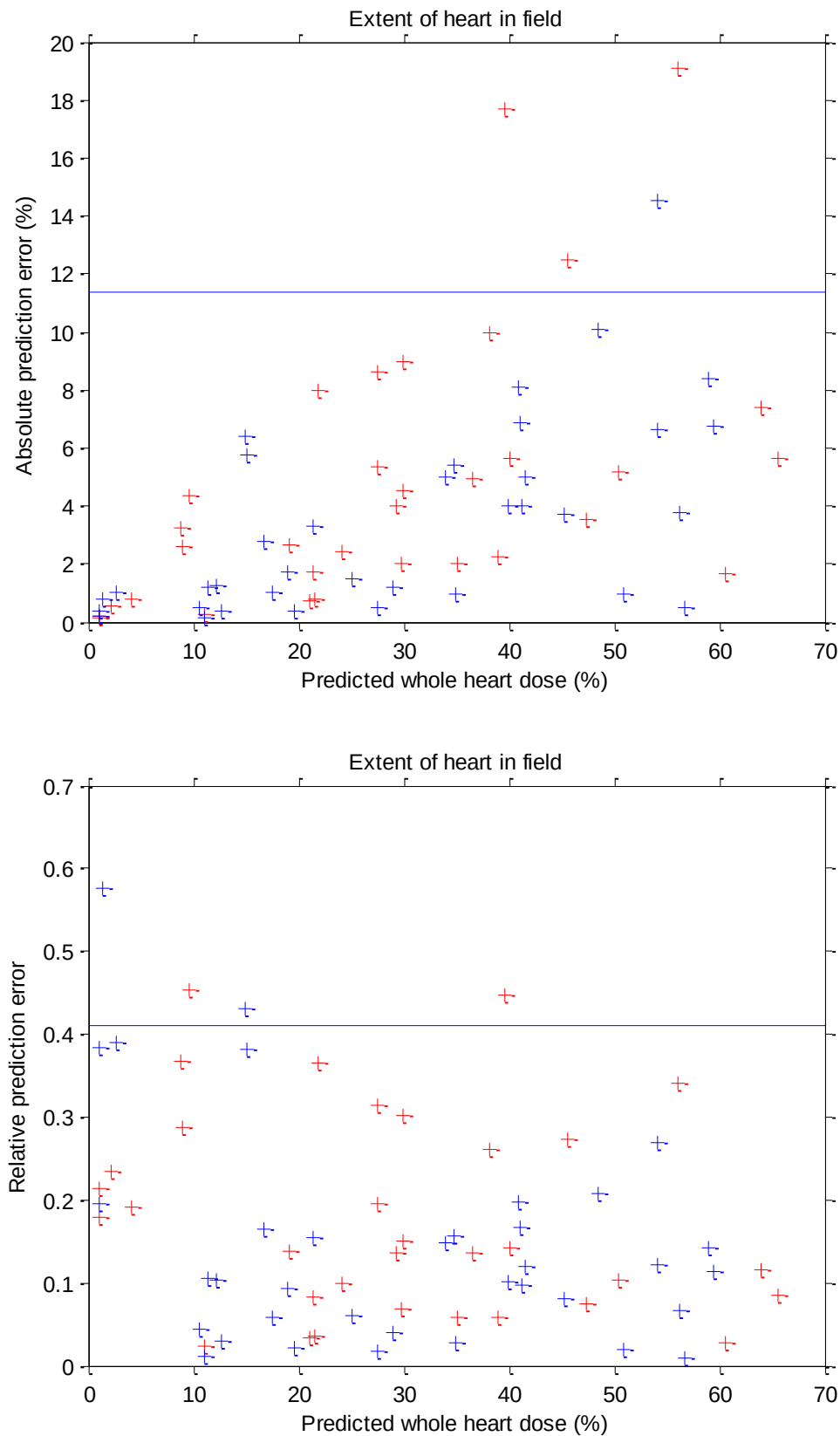


Figure 7.7b



**Figure 7.7c**



**Figure 7.7(a-c)** – The absolute (top panels) and relative (bottom panels) prediction errors for the models for the original 36 patients included in the models (blue crosses) and the additional 35 patients (red crosses). The blue lines represent 2 times the RMSEP (top panels) and RSD (bottom panels).



## **Discussion**

### **Clinical relevance**

The average MWHHD curves and figures produced by this study (Figure 7.5c and Table 7.3c) represent a tool that allows a clinician using IFRT to treat HL (or other nodal lymphoma) to predict the likely cardiac radiation exposure that may be expected from the course of mediastinal radiotherapy prior to treatment planning. This is possible as the lower border of the IFRT field is defined before treatment starts by the pre-chemotherapy limit of the disease, which is easily assessable from a baseline diagnostic CT and/or PET-CT scan. The accuracy of this rapid assessment would be expected to be within 20% of the actual MWHHD calculated when the patient is later planned using their individual CT-planning scan, which was 5-6% of the prescribed dose in absolute terms for the patients in this study (i.e. 1.5 to 1.8 Gy for a 30Gy prescribed dose). This degree of accuracy is sufficient to help inform a clinical decision between combined modality treatment including mediastinal radiotherapy versus chemotherapy alone where cardiac toxicity is of particular concern, perhaps due to pre-existing cardiovascular disease or known risk factors.

The curves and figures also allow an approximate estimate of the MWHHD that may have been received by patients treated with IFRT in the past where detailed CT-based dosimetry is not available but the position of the inferior border relative to the thoracic vertebral levels (Figure 7.5a and Table 7.3a) and/or the carina (Figure 7.5b and Table 7.3b) is known from clinical notes or radiotherapy planning and/or verification radiographs. They allow rapid estimations of mean whole heart dose for these patients that could help clinicians in follow-up clinics counsel patients who have received mediastinal radiotherapy in the past regarding the risk of future cardiovascular late effects and also to arrange the appropriate level of surveillance required.

## **Limitations**

The plans produced to create this tool are simplified compared to many that would be created in contemporary clinical practice using individualised CT-based planning. Specifically no dose compensation or altered field weighting was used and all plans were prescribed to the midline. This was done as, in order to produce the almost 400 plans created, a simplified approach was a necessity. Additionally only 6MV beams were used regardless of the anterior-posterior separation. The fact that the resulting tool adequately estimated the doses calculated by CT-based clinical plans that were administered within the context of the RAPID trial (Figure 7.5c), which used a much wider variety of radiotherapy techniques from 40 centres across the UK, indicates that this approach is valid.

Only standard IFRT fields were used to produce the tool and therefore the tool is most useful for predicting doses from IFRT. However, the tool may also be useful for predicting dose from involved site radiotherapy (ISRT)<sup>12</sup> as, although the cranio-caudal extent of the clinical target volume is less than for IFRT, the resulting radiotherapy fields are otherwise similar and the main determinant of MWHD for ISRT will remain the level of the inferior border of the radiation field relative to the heart. The model will not be applicable to involved node radiotherapy (INRT) techniques as the smaller irradiated volumes with this technique will very likely lead to lower cardiac doses compared to IFRT, especially when there is only unilateral hilar node involvement. However, as many RT centres continue to use IFRT or ISRT techniques to treat HL and other nodal lymphomas, the tool remains clinically useful.

The tool only gives an estimate of MWHD, whereas it is not known what are the most critical structures and dose-volume metrics for predicting RIHD.<sup>13</sup> However, MWHD is highly correlated with the mean dose to all other cardiac structures (see Appendix D, Table D.1) and the best

clinical data currently available to predict late cardiac effects use mean heart dose,<sup>5,6,14,15</sup> therefore MWHd remains a clinically relevant dose metric in this context.

Whole heart dose alone is not sufficient to completely assess an individual's risk of radiation-related heart disease, as the dose-response relationships between MWHd and fatal and non-fatal cardiac complications are not yet known with any degree of confidence.<sup>16</sup> An absolute excess risk of cardiac mortality can be estimated using an ERR per Gy MWHd adjusted for age at irradiation (See Chapter 6) in combination with an assessment of baseline cardiac risk. Age- and sex-based predictions of the risk of cardiac death can be produced by extrapolation from contemporary national mortality statistics (see Chapter 6). A more individualised assessment of coronary heart disease death may be made with knowledge of other major cardiac risk factors (diabetes, smoking, presence or absence of left ventricular hypertrophy, systolic blood pressure and cholesterol levels) using freely available risk calculators such as that produced by the Joint British Societies and advocated by the National Institute of Health and Clinical Excellence (see Chapter 8).<sup>17</sup> The most pragmatic method available to predict risk is to combine these individualised baseline risks with an ERR per Gy MWHd adjusted, where necessary, for age at irradiation (see Chapter 6). These methods would produce useful clinical tool.

## **Conclusion**

The data produced by this study allow a prediction of cardiac radiation exposure to be made at point of diagnosis for lymphoma patients that are scheduled for treatment including IFRT to the mediastinum. This prediction can be used to estimate the risk of late radiation induced cardiac morbidity and mortality for an individual patient. This allows more accurate information to be given during consent for radiotherapy and may, in exceptional circumstances, lead a clinician to consider possible alternatives to the current standard of combined modality therapy.

## References

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## **Chapter 8 - Characterisation of the Heart Using Cardiovascular Magnetic Resonance in Women Receiving Radiotherapy for Early Breast Cancer**

### **Introduction**

Breast cancer is the most common (non-skin cancer) malignancy and the second leading cause of cancer mortality among females in the United Kingdom, with approximately 50,000 incident cases and 12,000 deaths annually.<sup>1</sup> Breast cancer incidence has almost doubled over the past 40 years and 5-year survival has improved, from approximately 50% to greater than 80%, due to improved screening and more effective treatments. It is estimated that by the end of 2008 there were more than 500,000 breast cancer survivors in the UK alone.<sup>2</sup>

An important component of breast cancer treatment is radiotherapy, which is known to reduce both breast cancer recurrence and mortality.<sup>3</sup> Unfortunately, whilst breast cancer radiotherapy increases overall survival there is strong evidence that, due to incidental radiation exposure of the heart, it can also cause an increased risk of death from heart disease.<sup>4</sup> Radiation doses received by the heart are generally lower from contemporary radiotherapy than from techniques that were previously used,<sup>5,6</sup> therefore it is likely that the cardiac risk from modern treatments is lower than in the past. However the heart still receives a mean radiation dose of between 1 and 5 Gray (Gy) on average during treatment of the left breast and there is evidence that doses in this range confer risk<sup>7-10</sup> and, importantly, there appears to be no dose threshold below which there is no increased risk.<sup>10</sup> Additionally, although some modern conformal radiotherapy techniques such as inverse-planned intensity modulated radiotherapy (IMRT) allow reductions in the maximal heart dose received, they may actually result in an increase in the integral heart dose compared to previous techniques.<sup>11</sup> Given the increasing number of breast cancer survivors, it is important to determine whether the cardiac doses received during modern

breast radiotherapy have adverse effects on cardiac function that could be detected soon after treatment.

The imaging modality that has been used most frequently to study radiation-related heart disease following breast cancer is single photon emission computed tomography (SPECT) nuclear myocardial perfusion imaging.<sup>12</sup> More recently tissue Doppler echocardiography has also been used.<sup>13,14</sup> Compared to these modalities, cardiovascular magnetic resonance (CMR) imaging has theoretical advantages, as it can potentially detect multiple aspects of radiation-induced cardiac damage simultaneously by characterising tissue, measuring function and identifying structural or metabolic abnormalities.<sup>15</sup> Radiation-related cardiac disease is known to induce pathological changes including endothelial damage causing perfusion abnormalities, myocardial oedema, dysfunction, scarring and fibrosis, valvular disease, coronary artery disease and myocardial infarction<sup>16</sup> all of which may be demonstrable on CMR. CMR has advantages over echocardiography in terms of image quality, being less affected by patient habitus or operator experience, and a higher spatial resolution. Also importantly, unlike SPECT, CMR does not involve exposure to ionising radiation.

CMR imaging has recently been used to image acute left ventricular dysfunction in patients who received high cardiac radiation doses during concurrent chemoradiotherapy for oesophageal cancer<sup>17</sup> and it has also been used to study late cardiac effects of radiotherapy for Hodgkin lymphoma.<sup>18</sup> However, this is the first study to utilise the multi-modal potential of CMR imaging to look for acute and sub-acute effects of radiation alone in women receiving incidental doses to the heart during contemporary breast cancer radiotherapy.

## **Materials and Methods**

A single-institution prospective study of the potential of CMR imaging to detect early signs of radiation-induced cardiotoxicity from modern breast radiotherapy has been conducted. The study protocol was approved by the National Research Ethics Service and written informed consent was obtained from all participants.

### **Participants**

Women who were scheduled to have left-sided whole breast radiotherapy at the Oxford Cancer Centre following breast-conserving surgery for early breast cancer or ductal carcinoma in situ (DCIS) were eligible for enrolment. Exclusion criteria included age <18 or >65 years, adjuvant cytotoxic chemotherapy, previous significant heart disease, a baseline Framingham 10-year cardiac risk score of  $\geq 10\%$ , or diabetes. Patients with oestrogen receptor positive tumours received hormonal therapy.

### **Radiotherapy planning and delivery**

All radiotherapy treatments were planned using the CT-based Eclipse treatment planning system (TPS), Varian Medical Systems, Palo Alto, CA. Patients were CT-scanned supine, on a breast board with both arms elevated and a straight head. Images with a slice thickness of 2.5 to 5.0 mm were acquired. No intravenous contrast was given.

The planning target volume (PTV) was defined as the residual breast tissue on the affected side with a clinically acceptable margin (to include the deep fascia), but was not formally outlined. Tangential fields were positioned to cover the PTV using virtual simulation, with collimator rotation used to define the posterior border. If the heart was seen to protrude into the field then this was shielded with multi-leaf collimators (MLCs) at the planner's discretion as long as dose coverage of the PTV was not substantially compromised. The prescribed dose was 40 Gy in

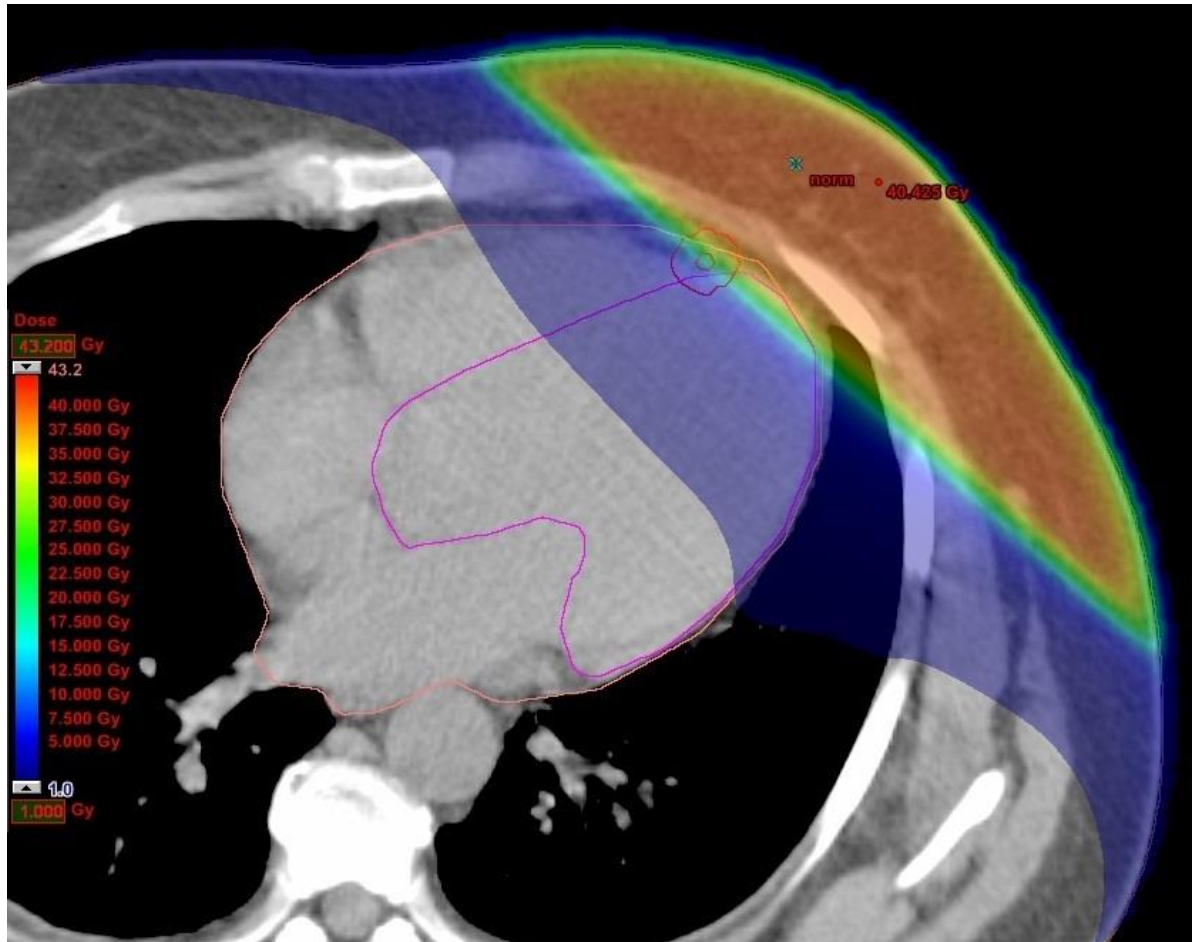
15 fractions, 5 fractions per week, prescribed to a normalisation point in the centre of the breast, with 50 Gy in 25 fractions used for exceptional cases (e.g. very large breasts). The treatments were administered on a Varian Clinac 2100iX linear accelerator using either 6 MV or a combination of 6 and 15 MV energy photon beams. A boost dose of 10 Gy in 5 daily fractions was given, where indicated, using electrons of appropriate energy to a clinically-defined tumour bed.

### **Cardiac outlining and dosimetry**

The whole heart, left ventricle and left coronary artery (comprising the left main stem and left anterior descending artery combined) were outlined on the planning CT of each patient with reference to a published cardiac atlas for radiation oncology<sup>19</sup> and a detailed online atlas of cardiac anatomy.<sup>20</sup> Given the uncertainty over the position of coronary arteries on a standard helical CT scan, especially without the use of intravenous contrast,<sup>21</sup> a 5 mm circumferential margin was added to the left coronary artery and this larger structure was used for radiation dosimetry.

The Eclipse TPS using an anisotropic analytical algorithm (AAA) calculation algorithm (version 8.1.1.7) was used to calculate three-dimensional dose distributions for each individual. A representative dose distribution is shown in Figure 8.1. Doses received by the cardiac structures of interest were calculated from dose volume histograms (DVHs) produced. Cardiac dose contributions from electron boosts are negligible and were not calculated.





**Figure 8.1** – A CT slice through the heart of a representative patient in the study, demonstrating the position of the heart, the left ventricle (pink) and the left anterior descending coronary artery (red), and the distribution of radiation dose delivered by treatment of the left breast (colour wash).

### **Cardiovascular assessments**

All participants were scheduled to undergo 4 cardiac assessments: the first after the CT planning scan but prior to the commencement of radiotherapy, the second within 72 hours of the final fraction of radiotherapy and the third and fourth at 3 months and 6 months after completion of radiotherapy. The assessment consisted of clinical examination, electrocardiogram (ECG), CMR imaging and blood biomarkers as described below. Participants will be invited back for a further assessment at 5 years to look for evidence of later cardiac effects.

### Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance imaging was performed using a 1.5 Tesla MR system (Avanto, Siemens Healthcare, Germany). CMR included: cine imaging for cardiac morphology, global and regional function; T2-weighted imaging to detect myocardial oedema; tagged cine CMR to measure peak systolic circumferential myocardial strain and strain rate; adenosine stress and rest perfusion imaging to assess for myocardial perfusion defects, and late gadolinium enhancement (LGE) imaging to detect myocardial scarring or fibrosis. LGE imaging was acquired using a T1-weighted phase-sensitive inversion recovery sequence<sup>22</sup> 8-10 minutes after intravenous administration of contrast agent (Gadodiamide, Omniscan, GE Healthcare, UK, total 0.13 mmol/kg). A 32-channel phased-array chest coil was used for all data acquisition, except for short-tau inversion recovery (STIR) imaging for which the body coil was used. Detailed acquisition parameters for each method are provided in Appendix E.

Quantitative and/or qualitative assessment of cine, oedema, perfusion and LGE images were undertaken by an experienced CMR cardiologist, Vanessa Ferriera (VF), with more than 4 years of expertise in performing and analysing both clinical and research CMR scans. VF was blinded to the radiation cardiac dose received by each patient. Strain rate analysis of tagged CMR images was performed under the supervision of VF. Further details on image analyses for each method are provided in Appendix E.

### Troponin and BNP assays

Troponin I (cTnI) levels were measured by using the second generation Tn-I-ultra assay, Siemens ADVIA Centaur analyser (Siemens Healthcare Diagnostics, Frimley, UK), in accordance with manufacturers recommendations with a lower limit of detection of 0.04 µg/L, corresponding to the 99<sup>th</sup> percentile reference value recommended by the manufacturer. The troponin inter-assay coefficient of variation (% CV) was 4.5%, 5.9% and 7.3%, with mean cTnI concentrations of

10.44 µg/L, 2.04 µg/L and 0.08 µg/L, respectively. Brain natriuretic peptide (BNP) was measured by using the Siemens ADVIA Centaur analyser (Siemens Healthcare Diagnostics, Frimley, UK) with a lower limit of detection of 0.6 pmol/L and an inter-assay coefficient of variation between 6.3% (at 12.6 pmol/L) and 5.6% (at 122.2 pmol/L).

### **Estimation of the absolute benefits and risks of breast irradiation**

#### **Estimation of breast cancer recurrence and mortality benefit from breast irradiation**

For each individual, age at irradiation, tumour size, tumour grade and ER status were used to estimate the absolute benefit of radiotherapy, in terms of reduction in breast cancer recurrence at 10 years, using data from the early breast cancer trialists collaborative group (EBCTCG) meta-analysis of radiotherapy after breast conserving surgery (see Appendix F).<sup>3</sup> The absolute benefit in terms of reduction in 15-year breast cancer mortality was estimated as one quarter of the reduction in breast cancer recurrence.

#### **Estimation of excess risk of developing coronary heart disease from breast irradiation**

For each individual, age at irradiation, smoking status (current or given up within 5 years vs. never or given up more than 5 years ago), systolic blood pressure (SBP) at study entry (or pre-treatment SBP if on anti-hypertensive medication), total cholesterol and high-density lipoprotein (HDL) were used to calculate a 10-year risk of developing coronary heart disease (CHD) without radiation exposure ( $R_0$ ), based on the Framingham equation.<sup>23</sup> The Framingham equation does not incorporate family history as a risk factor. In the case of a positive family history the estimated risk was multiplied by 1.5 as advised by the National Institute of Health and Clinical Excellence (NICE).<sup>24</sup> The absolute excess risk expected from incidental cardiac radiation exposure during breast irradiation was calculated by the equation:

$$\text{Absolute risk of CHD at 10 years} = R_0 * (1 + \text{MWHD} * 0.074)$$

Where mean whole heart dose (MWHHD) is the mean radiation dose to the whole heart for each individual. This utilises the estimated proportional increase of 7.4% per Gy MWHHD (95% confidence interval 2.9 to 14.5) obtained from the RACE case-control study (see Appendix F).<sup>10</sup>

#### Estimation of the Excess Risk of Cardiac Death from Breast Irradiation

For each individual the absolute risk of cardiac mortality following treatment was also estimated by the equation:

$$\text{Absolute risk of cardiac death at 15 years} = CM_0 * (1 + MWHHD * 0.047)$$

Where,  $CM_0$  is the 15-year probability of cardiac death for a woman of that age based on national mortality data. This utilises an estimate of the excess relative risk per Gy MWHHD obtained from EBCTCG of 4.7% (standard error  $\pm 1\%$ ).<sup>25</sup>

#### **Statistical Analysis**

Data are presented as percentages or means  $\pm$  standard deviation (SD). Analysis of variation in the end-points of interest (biomarkers and left ventricular functional indices, including strain and strain rate) over time-points were performed by two-way analysis of variance, taking into account which patient each end-point was measured in, as well as the time point at which it was measured.

## Results

### Participants enrolled

35 women were enrolled in the study between January 2010 and November 2011. 8 women withdrew from the study either at or after their first visit. 27 women had assessments at 2 or more study time points. 22 women had assessments at all 4 time points. 8 CMR scans in 3 women were performed without Gadolinium or adenosine due to lack of intravenous access. A further 5 scans in 3 women were performed without adenosine due to patient preference. The clinical and demographic characteristics of the study participants are given in Table 8.1.

| Characteristic                                    | All patients enrolled      | Patients with $\geq 2$ time points |
|---------------------------------------------------|----------------------------|------------------------------------|
| <b>Age</b> (years), mean (range)                  | 57.1 (42.0 to 65.2) (n=35) | 56.4 (42.0 to 63.3) (n=27)         |
| <b>Tumour Factors*</b>                            |                            |                                    |
| Tumour size (mm), mean $\pm$ SD                   | 14.5 $\pm$ 6.6 (n=33)      | 13.8 $\pm$ 5.8 (n=25)              |
| Tumour grade 1/2/3 (n)                            | 9/17/7 (n=33)              | 9/13/3 (n=25)                      |
| ER positivity (%)                                 | 85.3% (n=33)               | 96.0% (n=25)                       |
| HER2 positivity (%)                               | 6.1% (n=33)                | 4.0% (n=25)                        |
| <b>Cardiac Risk Factors</b>                       |                            |                                    |
| Smoking, current/previous (%)                     | 14.7%/41.2% (n=34)**       | 18.5%/40.7% (n=27)                 |
| Hypertension                                      | 11.4% (n=35)               | 11.1% (n=27)                       |
| Hypercholesterolaemia                             | 2.9% (n=35)                | 3.7% (n=27)                        |
| Family History                                    | 36.4% (n=33)†              | 36.0% (n=25)†                      |
| <b>Baseline cardiac function††</b>                |                            |                                    |
| LVEF (%), mean $\pm$ SD                           | 75.7 $\pm$ 5.6 (n=30)      | 75.2 $\pm$ 5.7 (n=27)              |
| LVEDV (ml) , mean $\pm$ SD                        | 122.9 $\pm$ 21.5 (n=30)    | 122.1 $\pm$ 21.3 (n=27)            |
| LVESV (ml) , mean $\pm$ SD                        | 30.2 $\pm$ 9.0 (n=30)      | 30.7 $\pm$ 9.4 (n=27)              |
| SV (ml) , mean $\pm$ SD                           | 92.8 $\pm$ 17.1 (n=30)     | 91.6 $\pm$ 16.1 (n=27)             |
| LV Mass (g) , mean $\pm$ SD                       | 70.1 $\pm$ 12.0 (n=30)     | 67.9 $\pm$ 10.5 (n=27)             |
| LV Mass Index (g/m <sup>2</sup> ) , mean $\pm$ SD | 39.4 $\pm$ 5.9 (n=30)      | 38.6 $\pm$ 5.6 (n=27)              |

**Table 8.1** – Baseline patient and tumour characteristics for all patients enrolled (n=35) and for the patients who were scanned at baseline and at least once at follow-up (n=27).

\* Not including 2 patients that had ductal carcinoma in-situ

\*\* One not recorded at baseline visit

† Two not known

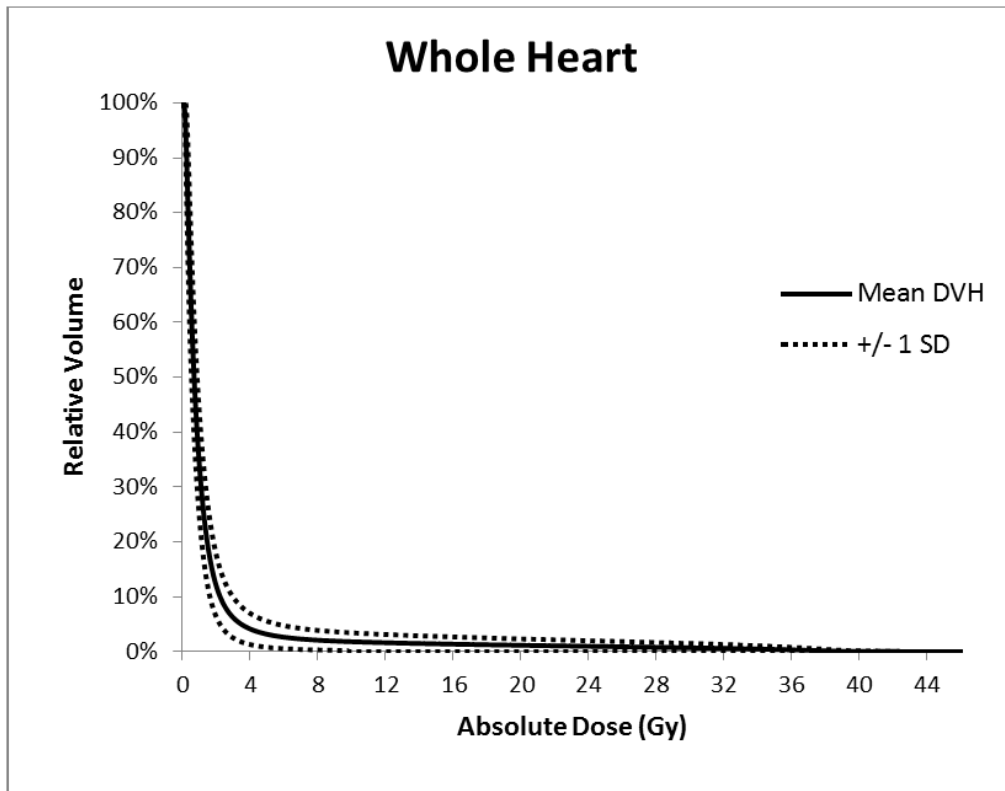
†† 5 patients enrolled did not have a baseline CMR assessment

### **Cardiac radiation dosimetry**

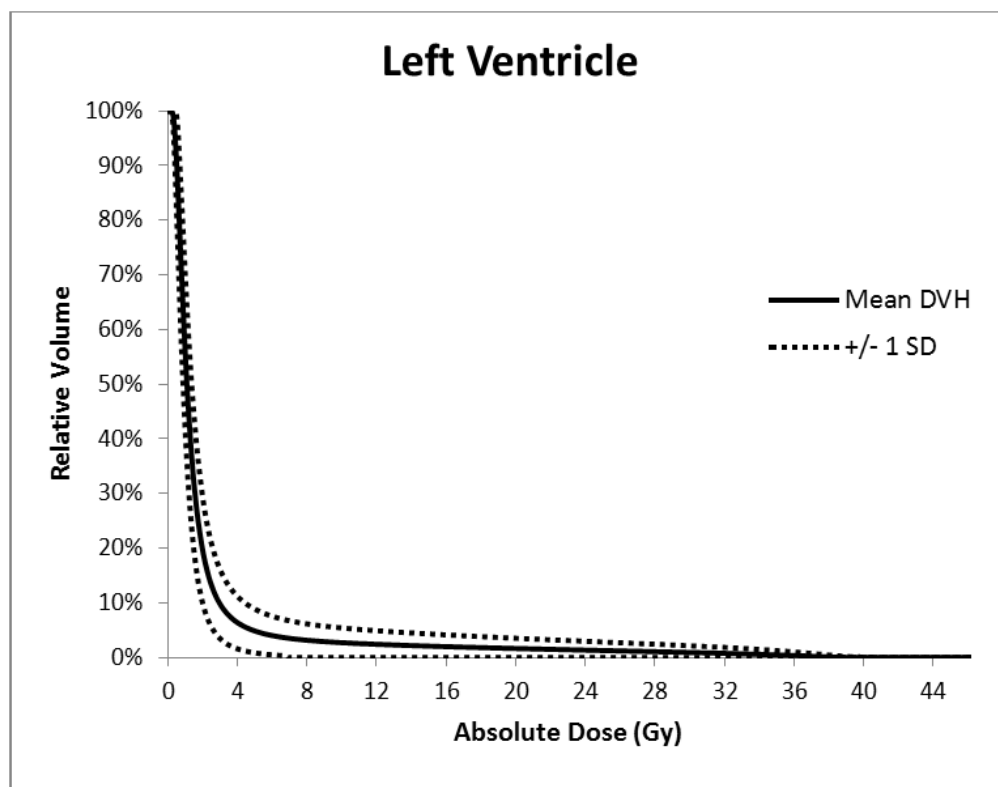
The cardiac radiation doses received are given in Table 8.2. The mean doses to the whole heart, left ventricle and left coronary artery for those women that had  $\geq 2$  study visits were 1.4 Gy, 2.0 Gy and 6.6 Gy respectively. Average cumulative dose volume histograms (DVHs) for the whole heart, left ventricle and left coronary artery are given in Figure 8.2. Only 3/35 patients (8.6%) overall, and 2/29 (6.9%) of the patients with  $\geq 2$  study visits, had  $>5\%$  of the left ventricle within the radiation field (as defined by the volume receiving  $\geq 50\%$  of the prescribed dose).

| <b>Cardiac radiation dose metric</b> | <b>All patients (n=35)</b>        | <b>Patients with <math>\geq 2</math> visits (n=27)</b> |
|--------------------------------------|-----------------------------------|--------------------------------------------------------|
|                                      | Average $\pm$ SD, (Range)         | Average $\pm$ SD, (Range)                              |
| <b><u>Whole heart</u></b>            |                                   |                                                        |
| Mean WH dose (Gy)                    | 1.49 $\pm$ 0.77, (0.62 to 4.40)   | 1.40 $\pm$ 0.59 (0.62 to 2.75)                         |
| Maximum WH dose (Gy)                 | 33.90 $\pm$ 9.92 (4.72 to 42.92)  | 32.89 $\pm$ 10.97 (4.72 to 42.92)                      |
| WH V <sub>30</sub> (%)               | 0.81 $\pm$ 1.19 (0.00 to 5.78)    | 0.69 $\pm$ 0.79 (0.00 to 3.05)                         |
| WH V <sub>20</sub> (%)               | 1.29 $\pm$ 1.55 (0.00 to 7.07)    | 1.08 $\pm$ 1.15 (0.00 to 4.38)                         |
| <b><u>Left ventricle</u></b>         |                                   |                                                        |
| Mean LV dose (Gy)                    | 2.12 $\pm$ 1.18 (0.83 to 6.81)    | 2.02 $\pm$ 0.89 (0.83 to 4.07)                         |
| Maximum LV dose (Gy)                 | 30.63 $\pm$ 11.54 (4.19 to 42.15) | 30.18 $\pm$ 12.64 (4.19 to 42.15)                      |
| LV V <sub>30</sub> (%)               | 1.11 $\pm$ 1.84 (0.00 to 9.43)    | 0.93 $\pm$ 1.23 (0.00 to 4.65)                         |
| LV V <sub>20</sub> (%)               | 1.84 $\pm$ 2.47 (0.00 to 11.72)   | 1.66 $\pm$ 1.87 (0.00 to 6.68)                         |
| LV V <sub>3</sub> (%)                | 10.53 $\pm$ 7.67 (0.47 to 38.37)  | 9.59 $\pm$ 6.24 (0.47 to 22.20)                        |
| <b><u>Left coronary artery</u></b>   |                                   |                                                        |
| Mean LCA dose (Gy)                   | 7.40 $\pm$ 5.26 (0.95 to 21.09)   | 6.64 $\pm$ 4.56 (0.95 to 15.50)                        |
| Maximum LCA dose (Gy)                | 32.36 $\pm$ 12.79 (3.68 to 46.02) | 30.50 $\pm$ 13.87 (3.68 to 43.42)                      |
| LCA V <sub>30</sub> (%)              | 9.40 $\pm$ 12.53 (0.00 to 45.82)  | 7.84 $\pm$ 9.55 (0.00 to 28.59)                        |
| LCA V <sub>20</sub> (%)              | 13.87 $\pm$ 14.59 (0.00 to 53.06) | 12.07 $\pm$ 12.49 (0.00 to 36.83)                      |

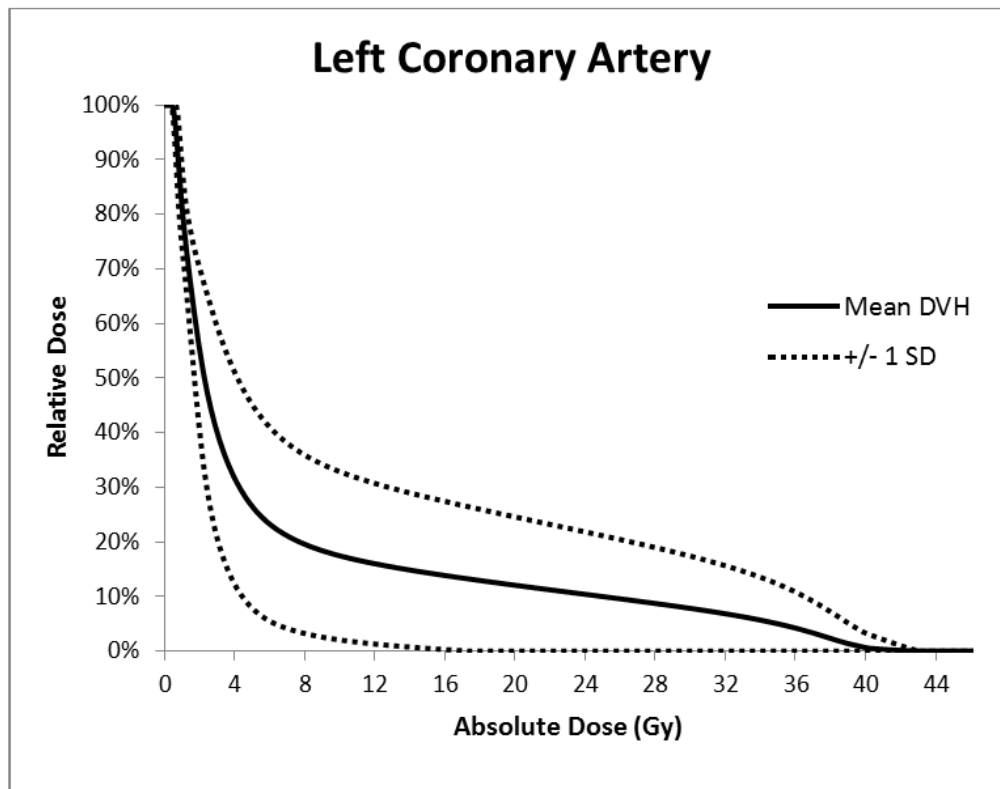
**Table 8.2** – Radiation doses to the whole heart (WH), left ventricle (LV) and left coronary artery (LCA) received by all patients enrolled in the study (n=35) and for the patients who were scanned at baseline and at least once at follow-up (n=27). V<sub>x</sub> = Percentage of the structure that received  $\geq X$  Gy.



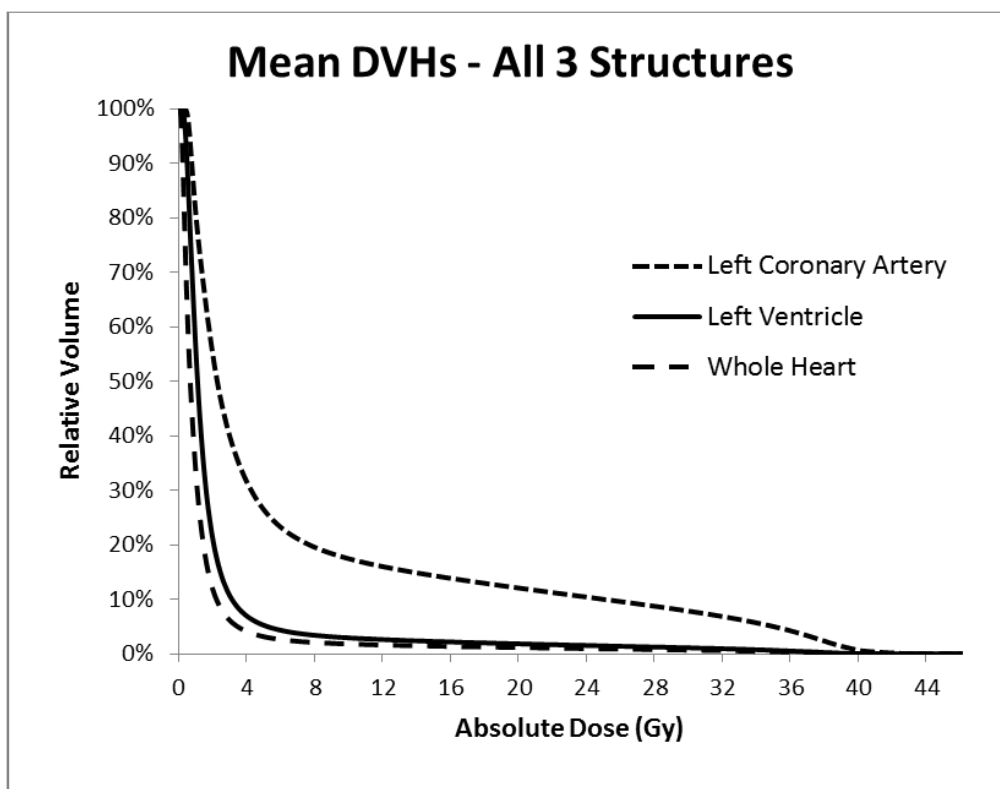
**Figure 8.2(a)** – Mean DVH for the whole heart for all 35 women recruited to the study.



**Figure 8.2(b)** – Mean DVH for the left ventricle for all 35 women recruited to the study.



**Figure 8.2(c)** – Mean DVH for the left coronary artery for all 35 women recruited to the study.



**Figure 8.2(d)** – Mean DVH for the whole heart, left ventricle, left coronary artery for all 35 women recruited to the study.



### **Blood biomarker results**

All patients had normal levels of Troponin I, below the limit of detection for the assay (<0.04 ug/L), at all time-points. All measures of brain natriuretic peptide (BNP) were also normal (0.6-28.9 pmol/L) with no evidence for heterogeneity of BNP between the time-points, see Table 8.3.

|                    | Time-point |           |          |          |
|--------------------|------------|-----------|----------|----------|
|                    | Baseline   | End of RT | 3 months | 6 months |
| BNP (mean, pmol/L) | 7.80       | 6.57      | 9.11     | 6.52     |
| BNP (SD, pmol/L)   | 5.53       | 5.90      | 9.31     | 5.50     |

**Table 8.3** – Brain natriuretic peptide levels for those women who had measurements taken at 2 or more time points. Two-way analysis of variance between time points, p=0.11.

### **Cardiovascular magnetic resonance results**

There was no evidence of any change in basic indices of LV function between the time points studied, nor was there any evidence of any change in global T2 signal intensity (SI) ratio (see Table 8.4).

|                           | Time Point   |              |              |              |          |
|---------------------------|--------------|--------------|--------------|--------------|----------|
|                           | Baseline     | End of RT    | 3 Months     | 6 Months     | p-value* |
| <b>LV Indices</b>         |              |              |              |              |          |
| LVEF                      | 75.1 ± 5.7   | 74.6 ± 4.9   | 73.7 ± 4.3   | 75.0 ± 6.1   | 0.25     |
| LVEDV                     | 122.1 ± 21.3 | 122.8 ± 17.7 | 125.2 ± 22.7 | 122.9 ± 21.8 | 0.87     |
| LVESV                     | 30.7 ± 9.4   | 31.2 ± 7.0   | 33.1 ± 8.5   | 31.0 ± 10.5  | 0.37     |
| SV                        | 91.6 ± 16.1  | 91.6 ± 15.0  | 92.2 ± 17.2  | 91.9 ± 16.3  | 0.94     |
| LV Mass                   | 67.9 ± 10.5  | 68.5 ± 11.9  | 67.4 ± 9.8   | 67.9 ± 10.8  | 0.38     |
| LV Mass Index             | 38.6 ± 5.6   | 38.8 ± 6.1   | 37.8 ± 4.7   | 38.2 ± 5.1   | 0.82     |
|                           |              |              |              |              |          |
| <b>T2 Global SI Ratio</b> | 1.41 ± 0.13  | 1.44 ± 0.11  | 1.40 ± 0.11  | 1.43 ± 0.10  | 0.25     |

**Table 8.4** – CMR imaging analysis for all patients who had scans performed at ≥2 or more time points. All values are given as mean ± SD. \* Test for variation over time-points by two-way analysis of variance.

There was no significant left ventricular myocardial oedema present in any CMR scan, with a mean percentage of oedema of 0.15% (SD 0.49%, range 0.00% to 3.40%) for all scans combined.

There were two individuals who had small areas of mid-wall late gadolinium enhancement at baseline; one very small area in the inferior apical wall of unclear significance and another in the basal infero-lateral wall, perhaps indicative of previous myocarditis. No new areas of LGE

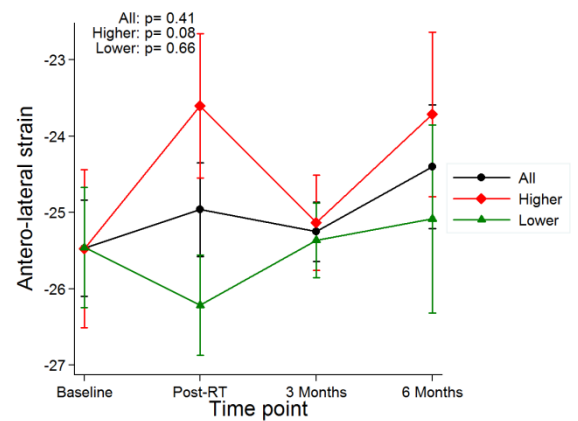
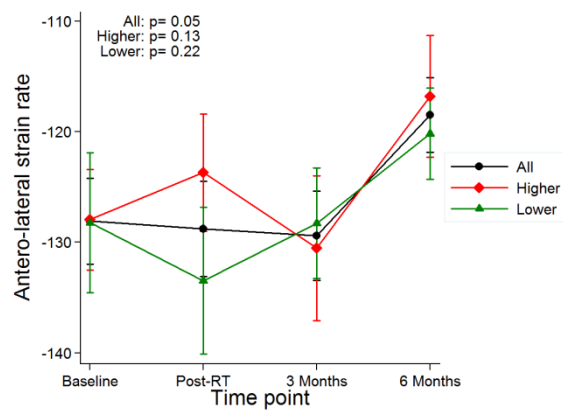
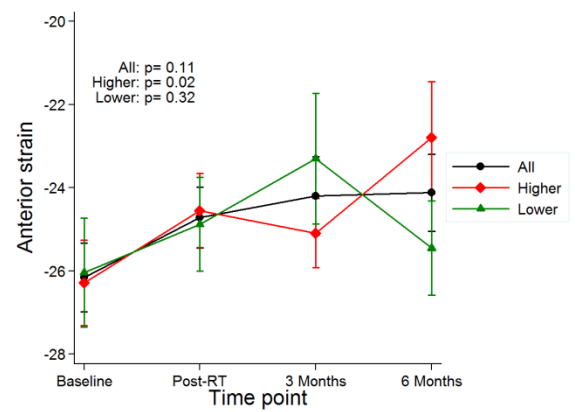
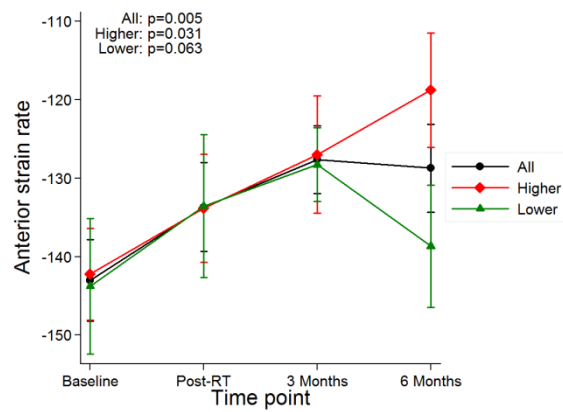
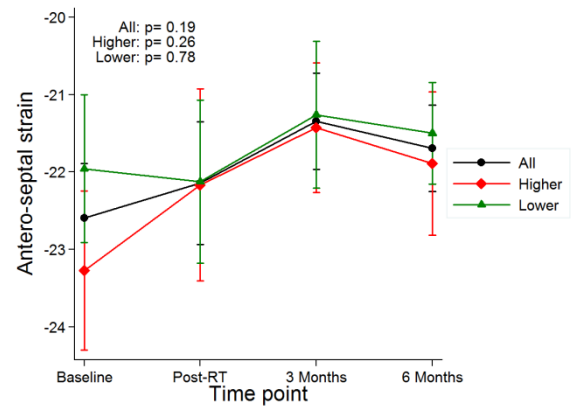
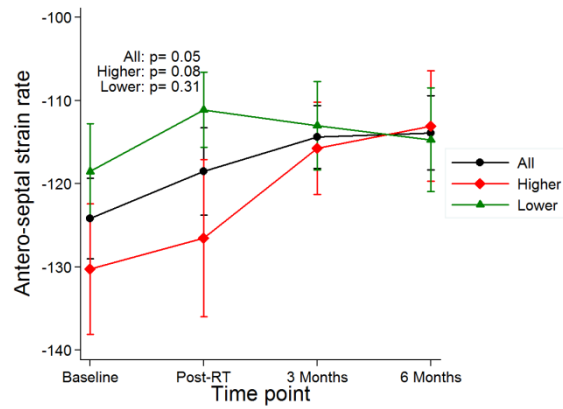
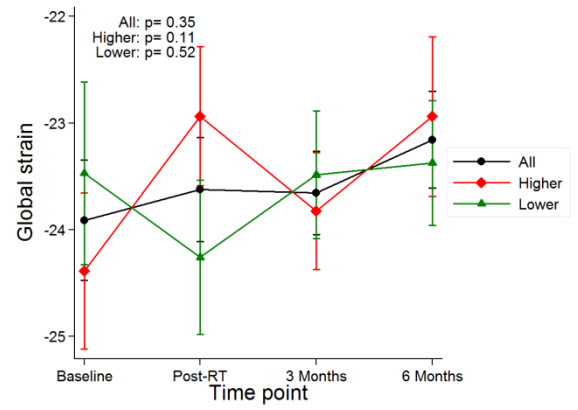
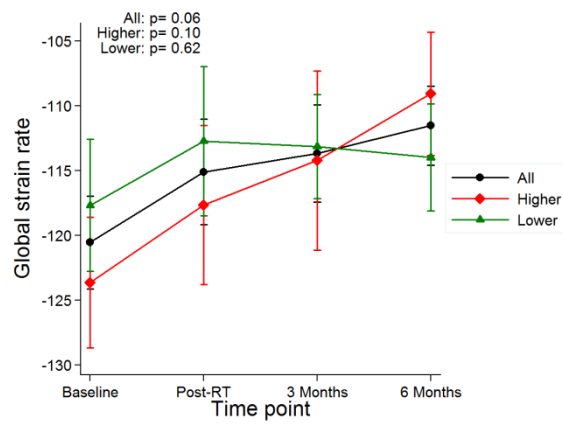
developed during the study. There were no qualitative perfusion abnormalities present on any scan.

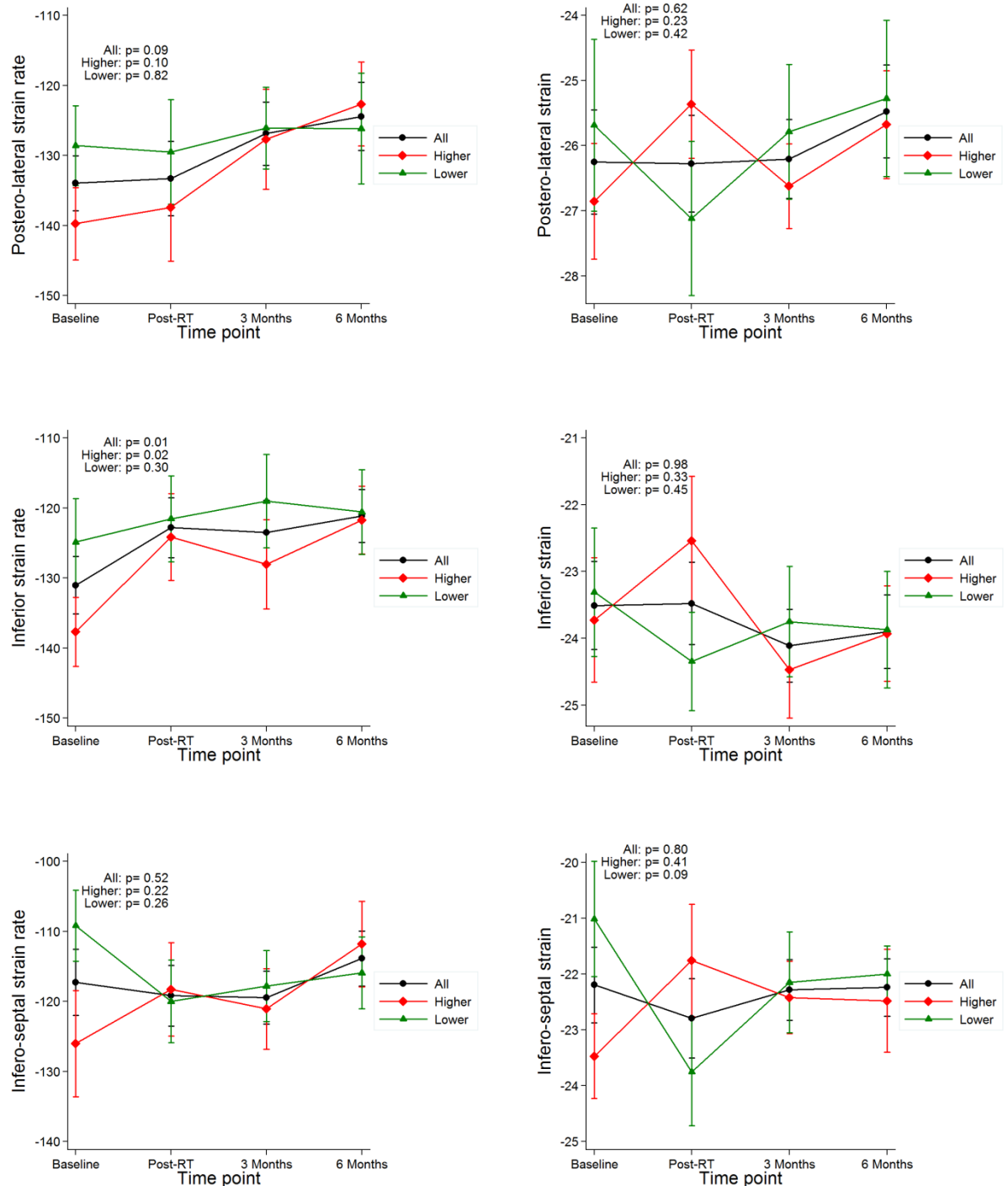
Strain rate imaging (SRI) analysis revealed evidence of a statistically significant reduction in peak systolic circumferential LV strain rate in the antero-septal, anterior, antero-lateral and inferior left ventricular segments (Table 8.5).

|                   | Time Point        |                   |                   |                   | p-value*     |
|-------------------|-------------------|-------------------|-------------------|-------------------|--------------|
|                   | Baseline          | End of RT         | 3 Months          | 6 Months          |              |
| Strain Rate (%/s) | (Mean $\pm$ SD)   | (Mean $\pm$ SD)   | (Mean $\pm$ SD)   | (Mean $\pm$ SD)   |              |
| Global            | -120.5 $\pm$ 18.5 | -115.1 $\pm$ 21.1 | -113.7 $\pm$ 19.5 | -111.5 $\pm$ 15.8 | 0.06         |
| Antero-septal     | -124.2 $\pm$ 25.2 | -118.5 $\pm$ 26.1 | -114.4 $\pm$ 18.4 | -113.9 $\pm$ 21.8 | <b>0.05</b>  |
| Anterior          | -143.0 $\pm$ 27.0 | -133.7 $\pm$ 28.3 | -127.6 $\pm$ 21.2 | -128.7 $\pm$ 27.5 | <b>0.005</b> |
| Antero-lateral    | -128.1 $\pm$ 20.1 | -128.8 $\pm$ 21.6 | -129.4 $\pm$ 19.8 | -118.5 $\pm$ 16.6 | <b>0.05</b>  |
| Postero-lateral   | -134.0 $\pm$ 20.4 | -133.3 $\pm$ 26.5 | -126.9 $\pm$ 22.1 | -124.4 $\pm$ 23.8 | 0.09         |
| Inferior          | -131.0 $\pm$ 21.3 | -122.8 $\pm$ 21.4 | -123.5 $\pm$ 22.6 | -121.2 $\pm$ 18.6 | <b>0.01</b>  |
| Infero-septal     | -117.3 $\pm$ 24.4 | -119.2 $\pm$ 21.7 | -119.4 $\pm$ 18.5 | -113.9 $\pm$ 19.3 | 0.52         |
| Strain (%)        |                   |                   |                   |                   |              |
| Global            | -23.91 $\pm$ 2.92 | -23.62 $\pm$ 2.54 | -23.66 $\pm$ 2.04 | -23.16 $\pm$ 2.35 | 0.35         |
| Antero-septal     | -22.59 $\pm$ 3.63 | -22.12 $\pm$ 3.96 | -21.34 $\pm$ 3.03 | -21.69 $\pm$ 2.73 | 0.19         |
| Anterior          | -26.16 $\pm$ 4.28 | -24.72 $\pm$ 3.65 | -24.20 $\pm$ 4.61 | -24.12 $\pm$ 4.56 | 0.11         |
| Antero-lateral    | -25.47 $\pm$ 3.28 | -24.96 $\pm$ 3.08 | -25.25 $\pm$ 1.90 | -24.40 $\pm$ 3.98 | 0.41         |
| Postero-lateral   | -26.25 $\pm$ 4.15 | -26.28 $\pm$ 3.70 | -26.20 $\pm$ 2.96 | -25.48 $\pm$ 3.50 | 0.61         |
| Inferior          | -23.51 $\pm$ 3.43 | -23.48 $\pm$ 3.08 | -24.11 $\pm$ 2.66 | -23.90 $\pm$ 2.71 | 0.98         |
| Infero-septal     | -22.20 $\pm$ 3.53 | -22.79 $\pm$ 3.56 | -22.28 $\pm$ 2.67 | -22.24 $\pm$ 2.52 | 0.80         |

**Table 8.5** – Myocardial peak systolic strain and strain rate (tagged CMR) imaging for the 27 patients who had scans at  $\geq 2$  time points. \*Test for variation over time-points by two-way analysis of variance.

The 27 individuals with 2 or more CMR scans performed were divided in half based on the estimated radiation dose of their left ventricle, with 13 individuals in the higher dose group (average mean LV dose = 2.74 Gy, range 1.88 to 4.07 Gy) and 14 individuals in the lower dose group (average mean LV dose = 1.35 Gy, range 0.83 to 1.86 Gy). These two groups were then analysed separately. In the lower dose group there was no statistically significant evidence of any reduction in global or segmental strain or strain rate. In contrast for the higher dose group there was a significant reduction in strain rate in the anterior and inferior segments ( $p=0.03$  and  $p=0.02$  respectively) and a significant reduction in anterior strain ( $p=0.02$ ). These results are presented graphically in Figure 8.3.





**Figure 8.3** - Plots of the peak systolic strain and strain rate by study time points, globally and for 6 left ventricular segments. The black lines are the averages for all patients who completed 2 or more study visits (n=27). The red lines are for those patients with the higher cardiac radiation doses (average mean LV dose=2.74 Gy, n=13). The green lines are for those patients with lower cardiac radiation doses (average mean LV dose = 1.35 Gy, n=14).

### **Individual absolute breast cancer benefit and cardiac risk calculations**

Table 8.6 details the benefits in terms of the absolute reduction in breast cancer recurrence and mortality and the absolute cardiac risks that would be predicted from the radiotherapy treatment received by women in the cohort. The average predicted reduction in breast cancer recurrence was 15.2% and the reduction in breast cancer mortality 3.8%. The average predicted increase in ischaemic heart disease risk was 1.0% and the increase in cardiac death 0.2%. Of note, the predicted increase in ischaemic heart disease risk exceeded the benefit in terms of breast cancer mortality reduction in only 9% of individuals (n=3).

| <b>Absolute benefits and risks for entire cohort (n=33)*</b> | <b>Mean, SD (range)</b>     |
|--------------------------------------------------------------|-----------------------------|
| Predicted reduction in 10 year breast cancer recurrence      | 15.2%, 6.7% (6.0% to 34.0%) |
| Predicted reduction in 15 year breast cancer mortality       | 3.8%, 1.7% (1.5% to 8.5%)   |
| Predicted increase in 10 year IHD incidence                  | 1.0%, 1.0% (0.1% to 5.0%)   |
| Predicted increase in 15 year cardiac mortality              | 0.2%, 0.1% (0.0% to 0.5%)   |

**Table 8.6** – The predicted breast cancer recurrence and mortality benefits and cardiac risk for the entire cohort. \*The two women treated following excision of DCIS are excluded from this analysis, the predicted absolute increases in 10 year IHD incidence for these women were 0.4% and 0.8% and the predicted absolute increases in 15 year cardiac mortality were 0.1% and 0.2%.

## **Discussion**

### **Main Findings**

Utilising a combination of multi-modality CMR and blood biomarkers, this study revealed no evidence of clinically significant adverse effects on the heart within 6 months of conventional 3D CT-planned left-sided tangential whole breast radiotherapy for early breast cancer in women with no previous cardiac disease. This is reassurance that the low estimated incidental cardiac doses received by patients in the study (average MWHd of 1.4, range 0.6 to 2.8), using standard tangential RT techniques in the absence of cardiotoxic chemotherapy, do not pose an immediate risk to cardiac function, in women with healthy hearts. Strain rate imaging analysis did, however, reveal evidence of subclinical effects on ventricular function within the anterior, antero-lateral and antero-septal segments of the left ventricle, which are known to be the

segments which receive the highest radiation dose during tangential RT to the left breast.<sup>14</sup> This suggests that strain rate imaging may represent an early surrogate marker of radiation-related heart damage, able to detect changes even at low cardiac radiation doses and in the absence of cardiotoxic chemotherapy. This modality therefore merits further investigation as a tool for the study of radiation-related heart disease. Specifically it will be important to investigate whether individual reductions in anterior peak systolic strain and/or strain rate correlate with the later occurrence of clinical cardiac events or with persistent abnormalities of cardiac function at later time points.

The cardiac risks predicted by dose-response relationships produced from the best available epidemiological evidence,<sup>10</sup> suggest that the radiation-related risk of developing or dying from cardiac disease for this cohort is low. These data would suggest that, by receiving these cardiac doses, just 1 extra woman in 100 would develop IHD by 10 years following treatment and only 1 more woman in 500 would have died from cardiac causes at 15 years. It remains possible therefore that although CMR strain rate imaging may be able to detect early subclinical markers of cardiac dysfunction, it may be insufficient to predict clinical events within the low risk population examined. The women in this study will be reassessed at 5 years in order to detect the development of any further cardiac dysfunction at this stage. Additionally, It may be rational to investigate the use of this imaging modality in higher risk patient populations where the heart receives higher incidental doses during treatment, e.g. mediastinal lymphoma.

This study has demonstrated that it is feasible to recruit women receiving radiotherapy for early breast cancer to such a study within a reasonable timescale, and that the protocol used was acceptable for the majority of women recruited. This supports the possibility that the study could be extended both in the number and risk profile of individuals recruited to further study the potential of CMR imaging in the context of radiation-related heart disease.

### **Comparison with other imaging studies**

A study utilising strain rate imaging (SRI) by tissue Doppler echocardiography in 20 women who received left-sided breast cancer radiotherapy revealed sub-acute (2 months after RT) dose-related regional decreases in myocardial function in segments of the left ventricle receiving >3 Gy.<sup>13</sup> The cardiac doses received in this study were higher with a mean LV dose of  $6.7 \pm 6$  Gy versus  $2.0 \pm 0.9$  Gy and a V30 of  $5.2 \pm 11.5\%$  versus  $0.9 \pm 1.2\%$ , when compared to our study. A proportion of patients within this study also received cytotoxic chemotherapy (60%), and some also received trastuzumab (20%), compared to none in the current study. There was a suggestion that chemotherapy was associated with the presence of the observed abnormalities ( $p=0.06$ ). A larger subsequent study by the same investigators recruited 51 further patients receiving radiotherapy for left-sided breast cancer.<sup>14</sup> All women had received prior adjuvant anthracycline-based chemotherapy, 22% received trastuzumab and 94% had the internal mammary nodes irradiated. Despite finding no significant decrease in conventional echocardiographic parameters for systolic and diastolic function, a significant decrease in strain and strain rate was observed for left-sided patients up to 14 months post-treatment. This was most marked in the anterior wall of the left ventricle, which received the highest radiation dose. Again, the heart doses received in this study were much higher than in our current study, with a mean LV dose of  $9 \pm 4$  Gy and a V30 of  $8 \pm 7\%$ . Therefore our study finds a similar subclinical effect detectable by SRI, but at lower left ventricular doses and in the absence of cardiotoxic chemotherapy, suggesting that SRI by CMR may be more sensitive than previously recognised when performed by Doppler echocardiography.

The current study revealed no evidence of the microvascular perfusion defects that were previously observed in the largest prospective imaging study of radiation-related cardiac dysfunction following breast cancer RT, which utilised single-photon emission computed

tomography (SPECT) imaging in 114 women.<sup>12,26</sup> There are several possible reasons for this difference. Firstly, the heart volumes incidentally irradiated in the SPECT study were greater. The internal mammary nodes were included in the radiation volume in 46.5% of patients and the volume of the left ventricle within the field exceeded 5% in 38.5% of cases. This contrasts with 0% and 6.9% of patients in the current study. Both these factors were related to an increased risk of perfusion defects. Secondly, 64% of patients received chemotherapy compared to none in our current study. Thirdly, patients with diabetes and/or previous coronary artery disease were included in the SPECT study, but excluded from our current study. Finally, the risk of perfusion defects was seen to increase from 27% at 6 months to 42% at 2 years, whereas our study has only so far scanned patient at up to 6 months post-RT.<sup>12</sup> Similar reasons likely account for the difference between our study and other nuclear medicine imaging studies where perfusion defects were found.<sup>27-30</sup>

The only published study to have so far utilised CMR to study radiation-related cardiac dysfunction in the acute setting was in patients receiving chemoradiotherapy for oesophageal cancer.<sup>17</sup> In the study there was a significant impairment of several different measures of LV function immediately after RT, in the group that received a high dose to the LV (n=21, mean LV dose of 3.6 to 41.2 Gy). However, there was also a significant decline in LV ejection fraction in the group that received a low dose to the LV (n=10, mean LV dose <0.6 Gy) with no significant difference in the extent of the decline when compared to the high LV dose group. This acute impairment of LV function was therefore interpreted as being predominantly an effect of the cisplatin and 5-fluorouracil chemotherapy that was given concomitantly to RT, rather than an effect of radiation. There were, however, differences between the high and low LV dose groups with respect to LV end-diastolic volume, stroke volume index and wall motion, suggesting a greater impairment of diastolic LV function in the high dose group. The study did not report on strain rate imaging analysis.



### **Comparison with other blood biomarker studies**

This study revealed no evidence of elevation of troponin or BNP up to 6 months following left breast radiotherapy. A recent study by D'Errico *et al* reported significant elevation of N-terminal pro-B-type natriuretic peptide (NT-proBNP, the inactive N-terminal fragment of proBNP) in 30 left-sided breast cancer patients 5 to 22 months (median 9 months) after RT compared to a control group.<sup>31</sup> For those women with higher levels of NT-proBNP (>125 pg/ml, n=8) there were significant correlations between plasma levels and several measures of radiation dose to the heart and left ventricle. Troponin I (TnI) levels were also measured and were not different between the irradiation women and the control group. The cardiac doses received in the study were higher with a MWHd of 2.5 Gy vs. 1.5 Gy and a mean LV dose of 3.7Gy vs. 2.1 Gy. Also 30% received anthracycline-based chemotherapy, the biomarker was slightly different and the follow-up period longer compared to the current study. These factors could account for the differences in results.

The previously mentioned study of SRI imaging following breast cancer radiotherapy<sup>14</sup> also measured troponin I and found significant elevations in troponin following left-sided RT ( $0.021 \pm 0.01 \mu\text{g/l}$  before RT and  $0.027 \pm 0.02 \mu\text{g/l}$  after RT,  $P=0.04$ ). However, these measurements were well below the stated analytic range of the assay used ( $0.13 \mu\text{g/l}$ ) and may be coincidental. One further study measured troponin T before, during and after left breast radiotherapy, but found no elevation after whole breast radiotherapy to 45-46 Gy in 50 women.<sup>32</sup>

Two studies have measured alternative cardiac biomarkers following breast radiotherapy. One found a significant elevation of atrial natriuretic peptide (ANP) in 43 breast cancer patients versus 67 healthy controls, 9.5 years following radiotherapy.<sup>33</sup> 20/43 (46.5%) of these women

also received either CMF or CAF chemotherapy. ANP levels were significantly higher in those women with clinical symptoms of cardiac disease compared to asymptomatic women. In the second study 105 breast cancer patients received intensive chemotherapy (either 9xFEC of 3xFEC followed by high dose chemotherapy).<sup>34</sup> Measured pro-ANP levels were significantly associated with cumulative epirubicin dose, but were on average 12% higher in women that received left-sided versus right-sided radiotherapy ( $p=0.031$ ) with no significant interaction with epirubicin dose. Numerous studies have shown, however that BNP (and NT-proBNP) plasma concentrations are a more sensitive and specific marker of cardiac dysfunction than ANP,<sup>31</sup> therefore it is unlikely that measuring ANP in the current study would yield positive findings. To confirm the negative findings of our study it would be appropriate to consider repeating measurements for NT-proBNP and for troponin I using a high sensitivity assay with a verified low analytic range.

## **Limitations**

### **Limitations of strain rate imaging**

Subjective operator input is required at both the image acquisition and software analysis stages of CMR tagging analysis and, as such, strain rate imaging is known to be sensitive to intra- and inter-observer variability. To reduce the variability from technical aspects of image acquisition all scans were acquired using the same scanner and according to a defined protocol. Whilst the reproducibility of LV strain measurement using CMR tagging has been demonstrated to be excellent, the reproducibility of strain rate measurement is more variable.<sup>35</sup> All tagging analysis this study was performed by one individual and therefore the strain and strain rate measurements given in the results above are not subject to any inter-observer variability. However in order to investigate the effect of intra-observer variability the analysis should, ideally be repeated by the same operator. Unfortunately the process is extremely time-consuming and due to time constraints this has not yet been performed. It would also be

informative for different operators to repeat the same tagging analysis to assess inter-observer variability. Any variation in results would be important to assess before the technique was used more widely to study radiation-related ventricular dysfunction.

As strain is deformation of an object relative to its initial dimension, and circumferential strain is the change in circumference during the cardiac cycle, the relative change is greater when the initial circumference is smaller.<sup>36</sup> For this reason LV strain varies within an individual at the basal-apical slice level chosen for image acquisition, with strain increasing as the slice is moved more apically. Slice orientation, however, only has a negligible effect on strain measurement.<sup>35</sup> It is difficult for images acquired during scans up to 6 months apart to correspond precisely in basal-apical level and, although the slices used for analysis were visually matched to equivalent slices across all time points, this imprecision may produce some artificial variation in strain and strain rate measurement.

#### Limitations of cardiac radiation dosimetry

The estimated cardiac doses acquired during the radiotherapy planning process are known to be subject to uncertainty with regards to how well they predict the radiation subsequently received during treatment. There are several sources of this uncertainty. Inter-observer variation in heart outlining is known to occur and have a greater effect on smaller, harder to define cardiac structures such as the coronary arteries.<sup>21</sup> It has also been demonstrated that daily treatment set-up errors reduce the accuracy of the predicted cardiac exposure.<sup>37</sup> Cardiac and respiratory motion that occurs during treatment should also be taken into account.<sup>38</sup> Were findings from imaging studies of radiation-induced cardiac dysfunction to be quantitatively correlated with individualised radiation dosimetry then these issues would need to be addressed. However, the cardiac radiation dosimetry in this study is largely presented for illustrative purposes and to divide the cohort in half in terms of predicted heart dose rather than to be used as an individual

quantitative variable for inclusion in the analysis. Therefore these inaccuracies with respect to CT-based cardiac radiation dosimetry are unlikely to have affected the interpretation of the above results.

#### Limitations of cardiac risk estimations

The individualised estimates of 10-year CHD risk and 15-year cardiac mortality are based on values for the relative risk per Gy MWHd as derived from the best evidence available.<sup>10,25</sup> However, the calculations of absolute risk inevitably rely on historical baseline cardiac risks and could be subject to inaccuracy. The 10-year CHD risks are based on the Framingham data<sup>23</sup> and could well be non-representative of risks over the coming decade. This method of CHD risk prediction is, however, that suggested for clinical use by the National Institute of Health and Clinical Excellence<sup>24</sup> and, as such, represents the best that is practically available. The 15-year cardiac mortality risks are based on UK population-based age and sex-matched figures from 2009 and can be considered a reliable baseline. The calculation does however assume that cardiac mortality will not change over the coming decade and, as cardiac mortality has been consistently decreasing over recent decades,<sup>39</sup> this may result in a slight overestimation of mortality risk.

#### **Conclusion**

This study is the first to utilise CMR as a tool to investigate the acute effects of incidental radiation exposure of the heart during breast cancer radiotherapy. Although there was no evidence of a clinically significant effect on cardiac function, there were subclinical reductions in left ventricular function detectable by strain rate imaging. This study is the first to demonstrate these subtle abnormalities at such low cardiac radiation doses, in the absence of other cardiotoxic therapy and in women with healthy hearts. These findings support the continued use of CMR as an investigational tool in the study of radiation-related cardiac dysfunction.

Comparison of the estimated absolute benefits of radiotherapy in terms of breast cancer recurrence and mortality versus the estimated absolute risk of radiation-related coronary heart disease for the study cohort demonstrates that, for the majority of cases, the estimated benefits substantially outweigh the risks. However, even in this small population of women, that was selected to be of low cardiovascular risk, in (3 women) 9% the situation arose where the estimated 10-year IHD risk was greater than the estimated reduction in breast cancer mortality. In a non-selected population that included women with diabetes or previous cardiac disease this situation would occur much more commonly as these women would have a higher baseline risk and hence a greater absolute increase as the relative risk per Gy MWHF does not vary with these factors.<sup>10</sup> These simple observations reinforce the message that although breast radiotherapy may incur less risk today than in previous decades due to lower cardiac doses, the decision to proceed with radiotherapy in a woman with low risk breast cancer and cardiac risk factors should always be considered on an individual basis.

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## **General Summary and Conclusions**

### **Radiation-Related Cardiovascular Disease Following Cancer Therapy**

This thesis adopts a variety of complementary approaches and applies them to the study of radiation-related cardiovascular disease (RRCD) following cancer therapy.

Chapter 4 makes use of the well-established British Childhood Cancer Survivor Study (BCCSS) and uses cohort techniques to acquire new knowledge that is relevant to contemporary clinical practice. It demonstrates that the absolute excess risk of dying from circulatory causes continues to increase with prolonged follow-up to more than 40 years following first cancer diagnosis and that there is no evidence of a decrease in the risk with more recent era of diagnosis over the period studied. In addition it revealed an increasing risk of death from cardiomyopathy and heart failure over the period studied. However, in terms of absolute risk and the potential to intervene and reduce this risk, it also showed that there should be as much, if not more, emphasis on ischaemic heart disease (IHD) as on cardiomyopathy and heart failure (CM/HF), which is currently not the case in survivorship programmes. These findings underline the importance of education and follow-up of childhood cancer survivors regarding circulatory disease and need for continued research into the nature and size of the risks that can be expected from contemporary treatments and how these risks can be ameliorated. The BCCSS is currently being extended to include more than 16,000 additional childhood cancer survivors diagnosed more recently than the members of the cohort analysed here.

Chapter 5 also makes use of a previously established cohort, this time of Hodgkin lymphoma (HL) survivors, and comprises a case-control study of valvular heart disease (VHD). It demonstrates a strong association between the estimated radiation dose to an affected valve and the risk of subsequent valvular heart disease ( $p < 0.001$ ). It also reveals, for the first time, a



dose-response relationship for radiation-related valvular heart disease (VHD) in HL survivors. This will allow clinicians treating patients with HL today, and following-up patients treated in the past, to form an estimation of the risk of VHD for these patients and educate and counsel them appropriately. The study will shortly be refined by the expansion of the cohort, with the addition of further cases of VHD and also the investigation of other cardiac endpoints including IHD and CM/HF. It will therefore continue to add knowledge regarding cardiac risks for HL survivors into the future.

Chapter 6 documents the cardiac doses received by a cohort of patients treated within the context of a national randomised clinical trial and explores the methods that can be used to predict long-term cardiac mortality following incidental cardiac radiation exposure. The predicted absolute risk is small (0.2% at 15 years, range 0.0 to 2.7%) and, for the majority of patients, would not in itself out-weigh the expected improvement in local control from the use of involved field radiotherapy (IFRT). However, for a small proportion of patients, the predicted cardiac risk of radiotherapy may exceed the expected treatment benefit. Therefore the study demonstrates the importance of making an individualised assessment of cardiac risk and how assessment using a model that does not consider the difference in baseline risk that occurs with gender and age, such as the relative seriality model, could be misleading.

Chapter 7 utilises a library of CT data sets from patients recently treated for HL to derive a clinical tool to estimate, at diagnosis and before any treatment has started, the likely cardiac dose that may result from a course of IFRT for their disease. This tool could help clinicians make a more informed decision regarding the risks and benefits of radiotherapy on an individualised basis without the need for more detailed CT-based planning. This study also highlights the observed variation in cardiac dose that occurs between patients due to individual differences in

cardiac anatomy which is relevant to the work in chapter 5 on retrospective dosimetry in HL and the planned extensions to this study.

Chapter 8 reports a prospective study of the utility of cardiovascular magnetic resonance (CMR) imaging as a sensitive marker of radiation-induced cardiac damage or dysfunction in a prospective cohort of women receiving modern radiotherapy for breast cancer. The women received low cardiac doses (mean whole heart dose = 1.5 Gy, SD = 0.8). Most of the women had a low predicted risk of cardiac morbidity and mortality but for a minority of women (9%, n=3) the predicted risk of ischaemic heart disease from radiotherapy exceeded the predicted benefit in terms of predicted reduction in breast cancer mortality. There was no evidence of any clinical effect on cardiac function by 6 months following RT, but strain rate imaging did reveal some subtle sub-clinical decline in function in the region of the left ventricle expected to receive the highest radiation dose. These results encourage the further use of CMR as a sensitive tool to employ in the study of radiation-related heart disease.

In conclusion, using a variety of methods this thesis has succeeded in adding to knowledge regarding RRCD which can be applied to the future management of cancer patients. Each of the component studies has natural extensions planned and will continue to contribute further knowledge into the future.

# Appendices

## Appendix A – Dose-Response Relationships for Radiation-Related Cardiovascular Disease

### Lyman-Kucher-Burman (LKB) model

$$NTCP = 1/\sqrt{2\pi} \int_{-\infty}^t \exp(-t^2/2) dt$$

$$v = V/V_{ref}$$

$$TD(v) = TD(1) * v - n$$

$$t = \frac{(D - TD_{50}(v))}{(m * TD_{50}(v))}$$

Where:

D = Radiation dose

v = Fraction of the organ irradiated to dose 'D'

Parameters:

TD<sub>50</sub> = Dose to the whole organ (or reference volume) giving an NTCP of 50%

m = Slope parameter with impact on the steepness of the dose-response curve

n = Volume dependence of the complication probability

V<sub>ref</sub> = Reference volume of the organ

The parameters for pericarditis are:<sup>1</sup>

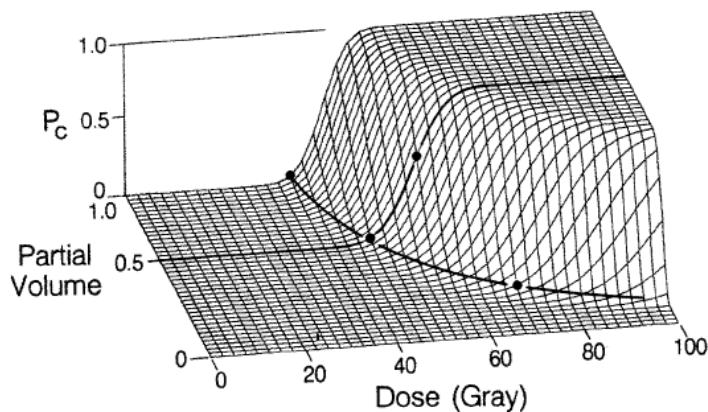
TD<sub>50</sub> = 48

m = 0.1

n = 0.35

V<sub>ref</sub> = Whole heart

Surface representation:<sup>2</sup>



P<sub>c</sub> = NTCP for pericarditis

### Logistic dose response curve

$$NTCP = \frac{1}{1 + \exp \left[ 4 * \gamma_{50} \left( 1 - \frac{D}{D_{50}} \right) \right]}$$

Parameters:

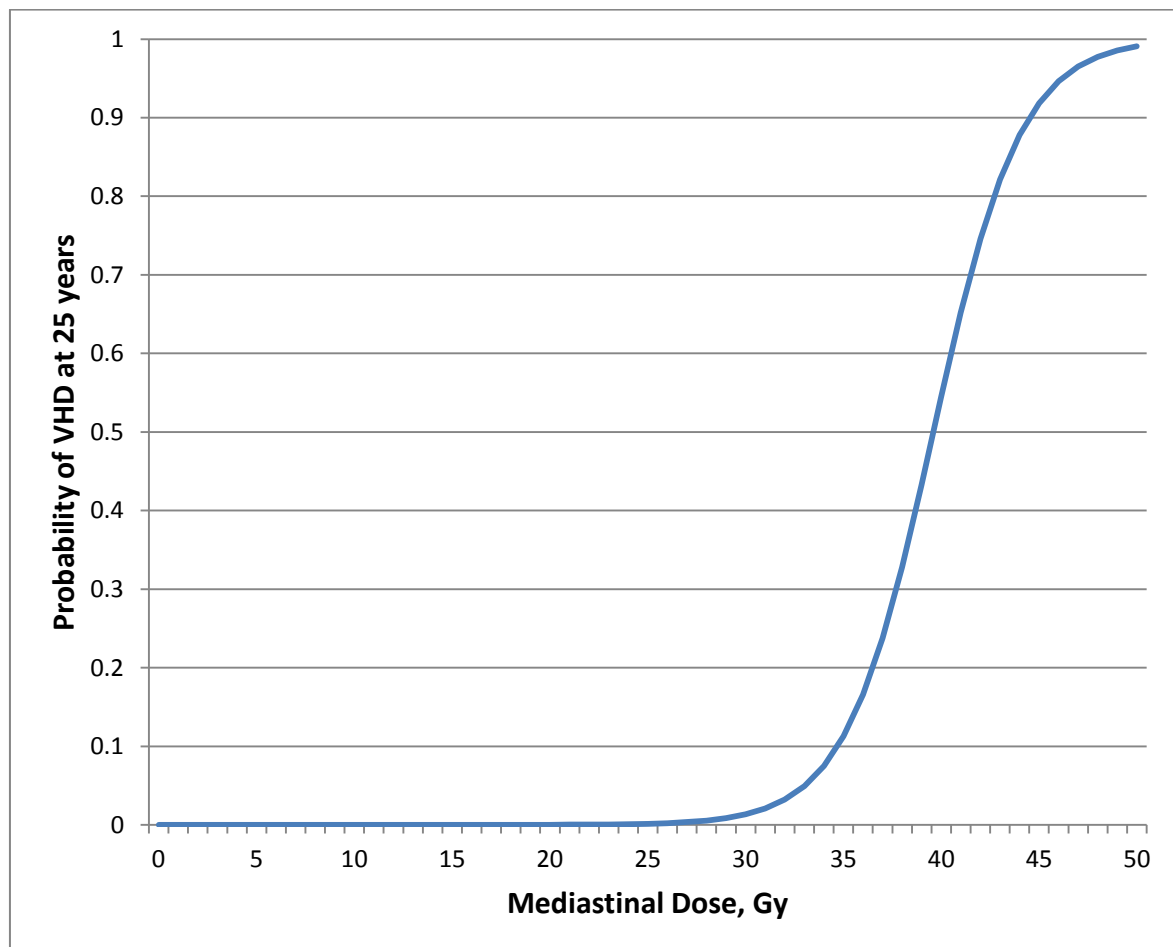
$\gamma_{50}$  = Normalised dose-response gradient at the 50% level

$D_{50}$  = Dose for a 50% response.

#### Example:

Probability of valvular heart disease at 25 years by mediastinal dose<sup>3</sup>

Where;  $\gamma_{50} = 4.4$  and  $D_{50} = 39.6$



1. Burman C, Kutcher GJ, Emami B, Goitein M. Fitting of normal tissue tolerance data to an analytic function. *Int J Radiat Oncol Biol Phys.* May 15 1991;21(1):123-135.
2. Lyman JT. Complication probability as assessed from dose-volume histograms. *Radiat Res Suppl.* 1985;8:S13-19.
3. Maraldo MV, Brodin NP, Vogelius IR, et al. Risk of Developing Cardiovascular Disease after Involved Node Radiotherapy versus Mantle Field for Hodgkin Lymphoma. *Int J Radiat Oncol Biol Phys.* Jan 21 2012.

## **Appendix B – Circulatory Mortality** **in the British Childhood Cancer Survivor Study**

| <b>Cause of Death</b>      | <b>ICD-5 (1940-49)</b>                                | <b>ICD-6 (1950-57)</b>                               | <b>ICD-7 (1958-67)</b>                                 | <b>ICD-8 (1968-78)</b>                          | <b>ICD-9 (1979-2000)</b>                                               | <b>ICD-10 (2001-09)</b>                                                             |
|----------------------------|-------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| <b>All Circulatory</b>     | 58a-c, 83a-c, 90a-b, 91a-c, 92-103, 111, 199, 200a(1) | 330-334, 401, 402.1, 410-468                         | 330-334, 401, 402.1, 410-468                           | 391, 392.0, 393-458                             | 391, 392.0, 393-459                                                    | I01, I02.0, I05-I99                                                                 |
| <b>All Cardiac</b>         | 58a-c, 90a-b, 91a-c, 92-95, 111b-c, 199, 200a(1)      | 401, 402.1, 410-416, 420-422, 430-434, 440-443       | 401, 402.1, 410-416, 420-422, 430-434, 440-443         | 391, 392.0, 393-398, 402, 404, 410-414, 420-429 | 391, 392.0, 393-398, 402, 404, 410-414, 416.1-9, 420-429.1, 429.3      | I01, I02.0, I05-I09, I11, I13, I20-I25, I27.1-9, I30-I52                            |
| Cardiomyopathy/CHF         | 58c, 93a-b, 93c(2-3), 93d, 111b-c, 200a(1)            | 401.2, 415, 422.0, 422.2, 431, 434.1-2               | 401.2, 415, 422.0, 422.2, 431, 434.1-2                 | 391.2, 422, 425, 427.0, 427.1, 428              | 391.2, 398.0, 422, 425, 428, 429.0, 429.1, 429.3                       | I01.2, I09.0, I11.0, I13.0, I13.2, I40-I43, I50, I51.4-5, I51.7                     |
| Valvular HD                | 92a, 92b(1), 92c                                      | 421                                                  | 421                                                    | 394.9, 395.9, 396.9, 397.0, 424                 | 424                                                                    | I34-I39                                                                             |
| Rheum Valvular HD          | 58b, 92b(2)                                           | 401.1, 410-414                                       | 401.1, 410-414                                         | 391.1, 394.0, 395.0, 396.0, 397.9               | 391.1, 394-397                                                         | I01.1, I05-I08, I09.1                                                               |
| Ischaemic HD               | 93c(1), 94a, 94b                                      | 420, 422.1                                           | 420, 422.1                                             | 410-414                                         | 410-414, 429.7                                                         | I20-I25                                                                             |
| Arrhythmias                | 199                                                   | 433.0-1                                              | 433.0-1                                                | 427.2-9                                         | 426-427                                                                | I44-49                                                                              |
| Pericardial                | 58a, 90a-b                                            | 401.0, 432                                           | 401.0, 432                                             | 391.0, 393, 420, 423                            | 391.0, 393, 420, 423                                                   | I01.0, I09.2, I30-I32                                                               |
| Other Cardiac              | 91a-c, 95                                             | 401.3, 402.1, 416, 430, 433.2, 434.0, 434.3, 440-443 | 401.3, 402.1, 416, 430, 433.2, 434.0, 434.3-4, 440-443 | 391.9, 392.0, 398, 402, 404, 421, 426, 429      | 391.8-9, 392.0, 389.9, 402, 404, 416.1-9, 421, 429.2, 429.4-6, 429.8-9 | I01.8-9, I02.0, I09.8-9, I11.9, I13.1, I13.9, I27.1-9, I33, I51.0-3, I51.6, I60-I69 |
| <b>Cerebrovascular</b>     | 83a-c                                                 | 330-334                                              | 330-334                                                | 430-438                                         | 430-438                                                                | I60-I69                                                                             |
| <b>Thromboembolic</b>      | 111a                                                  | 454, 463-466                                         | 454, 463-466                                           | 444, 450-453                                    | 415, 444, 451-453                                                      | I26, I74, I80-I82                                                                   |
| <b>Peripheral Vascular</b> | 96-100                                                | 450-453, 455-456, 460-462                            | 450-453, 455-456, 460-462                              | 440-443, 445-448, 454-456                       | 440-443, 446-448, 454-456                                              | I70-I73, I77-I79, I83-I87                                                           |
| <b>Other Circulatory</b>   | 101-103                                               | 444-447, 467-468                                     | 444-447, 467-468                                       | 400, 401, 403, , 457-458                        | 401, 403, 405, 416.0, 417, 457-459                                     | I10, I12, I15, I27.0, I28, I88-I89, I95-I99                                         |

**Table B.1 – ICD categorisations and sub-categorisations for circulatory causes of death as used in the analysis**

| Era of<br>Diagnosis | Years from Diagnosis |       |       |       |       |       |       |       |       |       |       |       |     |        |
|---------------------|----------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-----|--------|
|                     | 5-9                  | 10-14 | 15-19 | 20-24 | 25-39 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55-59 | 60-64 | 65+ | Totals |
| 1940-44             | 125                  | 118   | 104   | 95    | 90    | 90    | 90    | 90    | 80    | 75    | 70    | 65    | 26  | 1118   |
| 1945-49             | 374                  | 350   | 335   | 331   | 324   | 302   | 278   | 262   | 252   | 220   | 195   | 63    |     | 3285   |
| 1950-54             | 1352                 | 1246  | 1194  | 1139  | 1094  | 1058  | 1031  | 990   | 948   | 841   | 293   |       |     | 11187  |
| 1955-59             | 3323                 | 3093  | 2982  | 2908  | 2813  | 2719  | 2625  | 2521  | 2357  | 1058  |       |       |     | 26400  |
| 1960-64             | 5294                 | 4983  | 4806  | 4690  | 4591  | 4499  | 4364  | 4203  | 1863  |       |       |       |     | 39292  |
| 1965-69             | 6782                 | 6326  | 6131  | 5965  | 5820  | 5629  | 5426  | 2570  |       |       |       |       |     | 44649  |
| 1970-74             | 11025                | 10316 | 9987  | 9697  | 9407  | 9062  | 4044  |       |       |       |       |       |     | 63537  |
| 1975-79             | 14230                | 13428 | 13017 | 12716 | 12388 | 6023  |       |       |       |       |       |       |     | 71802  |
| 1980-84             | 16233                | 15494 | 15104 | 14798 | 7126  |       |       |       |       |       |       |       |     | 68756  |
| 1985-89             | 18160                | 17491 | 17026 | 8393  |       |       |       |       |       |       |       |       |     | 61070  |
| 1990-91             | 8301                 | 8013  | 6269  |       |       |       |       |       |       |       |       |       |     | 22583  |
| Totals              | 85200                | 80858 | 76955 | 60732 | 43653 | 29382 | 17857 | 10636 | 5500  | 2194  | 558   | 128   | 26  | 413681 |

**Table B.2** – Cohort distribution of person-years of follow-up by era of diagnosis and time since diagnosis

| Year of Diagnosis | Initial Surgery |              |              | Initial Radiotherapy |              |              | Initial Chemotherapy |              |              | Mean % Recorded |
|-------------------|-----------------|--------------|--------------|----------------------|--------------|--------------|----------------------|--------------|--------------|-----------------|
|                   | Yes             | No           | NR           | Yes                  | No           | NR           | Yes                  | No           | NR           |                 |
| 1940              | 3               | 0            | 1            | 2                    | 1            | 1            | 0                    | 3            | 1            | 75.0            |
| 1941              | 3               | 0            | 0            | 3                    | 0            | 0            | 0                    | 3            | 0            | 100.0           |
| 1942              | 3               | 1            | 0            | 3                    | 1            | 0            | 0                    | 4            | 0            | 100.0           |
| 1943              | 7               | 1            | 0            | 4                    | 3            | 1            | 0                    | 8            | 0            | 95.8            |
| 1944              | 5               | 1            | 1            | 6                    | 0            | 1            | 0                    | 6            | 1            | 85.7            |
| 1945              | 7               | 2            | 0            | 8                    | 1            | 0            | 0                    | 9            | 0            | 100.0           |
| 1946              | 10              | 0            | 0            | 9                    | 1            | 0            | 0                    | 10           | 0            | 100.0           |
| 1947              | 10              | 0            | 0            | 8                    | 2            | 0            | 0                    | 10           | 0            | 100.0           |
| 1948              | 18              | 2            | 0            | 16                   | 4            | 0            | 0                    | 20           | 0            | 100.0           |
| 1949              | 27              | 1            | 0            | 20                   | 8            | 0            | 0                    | 28           | 0            | 100.0           |
| 1950              | 24              | 5            | 2            | 21                   | 8            | 2            | 0                    | 29           | 2            | 93.5            |
| 1951              | 50              | 3            | 1            | 31                   | 21           | 2            | 1                    | 52           | 1            | 97.5            |
| 1952              | 38              | 13           | 2            | 40                   | 12           | 1            | 1                    | 51           | 1            | 97.5            |
| 1953              | 29              | 6            | 1            | 25                   | 11           | 0            | 0                    | 34           | 2            | 97.2            |
| 1954              | 97              | 20           | 0            | 84                   | 32           | 1            | 2                    | 115          | 0            | 99.7            |
| 1955              | 103             | 22           | 2            | 78                   | 44           | 5            | 3                    | 120          | 4            | 97.1            |
| 1956              | 113             | 30           | 4            | 102                  | 42           | 3            | 5                    | 140          | 2            | 98.0            |
| 1957              | 99              | 30           | 5            | 84                   | 44           | 6            | 3                    | 127          | 4            | 96.3            |
| 1958              | 111             | 22           | 7            | 89                   | 46           | 5            | 3                    | 132          | 5            | 96.0            |
| 1959              | 132             | 25           | 19           | 93                   | 63           | 20           | 8                    | 153          | 15           | 89.8            |
| 1960              | 142             | 39           | 20           | 119                  | 67           | 15           | 17                   | 172          | 12           | 92.2            |
| 1961              | 137             | 50           | 18           | 124                  | 66           | 15           | 21                   | 172          | 12           | 92.7            |
| 1962              | 184             | 36           | 9            | 131                  | 80           | 18           | 20                   | 167          | 42           | 90.0            |
| 1963              | 196             | 54           | 9            | 164                  | 81           | 14           | 29                   | 190          | 40           | 91.9            |
| 1964              | 186             | 53           | 13           | 147                  | 89           | 16           | 40                   | 179          | 33           | 91.8            |
| 1965              | 200             | 64           | 10           | 170                  | 71           | 33           | 58                   | 152          | 64           | 87.0            |
| 1966              | 208             | 77           | 12           | 188                  | 82           | 27           | 58                   | 153          | 86           | 86.0            |
| 1967              | 221             | 78           | 12           | 182                  | 72           | 57           | 69                   | 102          | 140          | 77.6            |
| 1968              | 212             | 55           | 12           | 177                  | 53           | 49           | 46                   | 89           | 144          | 75.5            |
| 1969              | 211             | 84           | 26           | 181                  | 74           | 66           | 93                   | 103          | 125          | 77.5            |
| 1970              | 236             | 123          | 33           | 225                  | 111          | 56           | 131                  | 157          | 104          | 83.6            |
| 1971              | 208             | 191          | 2            | 251                  | 133          | 17           | 185                  | 196          | 20           | 96.8            |
| 1972              | 271             | 228          | 9            | 366                  | 129          | 13           | 233                  | 255          | 20           | 97.2            |
| 1973              | 288             | 252          | 11           | 393                  | 132          | 26           | 281                  | 248          | 22           | 96.4            |
| 1974              | 251             | 257          | 5            | 377                  | 126          | 10           | 300                  | 206          | 7            | 98.6            |
| 1975              | 250             | 274          | 38           | 395                  | 127          | 40           | 339                  | 183          | 40           | 93.0            |
| 1976              | 275             | 299          | 38           | 435                  | 133          | 44           | 359                  | 208          | 45           | 93.1            |
| 1977              | 283             | 330          | 30           | 461                  | 153          | 29           | 410                  | 203          | 30           | 95.4            |
| 1978              | 299             | 293          | 29           | 457                  | 131          | 33           | 385                  | 202          | 34           | 94.8            |
| 1979              | 259             | 290          | 27           | 380                  | 166          | 30           | 371                  | 1776         | 29           | 95.0            |
| 1980              | 280             | 337          | 31           | 424                  | 190          | 34           | 427                  | 187          | 34           | 94.9            |
| 1981              | 239             | 326          | 83           | 406                  | 147          | 95           | 374                  | 182          | 92           | 86.1            |
| 1982              | 234             | 335          | 124          | 395                  | 165          | 133          | 400                  | 164          | 129          | 81.4            |
| 1983              | 278             | 309          | 115          | 400                  | 171          | 131          | 361                  | 222          | 119          | 82.7            |
| 1984              | 238             | 232          | 139          | 369                  | 184          | 147          | 372                  | 187          | 141          | 79.7            |
| 1985              | 238             | 355          | 185          | 410                  | 174          | 194          | 408                  | 177          | 193          | 75.5            |
| 1986              | 115             | 273          | 342          | 301                  | 104          | 325          | 303                  | 105          | 322          | 54.8            |
| 1987              | 114             | 254          | 404          | 278                  | 105          | 389          | 286                  | 98           | 388          | 49.0            |
| 1988              | 81              | 65           | 626          | 78                   | 85           | 609          | 96                   | 75           | 601          | 17.7            |
| 1989              | 56              | 61           | 588          | 80                   | 45           | 580          | 85                   | 42           | 578          | 17.4            |
| 1990              | 12              | 1            | 841          | 13                   | 21           | 820          | 18                   | 18           | 818          | 3.2             |
| 1991              | 3               | 0            | 851          | 12                   | 13           | 829          | 19                   | 8            | 827          | 2.1             |
| <b>Total</b>      | <b>7,294</b>    | <b>5,950</b> | <b>4,737</b> | <b>9,215</b>         | <b>3,824</b> | <b>4,942</b> | <b>6,620</b>         | <b>6,032</b> | <b>5,329</b> | <b>72.2%</b>    |

**Table B.3** – Initial treatments recorded as being received by year of diagnosis, NR = Not recorded



## **Numbers and Specific Causes of Cardiovascular Deaths in the BCCSS Cohort**

### **Cardiac (129)**

#### **Ischaemic Heart Disease (65)**

Acute myocardial infarction = 32  
Chronic ischaemic heart disease = 33

#### **Cardiomyopathy and Heart Failure (42)**

Cardiomyopathy = 32  
Myocarditis = 5  
Heart failure = 4  
Myocardial degeneration = 1

#### **Valvular Heart Disease (7)**

Aortic valve disease = 6  
Mitral valve disease = 1

#### **Cardiac Arrhythmias (2)**

Cardiac arrest = 1  
Cardiac arrhythmia, unspecified = 1

#### **Pericardial Disease (1)**

Constrictive pericarditis = 1

#### **Other Cardiac Disease (12)**

Kyphoscoliotic heart disease = 3  
Pulmonary heart disease = 3  
Heart disease, unspecified = 3  
Hypertensive heart disease = 2  
Bacterial endocarditis = 1

### **Cerebrovascular (59)**

#### **Haemorrhagic (25)**

Intracerebral haemorrhage = 15  
Subarachnoid haemorrhage = 8  
Unspecified haemorrhage = 1  
Subdural haemorrhage = 1

#### **Ischaemic (11)**

Cerebral infarction = 11

#### **Unspecified/Other (23)**

Stroke or cerebrovascular disease, unspecified = 22  
Hypertensive encephalopathy = 1

### **Other Cardiovascular (32)**

#### **Thromboembolic (20)**

Pulmonary embolism = 11  
Thrombosis of lower extremities = 8  
Budd-Chiari Syndrome = 1

#### **Peripheral Vascular (6)**

Unspecified peripheral vascular disease = 2  
Arteritis, unspecified = 2  
Oesophageal varices with bleeding = 1  
Aneurysm of carotid artery = 1

#### **Other Circulatory (6)**

Primary pulmonary hypertension = 4  
Lymphoedema = 1  
Malignant hypertension = 1

|                             |                       | Deaths<br>O/E | PYs FU  | SMR (95% CI)                                                                  | AER (95% CI)                                                                      |
|-----------------------------|-----------------------|---------------|---------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Gender</b>               | Male                  | 48/23.51      | 224,020 | 2.04 (1.51 to 2.71)                                                           | 1.09 (0.53 to 1.79)                                                               |
|                             | Female                | 17/4.76       | 189,661 | 3.57 (2.08 to 5.52)<br>Heterogeneity p=0.06                                   | 0.65 (0.27 to 1.18)<br>Heterogeneity p=0.23                                       |
| <b>Age at Diagnosis</b>     | 0-5                   | 21/6.98       | 195,054 | 3.01 (1.86 to 4.60)                                                           | 0.72 (0.31 to 1.29)                                                               |
|                             | 5-10                  | 15/6.53       | 107,702 | 2.30 (1.29 to 3.79)                                                           | 0.79 (0.17 to 1.69)                                                               |
|                             | 10-15                 | 29/14.77      | 110,925 | 1.96 (1.31 to 2.82)<br>Heterogeneity p=0.34<br>Trend p=0.15                   | 1.28 (0.42 to 2.42)<br>Heterogeneity p=0.55<br>Trend p=0.32                       |
| <b>Era of Diagnosis</b>     | 1940-49               | 4/2.34        | 4,403   | 1.71 (0.47 to 4.39)                                                           | 3.78 (-2.83 to 17.96)                                                             |
|                             | 1950-59               | 24/10.69      | 37,587  | 2.24 (1.44 to 3.34)                                                           | 3.54 (1.25 to 6.66)                                                               |
|                             | 1960-69               | 16/9.68       | 83,942  | 1.65 (0.95 to 2.69)                                                           | 0.75 (-0.06 to 1.94)                                                              |
|                             | 1970-79               | 18/4.38       | 135,340 | 4.11 (2.43 to 6.49)                                                           | 1.01 (0.46 to 1.78)                                                               |
|                             | 1980-91               | 3/1.19        | 152,408 | 2.53 (0.52 to 7.38)<br>Heterogeneity p=0.12<br>Trend p=0.14                   | 0.12 (-0.04 to 0.50)<br><b>Heterogeneity p=0.002</b><br><b>Trend p=0.0002</b>     |
| <b>Diagnostic Group</b>     | Leukaemia             | 2/1.43        | 91,864  | 1.40 (0.17 to 5.04)                                                           | 0.08 (-0.13 to 0.63)                                                              |
|                             | Hodgkin Lymphoma      | 14/3.46       | 30,351  | 4.05 (2.40 to 6.83)                                                           | 3.47 (1.38 to 6.60)                                                               |
|                             | NHL                   | 7/2.52        | 23,089  | 2.77 (1.11 to 5.70)                                                           | 1.94 (0.12 to 5.15)                                                               |
|                             | CNS (excl. PNET)      | 13/7.99       | 84,306  | 1.63 (0.87 to 2.78)                                                           | 0.59 (-0.13 to 1.69)                                                              |
|                             | PNET                  | 3/0.82        | 12,394  | 3.67 (0.76 to 10.72)                                                          | 1.76 (-0.16 to 6.41)                                                              |
|                             | Neuroblastoma         | 1/0.88        | 19,661  | 1.13 (0.03 to 6.30)                                                           | 0.06 (-0.44 to 2.38)                                                              |
|                             | Retinoblastoma (NH)   | 2/1.58        | 20,246  | 1.27 (0.15 to 4.58)                                                           | 0.21 (-0.66 to 2.79)                                                              |
|                             | Retinoblastoma (H)    | 3/1.04        | 16,468  | 2.88 (0.59 to 8.42)                                                           | 1.19 (-0.26 to 4.69)                                                              |
|                             | Wilms' Tumour         | 7/1.47        | 38,247  | 4.77 (1.92 to 9.83)                                                           | 1.45 (0.35 to 3.39)                                                               |
|                             | Bone Sarcoma          | 2/1.66        | 14,453  | 1.21 (0.15 to 4.37)                                                           | 0.24 (-0.98 to 3.85)                                                              |
|                             | Soft Tissue Sarcoma   | 6/2.84        | 29,741  | 2.12 (0.78 to 4.61)                                                           | 1.06 (-0.21 to 3.44)                                                              |
|                             | Non-CNS GCT           | 1/0.61        | 12,622  | 1.64 (0.04 to 9.13)                                                           | 0.31 (-0.46 to 3.93)                                                              |
|                             | Other                 | 4/1.97        | 20,238  | 2.03 (0.55 to 5.20)<br>Heterogeneity p=0.39                                   | 1.00 (-0.44 to 4.09)<br><b>Heterogeneity p=0.04</b>                               |
| <b>Initial Therapy</b>      | Surgery + No CT or RT | 10/7.30       | 70,070  | 1.37 (0.66 to 2.52)                                                           | 0.39 (-0.36 to 1.58)                                                              |
|                             | Surgery + CT or RT    | 24/10.63      | 82,454  | 2.26 (1.45 to 3.36)                                                           | 1.62 (0.58 to 3.04)                                                               |
|                             | Surgery + CT & RT     | 3/0.90        | 32,044  | 3.34 (0.69 to 9.75)                                                           | 0.66 (-0.09 to 2.46)                                                              |
|                             | CT or RT (No Surgery) | 18/4.63       | 41,350  | 3.88 (2.30 to 6.14)                                                           | 3.23 (1.46 to 5.76)                                                               |
|                             | CT & RT (No Surgery)  | 4/1.70        | 81,437  | 2.35 (0.64 to 6.01)                                                           | 0.28 (-0.08 to 1.05)                                                              |
|                             | Any Treatment N/R     | 6/3.10        | 106,325 | 1.94 (0.71 to 4.21)<br>Heterogeneity p=0.16                                   | 0.27 (-0.08 to 0.94)<br><b>Heterogeneity p=0.003</b>                              |
| <b>Years from Diagnosis</b> | 5-9                   | 1/0.08        | 85,200  | 12.77 (0.32 to 71.15)                                                         | 0.11 (-0.01 to 0.64)                                                              |
|                             | 10-19                 | 5/0.92        | 157,813 | 5.45 (1.77 to 12.72)                                                          | 0.26 (0.04 to 0.68)                                                               |
|                             | 20-29                 | 17/4.41       | 104,385 | 3.86 (2.25 to 6.17)                                                           | 1.21 (0.53 to 2.19)                                                               |
|                             | 30-39                 | 17/9.27       | 47,239  | 1.83 (1.07 to 2.94)                                                           | 1.64 (0.14 to 3.80)                                                               |
|                             | 40+                   | 25/13.60      | 19,042  | 1.84 (1.19 to 2.71)<br><b>Heterogeneity p=0.03</b><br><b>Trend p=0.003</b>    | 5.99 (1.35 to 12.24)<br><b>Heterogeneity p=0.001</b><br><b>Trend p=0.0004</b>     |
| <b>Attained Age</b>         | 5-19                  | 1/0.09        | 141,477 | 11.77 (0.30 to 65.58)                                                         | 0.06 (0.00 to 0.39)                                                               |
|                             | 20-29                 | 10/0.93       | 139,138 | 10.70 (5.13 to 19.68)                                                         | 0.65 (0.28 to 1.25)                                                               |
|                             | 30-39                 | 16/4.71       | 84,994  | 3.39 (1.94 to 5.51)                                                           | 1.33 (0.52 to 2.50)                                                               |
|                             | 40-49                 | 15/9.91       | 35,342  | 1.51 (0.85 to 2.50)                                                           | 1.44 (-0.43 to 4.20)                                                              |
|                             | 50+                   | 23/12.62      | 12,729  | 1.82 (1.15 to 2.73)<br><b>Heterogeneity p=0.0001</b><br><b>Trend p=0.0001</b> | 8.15 (1.54 to 17.19)<br><b>Heterogeneity p=0.0005</b><br><b>Trend p&lt;0.0001</b> |
| <b>Total</b>                |                       | 65/28.27      | 413,681 | 2.30 (1.77 to 2.93)<br><b>SMR ≠ 1, p&lt;0.0001</b>                            | 0.89 (0.53 to 1.32)<br><b>AER ≠ 0, p&lt;0.0001</b>                                |

**Table B.4** - SMRs and AERs for death from ischaemic heart disease by individual explanatory variables, with likelihood ratio tests for heterogeneity and trend where appropriate. Statistically significant tests are marked in bold.

## **Appendix C – Risk Factors for Valvular Heart Disease Following Hodgkin Lymphoma**

### **Definition of Equivalent Dose in 2 Gy Fractions (EQD2)**

$$EQD2 = D[(d + \alpha/\beta)/(2 + \alpha/\beta)]$$

Where; D = Total dose, d = dose per fraction and  $\alpha/\beta$  = the ratio of parameters in the linear quadratic model that are used to define the sensitivity of an effect in a tissue (assumed to be 2 for late heart effects for the purposes of this thesis).

|                                                    | Number of Cases |              | Number of Controls |              |
|----------------------------------------------------|-----------------|--------------|--------------------|--------------|
|                                                    | N               | %            | N                  | %            |
| <b>Initially selected</b>                          | <b>143</b>      | <b>100.0</b> | <b>428</b>         | <b>100.0</b> |
|                                                    |                 |              |                    |              |
| <b>Ineligible</b>                                  | <b>44</b>       | <b>30.8</b>  | <b>30</b>          | <b>7.0</b>   |
| - Prior cardiovascular event                       | 15              | 10.5         | 9                  | 2.1          |
| - No VHD                                           | 8               | 5.6          | -                  | -            |
| - Grade 1 VHD only                                 | 15              | 10.5         | -                  | -            |
| - Medical record lost                              | 3               | 2.1          | 4                  | 0.9          |
| - Lost to follow-up                                | -               | -            | 5                  | 1.2          |
| - Cut-off date changed                             | -               | -            | 7                  | 1.6          |
| - Other reasons                                    | 3               | 2.1          | 5                  | 1.2          |
| <b>Case excluded</b>                               | <b>-</b>        | <b>-</b>     | <b>93</b>          | <b>21.7</b>  |
| <b>Selected as third control, not used</b>         | <b>-</b>        | <b>-</b>     | <b>93</b>          | <b>21.7</b>  |
| - Of which case excluded                           | -               | -            | 45                 | 10.5         |
| <b>Administrative reasons for exclusion</b>        | <b>10</b>       | <b>7.0</b>   | <b>12</b>          | <b>2.8</b>   |
| - Case unconfirmed                                 | 7               | 4.9          | 9                  | 2.1          |
| - Case without controls                            | 3               | 2.1          | -                  | -            |
| - Control not abstracted                           | -               | -            | 2                  | 0.5          |
| - Control abstracted twice                         | -               | -            | 1                  | 0.2          |
|                                                    |                 |              |                    |              |
| <b>Total excluded</b>                              | <b>54</b>       | <b>37.8</b>  | <b>228</b>         | <b>53.3</b>  |
| <b>Total included in study</b>                     | <b>89</b>       | <b>62.2</b>  | <b>200</b>         | <b>46.7</b>  |
|                                                    |                 |              |                    |              |
| <b>Duplicate controls</b>                          | <b>-</b>        | <b>-</b>     | <b>43</b>          | <b>21.5</b>  |
| <b>Case as control</b>                             | <b>-</b>        | <b>-</b>     | <b>13</b>          | <b>6.5</b>   |
| - Once                                             | -               | -            | 12                 | 6            |
| - Twice                                            | -               | -            | 1                  | 0.5          |
| <b>Control as control</b>                          | <b>-</b>        | <b>-</b>     | <b>24</b>          | <b>12</b>    |
| - Once                                             | -               | -            | 20                 | 10           |
| - Twice                                            | -               | -            | 3                  | 1.5          |
| - Three times                                      | -               | -            | 1                  | 0.5          |
|                                                    |                 |              |                    |              |
| <b>Total number of unique individuals in study</b> | <b>89</b>       | <b>100.0</b> | <b>157</b>         | <b>78.5</b>  |

**Table C.1** – A flow chart of case and control selection indicating how the cases and controls for the study were selected from the original cohort.

Definition of EQD2

| Treatment Characteristic                            | Model A   |                |          | Model B   |                |          | Model E   |                |          | Model F   |                |          |
|-----------------------------------------------------|-----------|----------------|----------|-----------|----------------|----------|-----------|----------------|----------|-----------|----------------|----------|
|                                                     | Coeff     | 95% CI         | p        | Coeff     | 95% CI         | p        | Coeff     | 95% CI         | p        | Coeff     | 95% CI         | p        |
| <b>Dose (EQD2) to affected valve (per Gy):</b>      |           |                |          |           |                |          |           |                |          |           |                |          |
| Linear term                                         | -5.02     | -9.19 to -0.84 | 0.02     | -4.93     | -9.21 to -0.66 | 0.024    | -5.10     | -9.19 to -0.84 | 0.022    | -5.07     | -9.58 to -0.57 | 0.027    |
| Curvature term                                      | 0.08      | -0.01 to -0.16 | 0.09     | 0.07      | -0.02 to 0.16  | 0.12     | 0.07      | -0.01 to 0.16  | 0.11     | 0.07      | -0.03 to 0.16  | 0.15     |
| Model 2* vs. Model 3**                              |           |                | 0.02     |           |                | 0.041    |           |                | 0.037    |           |                | 0.06     |
| <b>Any splenectomy after HL diagnosis:</b>          | <b>OR</b> | <b>95% CI</b>  | <b>P</b> | <b>OR</b> | <b>95% CI</b>  | <b>P</b> | <b>OR</b> | <b>95% CI</b>  | <b>P</b> | <b>OR</b> | <b>95% CI</b>  | <b>P</b> |
| No                                                  | -         | -              | -        | 1         |                |          | -         | -              | -        | 1         | -              | -        |
| Yes                                                 | -         | -              | -        | 2.1       | 1.1 to 4.1     |          | -         | -              |          | 2.1       | 1.1 to 4.2     |          |
| <b>Procarbazine</b>                                 |           |                | -        |           |                | -        |           |                | 0.35     |           |                | 0.30     |
| No                                                  | -         | -              | -        | -         | -              | -        | 1         | -              | -        | 1         | -              | -        |
| Yes                                                 | -         | -              | -        | -         | -              | -        | 0.7       | 0.4 to 1.4     | -        | 0.7       | 0.4 to 1.4     | -        |
| <b>Dose (EQD2) to affected valve (categorical):</b> |           |                | <0.001   |           |                | 0.002    |           |                | 0.004    |           |                | 0.012    |
| No RT                                               | 1         | 0.2 to 4.9     |          | 1         | 0.2 to 4.6     |          | 1         | 0.2 to 5.1     |          | 1         | 0.2 to 4.9     |          |
| ≤30 Gy                                              | 1.4       | 0.5 to 3.6     |          | 1.3       | 0.5 to 3.4     |          | 1.4       | 0.5 to 3.7     |          | 1.2       | 0.4 to 3.2     |          |
| 31-35 Gy                                            | 3.4       | 1.9 to 6.0     |          | 2.8       | 1.5 to 5.0     |          | 3.0       | 1.7 to 5.3     |          | 2.3       | 1.3 to 4.2     |          |
| 36-40 Gy                                            | 5.6       | 4.0 to 7.0     |          | 4.7       | 3.3 to 6.5     |          | 4.8       | 3.4 to 6.8     |          | 3.9       | 2.7 to 5.5     |          |
| >40 Gy                                              | 12.2      | 5.1 to 29.0    |          | 9.9       | 4.1 to 23.8    |          | 10.5      | 4.4 to 25.0    |          | 8.1       | 3.3 to 19.7    |          |
| Unknown                                             | -         | -              | -        | -         | -              | -        | -         | -              | -        | -         | -              | -        |
| <b>Any splenectomy after HL diagnosis:</b>          |           |                | -        |           |                | 0.025    |           |                | -        |           |                | 0.022    |
| No                                                  | -         | -              | -        | 1         | -              | -        | -         | -              | -        | 1         | -              | -        |
| Yes                                                 | -         | -              | -        | 2.2       | 1.1 to 4.3     | -        | -         | -              | -        | 2.2       | 1.1 to 4.4     | -        |
| <b>Procarbazine</b>                                 |           |                | -        |           |                | -        |           |                | 0.48     |           |                | 0.41     |
| No                                                  | -         | -              | -        | -         | -              | -        | 1         | -              | -        | 1         | -              | -        |
| Yes                                                 | -         | -              | -        | -         | -              | -        | 0.8       | 0.4 to 1.5     | -        | 0.8       | 0.4 to 1.5     | -        |

**Table C.2** – Crude (A) and adjusted (B, E and F) logistic regression models of OR for VHD by radiation dose to affected valve, both per Gy (top) and by dose category (bottom). \*Linear model. \*\*Linear model with curvature.

| Treatment Characteristic                            | Model G   |                |          | Model H   |                |          |
|-----------------------------------------------------|-----------|----------------|----------|-----------|----------------|----------|
|                                                     | Coeff     | 95% CI         | P        | Coeff     | 95% CI         | P        |
| <b>Dose (EQD2) to affected valve (per Gy):</b>      |           |                |          |           |                |          |
| Linear term                                         | -5.14     | -9.92 to -0.35 | 0.04     | -4.98     | -9.55 to -0.42 | 0.32     |
| Curvature term                                      | 0.067     | -0.03 to 0.17  | 0.18     | 0.07      | -0.03 to 0.16  | 0.17     |
| Model 2* vs. Model 3**                              |           |                | 0.07     |           |                | 0.07     |
|                                                     | <b>OR</b> | <b>95% CI</b>  | <b>P</b> | <b>OR</b> | <b>95% CI</b>  | <b>P</b> |
| <b>Any splenectomy after HL diagnosis:</b>          |           |                | 0.02     |           |                | 0.027    |
| No                                                  | 1         | -              |          | 1         | -              |          |
| Yes                                                 | 2.2       | 1.1 to 4.3     |          | 2.2       | 1.1 to 4.3     |          |
| <b>Vincristine:</b>                                 |           |                | 0.12     |           |                | -        |
| No                                                  | 1         | -              |          | -         | -              |          |
| Yes                                                 | 0.6       | 0.3 to 1.2     |          | -         | -              |          |
| <b>Procarbazine:</b>                                |           |                | -        |           |                | 0.28     |
| No                                                  | -         | -              |          | 1         | -              |          |
| Yes                                                 | -         | -              |          | 0.7       | 0.3 to 1.4     |          |
| <b>Anthracyclines:</b>                              |           |                | >0.5     |           |                |          |
| No                                                  | 1         | -              |          | 1         | -              | >0.5     |
| Yes                                                 | 1.4       | 0.5 to 4.5     |          | 1.4       | 0.4 to 4.3     |          |
|                                                     |           |                |          |           |                |          |
| <b>Dose (EQD2) to affected valve (categorical):</b> |           |                | 0.02     |           |                | 0.01     |
| No RT                                               | 1         | 0.2 to 5.0     |          | 1         | 0.2 to 4.9     |          |
| ≤30 Gy                                              | 1.0       | 0.4 to 2.8     |          | 1.1       | 0.4 to 3.1     |          |
| 31-35 Gy                                            | 2.0       | 1.1 to 3.6     |          | 2.3       | 1.3 to 4.2     |          |
| 36-40 Gy                                            | 3.3       | 2.3 to 4.6     |          | 3.8       | 2.7 to 5.4     |          |
| >40 Gy                                              | 6.6       | 2.7 to 16.1    |          | 7.8       | 3.2 to 18.7    |          |
| Unknown                                             | -         | -              |          | -         | -              |          |
| <b>Any splenectomy after HL diagnosis:</b>          |           |                | 0.02     |           |                | 0.02     |
| No                                                  | 1         | -              |          | 1         | -              |          |
| Yes                                                 | 2.3       | 1.1 to 4.6     |          | 2.2       | 1.1 to 4.5     |          |
| <b>Vincristine:</b>                                 |           |                | 0.15     |           |                | -        |
| No                                                  | 1         | -              |          | -         | -              |          |
| Yes                                                 | 0.6       | 0.3 to 1.2     |          | -         | -              |          |
| <b>Procarbazine:</b>                                |           |                | -        |           |                | 0.36     |
| No                                                  | -         | -              |          | 1         | -              |          |
| Yes                                                 | -         | -              |          | 0.7       | 0.4 to 1.4     |          |
| <b>Anthracyclines:</b>                              |           |                | 0.38     |           |                | 0.42     |
| No                                                  | 1         | -              |          | 1         | -              |          |
| Yes                                                 | 1.7       | 0.5 to 5.4     |          | 1.6       | 0.5 to 5.1     |          |

**Table C.2** (continued) - Adjusted (G and H) logistic regression models of OR for VHD by radiation dose to affected valve, both per Gy (top) and by dose category (bottom). \*Linear model.

\*\*Linear model with curvature.

|                                             | Cases | Controls | Total |
|---------------------------------------------|-------|----------|-------|
| <b>All</b>                                  | 89    | 200      | 289   |
| <b>No second cancer</b>                     | 50    | 126      | 176   |
| <b>No second cancer before cut-off date</b> | 77    | 167      | 244   |
| <b>Second cancer before cut-off date</b>    | 12    | 33       | 45    |
| Treated with RT?                            |       |          |       |
| - Yes                                       | 2     | 1        | 3*    |
| - No                                        | 8     | 27       | 35    |
| - Unknown                                   | 2     | 5        | 7     |
| Treated with CT?                            |       |          |       |
| - Yes                                       | 2     | 16       | 18    |
| - Yes (regimen known)                       | 2***  | 10**     | 12    |
| - No                                        | 9     | 13       | 22    |
| - Unknown                                   | 1     | 4        | 5     |

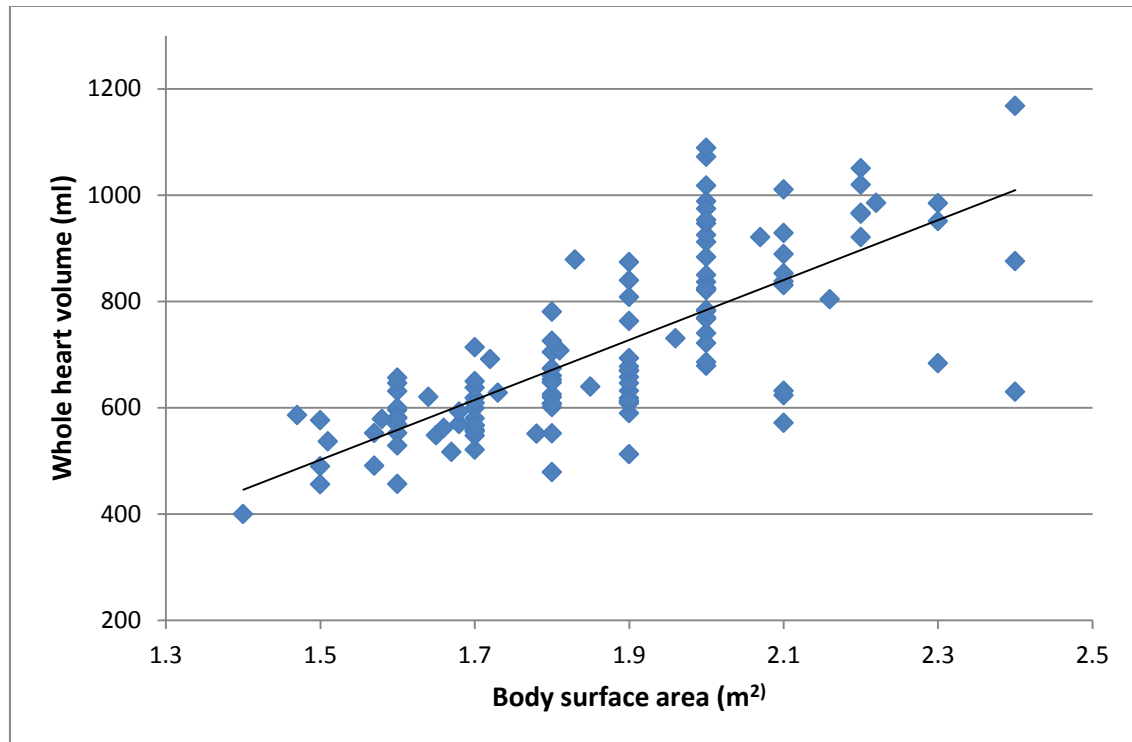
**Table C.3** – Cases and controls treated for a second cancer. \*3 patients known to have received RT for second cancer: 2 received RT with electrons for breast cancer; 1 received neck and mediastinal RT (20 Gy) for inoperable oesophageal cancer (diagnosed 28 days before cut-off); \*\*2xAC, 1xCHAP-6, 1xCHOP/DHAP-VIM-DHAP, 6xCMF; \*\*\*1xCHOP, 1xECC

|                                            | Cases | Controls | Total |
|--------------------------------------------|-------|----------|-------|
| <b>All</b>                                 | 89    | 200      | 289   |
| <b>No third cancer</b>                     | 83    | 181      | 264   |
| <b>No third cancer before cut-off date</b> | 87    | 193      | 280   |
| <b>Third cancer before cut-off date</b>    | 2     | 7        | 9*    |
| Treated with RT?                           |       |          |       |
| - Yes                                      | -     | -        | -     |
| - No                                       | 2     | 4        | 6     |
| - Unknown                                  | -     | 3        | 3     |
| Treated with CT?                           |       |          |       |
| - Yes                                      | -     | 2        | -     |
| - Yes (regimen known)                      | -     | 2**      | -     |
| - No                                       | 2     | 4        | 6     |
| - Unknown                                  | -     | 1        | 1     |

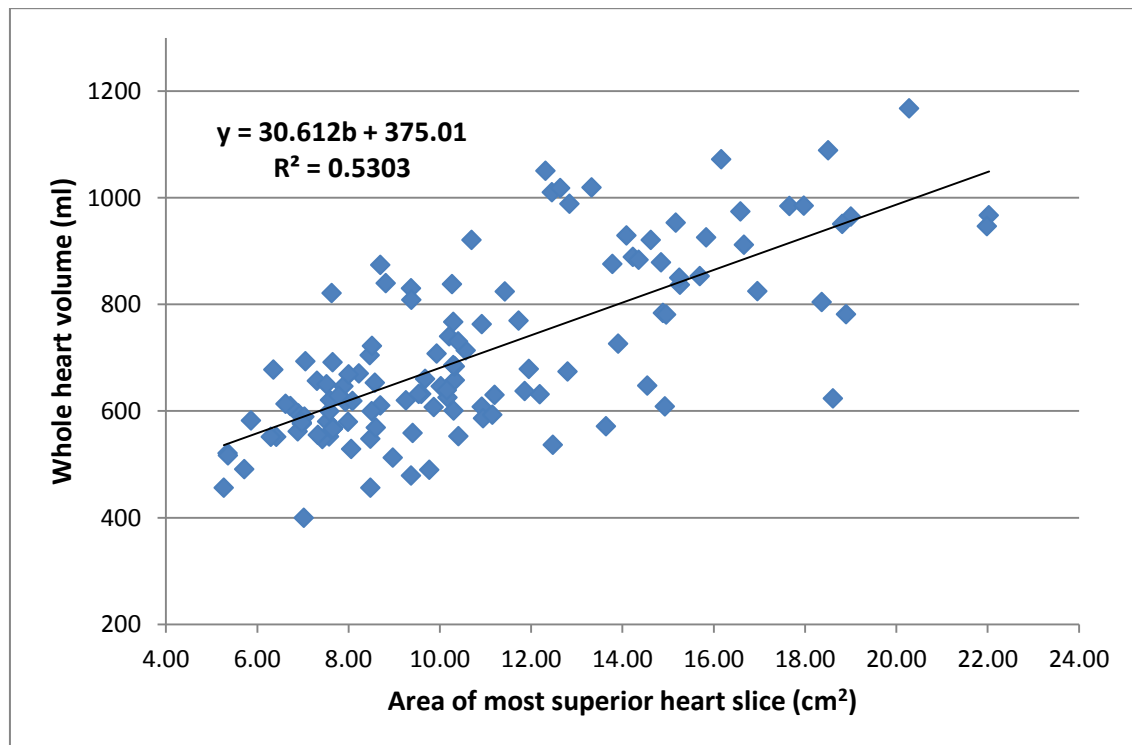
**Table C.4** – Cases and controls treated for a third cancer. \*None known to have received RT for third cancer; \*\*1xCP, 1xARA-C

## **Appendix D – Cardiovascular Dosimetry and Expected Cardiac Mortality in the RAPID Trial**

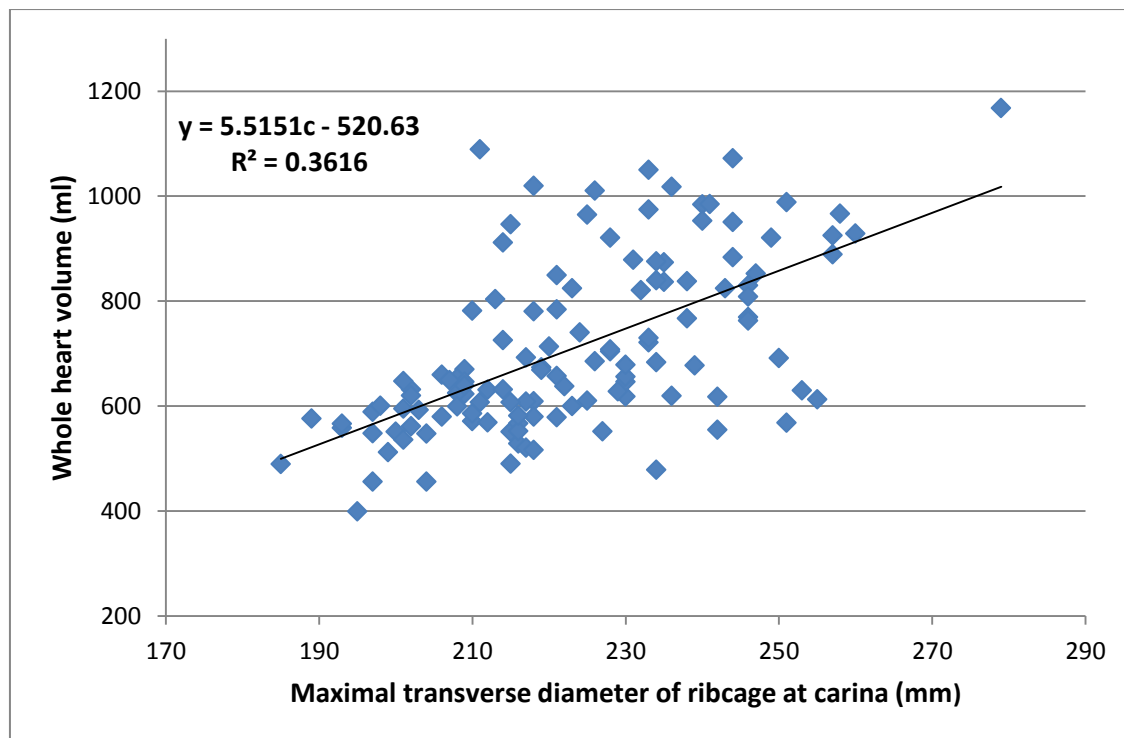
### **Appendix D.1 - A regression model to predict whole Heart volume**



**Figure D.1 – Scatter plot of body surface area (a) vs. whole heart volume**



**Figure D.2 – Scatter plot of the area of the most superior heart slice (b) vs. whole heart volume**



**Figure D.3** – Scatter plot of the maximal transverse diameter of the ribcage at the carina (c) vs. whole heart volume

Multiple linear regression model:

Co-efficient for explanatory variables (95% CI) =

Body surface area (a) = 238.1 (130.7 to 345.5)

Area of most superior heart slice (b) = 18.3 (13.0 to 23.5)

Maximal transverse diameter of ribcage at level of carina (c) = 2.5 (1.4 to 3.6)

Constant (95% CI) = -496.7 (-701.2 to -292.3)

Whole heart volume =  $238.1a + 18.3b + 2.5c - 496.7$

Adjusted  $R^2 = 0.72$

Calculated using STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station)



## Appendix D.2 - Linear correlations between mean radiation doses to cardiac structures

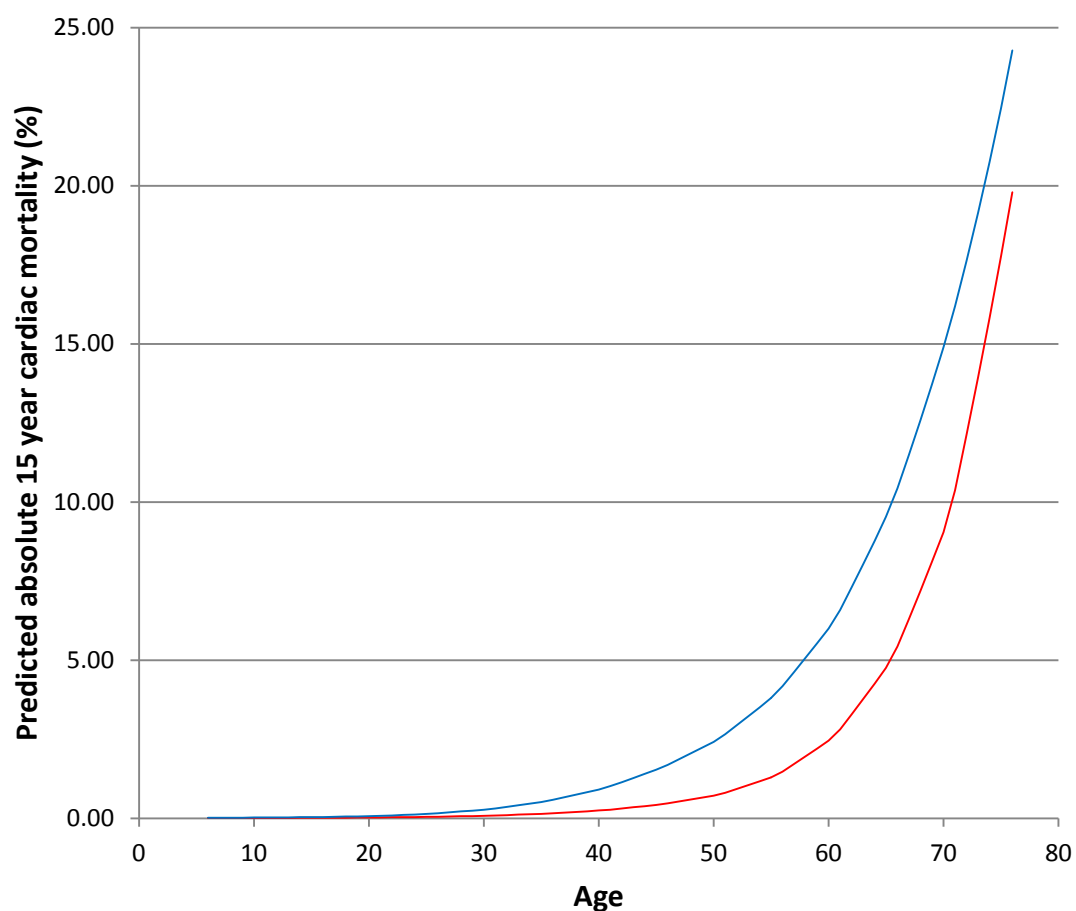
|                  | WH   | LCA  | RCA  | CCA  | MV   | TV   | AV   | PV   | LV   | RV   | LA   | RA   | SAN  | AVN  |
|------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| WH               | -    | 0.89 | 0.94 | 0.93 | 0.93 | 0.88 | 0.92 | 0.83 | 0.91 | 0.93 | 0.96 | 0.95 | 0.85 | 0.93 |
| LCA              | 0.89 | -    | 0.71 | 0.94 | 0.84 | 0.61 | 0.88 | 0.89 | 0.83 | 0.72 | 0.91 | 0.74 | 0.84 | 0.74 |
| RCA              | 0.94 | 0.71 | -    | 0.79 | 0.85 | 0.93 | 0.84 | 0.68 | 0.79 | 0.94 | 0.87 | 0.98 | 0.76 | 0.91 |
| CCA              | 0.93 | 0.94 | 0.79 | -    | 0.93 | 0.70 | 0.89 | 0.87 | 0.84 | 0.78 | 0.95 | 0.83 | 0.83 | 0.83 |
| MV               | 0.93 | 0.84 | 0.85 | 0.93 | -    | 0.80 | 0.84 | 0.72 | 0.89 | 0.86 | 0.90 | 0.88 | 0.72 | 0.94 |
| TV               | 0.88 | 0.61 | 0.93 | 0.70 | 0.80 | -    | 0.68 | 0.54 | 0.83 | 0.96 | 0.74 | 0.90 | 0.57 | 0.91 |
| AV               | 0.92 | 0.88 | 0.84 | 0.89 | 0.84 | 0.68 | -    | 0.88 | 0.75 | 0.77 | 0.97 | 0.87 | 0.93 | 0.79 |
| PV               | 0.83 | 0.89 | 0.68 | 0.87 | 0.72 | 0.54 | 0.88 | -    | 0.65 | 0.63 | 0.91 | 0.72 | 0.93 | 0.65 |
| LV               | 0.91 | 0.83 | 0.79 | 0.84 | 0.89 | 0.83 | 0.75 | 0.65 | -    | 0.89 | 0.80 | 0.81 | 0.64 | 0.88 |
| RV               | 0.93 | 0.72 | 0.94 | 0.78 | 0.86 | 0.96 | 0.77 | 0.63 | 0.89 | -    | 0.82 | 0.91 | 0.66 | 0.93 |
| LA               | 0.96 | 0.91 | 0.87 | 0.95 | 0.90 | 0.74 | 0.97 | 0.91 | 0.80 | 0.82 | -    | 0.90 | 0.92 | 0.85 |
| RA               | 0.95 | 0.74 | 0.98 | 0.83 | 0.88 | 0.90 | 0.87 | 0.72 | 0.81 | 0.91 | 0.90 | -    | 0.80 | 0.92 |
| SAN              | 0.85 | 0.84 | 0.76 | 0.83 | 0.72 | 0.57 | 0.93 | 0.93 | 0.64 | 0.66 | 0.92 | 0.80 | -    | 0.67 |
| AVN              | 0.93 | 0.74 | 0.91 | 0.83 | 0.94 | 0.91 | 0.79 | 0.65 | 0.88 | 0.93 | 0.85 | 0.93 | 0.67 | -    |
| R <sup>2</sup> * | -    | 0.78 | 0.88 | 0.86 | 0.87 | 0.77 | 0.84 | 0.68 | 0.83 | 0.87 | 0.92 | 0.91 | 0.72 | 0.87 |

**Table D.1** – Linear correlation coefficients between mean doses to the whole heart and cardiac substructures. \*R<sup>2</sup> values are between the whole heart and the cardiac structures

| Abbreviation | Structure                  | Regression co-efficient (a) |
|--------------|----------------------------|-----------------------------|
| LCA          | Left coronary artery       | 1.32                        |
| RCA          | Right coronary artery      | 0.87                        |
| CCA          | Circumflex coronary artery | 1.88                        |
| MV           | Mitral valve               | 1.39                        |
| TV           | Tricuspid valve            | 1.03                        |
| AV           | Aortic valve               | 2.46                        |
| PV           | Pulmonary valve            | 3.69                        |
| LV           | Left ventricle             | 0.40                        |
| RV           | Right ventricle            | 0.55                        |
| LA           | Left atrium                | 1.85                        |
| RA           | Right atrium               | 1.32                        |
| SAN          | Sino-atrial node           | 2.26                        |
| AVN          | Atrio-ventricular node     | 1.36                        |

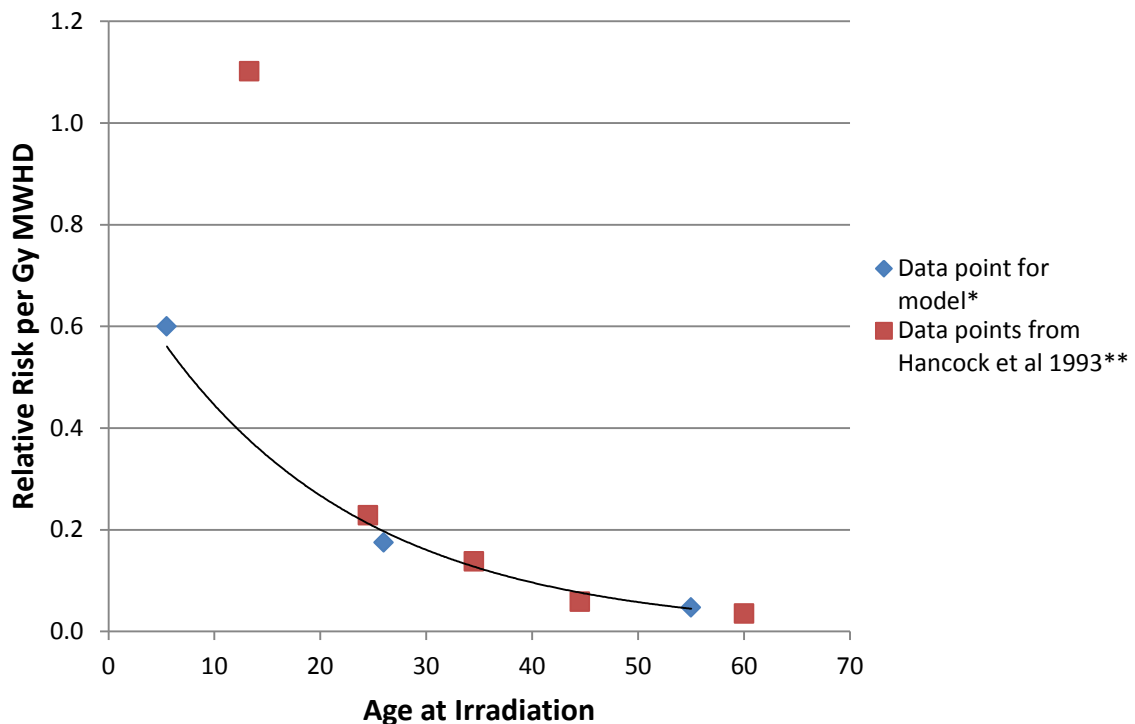
**Table D.2** – The abbreviations for individual structures and the regression co-efficient (a) to estimate the mean dose to a structure from the mean whole heart dose (MWHD), i.e. mean dose of structure = a(MWHD)

### Appendix D.3 - Variation of expected 15-year cardiac mortality with gender and age



**Figure D.4** – An Illustration of how expected 15-year cardiac mortality (calculated from national mortality statistics) varies with gender (blue = male, red = female) and age

#### Appendix D.4 - Data used for the ERR per Gy MWHHD model to predict 15 year cardiac NTCP



**Figure D.5** – Illustration of how the RR per Gy MWHHD varies by age at irradiation, including both the studies used to create the model\* and data from another large study of cardiac risk following RT for HL for comparison\*\*. The trend line represents an exponential regression equation fitted to the 3 data points. The RR per Gy MWHHD for a defined age at irradiation (x) is given by  $0.7418e^{-0.051x}$  ( $R^2=0.99$  for these three points).

\*Data points used from the following studies:

- Tukenova M, Guibout C, Oberlin O, et al: Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol 28:1308-15, 2010
- Aleman BM, van den Belt-Dusbout AW, Klokman WJ, et al: Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol 21:3431-9, 2003
- Darby SC, Taylor C: Long term toxicity of radiation therapy. 2006 update of the Early Breast Cancer Trialists' Collaborative Group overview of radiation therapy for early breast cancer, American Society of Clinical Oncology Annual Meeting. Chicago 2007

\*\*Data taken from:

- Hancock SL, Tucker MA, Hoppe RT: Factors affecting late mortality from heart disease after treatment for Hodgkin's disease. JAMA 270:1949-55, 1993

| Age at Irradiation (Yrs) | Mediastinal Dose (Gy) | Estimated Mean Heart Dose (Gy) | RR of Cardiac Death (O/E) | RR per Gy MHD |
|--------------------------|-----------------------|--------------------------------|---------------------------|---------------|
| 13.3                     | 35.4                  | 26.6                           | 30.3 (10/0.33)            | 1.10          |
| 24.5                     | 40.5                  | 30.4                           | 7.9 (15/1.89)             | 0.23          |
| 34.5                     | 38.8                  | 29.1                           | 5.0 (21/4.2)              | 0.14          |
| 44.5                     | 36.7                  | 27.5                           | 2.6 (12/4.6)              | 0.06          |
| 60.0                     | 28.7                  | 21.5                           | 1.8 (20/11.4)             | 0.04          |

**Table D.3** – The data used from Hancock *et al.* JAMA 1993

## **Appendix E – Cardiovascular Magnetic Resonance**

### **Imaging Protocol and Image Analysis**

Wording and images adapted with kind permission from Dr. Vanessa Ferreira (VF).

#### **Anatomical and functional imaging**

Cardiac volumes are acquired using a Siemens 1.5 Tesla Avanto MR system (Erlangen, Germany) using Steady State Free Precession (SSFP), retrospectively-gated imaging. Scan parameters are typically: voxel size = 2.0x2.0x8.0mm, FOV = 380x380mm, TR/TE = 39.6/1.12ms, flip angle = 55°, matrix = 192x192, generalised autocalibrating partially parallel acquisition (GRAPPA) = 3, 24 reference lines, segments = 15, concatenations = 1. Pilot, horizontal long axis, vertical long axis and short axis stack images are acquired with the patient in the supine position. The slices are obtained during a breath-hold at the end of normal expiration to minimize the effects of respiratory motion.

Using Argus post-processing software package software (version VA60C, Siemens AG, Siemens Medical Solutions, Erlangen, Germany), left ventricular (LV) short axis epicardial and endocardial borders are manually contoured at end diastole and end systole. LV end systolic (ESV) and end diastolic (EDV) volumes are used to calculate stroke volume (SV). Ejection fraction (EF) and cardiac output (CO) are calculated ( $EF = SV/EDV$ ,  $CO = SV \times HR$ ). Myocardial mass is also calculated by subtracting the endocardial volume from the epicardial volume. LV mass is calculated based on prior knowledge of myocardial specific gravity (1.05 g/cm<sup>3</sup>). Qualitative assessment of regional wall motion was undertaken by an experienced CMR cardiologist (VF) with more than 4 years of expertise in performing and analysing both clinical and research CMR scans.

#### **Oedema (T2-STIR) imaging**

T2-weighted turbo spin echo (TSE) images are acquired using an ECG-triggered Short-Tau Inversion Recovery (STIR) sequence with fat and moving blood suppression<sup>1,2</sup> in the short axis view at 1 cm intervals through the left ventricle using a body coil. Scan parameters are typically: voxel size = 1.9x1.5x10.0mm, FOV = 380x309mm, matrix = 166x256, TE = 61ms, TR = 80-85% of RR interval during breath-hold, flip angle = 180°, TI = 170ms, dark blood thickness 200%, dark blood flip angle = 180°, turbo factor = 25, echo trains per slice = 7, phases = 1, concatenations = 1.

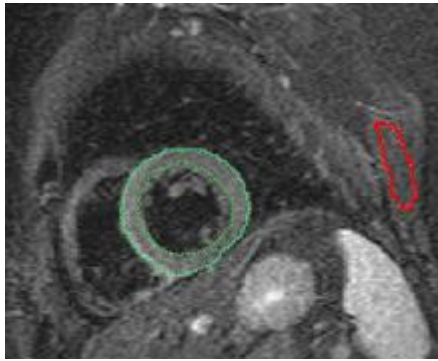
As previously described,<sup>2</sup> the short axis T2-weighted TSE image through the base of the left ventricle is reviewed for the presence of an adequate cross-section through skeletal muscle for later placement of a reference region of interest (ROI). If a satisfactory reference ROI is not available, the initial T2 TSE image is used to revise the graphic prescription by shifting the field of view more off-centre towards the left shoulder to include a suitable sample of chest wall/left shoulder/left upper arm skeletal muscle, adjusting the size of the field of view as necessary.

Offline post-processing involves manual tracing of LV endo- and epi-cardial contours using dedicated in-house software (MC-ROI). Care was taken to exclude non-suppressed blood pool signal due to slow-flow adjacent to the sub-endocardium and to avoid using areas with abnormally low signal for normalization.

Semi-quantitative analysis by normalizing the signal intensity of the myocardium to that of skeletal muscle allows detection of a global T2 signal abnormality:

$$\text{T2 ratio} = \text{Signal intensity}_{\text{myocardium}} / \text{Signal intensity}_{\text{skeletal muscle}}$$

Areas of myocardial oedema were defined as any contiguous area of at least 40 mm<sup>2</sup> (or 10 adjacent pixels) with a T2 SI ratio of  $\geq 2.0$ , as previously published.<sup>3</sup>

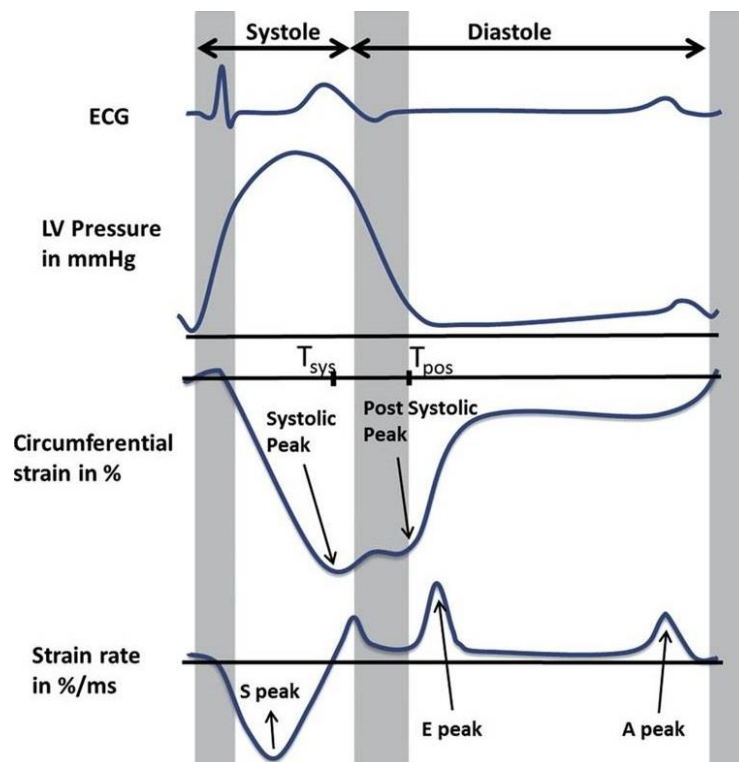


**Figure E.1** – Dark-blood T2-weighted MRI image with myocardial contours (green contours) and a reference region of interest (ROI) over skeletal muscle (red contour).

#### Myocardial strain (Tagged CMR) imaging

Tagged cine MRIs are acquired with an ECG-triggered segmented k-space gradient echo sequence with spatial modulation of magnetization in orthogonal planes. Tag imaging is performed before administration of gadolinium. Multiple short axis (basal, mid-ventricular and apical) and two long axis (horizontal and vertical) scans were obtained. The scan parameters were typically: voxel size = 2.1 x 1.4 x 8.0 mm, FOV = 360x292mm, matrix = 141x256, TR/TE = 40.45/3.89ms, flip angle = 14°, segments = 9, phases = 16, concatenations = 1, grid tag distance = 7mm, bandwidth = 184 Hz/Px.

Post-processing analysis was performed using the Cardiac Image Modeller software (CIM Tag2D v.7, Auckland MRI Research Group, New Zealand) by aligning a grid to the myocardial tagging planes at end diastole, indicating the LV/RV insertion points. End systole is determined visually, and the tags adjusted at each frame through the cardiac cycle. From the short-axis stack, peak systolic 2D peak circumferential strain and strain rate were derived. Figure E.2 indicates these points within the cardiac cycle. Tagging analysis was for each subject at all 4 time points in a single session to prevent learner bias and to ensure consistent selection of comparable slices within the same subject for time-point comparisons.



**Figure E.2** – A figure illustrating the cardiac cycle. More negative strain values indicate greater circumferential fractional shortening. Peak systolic circumferential strain is measured at the systolic peak and peak systolic strain rate is measured at 'S peak'. Adapted from Ambale-Venkatesh *et al.*<sup>4</sup>

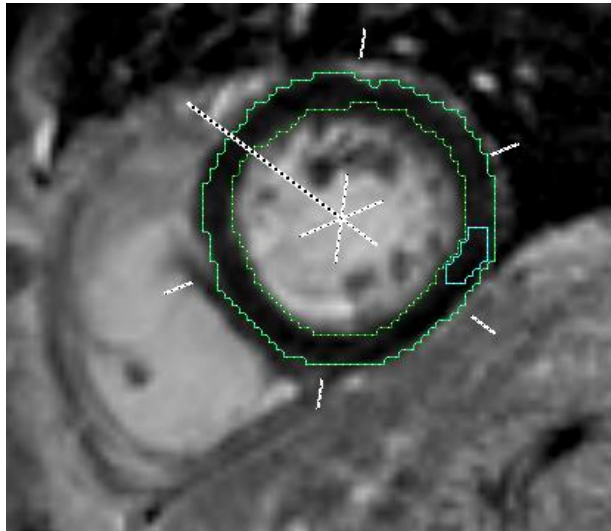
#### Perfusion imaging (stress and rest)

Perfusion imaging was performed every cardiac cycle during the first pass using a T1-weighted fast (spoiled) gradient echo sequence. Three short axis cine images (base, mid-ventricular and apical) are chosen from the short axis stack, taking care to avoid the LV outflow in systole. Scan parameters are typically: voxel size = 2.8 x 2.3 x 10.0 mm, FOV = 360x270mm, matrix = 96x160, TR/TE = 160.76/1.05 ms, flip angle = 12°, TI = 100ms, GRAPPA = 2, 18 reference lines, measurements = 50, segments = 57, concatenations = 1, phases = 1, 1 shot per slice, bandwidth 651 Hz/Px. Where stress perfusion is required, adenosine (3mg/ml) is infused through a large bore cannula in the ante-cubital fossa at 140µg/kg/min. Images are acquired at peak stress typically around 1-2 minutes after commencement of adenosine. A satisfactory response was achieved if the heart rate increased by 10 bpm or 20% over the resting heart rate. Heart rate and blood pressure are measured before, at one minute intervals during, and after adenosine stress. To assess regional perfusion, a bolus of intravenous MR contrast agent (0.03 mmol/kg body weight of Gd-DTPA) is given at the end of the adenosine infusion, and stress first pass perfusion is measured as previously described.<sup>5,6</sup> Rest perfusion is imaging performed using the same imaging sequence 20 minutes later without adenosine and another dose of contrast (0.03 mmol/kg body weight) is given. Qualitative assessment for stress and rest perfusion defects was performed by an experienced CMR cardiologist (VF).

#### Late gadolinium enhancement (LGE) imaging

Delayed enhancement imaging is acquired using a T1-weighted phase-sensitive inversion recovery<sup>7</sup> sequence 8-15 minutes after the administration of top-up intravenous contrast agent

and provides quantification of fibrotic tissue. The inversion time was adjusted for optimal nulling of remote normal myocardium. The scan parameters are typically: voxel size = 2.0 x 1.5 x 8.0 mm, matrix = 144x256, FOV = 380x285mm, TR/TE = 800.20/3.36ms, flip angle = 25°, GRAPPA = 2, 24 reference lines, segments = 25, phases = 1, concatenations = 1, measurements = 1, bandwidth = 130Hz/Px. LGE images were evaluated qualitatively by an experienced CMR cardiologist (VF) for the presence or absence, pattern (subendocardial, midwall, subepicardial, transmural) and regional distribution of LGE areas.



**Figure E.3** - Late gadolinium enhancement (LGE) image with myocardial contours (green contour) and a reference region of interest over remote myocardium (blue contour)

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## **Appendix F – Authored Published Papers Cited Within the Thesis**

|                                                                                            |               |
|--------------------------------------------------------------------------------------------|---------------|
| Radiation-Related Heart Disease: Current Knowledge and Future Prospects <sup>1</sup> ..... | pages 246-255 |
| Risks of Heart Disease after Radiotherapy <sup>2</sup> .....                               | pages 256-257 |
| EBCTCG: Radiotherapy after Breast-Conserving Surgery <sup>3</sup> .....                    | pages 258-267 |
| Risk of IHD in Women after Radiotherapy for Breast Cancer <sup>4</sup> .....               | pages 268-279 |

## **References**

1. Darby SC, Cutter DJ, Boerma M, et al. Radiation-related heart disease: current knowledge and future prospects. *Int J Radiat Oncol Biol Phys*. Mar 1 2010;76(3):656-665.
2. Cutter DJ, Darby SC, Yusuf SW. Risks of heart disease after radiotherapy. *Tex Heart Inst J*. 2011;38(3):257-258.
3. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. Nov 12 2011;378(9804):1707-1716.
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## CRITICAL REVIEW

# RADIATION-RELATED HEART DISEASE: CURRENT KNOWLEDGE AND FUTURE PROSPECTS

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## INTRODUCTION

It has been recognized since the 1960s that the heart may be damaged by substantial doses of radiation [ $>30$  Gray (Gy)], such as used to occur during mantle radiotherapy for Hodgkin lymphoma. During the last few years, however, evidence that radiation-related heart disease (RRHD) can occur following doses below 20 Gy has emerged from several independent sources. Those sources include studies of breast cancer patients who received mean cardiac doses of 3 to 17 Gy when given radiotherapy following surgery and studies of survivors of the atomic bombings of Japan who received doses of up to 4 Gy.

At doses above 30 Gy, an increased risk of RRHD can become apparent within a year or two of exposure, and the risk increases with higher radiotherapy dose, younger age at irradiation, and the presence of conventional risk factors. At lower doses, the typical latency period is much longer and is often more than a decade. The nature and magnitude of the risk following lower doses is not well characterized, and it is not yet clear whether there is a threshold dose below which there is no risk.

The evidence regarding RRHD comes from several different disciplines. The present review brings together information from pathology, radiobiology, cardiology, radiation oncology, and epidemiology; it summarizes current knowledge, identifies gaps in that knowledge, and outlines some potential strategies for filling them.

## CURRENT KNOWLEDGE

### Pathology

The pathological expressions of RRHD documented following therapeutic irradiation can be broadly reduced to four conditions: pericarditis, pericardial fibrosis, diffuse myocardial fibrosis, and coronary artery disease (CAD) (1, 2). Radiation may also cause valvular disease, although the evidence for this is not as strong. None of these conditions is specific to radiation.

Radiation-related pericarditis is characterized by an exudate of a variable amount of protein-rich fluid within the pericardial sac (pericardial effusion). Rapid accumulation of this fluid can, in rare cases, cause potentially fatal cardiac tamponade. Almost invariably, fibrin accumulates on the

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Conflict of interest: none.

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whose insights contributed greatly to the ideas presented in this paper. The paper has been submitted for publication with permission from the National Academy, but the Academy has not been involved in its preparation, and the views expressed do not necessarily represent the views of the Academy or any of its constituent units. The authors also thank colleagues in the Clinical Trial Service Unit for helpful comments on an earlier draft of the paper.

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mesothelial lining of the epicardium or the parietal pericardium.

Pericardial fibrosis consists of collagen deposition, usually in the parietal pericardium, replacing the peripheral adipose layer and increasing the thickness of the fibrous layer (normally, < 0.5 mm) to as much as 8 mm. This results in a rigid pericardial sac (Fig. 1) that may produce constriction and is often accompanied by effusion. Fibrin also accumulates interstitially in the thickened pericardium (1).

As the name implies, diffuse myocardial fibrosis consists of diffuse proliferation of bands of collagen separating and/or replacing myocytes (Fig. 2). It occurs in patches, often in the anterior wall of the left ventricle. Experimental studies have demonstrated that this condition results from damage to the endothelium of the myocardial blood capillaries and can lead to ischemia and ultimately fibrosis (3). If it is extensive, myocardial fibrosis may lead to congestive heart failure.

The morphology of radiation-related CAD is essentially the same as CAD resulting from atherosclerosis from other causes: intimal proliferation of myofibroblasts, with lipid-containing macrophages forming plaques that may fissure causing thrombosis (4). This reduces the arterial lumen to various degrees (Fig. 3), resulting in the clinical manifestations of ischemic heart disease: stable angina pectoris, unstable angina, myocardial infarction (MI), and chronic ischemic heart disease. Endovascular irradiation (used until recently to prevent coronary arterial restenosis postangioplasty) often causes fibrosis of the adventitia in swine and probably also in humans. However, that feature is often absent in CAD resulting from external irradiation. Valvular lesions character-

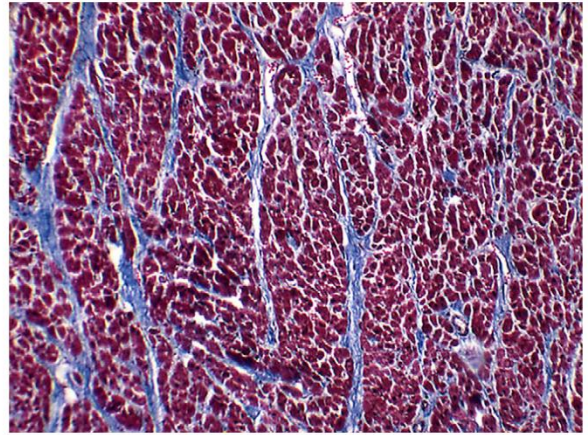


Fig. 2. Fatal diffuse myocardial fibrosis several years after irradiation for Hodgkin's disease. Whereas normally there should be very little collagen among the dark red myocytes, this heart muscle is criss-crossed by multiple bands of blue collagen. Gomori trichrome stain.

ized by fibrosis and calcification have been described in irradiated patients (5).

#### Experimental models

Pericardial, myocardial, and coronary artery lesions can all be reproduced by irradiating appropriate animal models (1-3), but direct experimental proof regarding radiation-induced valvular disease is lacking at present. Experimental models commonly used to study RRHD include rat, rabbit, and

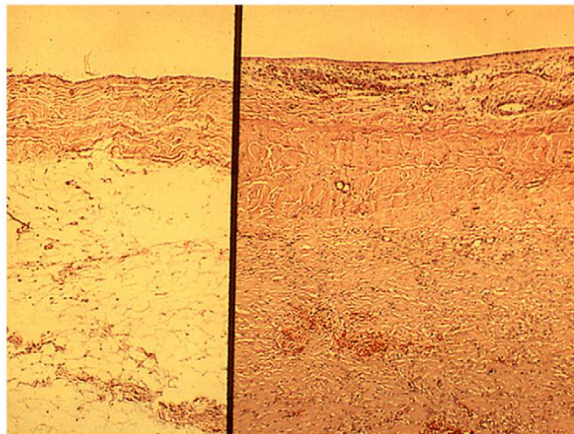


Fig. 1. Perpendicular sections of human pericardium. The left panel illustrates the normal parietal pericardium with a thin, uniform fibrous layer that faces the heart (upper section) and an outer layer of adipose tissue (lower section). The right panel is a typical example of irradiated pericardium at 17 months after receiving 67 Gy. The adipose tissue has been replaced by dense fibrous tissue that actually extends well below the limits of this micrograph. Hematoxylin-eosin stain. (From Fajardo LF. The pathology of ionizing radiation as defined by morphologic patterns. Keynote lecture, 5th Nordic Conference on Radiation Oncology, Bergen, Norway. *Acta Oncologica* 2005;44:13-22, with permission.)

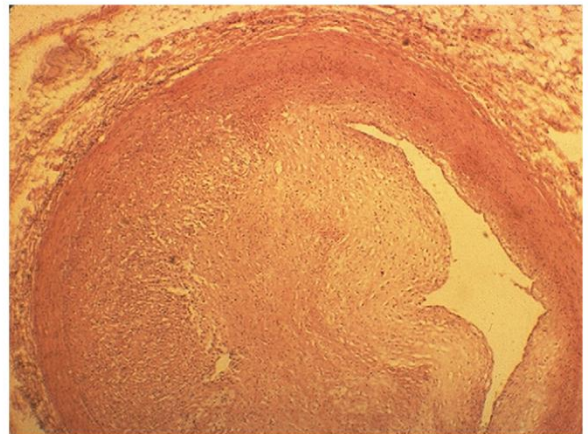


Fig. 3. Left anterior descending coronary artery in a 16-year-old boy 1 year after receiving 40 Gy mantle radiotherapy for Hodgkin's disease. Myointimal proliferation has considerably narrowed the lumen. Fatal cases like this in a patient who had no cardiac risk factors other than radiation illustrate that the morphology of arterial disease due to radiation is essentially no different from that of age-related atherosclerosis. Hematoxylin-eosin stain. (From Fajardo LF. The pathology of ionizing radiation as defined by morphologic patterns. Keynote lecture, 5th Nordic Conference on Radiation Oncology, Bergen, Norway. *Acta Oncologica* 2005;44:13-22; with permission.)



dog. Myocardial fibrosis and loss of cardiac function develop several months after irradiation in all three species, although interstrain and interspecies differences in expression (3, 6, 7) mean that caution is required in extrapolating to humans. Nevertheless, these animal models have provided insight into possible mechanisms of RRHD.

Evidence from rodent models suggests that radiation can cause both microvascular and macrovascular cardiac pathology. The microvascular pathology is characterized by a decrease in capillary density, causing chronic myocardial ischemia and fibrosis. Macrovascular disease occurs through an accelerated development of age-related atherosclerosis.

Experiments investigating the effects of high-precision X-ray irradiation of the whole heart in rats demonstrate that observable congestive heart failure develops in 100% of irradiated animals within their normal lifespan following single doses of >15 Gy (2, 8). At 10 Gy, reduced capillary density has also been observed, but damage progression was slow, and latency to clinical symptoms exceeded the normal life span of rats. Analysis of the effect of varying dose fractionations on median latency to heart failure in experiments with up to 10 fractions yields alpha/beta ratios of <4 Gy (9). The low ratio suggests that the myocardium behaves as a classical late-reacting tissue.

Studies of radiation-induced microvascular pathology in rats demonstrate focal loss of alkaline phosphatase activity within a few weeks of heart irradiation. Loss of capillaries, preceded by increased endothelial proliferation, occurs in enzyme-negative areas only (10). Those foci start small and gradually increase in size, with a progressive decrease in local capillary density. Histopathology at the time of heart failure demonstrates foci of ischemic necrosis and reparative fibrosis unrelated to the distribution of major blood vessels. Myocytes are terminally differentiated cells and are therefore relatively resistant to the direct cytotoxic effects of irradiation. Experimental evidence suggests that radiation-induced heart failure is an effect of indirect myocyte toxicity secondary to microvascular damage and ischemia. This is in contrast to anthracycline-induced heart failure, where anthracyclines are known to be directly toxic to myocytes.

The pathogenesis of radiation-related atherosclerosis in large arteries has been studied in ApoE<sup>-/-</sup> mice. These rodents spontaneously develop atherosclerotic plaques within 6 to 12 months, but radiation of vessels speeds this process due to local effects on the vascular endothelium. The phenotype of the plaques is also altered by doses of  $\geq 14$  Gy, with an increased frequency of intraplaque hemorrhage and inflammatory cells, so that they are more vulnerable to rupture, causing thrombosis (11).

Based on these experimental findings, it is reasonable to formulate two hypotheses for the biological mechanisms that lead to increased morbidity and mortality from coronary artery disease after radiation exposure in humans. The first hypothesis is that radiation increases the frequency of MI by interacting with the pathological pathway of age-related coronary artery atherosclerosis, resulting in accelerated atherosclerosis in which disease is seen at a younger age than

would normally occur. The second hypothesis is that radiation increases the lethality of age-related MI by reducing the heart's tolerance to acute infarctions as a result of microvascular damage to the myocardium. As shown in Fig. 4, these hypotheses are not mutually exclusive, and the two mechanisms may act together to produce clinical heart disease.

Animal models have also been used to test potential intervention strategies both before and after local heart irradiation. Those strategies include use of methylprednisolone or ibuprofen (12), captopril (13), amifostine (14), and a combination of pentoxifylline and alpha-tocopherol (15). All agents showed some potential benefit in preventing morphologic or functional deterioration experimentally, but their clinical usefulness has not yet been demonstrated.

#### Clinical manifestations and management

A wide range of clinical cardiovascular problems can arise from radiation therapy (RT) for thoracic malignancy. Radiation-related pericardial and myocardial diseases are less common today than in the past, due to modifications in RT techniques, particularly for lymphomas (16), resulting in lower radiation doses to the heart. The predominant clinical manifestation of RRHD today is probably CAD, but the frequency with which it occurs is unknown, as it does not differ clinically from CAD from other causes, and many radiation-related cases may not be recognized as such.

Acute pericarditis is still occasionally seen within weeks after cardiac irradiation. Patients present with pleuritic chest pain, fever, tachycardia, a pericardial rub, and characteristic electrocardiographic abnormalities. Those signs and symptoms usually resolve quickly and without consequence with nonsteroidal anti-inflammatory drug therapy. A proportion of patients, however, develop chronic pericarditis up to 10 years later. The incidence of disease is related to the volume of pericardium irradiated, the dose received, and possibly the presence of effusion during the acute phase. The severity is variable, ranging from asymptomatic pericardial thickening found incidentally to cardiac tamponade requiring urgent pericardiocentesis. For those patients with recurrent effusion,

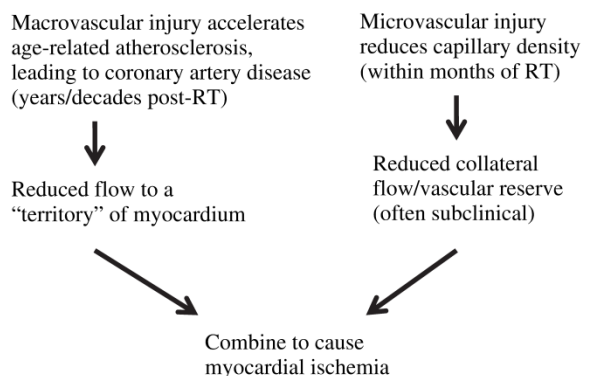


Fig. 4. An outline of how microvascular and macrovascular radiation-related cardiac injury could theoretically combine to cause myocardial ischemia after RT.

some authorities recommend subtotal pericardiectomy to prevent the development of severe constrictive pericarditis, which can be difficult to treat effectively at a later stage (17).

Radiation-related myocardial fibrosis is often asymptomatic and is picked up only incidentally on echocardiography more than 10 years after radiation therapy (18). Clinically significant ventricular dysfunction is uncommon but can occur, particularly in the context of anthracycline chemotherapy and high radiation doses (>30 Gy) to large volumes of the heart. The management of radiation-related cardiomyopathy currently follows guidelines for the management of cardiac failure due to other causes.

Radiotherapy has been associated with valvular heart disease, which is common in some series (18). The incidence has been related to mediastinal radiation doses of >30 Gy (19–21) and younger age at irradiation (22–24), with an average latency of >10 years for asymptomatic and longer (median, 22 years) for symptomatic disease (20). Aortic disease usually consists of mixed stenosis and regurgitation and is more common than mitral and right-sided disease.

Conduction system abnormalities have also been reported, often in association with other types of RRHD. A variety of arrhythmias and conduction blocks have been observed, but these are rarely clinically serious. Autonomic nervous system dysfunction with a persistent nonvariable tachycardia has also been described (25).

Thoracic RT is now firmly established as a risk factor for CAD. Radiation-related CAD is usually not detected until at least 10 years after exposure, and the magnitude of the risk with modern RT techniques is not yet well defined. Relative risks increase with higher radiotherapy doses (19, 26), younger age at irradiation (23, 26), and the presence of conventional risk factors for coronary artery disease (20). Radiation-related CAD is managed conventionally, with medical control of risk factors and percutaneous coronary intervention or surgical bypass if indicated. Surgery may be technically challenging due to the presence of mediastinal scarring, friability of the vessels, and a possible increased restenosis rate of irradiated internal mammary vessels when they are chosen for coronary artery bypass grafting (27). Patients most commonly presenting with RRHD are survivors of breast cancer or HL, although RRHD has also been reported after radiotherapy for testicular cancer (28) and peptic ulcer disease (29).

#### *Studies of patients with HL*

In the general population, early changes indicative of atherosclerosis can be seen in young adults, but clinical manifestations, such as angina and MI, rarely present until patients are at least in their 50s. In contrast, young patients without conventional cardiac risk factors who received mediastinal irradiation for HL can present with CAD in their 20s. In such individuals the likely cause is clear, and they may provide an example of the hypothesis of accelerated atherosclerosis referred to above.

In older people, among whom heart disease in the absence of radiotherapy is common, RRHD is harder to identify, and

much of our information about the risk comes from studies in which a large population of HL patients treated with RT have been identified and followed over many years. Information about heart disease is obtained either from patients' medical records or from disease registers or death certificates, and the risk of developing or dying from heart disease in the HL group can then be compared with that of the general population or with another suitable control group.

A recent study of 1,474 5-year survivors treated for HL before age 40 found relative risk (RR) values of 3 to 5 for cardiac morbidity of all types compared with the general population, suggesting that 66 to 80% of all cardiac disease in the HL population was due to therapy (30), while estimates of the RR of death from MI in HL patients compared with the general population are in the range 2 to 9 (31, 32).

Both the radiotherapy techniques and the chemotherapy regimens used to treat HL are evolving with time. Therefore, the impact of cardiac disease in HL survivors requires periodic reevaluation. The modification of radiotherapy techniques has resulted in a reduction in the risk of death from some cardiac causes. For example, among 2,232 HL patients treated at Stanford from 1960 to 1991, the RR for non-MI cardiac death fell from 5.3 to 1.4 when subcarinal blocking was introduced (26). However, the RR for fatal MI was not changed significantly in this series, possibly due to continued RT exposure of the proximal coronary arteries. Patients treated during the 1990s in Canada still had an increased risk of hospitalization for cardiac disease that was more marked in those who received combination therapy with anthracyclines (33), suggesting that an increased risk of late cardiac effects had not yet been eliminated.

The proportional increase in the cardiac death rate is greater in survivors of childhood HL than in adults. In a report from the U.S. Childhood Cancer Survivor Study (22), which included 2,717 5-year survivors of childhood HL, the RR of death from all cardiac causes compared with that of the general population was 11.9 (95% confidence interval [CI], 9.1–15.3), while the RR of death from MI following mediastinal irradiation in childhood has been estimated to be as high as 41.5 (95% CI, 18.1–82.1) with RT doses of  $\geq 42$  Gy (23).

#### *Studies of patients with breast cancer*

In studies of patients with HL, the death rates from heart disease have, in the past, often been so large that comparisons with rates in the general population gave a clear indication of the magnitude of the risk. For breast cancer patients, cardiac doses from RT have been lower and risks smaller. Therefore, the phenomenon of RRHD is less obvious in breast cancer patients than in HL patients. In breast cancer, much of our knowledge of the effect of RT on cardiovascular disease has come from long-term follow-up of women entered into trials in which all women received similar treatment in terms of surgery and drugs, and then half of the women were allocated at random also to receive adjuvant radiotherapy.

One of the first studies to examine the effect of RT on long-term survival in breast cancer was published by Cuzick *et al.* in 1987 (34). This meta-analysis of randomized trials showed



that survival beyond 10 years was significantly worse for those receiving RT. This study was unable to determine the disease responsible for the detrimental effect on survival, but subsequent meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have shown that mortality from heart disease was increased by 27% ( $2p = 0.0001$ ) in women randomized to surgery plus RT compared with women randomized to surgery alone (35). Most of the increase was due to CAD. Aspects of the radiotherapy techniques used in the earlier trials that contributed to the increased cardiac mortality included field placement near the heart (particularly anterior fields used to treat the internal mammary nodes), orthovoltage radiation that delivered high doses to the anterior part of the heart, large daily fractions, and high total doses (36).

Recently, a preliminary analysis of updated EBCTCG data has related mortality from heart disease to estimated cardiac doses in over 30,000 women followed for up to 20 years. There is clear evidence that the radiation-related increase is higher in trials with larger mean cardiac RT doses and that the risk of death from heart disease increases by 3% per Gy (95% CI, 2%-5%;  $2p < 0.00001$ ) (37). That estimate can only be taken as an approximate indication of the risk, as individual treatment plans were not available for the women in those trials. Nevertheless, the data provide strong evidence that risk of RRHD was related to cardiac dose in irradiated breast cancer patients.

Outside the context of a randomized trial, comparisons of mortality after various different treatment regimens are often misleading because the prognosis of patients given different treatments will vary (38). In breast cancer, however, a reliable

indication of the effect of radiotherapy on heart disease can be obtained by comparing the experience of irradiated women with left-sided tumors with that of women with right-sided tumors (39). This can be done because cardiac radiation doses in women given radiotherapy for left-sided tumors are usually larger than the cardiac radiation doses in women with right-sided tumors, and breast cancer laterality has, in the past, played little part in determining who should be given radiotherapy.

As shown in Fig. 5, for breast cancer patients who were not treated with radiotherapy, the subsequent risk of heart disease was independent of tumor laterality, while for irradiated patients, the heart disease mortality ratio, left-sided vs. right-sided tumors, increased with increasing time since diagnosis (*i.e.*, with increasing time since irradiation). The increase was specific to heart disease as, for mortality from all other known causes, the left-sided vs. right-sided mortality ratio was close to unity in both irradiated and unirradiated patients. That suggests that the increasing trend in the left-sided vs. right-sided mortality ratio for heart disease shown in Fig. 5 is caused by radiotherapy, with the bulk of the risk occurring more than a decade after exposure. The proportional increase was higher for women irradiated at ages 20 to 49 than at older ages, but the trend did not reach statistical significance.

A recent study examining the incidence of CAD following breast irradiation (40) revealed a higher prevalence of stress test abnormalities in left-sided than in right-sided tumor patients (59% vs. 8%;  $p = 0.001$ ). Among left-sided tumor patients, the disease distribution differed from that expected in women, with a preponderance of left anterior descending artery disease. The anterior portion of the heart and the left anterior descending artery territory are the parts of the heart

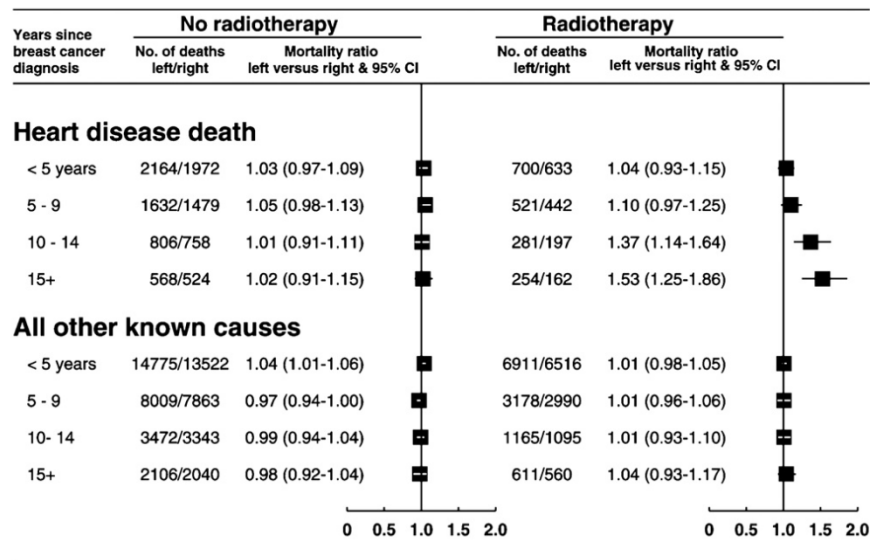


Fig. 5. Left-sided vs. right-sided breast cancer. Mortality ratios by radiotherapy status, cause, and years since diagnosis in 300,000 women with breast cancer and registered in the Surveillance Epidemiology and End Results (SEER) cancer registries, 1973 to 2001 (From Darby SC, McGale P, Taylor CW, *et al.* Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005;6:557-565; with permission.)

most often within the tangential radiation fields used to treat breast cancer. Hence, this finding provides direct evidence of a causal effect of radiotherapy on the development of CAD.

#### *Imaging studies*

The long latency between radiation exposure and development of symptomatic RRHD prevents a direct assessment of the cardiovascular risks of current or planned radiotherapy regimens within a practical time scale. Therefore, early surrogate endpoints predictive of the development of later cardiac events would be useful.

Nuclear medicine imaging can assess quantitatively acute and early chronic myocardial perfusion changes and functional deficits due to ischemic heart disease (41). Marks *et al.* (42) initiated a prospective study to assess changes in myocardial perfusion and function following tangential photon irradiation of left-sided breast cancer. Patients underwent preradiotherapy and serial 6-month postradiotherapy cardiac single-photon emission computed tomography (SPECT) scans. The frequency of perfusion defects was related to the percentage of the left ventricle within the tangential photon fields. Wall motion abnormalities were more common in patients with perfusion abnormalities than in those without. Typically, perfusion defects and the associated wall motion abnormality were in the anterior wall of the left ventricle, corresponding to the region of the heart within the radiotherapy field (Fig. 6).

Repeat scanning at 3 to 8 years after radiotherapy of patients with abnormalities at earlier time points demonstrated that perfusion defects persisted (43). Such defects have been associated with modest wall motion abnormalities but at present have not been shown to be predictive of clinical cardiac events such as congestive heart failure or MI. Thus, their clinical significance remains unproven. Nevertheless, as patients irradiated in the past for left-sided breast cancer

have been shown to be at increased risk of cardiac events at more than 10 years after breast radiotherapy (39), it is tempting to hypothesize that these perfusion defects are related in some way to the longer-term clinical manifestations.

Since the perfusion abnormalities follow the contour of the radiation treatment field rather than the territorial distribution of coronary arteries, they are likely to represent a radiation-related microvascular injury to the myocardial capillary network. That, if true, would perhaps increase the likelihood or severity of a subsequent ischemic event. One would hypothesize that a later MI in such an irradiated patient may produce a larger perfusion defect and clinical consequence than would have been expected based on the location and severity of their coronary artery lesion due to a reduction in vascular reserve (Fig. 4).

#### *Studies of atomic bomb survivors*

Mortality from heart disease has been studied among atomic bomb survivors in the Hiroshima-Nagasaki Life Span Study (LSS) for over 55 years (44). Distinctive features of the LSS are a population of >86,000 survivors who received whole-body uniform doses; individual radiation doses; a dose range of 0 to ~4 Gy; and complete mortality ascertainment and cause-of-death information.

Dose-related increases in heart disease mortality in the LSS occur in both genders, based on >8,400 heart disease deaths. The risk increased by 14% per Gy (95% CI, 6–23%), although it is not certain that there was any increase below about 0.5 Gy (44). It is unclear when the increase started, as there were substantial healthy survivor selection effects for at least a decade. However, even 50 years after irradiation, there is no suggestion that the risk has diminished.

The 14% increase in risk per Gy seen in the LSS is larger than the 3% per Gy seen in women in randomized trials of breast cancer patients. Confounding is unlikely to be responsible for the difference, as controlling for smoking, alcohol

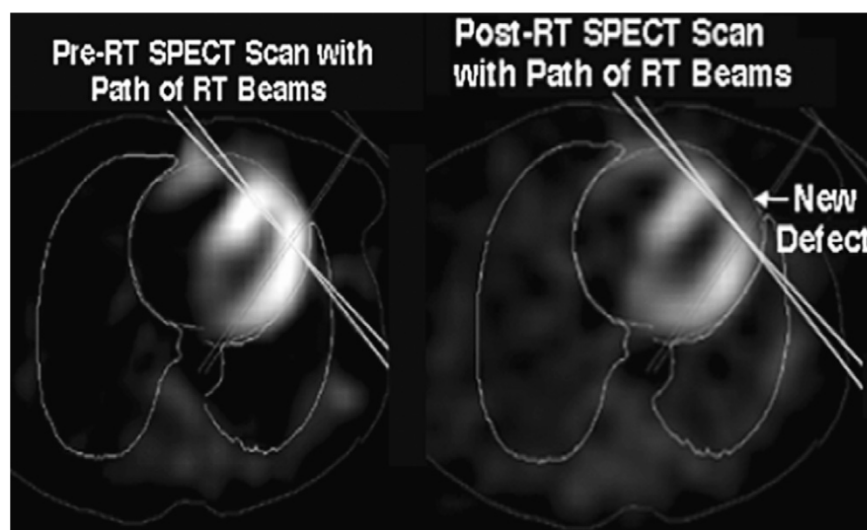


Fig. 6. Representative axial images pre-RT (left panel) and post-RT (right panel) cardiac SPECT scans. The deep borders of the tangential RT beams are shown as solid lines. A new perfusion defect in the anterior left ventricle after radiation is seen.

consumption, diabetes, obesity, education, and occupation had almost no effect on the estimates in the LSS. Also, the Adult Health Study biennial examinations of a subset of atomic bomb survivors provide additional support for an effect of radiation on heart disease in this population through associations of radiation exposure with alterations in blood pressure (45) and preclinical cardiovascular disease effects, including inflammatory markers (46) and lipid metabolism (47). The nominal difference in risk per Gy may be due to the fact that irradiation of the breast cancer patients is fractionated (2). Other possible reasons include Japanese/Western baseline differences in heart disease mortality rates, differences in age at exposure, and substantially less homogeneous cardiac radiation doses during breast cancer radiotherapy.

#### *Occupational studies*

Radiologists and radiologic technologists undoubtedly received substantial fractionated radiation doses in the early years. Although individual dose estimates are not available, several studies have subdivided them by year of registration to groups likely to have received different doses (48–50). In the United Kingdom, cancer mortality was higher in radiologists than in other medical practitioners for those registered during 1897 to 1920, suggesting a radiation-related excess (RR = 1.75; 95% CI, 1.34–2.26), and mortality declined significantly with the increasing year of registration, as would be expected from the declining doses over the 20th Century. In contrast, mortality from circulatory disease for those registered during 1897 to 1921 was lower in radiologists than in other medical practitioners (RR = 0.79; 95% CI, 0.66–0.94), and there was no suggestion of any trend with year of registration. Those data appear incompatible with a substantial radiation-related excess of circulatory disease in the early group. However, a study of 90,000 US radiologic technologists found increased risks of circulatory disease in those starting work prior to 1940 compared with those starting after 1960 (RR = 1.42; 95% CI, 1.04–1.94). This increase was mostly due to cerebrovascular disease (RR = 2.40; 95% CI, 1.09–5.31), rather than ischemic heart disease (RR = 1.22; 95% CI, 0.81–1.82) (50).

### **FUTURE PROSPECTS**

#### *Gaps in knowledge*

There are major gaps in current knowledge of the structures at risk and mechanisms of damage in RRHD. It is uncertain whether there is a threshold dose of radiation to the heart below which no risk is incurred. Even at doses sufficient to increase risk, estimates of its magnitude for a given cardiac dose are still subject to considerable uncertainty, and knowledge about the shape of the dose-response relationship and factors that modify it is rudimentary, both for heart disease as a whole and for specific heart diseases. There are substantial dose inhomogeneities within the heart during radiation therapy, but it is not known which part of the heart is the most radiosensitive, nor which structure or structures at risk should be chosen as a reference point for tolerance doses in clinical practice. Additional important gaps in current knowl-

edge include the relationship between short-term effects and long-term risk and the extent to which cardiac risk may be modified by other factors such as irradiation of other organs (e.g., kidneys), preexisting cardiovascular disease or diabetes, lifestyle factors including smoking, and interactions with cardiotoxic drugs used in combination with radiotherapy during cancer treatment.

#### *Experimental models*

Experimental models offer the greatest scope for increasing understanding of the cellular and molecular mechanisms of RRHD. A project utilizing high-precision cardiac irradiation of established murine models with prolonged follow-up, in combination with *ex vivo* and *in vitro* techniques, is presently underway (51). That project should eventually shed light on whether radiation operates predominantly by accelerating age-related coronary artery atherosclerosis by reducing the heart's tolerance to acute infarctions through microvascular damage to the myocardium, or whether both mechanisms are important.

Other topics that may be amenable to study experimentally include the sensitivities of specific cardiac substructures and the effect of irradiation of organs such as the kidney on risk of heart disease. Experimental models may also shed light on possible intervention strategies to reduce the risk in patients receiving radiotherapy, although the possibility of appreciable interspecies differences complicates the immediate application of promising findings to humans.

#### *Scientific studies of exposed individuals*

Further insight into the way in which the risk of death from RRHD varies with time since exposure and age is expected soon from a multinational study of cause-specific mortality after left-sided vs. right-sided breast cancer irradiation in over 1 million women (52). Information on cardiac morbidity and also on the possible modifying effects of preexisting heart disease and conventional cardiovascular risk factors such as diabetes, kidney disease, and hypertension will be available for a subset of the data (52, 53).

In some countries it is possible to link information on the subsequent morbidity and mortality of cancer patients with estimates of dose to the whole heart and some cardiac substructures derived from individual radiotherapy charts (36). Although retrospective dose estimates lack the accuracy of prospective studies due to an absence of individual three-dimensional treatment plans, they should provide a broad dose-response relationship for radiation-induced heart disease for doses ranging from about 1 to 20 Gy (53). They should also provide insight into the combined cardiotoxicity of radiation and drugs, such as anthracyclines, taxanes, or trastuzumab.

Studies of irradiated breast cancer patients can avoid selection biases by making use of the left-right comparison. Clearly, however, they can provide no information about the effects of cardiac irradiation in children or in men. It may be possible to derive quantitative risk estimates in patients with childhood cancer or from men with cancers such



as HL who have taken part in randomized trials of radiotherapy, but quantitative estimates from nonrandomized studies need to be interpreted with caution unless it can be established that the effects of selection are small.

Clinical studies of the atomic bomb survivors that employ a broad range of physical, imaging, and biomarker measurements are underway. Those studies aim to evaluate prospectively various potential mechanisms of radiation-related subclinical and clinical cardiovascular disease.

Several studies that were initiated to study radiation-related cancer in nuclear industry workers have large population sizes, long follow-up, and generally well-characterized doses, mostly of <0.5 Gy. It is possible that they may eventually provide information on the risks of RRHD. The low doses involved in such studies limit their statistical power. In addition, a major concern is that any dose-response relationship may be subject to confounding by smoking and other lifestyle factors. So far, little has been done to control for such factors in those studies.

#### *Monitoring and prevention of risk in exposed individuals*

The cardiac doses delivered by contemporary radiotherapy for cancer are lower than those delivered in previous decades (54). Cardiac risks are therefore likely to be correspondingly lower, but in the absence of reliable dose-response relationships, the extent of any risks from current therapies remains uncertain. The current era of three-dimensional computerized tomography treatment planning for radiotherapy enables the dose delivered to the whole heart and to specific cardiac substructures in any specific treatment plan to be estimated precisely. Hence, those carrying out treatment planning may have more control over cardiac doses than ever before. If reliable dose-response relationships for cardiac risk were available, useful prospective treatment-planning parameters could be derived (55), especially if the dose-response relationships also considered the impact of adjuvant systemic therapies and patient-specific factors.

The recognition and treatment of conventional cardiovascular risk factors, such as hypertension and hypercholesterolemia, can improve outcomes. As studies have suggested that the presence of conventional risk factors is a major modifier in the development of radiation-induced cardiovascular disease (20), there is an argument that those given thoracic radiotherapy may benefit from increased surveillance of these risk factors. Thus, a first step is to increase awareness among practicing physicians of radiation as an additional risk factor. An American Society of Clinical Oncology (ASCO) clinical

evidence review published in 2007 (56) emphasized the absence of high-quality evidence regarding the best methods and possible benefits of screening for late cardiac effects of cancer therapies. This deficit in knowledge will become increasingly important as the number of long-term cancer survivors is predicted to increase dramatically over the next decade. Further research is required into surveillance and targeted intervention strategies, so that evidence-based guidelines for long-term cardiac follow-up of those patients at risk can be developed.

#### *Radiological protection*

There are approximately 400 million diagnostic medical examinations performed annually in the United States and some 3.6 billion worldwide. In addition, there are almost 4 million workers monitored occupationally for potential radiation exposure in the United States and over 15 million worldwide. Present radiological protection guidelines and regulations are concerned solely with radiation-related cancers and hereditary effects and do not consider RRHD. Virtually all the exposure occurs at doses of below 0.5 Gy, and, at the present time, it is unclear whether such low doses pose any cardiac risk. Therefore, it is as yet unclear whether there will be any future need to take explicit account of RRHD in radiation protection.

## CONCLUSIONS

Further knowledge about the nature and magnitude of radiation-related heart disease would have immediate application in radiation oncology. It would also provide a basis for radiation protection policies for use in diagnostic and occupational exposure.

To our knowledge, this review is first time that individuals from such a wide range of disciplines, including pathology, radiobiology, cardiology, radiation oncology, epidemiology, statistics, and diagnostic radiology have collaborated to share knowledge about RRHD. All those different disciplines have roles to play in furthering knowledge and in reducing the future burden of RRHD. Knowledge accumulated in one discipline may often be published in specialized journals that are not regularly read by those working in other disciplines, and technical terminology often impedes ready interpretation by those in other disciplines. We therefore conclude that future multidisciplinary reviews examining the topics raised here in greater depth and summarizing new findings are needed.

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## Risks of Heart Disease after Radiotherapy

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*Texas Heart Institute Journal*

**H**eart disease and cancer are the 2 leading causes of morbidity and death world-wide.<sup>1</sup> The prognosis of many cancers has improved, and an increasing number of patients go on to live for many years as cancer survivors. More than 50% of cancer patients receive radiotherapy during treatment, and it is well established that therapeutic irradiation can result in late cardiovascular morbidity and death.<sup>2</sup> Much of the evidence for this risk comes from patients treated decades ago for Hodgkin lymphoma (HL) using older radiotherapy techniques.<sup>3</sup> Although more modern treatment often involves lower cardiac doses and can therefore result in lower risk, there is evidence that an increased risk of cardiac morbidity remains for HL patients treated more recently<sup>4</sup> and might also remain for patients who are being treated today, whether for HL or for some other cancers, such as breast cancer.

In the past, the heart was thought to be relatively resistant to the effects of radiation and damaged only by doses of  $\geq 30$  Gy. More recent data from several independent sources have provided substantial evidence that mean heart doses of  $\leq 20$  Gy, and even  $\leq 5$  Gy, can increase the risk. These sources include information pertaining to atomic bomb survivors<sup>5</sup> and patients treated for childhood cancers,<sup>6</sup> peptic ulcer disease,<sup>7</sup> and breast cancer.<sup>8,9</sup> Data from the Early Breast Cancer Trialists' Collaborative group include women who were randomized within trials to radiotherapy or no radiotherapy. Retrospective estimation of mean heart doses, by 3-dimensional reconstruction of radiotherapy techniques specified within the trial protocols, yields an increase in relative risk of cardiac death of 3.1% per Gy.<sup>10</sup>

Modern techniques of radiation therapy, such as intensity-modulated radiotherapy (IMRT) and tomotherapy, enable radiation oncologists to deliver doses with far more accuracy than was previously possible. Unfortunately, these techniques have advanced beyond the current knowledge of normal cardiovascular tissue complications. The critical dose and volume relationships for individual cardiac structures, and for individual cardiovascular endpoints, are not known with any accuracy. For example, it is not known whether it might be advantageous to deliver a high dose to a small volume of the heart or a smaller dose to a larger volume of the heart. There is a general view that the avoidance of cardiac doses of  $> 30$  Gy will eliminate any significant risk of late effects, but evidence for increased risks from lower doses, as described above, appears to contradict this. In addition, only limited data are available, as yet, on the potential interactions of radiation, both with drug treatments (such as anthracyclines and tyrosine kinase inhibitors) and with conventional cardiovascular risk factors (such as smoking and hypertension). These data will be essential to enable the accurate prediction of risks on an individual basis.

The study of radiation-induced cardiovascular effects is complicated by the wide spectrum of disease that can occur, including coronary artery disease, pericardial disease, valvular disease, and cardiomyopathy.<sup>2</sup> It is further complicated by the prolonged latency of many of the endpoints. This necessitates the imaginative use of a variety of scientific approaches and data sets in attempts to answer the outstanding questions. The development of validated early-surrogate markers of late cardiovascular risks, perhaps by using modern imaging techniques such as cardiovascular magnetic resonance, might also prove vital to the more rapid acquisition of data relevant to modern treatments. At present, the clinical relevance of recognized early abnormalities, such as perfusion defects after breast cancer treatment,<sup>11</sup> is unknown. It is also not known whether interventions after exposure—for example, with antiplatelet drugs, angiotensin-converting enzyme inhibitors, or statins—may lower cardiovascular risks.

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Improved knowledge in the emerging field of oncocardiology is important for numerous reasons: 1) to better inform patients of risks during consent; 2) to enable informed management decisions that are based on the risks of late effects, as well as on oncologic effectiveness; 3) to aid radiotherapy planning in the era of sophisticated dose delivery; and 4) to enable, for cancer survivors, better targeted follow-up, screening, and intervention. It is vital to pay appropriate attention to the risks of heart disease after radiotherapy.

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# Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials



Early Breast Cancer Trialists' Collaborative Group (EBCTCG)\*

## Summary

**Background** After breast-conserving surgery, radiotherapy reduces recurrence and breast cancer death, but it may do so more for some groups of women than for others. We describe the absolute magnitude of these reductions according to various prognostic and other patient characteristics, and relate the absolute reduction in 15-year risk of breast cancer death to the absolute reduction in 10-year recurrence risk.

**Methods** We undertook a meta-analysis of individual patient data for 10 801 women in 17 randomised trials of radiotherapy versus no radiotherapy after breast-conserving surgery, 8337 of whom had pathologically confirmed node-negative (pN0) or node-positive (pN+) disease.

**Findings** Overall, radiotherapy reduced the 10-year risk of any (ie, locoregional or distant) first recurrence from 35·0% to 19·3% (absolute reduction 15·7%, 95% CI 13·7–17·7,  $2p<0\cdot00001$ ) and reduced the 15-year risk of breast cancer death from 25·2% to 21·4% (absolute reduction 3·8%, 1·6–6·0,  $2p=0\cdot00005$ ). In women with pN0 disease ( $n=7287$ ), radiotherapy reduced these risks from 31·0% to 15·6% (absolute recurrence reduction 15·4%, 13·2–17·6,  $2p<0\cdot00001$ ) and from 20·5% to 17·2% (absolute mortality reduction 3·3%, 0·8–5·8,  $2p=0\cdot005$ ), respectively. In these women with pN0 disease, the absolute recurrence reduction varied according to age, grade, oestrogen-receptor status, tamoxifen use, and extent of surgery, and these characteristics were used to predict large ( $\geq 20\%$ ), intermediate (10–19%), or lower ( $<10\%$ ) absolute reductions in the 10-year recurrence risk. Absolute reductions in 15-year risk of breast cancer death in these three prediction categories were 7·8% (95% CI 3·1–12·5), 1·1% ( $-2\cdot0$  to 4·2), and 0·1% ( $-7\cdot5$  to 7·7) respectively (trend in absolute mortality reduction  $2p=0\cdot03$ ). In the few women with pN+ disease ( $n=1050$ ), radiotherapy reduced the 10-year recurrence risk from 63·7% to 42·5% (absolute reduction 21·2%, 95% CI 14·5–27·9,  $2p<0\cdot00001$ ) and the 15-year risk of breast cancer death from 51·3% to 42·8% (absolute reduction 8·5%, 1·8–15·2,  $2p=0\cdot01$ ). Overall, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10, and the mortality reduction did not differ significantly from this overall relationship in any of the three prediction categories for pN0 disease or for pN+ disease.

**Interpretation** After breast-conserving surgery, radiotherapy to the conserved breast halves the rate at which the disease recurs and reduces the breast cancer death rate by about a sixth. These proportional benefits vary little between different groups of women. By contrast, the absolute benefits from radiotherapy vary substantially according to the characteristics of the patient and they can be predicted at the time when treatment decisions need to be made.

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## Introduction

For many women with early-stage breast cancer, breast-conserving surgery can remove any macroscopic disease that has been detected; however, some microscopic tumour foci might remain in the conserved breast that could, if untreated, lead to locoregional recurrence or life-threatening distant metastases, or both. This report updates previous analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) of individual patient data from the randomised trials of radiotherapy after breast-conserving surgery.<sup>1–5</sup> It includes further follow-up for nine of the ten trials analysed previously;<sup>5</sup> adds data from seven new trials, six of which were in

low-risk women; and increases the total number of women analysed by nearly 50%. The report focuses mainly on women for whom pathological axillary lymph node status is known (negative [pN0] or positive [pN+]), because such information is usually available nowadays. It assesses the extent to which the radiotherapy-related absolute reduction in 10-year risk of first recurrence at any site (locoregional or distant) varies for women with different prognostic and other factors. It then relates the absolute reduction in the 15-year risk of breast cancer death to the absolute reduction in the 10-year risk of a recurrence.

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\*Collaborators listed in [Articles](#)  
Lancet 2011; 378: 771–84 and  
webappendix p 48

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See Online for webappendix

## Methods

### Study design

Eligible trials were those beginning before the year 2000 of adjuvant radiotherapy versus no radiotherapy following breast-conserving surgery for invasive cancer. Trial identification and data handling were as previously reported.<sup>5</sup> For every woman, information was sought regarding initial characteristics, allocated treatment, time to first recurrence, whether the first recurrence was locoregional or distant (excluding contralateral breast cancer), and date last known alive or date and underlying cause of death. When no recurrence was reported before breast cancer death, distant recurrence was assumed to have just preceded it. If contralateral breast cancer occurred before any other recurrence, follow-up was censored on that date in recurrence analyses.

### Statistical analysis

The method used in this study differs from that used previously.<sup>5</sup> First, to avoid assumptions about how locoregional and distant recurrence relate to each other, the main emphasis is on analyses of any first recurrence rather than, as before, of time to locoregional recurrence as a first event. Second, most analyses of recurrence present data for only 10 years, because many of these trials did not follow up women beyond this time for recurrence. This absence of follow-up should not bias the estimated proportional effect on recurrence after year 10, but could affect estimates of the absolute recurrence risk after year 10 substantially. Third, deaths of unknown cause before recurrence are no longer attributed to breast cancer, because most occurred many years after trial entry, by

which time non-breast-cancer mortality predominated. Other aspects of the methods used are as before.<sup>5</sup> Log-rank analyses are stratified by trial, individual follow-up year, and nodal status. They are also stratified by age, either in five groups (<40, 40–49, 50–59, 60–69, 70+ years) or, when data are also subdivided by other factors, in two groups (<50 and 50+ years).

Analyses of the dependence of absolute risk, and absolute risk reduction, on several factors simultaneously use Poisson regression fitted by maximum likelihood (webappendix pp 20–25). In these analyses absolute risk of any first recurrence is adjusted for trial, individual follow-up year, nodal status, and age (five groups), and also for tumour grade, tumour size, oestrogen-receptor (ER) status, and whether or not tamoxifen had been used in both randomised groups in the trial.

Preliminary results were presented to collaborators in September, 2010. A report was circulated to collaborators for comment in January, 2011, and then revised centrally.

### Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The Secretariat had full access to all data and analyses. Submission for publication was decided only by the writing committee.

## Results

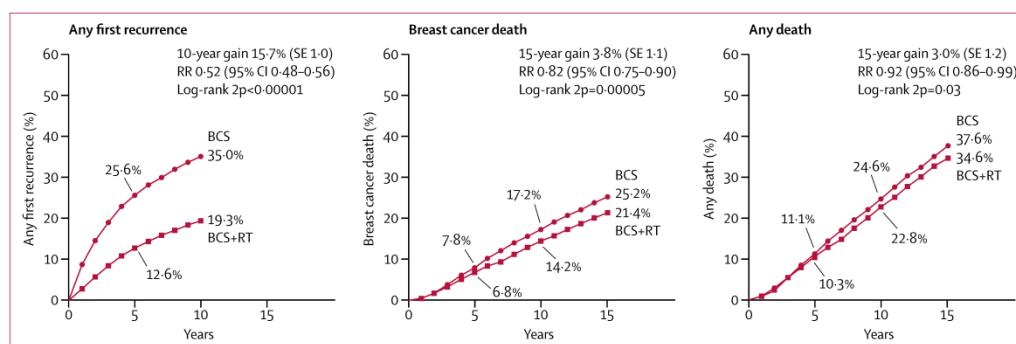
Information was available for 10 801 women in 17 trials (table 1). Six trials were of radiotherapy after lumpectomy and included both low-risk and high-risk women

| Trial category†                                         | Number of trials available* | Years trials began | Women  | Deaths | Woman-years at risk |                      |                                                      |      |       |       |     |
|---------------------------------------------------------|-----------------------------|--------------------|--------|--------|---------------------|----------------------|------------------------------------------------------|------|-------|-------|-----|
|                                                         |                             |                    |        |        | Median/<br>woman    | Total<br>(thousands) | Distribution by years since diagnosis<br>(thousands) |      |       |       |     |
|                                                         |                             |                    |        |        |                     |                      | <5                                                   | 5–9  | 10–14 | 15–19 | 20+ |
| (A) Lumpectomy, original trials <sup>5–11</sup>         | 6                           | 1976–86            | 4398   | 1982   | 11.8                | 52.9                 | 20.3                                                 | 16.0 | 10.1  | 4.8   | 1.7 |
| (B) Sector resection or quadrantectomy <sup>12–15</sup> | 4                           | 1981–91            | 2399   | 708    | 12.4                | 29.4                 | 11.6                                                 | 10.3 | 6.0   | 1.4   | 0.1 |
| (C) Lumpectomy in low-risk women <sup>16–22</sup>       | 7                           | 1989–99            | 4004   | 453    | 6.6                 | 26.9                 | 17.9                                                 | 7.9  | 1.1   | 0.0   | 0.0 |
| Pathological nodal status                               |                             |                    |        |        |                     |                      |                                                      |      |       |       |     |
| Negative (pN0)                                          | ..                          | ..                 | 7287   | 1801   | 9.7                 | 73.7                 | 34.0                                                 | 23.3 | 11.3  | 3.9   | 1.2 |
| Positive (pN+)                                          | ..                          | ..                 | 1050   | 585    | 10.3                | 11.8                 | 4.6                                                  | 3.2  | 2.2   | 1.3   | 0.5 |
| Unknown                                                 | ..                          | ..                 | 2464   | 757    | 8.8                 | 23.6                 | 11.3                                                 | 7.6  | 3.7   | 1.0   | 0.0 |
| All women                                               | 17                          | 1976–99            | 10 801 | 3143   | 9.5                 | 109.1                | 49.8                                                 | 34.1 | 17.2  | 6.3   | 1.7 |

\*Only unconfounded trials are considered—ie, trials in which there was no difference between the treatment groups in the type or extent of surgery or in the use of systemic therapy. Two further eligible trials,<sup>13,24</sup> both category A with a total of 133 women, were identified but data were unavailable. Details of the 17 available trials are given in webappendix pp 4, 45–47. †Elsewhere, these trial categories are abbreviated to: (A) Lumpectomy: original; (B) >Lumpectomy; (C) Lumpectomy: low risk. In category A, 55% were pathologically node negative, 5% were aged 70+ years, 10% had low-grade tumours, 54% had T1 tumours (1–20 mm), 81% had oestrogen-receptor (ER)-positive disease or unknown status, and 44% were in trials in which tamoxifen was used in both trial groups. In category B, 81% were pathologically node negative, 10% were aged 70+ years, 9% had low-grade tumours, 89% had T1 tumours, 86% had ER positive disease or unknown status, and 6% were in trials in which tamoxifen was used in both trial groups. In category C, 73% were pathologically node negative, 40% were aged 70+ years, 33% had low-grade tumours, 90% had T1 tumours, 98% had ER positive disease or unknown status, and 88% were in trials in which tamoxifen was used in both trial groups.

**Table 1: Availability of data from randomised trials of radiotherapy after breast-conserving surgery for invasive cancer that began before the year 2000**



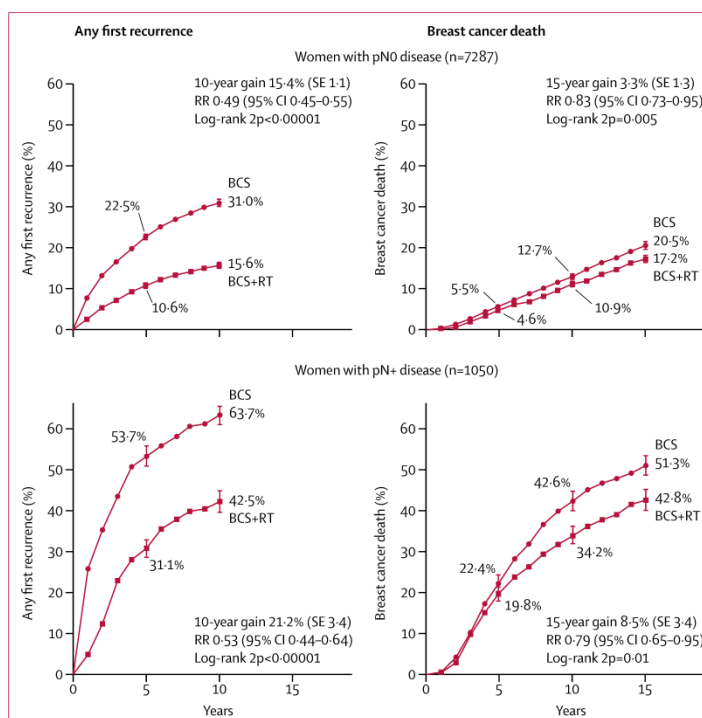


**Figure 1:** Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10 801 women (67% with pathologically node-negative disease) in 17 trials. Further details are in webappendix p 5. RR=rate ratio. Rate ratios in this figure include all available years of follow-up.

(category A, 4398 women), four were of radiotherapy after sector resection or quadrantectomy (category B, 2399 women), and seven more recent trials were of radiotherapy after lumpectomy in low-risk women (category C, 4004 women). In most of the trials radiotherapy was to the conserved breast only (webappendix p 4). Median follow-up was 9.5 years at risk per woman and 25% of women were followed up for more than a decade. 3143 (29%) had died by the final follow-up date of Sept 30, 2006.

The 10-year risk of any (locoregional or distant) first recurrence was 19.3% in women allocated to radiotherapy and 35.0% in women allocated to breast-conserving surgery only, corresponding to an absolute risk reduction of 15.7% (95% CI 13.7–17.7, 2p<0.00001; figure 1). Nearly three-quarters of first recurrences in the no radiotherapy group were locoregional (25% locoregional first, 10% distant first), compared with fewer than half of those in the radiotherapy group (8% locoregional first, 12% distant first; webappendix p 9). In addition to reducing recurrence substantially, radiotherapy also reduced breast cancer death by a moderate amount: the 15-year absolute risk reduction was 3.8% (95% CI 1.6–6.0, 2p=0.00005), suggesting on average about one breast cancer death avoided for every four recurrences avoided by radiotherapy.

Allocation to radiotherapy halved the average annual rate of any first recurrence (rate ratio [RR] 0.52, 95% CI 0.48–0.56, figure 1). The proportional reduction was greatest in the first year (0.31, 0.26–0.37), but was still substantial during years 5–9 (0.59, 0.50–0.70; webappendix p 13). Beyond year 10 there was no evidence of any further effect on the first recurrence rate, but information about recurrence in this period was incomplete so the number of events was small and the CI wide (figure 1). Radiotherapy reduced the annual breast cancer death rate by a sixth (RR 0.82, 0.75–0.90). The timing of breast cancer death differed from that of first recurrence, with few events during the first year

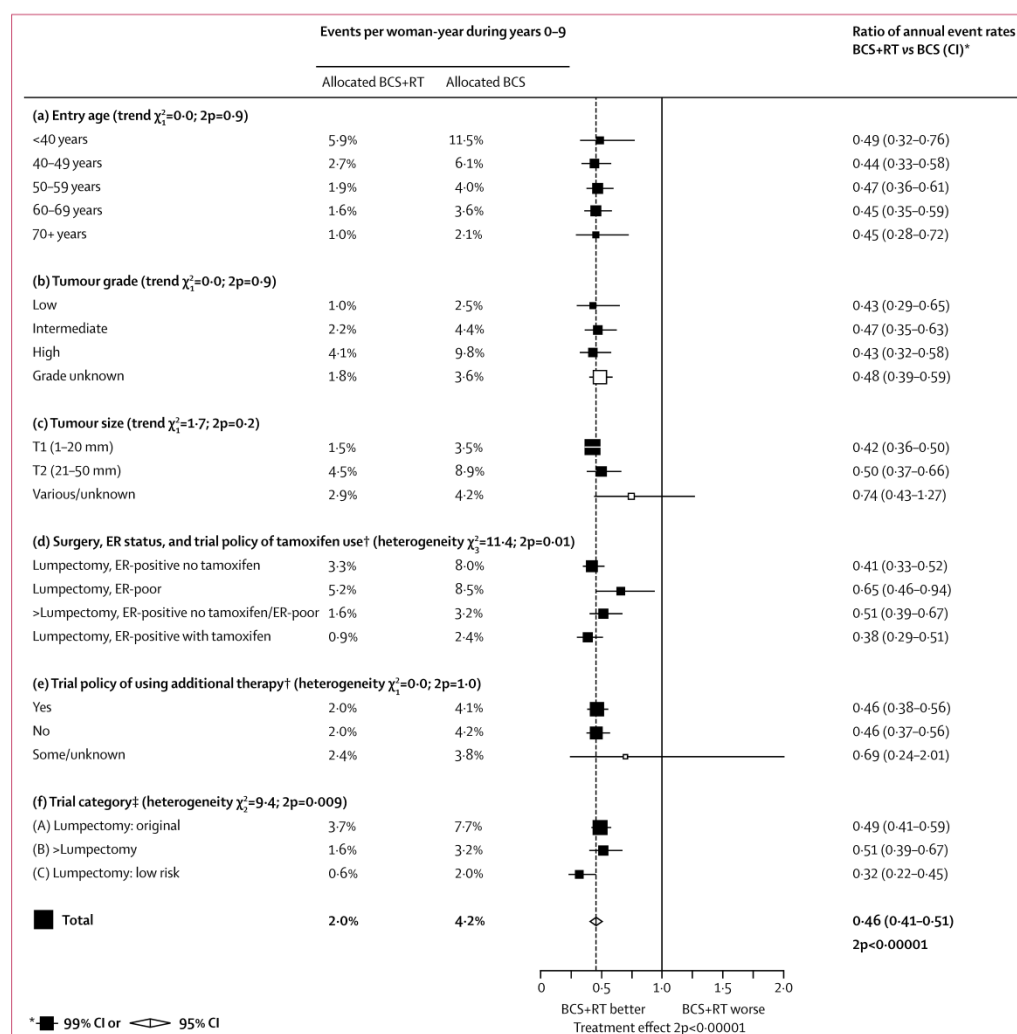


**Figure 2:** Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risk of breast cancer death in women with pathologically verified nodal status

Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages. Further details are in webappendix pp 6–7. pN0=pathologically node-negative. pN+=pathologically node-positive. RR=rate ratio. Rate ratios in this figure include all available years of follow-up.

(figure 1), and there were substantial numbers of breast cancer deaths after year 10.

Mortality without recurrence from non-breast-cancer causes was slightly higher in women allocated to radiotherapy than in women allocated to breast-conserving



**Figure 3:** Event rates for any (locoregional or distant) first recurrence (% per year) and recurrence rate ratios for various factors, considered separately, during years 0–9 in women with pathologically node-negative disease (n=7287)

BCS=breast-conserving surgery. RT=radiotherapy. ER=oestrogen receptor. Categories including unknowns excluded from tests for trend and heterogeneity. †A trial policy of tamoxifen use gives tamoxifen to both treatment groups if the disease is ER positive (or ER unknown, here counted with ER positive); additional therapy could be chemotherapy (usually cyclophosphamide, methotrexate, fluorouracil [CMF]) for both treatment groups, or additional RT (nodal RT or a boost or both) for those allocated BCS+RT. ‡Definitions of trial categories A, B, and C are in table 1. Further details are in webappendix p 14.

surgery only, but the excess was not significant (RR 1.09, 95% CI 0.97–1.22, 2p=0.14). If the mortality rate from non-breast-cancer causes in women allocated to radiotherapy had been identical to that in women allocated to breast-conserving surgery only, then the 15-year absolute risk reduction in all-cause mortality would have been 3.2%. In fact, the 15-year absolute risk reduction in all-cause mortality was 3.0% (95% CI 0.6–5.4, 2p=0.03; figure 1).

Most women (n=7287) had pN0 disease. In this group, allocation to radiotherapy halved the average annual

recurrence rate during the first decade (RR 0.46, 95% CI 0.41–0.51), reducing the 10-year risk of any first recurrence from 31.0% to 15.6%, an absolute reduction of 15.4% (95% CI 13.2–17.6, 2p<0.00001 figure 2). For these women, radiotherapy reduced breast cancer death by about a sixth (RR 0.83, 95% CI 0.73–0.95), and reduced the 15-year risk of breast cancer death from 20.5% to 17.2%, an absolute reduction of 3.3% (95% CI 0.8–5.8, 2p=0.005; figure 2).

For the 1050 women with pN+ disease, allocation to radiotherapy reduced the 1-year recurrence risk from



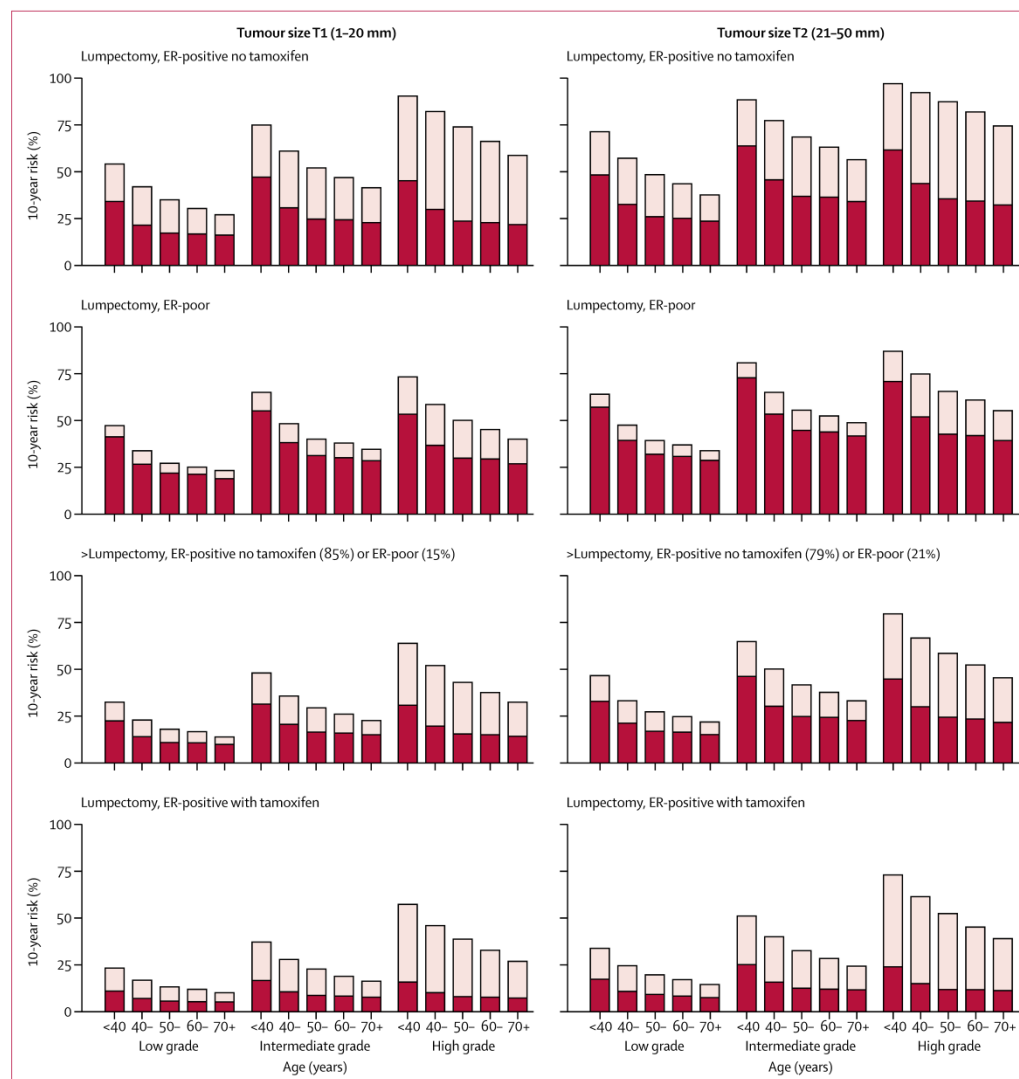
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Number allocated<br>BCS+RT/BCS | 10-year risk of a locoregional or distant recurrence (%) |      |                                     | Test for trend/heterogeneity in absolute reduction |                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|----------------------------------------------------------|------|-------------------------------------|----------------------------------------------------|--------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                | BCS+RT                                                   | BCS  | Absolute reduction with RT (95% CI) | 2p unadjusted*                                     | 2p adjusted*                         |
| (a) Entry age (years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                |                                                          |      |                                     |                                                    |                                      |
| <40                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 189/174                        | 36.1                                                     | 60.7 | 24.6 (13.2 to 36.0)                 | <0.00001                                           | 0.0002                               |
| 40–49                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 576/582                        | 20.8                                                     | 41.4 | 20.6 (15.1 to 26.1)                 |                                                    |                                      |
| 50–59                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1093/1028                      | 15.0                                                     | 29.7 | 14.7 (10.8 to 18.6)                 |                                                    |                                      |
| 60–69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1138/1167                      | 14.2                                                     | 28.3 | 14.1 (10.4 to 17.8)                 |                                                    |                                      |
| 70+                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 679/661                        | 8.8                                                      | 17.7 | 8.9 (4.0 to 13.8)                   |                                                    |                                      |
| (b) Tumour grade                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                |                                                          |      |                                     |                                                    |                                      |
| Low                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 750/757                        | 11.0                                                     | 22.4 | 11.4 (6.3 to 16.5)                  | <0.00001                                           | <0.00001                             |
| Intermediate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 816/843                        | 16.4                                                     | 31.6 | 15.3 (10.4 to 20.2)                 |                                                    |                                      |
| High                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 448/431                        | 28.6                                                     | 53.3 | 24.7 (17.6 to 31.8)                 |                                                    |                                      |
| Grade unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 1661/1581                      | 14.7                                                     | 28.2 | 13.5 (10.4 to 16.6)                 |                                                    |                                      |
| (c) Tumour size                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                |                                                          |      |                                     |                                                    |                                      |
| T1 (1–20 mm)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2942/2920                      | 12.4                                                     | 27.5 | 15.1 (12.7 to 17.5)                 | 0.02                                               | 0.06                                 |
| T2 (21–50 mm)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 513/487                        | 30.7                                                     | 50.0 | 19.3 (12.6 to 26.0)                 |                                                    |                                      |
| Various/unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 220/205                        | 24.9                                                     | 32.6 | 7.6 (–1.8 to 17.0)                  |                                                    |                                      |
| (d) ER status and trial policy of tamoxifen use†                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                |                                                          |      |                                     |                                                    |                                      |
| ER-poor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 448/427                        | 28.9                                                     | 43.8 | 14.9 (8.0 to 21.8)                  | <0.00001                                           | 0.003                                |
| ER-positive no tamoxifen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1686/1626                      | 18.6                                                     | 36.0 | 17.4 (14.3 to 20.5)                 |                                                    |                                      |
| ER-positive with tamoxifen                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 1541/1559                      | 8.7                                                      | 22.0 | 13.3 (10.0 to 16.6)                 |                                                    |                                      |
| (e) Trial policy of using additional therapy‡                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                |                                                          |      |                                     |                                                    |                                      |
| No                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1498/1471                      | 15.8                                                     | 31.6 | 15.8 (12.7 to 18.9)                 | 0.06                                               | 0.45                                 |
| Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 2127/2085                      | 16.1                                                     | 31.8 | 15.6 (12.3 to 18.9)                 |                                                    |                                      |
| Some/unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 50/56                          | ..                                                       | ..   | ..                                  |                                                    |                                      |
| (f) Trial category‡                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                |                                                          |      |                                     |                                                    |                                      |
| (A) Lumpectomy: original                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1223/1197                      | 27.8                                                     | 47.9 | 20.1 (16.0 to 24.2)                 | <0.00001 (A vs C);<br>0.90 (A+C vs B)              | 0.16 (A vs C);<br>0.00003 (A+C vs B) |
| (B) >Lumpectomy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 986/970                        | 14.3                                                     | 25.9 | 11.6 (7.9 to 15.3)                  |                                                    |                                      |
| (C) Lumpectomy: low risk                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1466/1445                      | 6.3                                                      | 19.9 | 13.6 (9.7 to 17.5)                  |                                                    |                                      |
| Total                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3675/3612                      | 15.6                                                     | 31.0 | 15.4 (13.2 to 17.6)                 |                                                    |                                      |
| Information about numbers of events and woman-years is in webappendix p 26. Results for 5-year risks are in webappendix p 31. ER=estrogen receptor. *Unadjusted: each factor alone. Adjusted: each factor adjusted for all other factors by means of regression modelling. Categories including unknowns excluded from test for trend or heterogeneity. †A trial policy of tamoxifen use gives tamoxifen to both treatment groups if the disease is ER positive (or ER unknown, here counted with ER positive); additional therapy could be chemotherapy (usually cyclophosphamide, methotrexate, fluorouracil [CMF]) for both treatment groups, or additional RT (nodal RT or a boost or both) for those allocated BCS+RT. ‡Definitions of trial categories A, B, and C are in table 1. |                                |                                                          |      |                                     |                                                    |                                      |
| Table 2: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence in women with pathologically node-negative disease (n=7287), subdivided by patient and trial characteristics                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                |                                                          |      |                                     |                                                    |                                      |

26.0% to 5.1%, which is a five-fold reduction (RR 0.20, 95% CI 0.14–0.29). There was a moderate additional effect over the next few years but little further effect after year 5 (figure 2). When these very different proportional effects in different periods since treatment were combined, the mean annual recurrence rate during the whole of the first decade was halved in pN+ disease (RR 0.50, 95% CI 0.41–0.61). Although the proportional reductions in the mean annual recurrence rate were similar in pN0 and pN+ disease, the absolute 10-year recurrence reduction seemed to be somewhat larger in pN+ disease at 21.2% (95% CI 14.5–27.9, 2p<0.00001, 42.5% vs 63.7%). Radiotherapy also reduced breast cancer death in pN+ disease (RR 0.79, 95% CI 0.65–0.95, 2p=0.01), with

a 15-year absolute reduction of 8.5% (95% CI 1.8–15.2; 42.8% vs 51.3%).

In both pN0 and pN+ disease, the first recurrence was locoregional for a higher proportion of women allocated to breast-conserving surgery only than of women allocated to breast-conserving surgery plus radiotherapy (webappendix p 10).

Analyses of the effects of treatment in various subgroups of women with pN0 disease are much more likely to identify differences reliably if they are based on recurrence than on mortality, because the significance level of the effect of radiotherapy is much more extreme for recurrence than for mortality (2p<0.00001 for recurrence [ $\chi^2=209.0$ ], 2p=0.005 for breast cancer death [ $\chi^2=7.8$ ]).



**Figure 4: Absolute 10-year risks (%) of any (locoregional or distant) first recurrence with and without radiotherapy (RT) following breast-conserving surgery (BCS) in pathologically node-negative women by patient and trial characteristics, as estimated by regression modelling of data for 7287 women** Further details are in webappendix pp 27–30. Results for 5-year risks are in webappendix pp 31–34. Bars show 10-year risks in women allocated to BCS only, dark sections show 10-year risks in women allocated to BCS plus RT, light sections show absolute reduction with RT. ER=oestrogen receptor.

In a series of analyses which focus first on proportional and then on absolute reductions in recurrence, women were subdivided into different groups to ascertain whether some groups benefit more than others from radiotherapy. In the first analysis, the proportional effect of radiotherapy on the rate of any first recurrence in pN0 disease during the first 10 years was estimated for each of several factors considered separately (figure 3). In most subgroups, radiotherapy roughly halved the annual recurrence rate (except that among women who had been

given lumpectomy the proportional recurrence reduction was somewhat less extreme in ER-poor disease [ $2p=0.01$ , section (d) of figure 3] and somewhat more extreme in the low-risk [category C] trials [ $2p=0.009$ , section (f) of figure 3]).

Halving a big risk produces a bigger absolute benefit than halving a small risk. In women with pN0 disease, the annual recurrence rate without radiotherapy was strongly correlated with age (inversely), tumour grade, tumour size, ER status (especially when tamoxifen was

used in ER-positive disease), and extent of surgery (inversely). The absolute recurrence reduction produced by radiotherapy also depended strongly on these factors (table 2). In the second analysis, the way in which the absolute reduction in 10-year recurrence risk produced by radiotherapy depended on all the potential explanatory factors listed in table 2 considered together was modelled. The modelling was carried out by considering information both for women allocated to radiotherapy and for those allocated to no radiotherapy (webappendix pp 20–25 shows methodological details).

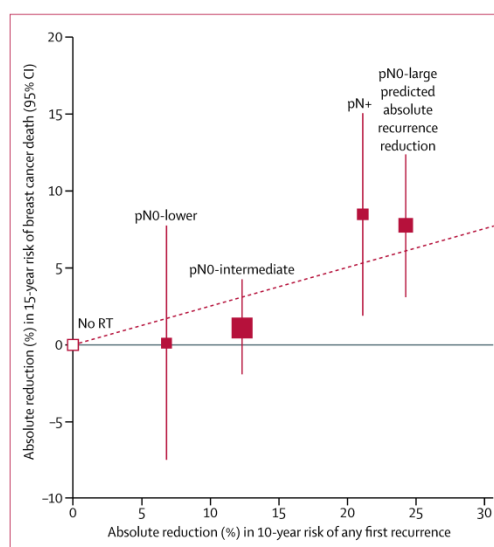
The absolute recurrence reduction produced by radiotherapy and the absolute recurrence risk remaining even with radiotherapy varied significantly with age, tumour grade, ER status, and tamoxifen use, even after adjustment for all other factors (table 2). Tumour size was independently predictive of absolute recurrence risk although not of the absolute risk reduction.

When the original trials with lumpectomy (category A) and the later trials with lumpectomy in low-risk women (category C) were compared, there was a substantial difference in the absolute recurrence risk without radiotherapy and in the absolute reduction in this risk produced by radiotherapy, but these differences were largely accounted for by the other recorded factors (table 2; webappendix pp 15–17, 19).

Surgery that is more extensive than lumpectomy (as in the category B trials) reduced the absolute recurrence risk without radiotherapy and reduced the absolute reduction in this risk produced by radiotherapy. However, because the category B trials did not give tamoxifen, this effect of the extent of surgery on the absolute effect of radiotherapy was apparent only after adjustment for tamoxifen use (and the other recorded factors), but not before (table 2; webappendix p 18).

The characteristics that were independently predictive of the absolute risk of recurrence, or of the absolute risk reduction with radiotherapy, were included in a model to show how 10-year recurrence risks with and without radiotherapy depended in these trials on age, grade, ER status, tamoxifen (which was given much more often in the recent category C trials of low-risk patients than in the original category A trials), and extent of surgery. Figure 4 shows estimates based on this model. Within each section of the figure, younger women and those with high-grade tumours had substantially larger absolute recurrence risks without radiotherapy and substantially larger absolute risk reductions with radiotherapy than did older women and those with low-grade tumours (figure 4). Among women given lumpectomy but not radiotherapy, for a specific age and grade, the highest risks and largest absolute reductions with radiotherapy were for women with ER-positive disease not given tamoxifen; however, even with tamoxifen the additional effects of radiotherapy were substantial for women with high-grade tumours and younger women with intermediate-grade tumours (figure 4).

Each woman with pN0 disease was assigned a predicted absolute reduction in 10-year recurrence risk from radiotherapy on the basis of her individual characteristics, the characteristics of the trial that she was in, and the model-based estimates in figure 4. The absolute reduction in 10-year recurrence risk was large ( $\geq 20\%$ ) for 1924 women (56% of women in trial category A, 16% of trial category B, and 9% of trial category C), intermediate (10–19%) for 3763 women (32%, 74%, and 53% of trial categories A, B, and C respectively), and lower ( $<10\%$ ) for 1600 women (12%, 10%, and 38% of trial categories A, B, and C respectively). For these three groups (pN0-lower, pN0-intermediate, and pN0-large), the observed 10-year recurrence risks with and without radiotherapy, calculated directly from data for individual women, were 26.0% versus 50.3% (absolute reduction of 24.3%, 95% CI 19.6–29.0), 12.4% versus 24.8% (absolute reduction of 12.4%, 9.7–15.1), and 12.0% versus 18.9% (absolute reduction of 6.9%, 2.2–11.6), respectively. The corresponding absolute reductions in 15-year risk of breast cancer death in the three groups were 7.8% (95% CI 3.1–12.5), 1.1% (–2.0 to 4.2), and 0.1% (–7.5 to 7.7), respectively (trend in absolute mortality reduction:  $2p=0.03$ ; figure 5, webappendix pp 35–37). For all three groups, the first recurrence was locoregional for a much larger proportion of women allocated to



**Figure 5: Absolute reduction in 15-year risk of breast cancer death with radiotherapy (RT) after breast-conserving surgery versus absolute reduction in 10-year risk of any (locoregional or distant) recurrence**  
Women with pN0 disease are subdivided by the predicted absolute reduction in 10-year risk of any recurrence suggested by regression modelling (pN0-large  $\geq 20\%$ , pN0-intermediate 10–19%, pN0-lower  $<10\%$ ; further details are in webappendix pp 35–39). Vertical lines are 95% CIs. Sizes of dark boxes are proportional to amount of information. Dashed line: one death from breast cancer avoided for every four recurrences avoided. pN0=pathologically node-negative. pN+=pathologically node-positive.

breast-conserving surgery only than for those allocated to breast-conserving surgery plus radiotherapy (webappendix pp 38–39). Because only 1050 women had pN+ disease in these trials, the relevance of prognostic factors and other characteristics could not be explored reliably in this group (webappendix pp 40–44).

On average, in all the women in these trials, about one breast cancer death was avoided by year 15 for every four recurrences avoided by year 10 (figure 1). For pN+ disease and for pN0 disease with large predicted absolute recurrence benefit the observed ratio was slightly larger, whereas for pN0 disease with intermediate or lower predicted absolute benefit it was somewhat smaller (figure 5). However, the departure from linearity was not statistically significant ( $2p=0.11$ ).

### Discussion

The overall findings from these trials show that radiotherapy after breast-conserving surgery not only substantially reduces the risk of recurrence but also moderately reduces the risk of death from breast cancer. These results suggest that killing microscopic tumour foci in the conserved breast with radiotherapy reduces the potential for both local recurrence and distant metastasis. Both proportional and absolute reductions in the annual recurrence rate are largest in the first year but the recurrence rate continues to be somewhat lower throughout the first decade, whereas the reduction in breast cancer death rate becomes definite only after the first few years and appears to continue into the second decade. Non-breast-cancer mortality and the incidence of contralateral and other second cancers in these and other trials of radiotherapy in early breast cancer will be reported elsewhere, but there appeared to be little adverse effect on 15-year mortality from the aggregate of all causes other than breast cancer, so 15-year all-cause mortality was reduced by almost as much as would be expected from the reduction in breast cancer mortality.

Previous analyses had shown that in pN0 disease young age, large tumour size, and high grade were each strongly predictive of the risk of locoregional recurrence and of the absolute reduction in that risk with radiotherapy.<sup>5</sup> This report combines the predictive value of these and other factors, such as wider tamoxifen use in recent trials. Taken together, they account for the fact that the absolute recurrence reduction with radiotherapy is lower in the more recent postlumpectomy trials (ie, category C trials) than in the original postlumpectomy trials (ie, category A trials, table 2). However, even for women with pN0 disease in the recent low-risk trials the predicted absolute 10-year recurrence reduction with radiotherapy exceeded 10% in most women and exceeded 20% in some women.

Almost a quarter of women with pN0 disease were in trials in which sector resection or quadrantectomy, rather than lumpectomy, was undertaken and tamoxifen was not trial policy for pN0 disease in any of these trials. Recurrence rates were, however, lower than those for women with

similar characteristics in trials in which lumpectomy was performed (figure 4). This difference accords with the findings of the one randomised trial of quadrantectomy versus lumpectomy, both with radiotherapy, in 700 women, two-thirds of whom were node negative.<sup>25</sup> Most of the trials of radiotherapy after lumpectomy required negative surgical margins for invasive cancer (although not for ductal carcinoma in situ). However, pathological techniques have become more sensitive since the women entered these trials, and some would probably have been positive with modern techniques. Therefore, whether the lower recurrence rates recorded in trials of radiotherapy in women given sector resection or quadrantectomy are simply the result of a reduction in the proportion of women with positive margins, or whether there is further benefit to be derived from more extensive surgery, is unknown.

The classification of pN0 disease into three groups with large, intermediate, and lower predicted absolute recurrence benefit from radiotherapy was derived from the recurrence data in these trials. The classification cannot be validated externally and so should not be over-interpreted. Nevertheless, the size of the difference in the absolute recurrence reduction between the three groups is striking. Furthermore, the 15-year reduction in risk of breast cancer death was about as big in pN0 disease with large predicted absolute recurrence benefit as it was in pN+ disease, whereas in pN0 disease with intermediate or lower predicted recurrence benefit the mortality reduction was smaller and neither differed significantly from zero. Therefore the number of breast cancer deaths avoided per recurrence avoided might be more than one in four in pN+ disease and in pN0 disease with large predicted absolute recurrence benefit, and less than one in four for women with intermediate or lower predicted absolute benefit (figure 5). However, the present data do not depart significantly from the one-in-four relationship.

The main analyses presented are of first recurrence of any type rather than, as previously, locoregional recurrence as a first event. This difference is partly because it is now clear that radiotherapy after breast-conserving surgery reduces breast cancer death, so it must also reduce distant recurrence. It is also because women with higher risk of locoregional recurrence have higher risk of distant recurrence (ie, the probabilities of locoregional and of distant recurrence are not statistically independent), so valid estimates of the separate effects of radiotherapy on local and distant recurrence cannot be obtained.<sup>26,27</sup> These issues are more important at 10 years than at 5 years (as presented previously), because more distant recurrences occur by 10 years than by 5 years. The fact that the proportion of first recurrences that were locoregional was much lower in irradiated women than in controls does, however, suggest that the main effect of radiotherapy was to reduce locoregional recurrence, whereas the reduction of the breast cancer death rate by a sixth suggests that the distant recurrence rate was



reduced by at least as much. No analyses have been undertaken of recurrences after the first, because they are affected by treatment policies for the first recurrence, and many trials did not record further recurrences.

Screening, surgery, pathology, radiotherapy, and systemic therapy<sup>28,29</sup> have all changed substantially since most of the women entered these trials, so the absolute recurrence reduction with radiotherapy in future patients might differ greatly from that recorded in these trials. Moreover, information about additional risk factors will often be available (eg, HER2, gene expression profile, margin status) and a radiotherapy boost may be given.<sup>30,31</sup> Nevertheless, the finding that radiotherapy roughly halved the recurrence rate after breast-conserving surgery in a wide range of patients with very different absolute risks (figure 3) suggests that it might also roughly halve the recurrence rate in future patients given breast-conserving surgery but who are not comparable with the women included in the trials analysed here. If so, then in these future patients, a reasonable way to predict the absolute recurrence benefit of radiotherapy would be to construct contemporary estimates of the absolute risk of first recurrence of any type and to assume that radiotherapy will approximately halve it.

#### Contributors

SD, PMcG, and CC designed and undertook the analyses with DC, RP, and CT as internal advisers and TW, ME, LP, and RA as external advisers. All writing committee members contributed to the report. The EBCTCG secretariat, including SD, PMcG, CC, CT, MC, DC, CD, JG, RG, YW, and RP, identified trials, and received, collated, and checked datasets.

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EBCTCG collaborators are listed in webappendix p 48 and in reference 29.

#### Conflicts of interest

Any interests of trialists in treatments or diagnostics and company support of trials (see trial publications) have not affected data availability or EBCTCG meta-analyses of these datasets. EBCTCG is funded from the general long-term financial support from the Cancer Research UK, the British Heart Foundation, and the UK Medical Research Council to the CTSU, University of Oxford (<http://www.ctsu.ox.ac.uk/about/>). CTSU also performs trials funded by industry grants to the University of Oxford that are initiated, conducted, and interpreted independently of study funders. CTSU staff policy excludes honoraria or consultancy fees. All secretariat and writing committee members declare that they have no conflicts of interest.

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## Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

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### ABSTRACT

#### BACKGROUND

Radiotherapy for breast cancer often involves some incidental exposure of the heart to ionizing radiation. The effect of this exposure on the subsequent risk of ischemic heart disease is uncertain.

#### METHODS

We conducted a population-based case-control study of major coronary events (i.e., myocardial infarction, coronary revascularization, or death from ischemic heart disease) in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark; the study included 963 women with major coronary events and 1205 controls. Individual patient information was obtained from hospital records. For each woman, the mean radiation doses to the whole heart and to the left anterior descending coronary artery were estimated from her radiotherapy chart.

#### RESULTS

The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72). Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray (95% confidence interval, 2.9 to 14.5;  $P < 0.001$ ), with no apparent threshold. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy. The proportional increase in the rate of major coronary events per gray was similar in women with and women without cardiac risk factors at the time of radiotherapy.

#### CONCLUSIONS

Exposure of the heart to ionizing radiation during radiotherapy for breast cancer increases the subsequent rate of ischemic heart disease. The increase is proportional to the mean dose to the heart, begins within a few years after exposure, and continues for at least 20 years. Women with preexisting cardiac risk factors have greater absolute increases in risk from radiotherapy than other women. (Funded by Cancer Research UK and others.)

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RANDOMIZED TRIALS HAVE SHOWN THAT radiotherapy for early-stage breast cancer can reduce the rates of recurrence and of death from breast cancer.<sup>1,2</sup> However, long-term follow-up in some trials has shown that radiotherapy can also increase the risk of ischemic heart disease, presumably through incidental irradiation of the heart.<sup>1,3</sup>

Radiotherapy regimens for breast cancer have changed since the women in these trials were irradiated, and the doses of radiation to which the heart is exposed are now generally lower.<sup>4</sup> Nevertheless, in most women, the heart still receives doses of 1 to 5 Gy.<sup>5-11</sup> Several studies have suggested that exposures at this level can cause ischemic heart disease,<sup>12-14</sup> but the magnitude of the risk after any given dose to the heart is uncertain, as are the time to the development of any radiation-related disease and the influence of other cardiac risk factors. We therefore conducted a study relating the risk of ischemic heart disease after radiotherapy to each woman's radiation dose to the heart and to any cardiac risk factors she had at the time of radiotherapy.

## METHODS

### STUDY POPULATION

A population-based case-control study of major coronary events was conducted in women in Sweden and Denmark who received external-beam radiotherapy for invasive breast cancer. Major coronary events were defined as a diagnosis of myocardial infarction (*International Classification of Diseases, 10th Revision* [ICD-10] codes I21-I24), coronary revascularization, or death from ischemic heart disease (ICD-10 codes I20-I25). Patients with a diagnosis of angina alone were not included, because pilot studies showed that we could not reliably identify angina. Patient records from hospital oncology departments were used to obtain data on each woman's medical history before her diagnosis of breast cancer, tumor characteristics, and radiotherapy.

### ELIGIBILITY CRITERIA

A single study protocol was used, but the selection of case patients and controls varied slightly between the two countries. In Sweden, all women living in Stockholm for whom data were recorded in the Swedish National Cancer Register<sup>15</sup>

were considered for the study if they received a diagnosis of breast cancer between 1958 and 2001, were younger than 70 years of age at the time of diagnosis, and had received radiotherapy. Because information on radiotherapy is not kept by the Swedish Register, hospital records were used to determine which women had received radiotherapy. In Denmark, all women for whom data were recorded in the register held by the Danish Breast Cancer Cooperative Group<sup>16</sup> were considered for the study if they received the diagnosis of breast cancer between 1977 and 2000, were younger than 75 years at the time of diagnosis, and received radiotherapy. The study was approved by the Danish Data Protection Agency and by the ethics review board of the Karolinska Institutet in Stockholm. The requirement for informed consent was waived because of the nature of the study.

In both countries, women without histopathological confirmation of breast cancer, with bilateral or metastatic disease at the time of diagnosis, or with a history of cancer (excluding nonmelanoma skin cancer) or previous radiotherapy to the thoracic area were excluded. All other women who received radiotherapy were cross-matched with nationwide registers of diagnosis at the time of hospital discharge and cause of death (up to 2002 in Sweden and 2007 in Denmark).<sup>17</sup> Women whose primary diagnosis was a major coronary event that occurred after a diagnosis of breast cancer but before any recurrence or diagnosis of a second cancer were classified as case patients. Whenever possible, hospital cardiology or autopsy records were reviewed, and if the case-defining event was refuted, the woman was excluded from the study. For each remaining case patient, we defined "time period" as the time from breast-cancer diagnosis to the time of first major coronary event. Controls (one per case patient in Sweden and two per case patient in Denmark) were selected at random from all eligible women in the study population. Eligibility criteria for controls included fulfillment of the matching criteria (country of residence, age at the time of breast-cancer diagnosis, and year of diagnosis, with both age and year matched within 5 years); receipt of radiotherapy; and no recurrence of breast cancer, no diagnosis with another cancer, and no major coronary event before the index date (defined as the date of breast-cancer diagnosis plus the time period of the matched case).



#### RADIATION DOSIMETRY

Individual radiotherapy charts, including a diagram or photograph of the treatment fields and a dose plan (where available) were copied. Virtual simulation and planning based on computed tomography (CT) (or, for a few regimens, manual planning) were used to reconstruct each radiotherapy regimen on the CT scan of a woman with typical anatomy. Virtual simulation and CT planning involved the reconstruction of radiotherapy fields on a CT scan. Radiation doses to the structures of interest were then estimated with the use of the treatment-planning system Helax-TMS, version 6.1B (Nucletron). In manual planning, the doses were estimated on the basis of charts on which isodose curves (i.e., lines delimiting areas receiving the same radiation dose) had been drawn. As previously described,<sup>18,19</sup> dose-volume histograms for the whole heart and for the left anterior descending coronary artery (which often receives the highest dose of radiation from radiotherapy for cancer of the left breast) were obtained for the regimens used, and the mean doses received by these two structures were calculated. Equivalent doses delivered in 2-Gy fractions (EQD2)<sup>20</sup> were calculated from the dose-volume histograms as  $nd[(d+\alpha/\beta)/(2+\alpha/\beta)]$ , where  $n$  was the number of fractions,  $d$  was the dose to the heart per fraction (in Gy), and  $\alpha/\beta$  was 2 Gy.<sup>21</sup>

#### STATISTICAL ANALYSIS

Rate ratios were estimated with the use of conditional logistic regression after stratification according to country and to age at the time of cancer diagnosis, year of cancer diagnosis, and years from cancer diagnosis to first subsequent major coronary event (for case patients) or the index date (for controls) (all in 5-year categories).<sup>22,23</sup> To estimate the proportional increase in the rate of major coronary events per gray of radiation, the data were also stratified according to presence or absence of a cardiac risk factor. The rate of major coronary events was modeled as  $B_s(1+KX)$ , where  $B_s$  was the stratum-specific rate of major coronary events in the absence of radiotherapy,  $X$  was the dose (or EQD2) of cardiac radiation (in Gy), and  $K$  was the percentage increase in the rate of major coronary events per gray. The form  $1+KX$  was chosen for the dose-response relationship because a wide variety of functions are approximately linear for small values of  $X$ . The adequacy of  $1+KX$  for summarizing the dose-response re-

lationship was examined by carrying out analyses based on categories of radiation dose. In these analyses and in tests for interactions between radiation dose and other factors, models similar to the model described above were used. Significance tests were two-sided, and both significance tests and confidence intervals were based on the likelihood ratio. For analyses in which the explanatory variable was categorical, the confidence intervals for every category, including the reference category, were estimated from the amount of information in that category.<sup>24</sup> Calculations were performed with the use of Stata Statistical Software, release 12 (StataCorp),<sup>25</sup> and EpiWin, release 1.8 (Hirosoft International).<sup>26</sup>

### RESULTS

#### CHARACTERISTICS OF THE PATIENTS

A total of 963 women with major coronary events and 1205 controls were included in the study. Among the case-defining major coronary events (i.e., the event resulting in inclusion in the study), 44% occurred less than 10 years after breast cancer was diagnosed, 33% occurred 10 to 19 years afterward, and 23% occurred 20 or more years afterward. Hospital cardiology or autopsy records confirmed the case-defining major coronary event in 65% of case patients and were consistent with the event in 9% of case patients; for the remaining 26% of case patients, no relevant record could be found. A total of 54% of case patients were known to have died from ischemic heart disease, either at the time of their case-defining event or subsequently. (For further information, see Tables S1, S2, and S3 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

#### RISK FACTORS FOR A MAJOR CORONARY EVENT

Women irradiated for cancer of the left breast had higher rates of major coronary events than women irradiated for cancer of the right breast ( $P=0.002$ ), but there were no other strong associations between the rate of major coronary events and tumor characteristics or the cancer treatments administered in addition to radiotherapy (rate ratio, 1.20;  $P=0.06$  for nodal status and  $P\geq 0.10$  for all other tumor or treatment characteristics) (Table 1). In contrast, the overall rate ratio for a major coronary event among women with a history of ischemic heart disease as com-

**Table 1.** Characteristics of the Women in the Study at the Time of Breast-Cancer Diagnosis and Association between the Characteristics and the Subsequent Rate of Major Coronary Events.\*

| Characteristic                                                     | No. of Case Patients<br>(N=963) | No. of Controls<br>(N=1205) | Rate Ratio | P Value† |
|--------------------------------------------------------------------|---------------------------------|-----------------------------|------------|----------|
| <b>Tumor characteristics</b>                                       |                                 |                             |            |          |
| Nodal status                                                       |                                 |                             |            | 0.06     |
| Negative                                                           | 482                             | 610                         | 1.00       |          |
| Positive                                                           | 463                             | 579                         | 1.20       |          |
| Unknown                                                            | 18                              | 16                          | 0.96       |          |
| Size                                                               |                                 |                             |            | 0.97     |
| <2 cm                                                              | 331                             | 449                         | 1.00       |          |
| 2–5 cm                                                             | 494                             | 604                         | 1.00       |          |
| Other or unknown                                                   | 138                             | 152                         | 1.08       |          |
| Location                                                           |                                 |                             |            | 0.22     |
| Outer quadrants                                                    | 350                             | 572                         | 1.00       |          |
| Inner quadrants                                                    | 114                             | 204                         | 0.84       |          |
| Other or unknown                                                   | 499                             | 429                         | 0.82       |          |
| Laterality of breast cancer                                        |                                 |                             |            | 0.002    |
| Right                                                              | 420                             | 604                         | 1.00       |          |
| Left                                                               | 543                             | 601                         | 1.32       |          |
| <b>Cancer treatment</b>                                            |                                 |                             |            |          |
| Surgery                                                            |                                 |                             |            | 0.22     |
| Mastectomy                                                         | 748                             | 860                         | 1.00       |          |
| Breast-conserving surgery                                          | 212                             | 337                         | 0.86       |          |
| None                                                               | 3                               | 8                           | 0.39       |          |
| Adjuvant hormonal therapy‡                                         |                                 |                             |            | 0.10     |
| No                                                                 | 732                             | 892                         | 1.00       |          |
| Yes                                                                | 229                             | 311                         | 1.23       |          |
| Unknown                                                            | 2                               | 2                           | 0.80       |          |
| Adjuvant chemotherapy§                                             |                                 |                             |            | 0.13     |
| No                                                                 | 889                             | 1057                        | 1.00       |          |
| Yes                                                                | 74                              | 148                         | 0.73       |          |
| Ovarian ablation¶                                                  |                                 |                             |            | 0.54     |
| No                                                                 | 774                             | 1027                        | 1.00       |          |
| Yes                                                                | 70                              | 89                          | 0.89       |          |
| Unknown                                                            | 119                             | 89                          | 1.54       |          |
| <b>Factors associated with subsequent coronary event</b>           |                                 |                             |            |          |
| No known cardiac risk factors                                      | 353                             | 600                         | 1.00       | <0.001   |
| History of ischemic heart disease                                  | 109                             | 38                          | 6.67**     |          |
| Risk factors other than ischemic heart disease††                   | 458                             | 527                         | 1.96**     |          |
| Unknown                                                            | 43                              | 40                          | 1.23       |          |
| History of circulatory disease other than ischemic heart disease‡‡ |                                 |                             |            | <0.001   |
| No                                                                 | 536                             | 845                         | 1.00       |          |
| Yes                                                                | 265                             | 269                         | 1.88       |          |
| Unknown                                                            | 53                              | 53                          | 1.04       |          |
| History of diabetes§§                                              |                                 |                             |            | <0.001   |
| No                                                                 | 704                             | 1056                        | 1.00       |          |
| Yes                                                                | 55                              | 29                          | 3.23       |          |
| Unknown                                                            | 95                              | 82                          | 1.19       |          |
| History of COPD¶¶                                                  |                                 |                             |            | <0.001   |
| No                                                                 | 736                             | 1076                        | 1.00       |          |
| Yes                                                                | 15                              | 6                           | 6.33       |          |
| Unknown                                                            | 103                             | 85                          | 1.24       |          |

Table 1. (Continued.)

| Characteristic              | No. of Case Patients<br>(N = 963) | No. of Controls<br>(N = 1205) | Rate Ratio | P Value† |
|-----------------------------|-----------------------------------|-------------------------------|------------|----------|
| Current smoker§§            |                                   |                               |            | <0.001   |
| No                          | 160                               | 344                           | 1.00       |          |
| Yes                         | 167                               | 195                           | 1.87       |          |
| Unknown                     | 527                               | 628                           | 1.39       |          |
| BMI§§§                      |                                   |                               |            | 0.002    |
| <30                         | 321                               | 574                           | 1.00       |          |
| ≥30                         | 139                               | 165                           | 1.57       |          |
| Unknown                     | 394                               | 428                           | 1.00       |          |
| Analgesic medication§§§     |                                   |                               |            | 0.02     |
| No                          | 509                               | 836                           | 1.00       |          |
| Yes                         | 50                                | 54                            | 1.65       |          |
| Unknown                     | 295                               | 277                           | 1.01       |          |
| Other medications           |                                   |                               |            |          |
| Hormone-replacement therapy |                                   |                               |            | 0.006    |
| No                          | 495                               | 731                           | 1.00       |          |
| Yes                         | 79                                | 178                           | 0.66       |          |
| Unknown                     | 389                               | 296                           | 1.70       |          |
| Thyroid medication          |                                   |                               |            | 0.60     |
| No                          | 635                               | 888                           | 1.00       |          |
| Yes                         | 26                                | 37                            | 0.87       |          |
| Unknown                     | 302                               | 280                           | 0.90       |          |
| Other medications¶¶¶        |                                   |                               |            | 0.08     |
| No                          | 740                               | 958                           | 1.00       |          |
| Yes                         | 38                                | 70                            | 0.69       |          |
| Unknown                     | 185                               | 177                           | 0.84       |          |

\* The category listed first is the baseline category. Rate ratios were estimated after stratification according to country and age at breast-cancer diagnosis, year of breast-cancer diagnosis, and years from breast-cancer diagnosis to first subsequent major coronary event (for case patients) or index date (for controls) (all in 5-year categories). BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters).

† The test for heterogeneity between categories did not include the categories of “unknown” or “other or unknown.”

‡ Adjuvant hormonal therapy consisted of tamoxifen in 197 case patients and 258 controls, an aromatase inhibitor in 6 case patients and 16 controls, and another medication in 26 case patients and 37 controls.

§ Chemotherapy consisted of cyclophosphamide, methotrexate, and fluorouracil in 44 case patients and 105 controls; an anthracycline-based regimen in 8 case patients and 9 controls; and other chemotherapy (but without an anthracycline) in 22 case patients and 34 controls.

¶ For 34 case patients and 55 controls, ovarian ablation consisted of oophorectomy before the diagnosis of breast cancer.

|| Women with a history of ischemic heart disease were defined as those for whom myocardial infarction or angina had been cited in their oncology record at the time of breast-cancer diagnosis or for whom ischemic heart disease had been recorded as a primary diagnosis in the hospital discharge register before the breast-cancer diagnosis.

\*\* These rate ratios can be subdivided according to the time since breast-cancer diagnosis. Rate ratios for major coronary events in women with a history of ischemic heart disease up to 10 years and 10 or more years after breast-cancer diagnosis were 13.43 (95% confidence interval [CI], 7.65 to 23.58) and 2.09 (95% CI, 1.05 to 4.13), respectively ( $P < 0.001$ ). Rate ratios for major coronary events in women without a history of ischemic heart disease but with other cardiac risk factors for up to 10 years and for 10 years or more after the breast-cancer diagnosis were 2.60 (95% CI, 1.89 to 3.57) and 1.63 (95% CI, 1.24 to 2.15), respectively ( $P = 0.03$ ). See Table S4 in the Supplementary Appendix for further details.

†† The factors associated with a subsequent risk of heart disease in women without a history of ischemic heart disease included factors for which the association was likely to be causal (e.g., current smoker) and factors for which the association was indirect (e.g., history of chronic obstructive pulmonary disease).

‡‡ This category excludes 109 case patients and 38 controls who had a history of ischemic heart disease (as defined above) and indicates which of the remaining women who, before their diagnosis of breast cancer, had received a primary diagnosis of circulatory disease (*International Classification of Diseases, 10th Revision*, codes I-00 to I-15 or I-26 to I-99), according to the hospital discharge register, or had received medication for cardiac disease or hypertension according to their oncology record.

§§ This category excludes 109 case patients and 38 controls who had a history of ischemic heart disease (as defined above) and indicates which of the remaining women appeared in the hospital discharge register with this condition as a primary diagnosis before breast-cancer diagnosis or had an oncology record in which this factor was cited.

¶¶ This category excludes women who at the time of their diagnosis were receiving medication for cardiac disease or hypertension or an analgesic medication, according to the oncology record.

pared with women with no such history was 6.67 (95% confidence interval [CI], 4.37 to 10.18). The rate ratio was 13.43 (95% CI, 7.65 to 23.58) during the first 10 years after the cancer diagnosis as compared with 2.09 (95% CI, 1.05 to 4.13) during later years ( $P<0.001$ ) (Table S4 in the Supplementary Appendix). Rates of major coronary events were also elevated among women with a history of other circulatory diseases, diabetes, or chronic obstructive pulmonary disease; among women who smoked; and among women with a high body-mass index or a history of regular analgesic use. The rate ratio for the presence of one or more of these factors but no ischemic heart disease was 1.96 overall (95% CI, 1.60 to 2.40); during the first 10 years after the cancer diagnosis, the rate ratio was 2.60 (95% CI, 1.89 to 3.57) as compared with 1.63 (95% CI, 1.24 to 2.15) during later years ( $P=0.03$ ).

#### EFFECT OF RADIOTHERAPY

The overall average of the estimated mean doses of radiation to the heart was 6.6 Gy for women with tumors in the left breast, 2.9 Gy for those with tumors in the right breast, and 4.9 Gy overall (range, 0.03 to 27.72). The rate of major coronary events increased by 7.4% for each increase of 1 Gy in the mean radiation dose delivered to the heart (95% CI, 2.9 to 14.5;  $P<0.001$ ) (Fig. 1). When women were grouped according to whether the mean radiation dose to the heart was less than 2 Gy, 2 to 4 Gy, 5 to 9 Gy, or 10 or more Gy, the percentage increases in the rate of major coronary events in these four categories, as compared with the estimated rate if the cardiac dose had been zero, were 10% (95% CI, -9 to 33), 30% (95% CI, 14 to 49), 40% (95% CI, 15 to 72), and 116% (95% CI, 59 to 195), respectively. The percentage increase per gray did not differ significantly according to any of the matching factors used in the selection of controls, tumor characteristics (including whether the tumor was in the left or right breast), or cancer treatments in addition to radiotherapy. Despite the fact that the rate of major coronary events was higher among women with cardiac risk factors than among those without such risk factors, the percentage increase in the rate of major coronary events per gray was similar for women with and those without a cardiac risk factor at the time of breast-cancer diagnosis (Table 2).

#### VARIATION WITH TIME SINCE EXPOSURE

The percentage increases in the rate of major coronary events per gray of radiation according to the number of years since radiation exposure were as follows: 0 to 4 years, 16.3% (95% CI, 3.0 to 64.3); 5 to 9 years, 15.5% (95% CI, 2.5 to 63.3); 10 to 19 years, 1.2% (95% CI, -2.2 to 8.5); and 20 or more years, 8.2% (95% CI, 0.4 to 26.6) (Table 3). The variation among these values was consistent with random variation ( $P=0.16$  for heterogeneity;  $P=0.26$  for trend). Findings were similar when the analysis was repeated separately according to age at the time of the breast-cancer diagnosis, the presence or absence of preexisting cardiac risk factors, whether the case patient had died from ischemic heart disease, and whether the case patient's hospital cardiology record or autopsy record had been reviewed (Tables S5 through S8 in the Supplementary Appendix).

#### OTHER MEASURES OF DOSE

The overall average of the mean EQD2 doses to the heart was 3.9 Gy (range, 0.1 to 30.4). The mean doses and the EQD2 doses to the heart were highly correlated (correlation coefficient, 0.98). The results of analyses based on dose and EQD2 dose were therefore similar (Fig. S1 in the Supplementary Appendix). Estimated mean doses to the left anterior descending coronary artery and to the heart were also correlated (correlation coefficient, 0.76) (Table S9 in the Supplementary Appendix). The mean dose of radiation to the heart was a better predictor of the rate of major coronary events than the mean dose to the left anterior descending coronary artery ( $P<0.001$  for mean dose to the heart;  $P=0.001$  for mean dose to the left anterior descending coronary artery). The mean dose of radiation to the heart remained significantly associated with the rate of major coronary events after the mean dose to the left anterior descending coronary artery was taken into account ( $P=0.04$ ). However, the converse did not apply: the mean dose to the left anterior descending coronary artery was not significantly associated with the rate of major coronary events after the mean dose to the heart was taken into account ( $P=0.62$ ).

#### DISCUSSION

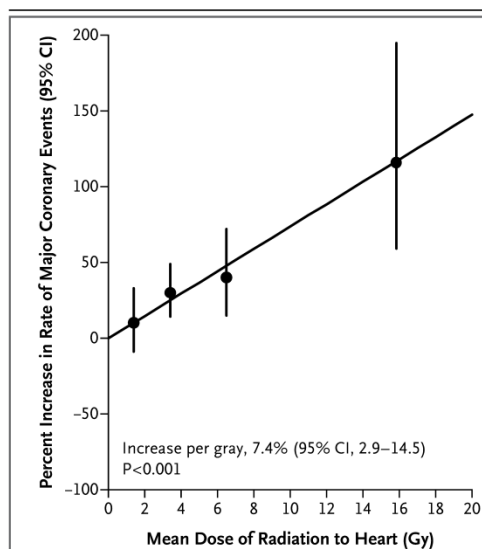
Breast cancer is the most common cancer in women worldwide, with more than 1 million new



diagnoses each year.<sup>27</sup> Moreover, every year, tens of thousands of women worldwide receive a diagnosis of ductal carcinoma in situ. The overall 5-year survival rate for these two diagnostic groups combined is approximately 90%, and in both groups many of the survivors will have received radiotherapy.<sup>28</sup> Current mean doses of radiation to the heart from radiotherapy for breast cancer are typically about 1 or 2 Gy for disease of the right breast. For disease of the left breast, the doses are usually higher but vary widely, and for some women, including those in whom the distance of the heart to the thoracic wall is small and those who require internal mammary irradiation, the mean dose may be around 10 Gy.<sup>5-11</sup>

Among the 2168 women in this study, the mean dose to the heart ranged from 0.03 Gy to 27.72 Gy, with an overall average of the mean doses of 4.9 Gy. The risk of a major coronary event increased linearly with the mean dose to the heart. The magnitude of the risk was 7.4% per gray, with no apparent threshold below which there was no risk. The risk started to increase within the first 5 years after exposure and continued for at least 20 years. The percentage increase in risk per gray was similar for women with and those without cardiac risk factors at the time of radiotherapy.

A strength of this study is that it relates the risk of ischemic heart disease among women who have received radiotherapy for breast cancer to individual doses of cardiac radiation and individual cardiac risk factors at the time of their cancer diagnosis. Other strengths of the study are that it was carried out in women with cancer that had not recurred (thus avoiding confusion with the influence of further treatment); that it was population-based, including all women recorded as receiving radiotherapy for breast cancer in Denmark or Stockholm during the period of interest (thus avoiding the tendency in randomized trials to omit patients in poor health); and that the majority of cardiac events were confirmed by a review of cardiology or autopsy records. Because health status may play a role in the selection of women for radiotherapy, we included in the study only women who had received radiotherapy; nonrandomized comparisons of women who underwent irradiation with those who did not could produce misleading estimates of risk.<sup>29</sup>



**Figure 1. Rate of Major Coronary Events According to Mean Radiation Dose to the Heart, as Compared with the Estimated Rate with No Radiation Exposure to the Heart.**

Major coronary events included myocardial infarction, coronary revascularization, and death from ischemic heart disease. The values for the solid line were calculated with the use of dose estimates for individual women. The circles show values for groups of women, classified according to dose categories; the associated vertical lines represent 95% confidence intervals. All estimates were calculated after stratification for country and for age at breast-cancer diagnosis, year of breast-cancer diagnosis, interval between breast-cancer diagnosis and first major coronary event for case patients or index date for controls (all in 5-year categories), and presence or absence of a cardiac risk factor. The radiation categories were less than 2, 2 to 4, 5 to 9, and 10 Gy or more, and the overall averages of the mean doses to the heart of women in these categories were 1.4, 3.4, 6.5, and 15.8 Gy, respectively.

A limitation of our study was that individual CT-based information on radiotherapy was unavailable for the women studied, because they were treated before the era of three-dimensional CT-based planning. However, we have used 20 consecutive individual CT-based, three-dimensional planning scans to show that for left and right tangential radiotherapy and for left and right direct internal mammary fields, the patient-to-patient variation in mean radiation dose to the heart is small (coefficients of variation, 30%, 11%, 11%, and 21%, respectively).<sup>4</sup> We have also confirmed that the patient with typical anatomy who

was used to calculate the dose estimates in this study was average in terms of the radiation dose to her heart. Consideration of irradiated structures within the heart<sup>30,31</sup> may prove fruitful in the future, but in the present study, inclusion of the estimated mean dose to the left anterior descending coronary artery did not improve prediction of the rate of major coronary events.

Since our study included few women who were

younger than 40 years of age at the time of radiotherapy, caution is needed in applying our results to women in this age group, and the possibility of larger increases in the rate of major coronary events per gray of radiation for this group cannot be ruled out. Few women in this study were treated with anthracyclines, and none with taxanes or trastuzumab, all of which are known to affect the heart, even in the absence of radiotherapy.<sup>32</sup>

**Table 2.** Radiation Dose to the Heart and Percentage Increase in the Rate of Major Coronary Events per Gray, According to Risk Factors and Other Characteristics.\*

| Characteristic                                          | Radiation Dose to Heart<br>Gy | Increase in Rate of Major<br>Coronary Events (95% CI)†<br>% increase/Gy | P Value<br>for Heterogeneity‡ |
|---------------------------------------------------------|-------------------------------|-------------------------------------------------------------------------|-------------------------------|
| Characteristics used for selection of matched controls§ |                               |                                                                         |                               |
| Country                                                 |                               |                                                                         | 0.38                          |
| Sweden                                                  | 5.4±5.7                       | 5.7 (1.2 to 13.7)                                                       |                               |
| Denmark                                                 | 4.4±2.7                       | 11.2 (2.5 to 30.7)                                                      |                               |
| Age at diagnosis of breast cancer (yr)                  |                               |                                                                         | 0.99                          |
| 20–39                                                   | 4.7±4.8                       | –1.5 (<–25.3 to 61.6)                                                   |                               |
| 40–49                                                   | 4.9±4.8                       | 6.3 (–2.0 to 41.3)                                                      |                               |
| 50–59                                                   | 5.1±4.8                       | 7.1 (0.4 to 22.2)                                                       |                               |
| 60–69                                                   | 4.8±4.2                       | 7.8 (1.7 to 19.7)                                                       |                               |
| 70–74                                                   | 4.9±3.1                       | 9.7 (–2.9 to 116)                                                       |                               |
| Year of breast-cancer diagnosis                         |                               |                                                                         | 0.13                          |
| 1958–1969                                               | 3.7±4.1                       | 6.6 (–0.2 to 20.7)                                                      |                               |
| 1970–1979                                               | 7.3±6.3                       | 20.4 (5.4 to 79.2)                                                      |                               |
| 1980–1989                                               | 4.9±3.6                       | 0.8 (–2.8 to 8.7)                                                       |                               |
| 1990–2001                                               | 4.2±2.7                       | 11.8 (–0.1 to 56.2)                                                     |                               |
| Tumor characteristics                                   |                               |                                                                         |                               |
| Nodal status                                            |                               |                                                                         | 0.26                          |
| Negative                                                | 4.8±4.4                       | 4.0 (–1.0 to 14.1)                                                      |                               |
| Positive                                                | 5.0±4.3                       | 11.8 (2.7 to 33.6)                                                      |                               |
| Size                                                    |                               |                                                                         | 0.24                          |
| <2 cm                                                   | 4.9±4.2                       | 20.4 (3.6 to 98.3)                                                      |                               |
| 2–5 cm                                                  | 4.9±4.5                       | 6.9 (1.1 to 18.0)                                                       |                               |
| Location                                                |                               |                                                                         | 0.17                          |
| Outer quadrants                                         | 4.4±2.8                       | 10.0 (1.1 to 32.8)                                                      |                               |
| Inner quadrants                                         | 4.8±3.5                       | –2.1 (<–6.9 to 21.2)                                                    |                               |
| Laterality of breast cancer                             |                               |                                                                         | 0.88                          |
| Right                                                   | 2.9±2.5                       | 5.0 (–2.2 to 22.5)                                                      |                               |
| Left                                                    | 6.6±4.9                       | 4.1 (–0.4 to 13.8)                                                      |                               |

**Table 2. (Continued.)**

| Characteristic                                                       | Radiation Dose to Heart<br>Gy | Increase in Rate of Major<br>Coronary Events (95% CI) <sup>†</sup><br>% increase/Gy | P Value<br>for Heterogeneity <sup>‡</sup> |
|----------------------------------------------------------------------|-------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------|
| Cancer treatment                                                     |                               |                                                                                     |                                           |
| Surgery                                                              |                               |                                                                                     | 0.59                                      |
| Mastectomy                                                           | 5.1±4.7                       | 8.7 (3.2 to 18.0)                                                                   |                                           |
| Breast-conserving surgery                                            | 4.3±3.1                       | 14.9 (−0.1 to 77.6)                                                                 |                                           |
| Adjuvant hormonal therapy                                            |                               |                                                                                     | 0.55                                      |
| No                                                                   | 5.0±4.7                       | 10.0 (3.9 to 20.4)                                                                  |                                           |
| Yes                                                                  | 4.7±3.4                       | 5.2 (−2.1 to 29.0)                                                                  |                                           |
| Adjuvant chemotherapy                                                |                               |                                                                                     | 0.47                                      |
| No                                                                   | 5.0±4.5                       | 7.6 (2.9 to 15.2)                                                                   |                                           |
| Yes                                                                  | 4.6±3.3                       | −0.4 (−6.7 to 70.2)                                                                 |                                           |
| Ovarian ablation                                                     |                               |                                                                                     | 0.94                                      |
| No                                                                   | 4.9±4.2                       | 5.5 (1.1 to 12.9)                                                                   |                                           |
| Yes                                                                  | 4.3±4.2                       | 6.5 (−3.6 to 77.7)                                                                  |                                           |
| Factors associated with subsequent major coronary event <sup>¶</sup> |                               |                                                                                     | 0.99                                      |
| No                                                                   | 5.1±4.7                       | 7.4 (1.8 to 17.8)                                                                   |                                           |
| Yes                                                                  | 4.9±4.1                       | 7.4 (1.1 to 19.5)                                                                   |                                           |
| Other medications <sup>  </sup>                                      |                               |                                                                                     | 0.58                                      |
| No                                                                   | 4.8±4.1                       | 8.4 (1.9 to 21.3)                                                                   |                                           |
| Yes                                                                  | 4.7±3.6                       | 2.8 (−4.3 to 47.3)                                                                  |                                           |
| Death of case patient from ischemic heart disease <sup>**</sup>      |                               |                                                                                     | 0.81                                      |
| No                                                                   | 4.9±4.2                       | 8.0 (2.3 to 17.2)                                                                   |                                           |
| Yes                                                                  | 4.9±4.5                       | 7.2 (2.4 to 14.9)                                                                   |                                           |
| Cardiology record of case patient reviewed <sup>††</sup>             |                               |                                                                                     | 0.60                                      |
| No                                                                   | 4.5±3.1                       | 9.2 (1.8 to 21.7)                                                                   |                                           |
| Yes                                                                  | 5.1±4.8                       | 7.0 (2.5 to 14.2)                                                                   |                                           |
| All women                                                            | 4.9±4.4                       | 7.4 (2.9 to 14.5)                                                                   |                                           |

\* Radiation doses to the heart are arithmetic averages of mean doses to the whole heart for cases and controls combined, with standard deviations.

† Rates were estimated after stratification according to country, age at breast-cancer diagnosis, year of breast-cancer diagnosis, and years from breast-cancer diagnosis to first major coronary event (for case patients) or index date (for controls) (in 5-year categories), the presence or absence of a cardiac risk factor, and the characteristic under examination.

‡ P values are based on tests for heterogeneity between the percentage increases in the rate of major coronary events per gray of radiation for the categories listed for each characteristic.

§ The numbers of women in each category for the variables used as the basis of selection are listed in Table S2 in the Supplementary Appendix.

¶ Women for whom information about cardiac risk factors was unavailable were classified as not having the risk factors.

|| This category includes medications other than those prescribed for cardiac disease or hypertension and analgesic medications.

\*\* "Yes" indicates case patients for whom ischemic heart disease was known to be the underlying cause of death and their matched controls.

"No" indicates case patients for whom it was not the underlying cause of death and their matched controls.

†† "Yes" indicates case patients for whom a hospital cardiology or autopsy record was reviewed and was found to confirm or to be consistent with the case-defining event and their matched controls. "No" indicates case patients for whom no information was available for cardiology review and their matched controls.

**Table 3.** Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

| Time since Radiotherapy* | No. of Case Patients | No. of Controls | Increase in Rate of Major Coronary Events (95% CI)†<br>% increase/Gy |
|--------------------------|----------------------|-----------------|----------------------------------------------------------------------|
| 0 to 4 yr                | 206                  | 328             | 16.3 (3.0 to 64.3)                                                   |
| 5 to 9 yr                | 216                  | 296             | 15.5 (2.5 to 63.3)                                                   |
| 10 to 19 yr              | 323                  | 388             | 1.2 (–2.2 to 8.5)                                                    |
| ≥20 yr                   | 218                  | 193             | 8.2 (0.4 to 26.6)                                                    |
| 0 to ≥20 yr              | 963                  | 1205            | 7.4 (2.9 to 14.5)                                                    |

\* The values shown are the numbers of years since the breast-cancer diagnosis. The median time from the breast-cancer diagnosis to the start of radiotherapy was 42 days.

† The percentage increase was estimated after stratification according to country, age at breast-cancer diagnosis, year of breast-cancer diagnosis, years from breast-cancer diagnosis to first major coronary event (for case patients) or index date (for controls), and the presence or absence of a cardiac risk factor. Chi-square for heterogeneity=5.2 with 3 df, P=0.16; chi-square for trend=1.2 with 1 df, P=0.26.

Studies comparing rates of cardiac disease among women who received radiotherapy for cancer of the left breast and women who received radiotherapy for cancer of the right breast have been reviewed elsewhere.<sup>33–35</sup> Such studies are likely to underestimate the extent of any radiation-related risk because they rely on any difference in cardiac dose between women irradiated for tumors in the left breast and those irradiated for tumors in the right breast. In addition, these studies have generally not had information on whether a woman had prior heart disease, and thus could not account for any tendency to avoid irradiation in women with preexisting cardiac risk factors and cancer of the left breast or for the exclusion of women whose only diagnosis was angina (which may be unreliably recorded in routine records). In our study, the radiation-related increase in the risk of major coronary events began within the first 5 years after exposure. Early increases in risk have been reported in studies of patients with Hodgkin's lymphoma who received radiotherapy.<sup>36–38</sup> The effect of preexisting cardiac risk factors on the risk of radiation-related ischemic heart disease has not been well studied, but one report on patients with breast cancer indicated that the absolute effect of radiotherapy was greater in smokers than in nonsmokers.<sup>39</sup> Several studies have empirically investigated the relationship between cardiac radiation dose and risk of heart

disease (Table S10 in the Supplementary Appendix). The estimates vary considerably, but this is to be expected, since both the populations studied and the end points reported were diverse.

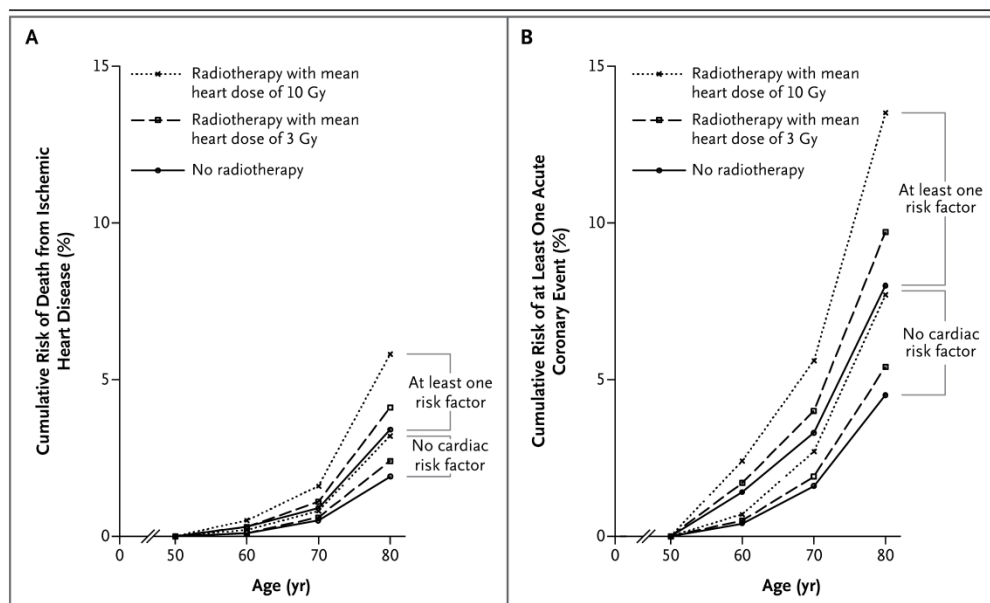
The relevance of our findings to a woman receiving radiotherapy for breast cancer today is that they make it possible to estimate her absolute risk of radiation-related ischemic heart disease. This absolute risk can be weighed against the probable absolute reduction in her risk of recurrence or death from breast cancer that would be achieved with radiotherapy.<sup>2</sup> The percentage increases in risk per unit increase in the mean dose of radiation to the heart are similar for women with and women without preexisting cardiac risk factors. Therefore, absolute radiation-related risks are greater for women with preexisting cardiac risk factors than for other women.

Data from a case-control study do not by themselves permit estimation of absolute risks. Therefore, we have illustrated our results on the risk of fatal ischemic heart disease by combining them with recent data on rates of death from ischemic heart disease for the 15 westernmost countries of the European Union combined (Table S11 in the Supplementary Appendix). We have also illustrated the effect of radiotherapy for breast cancer on the risk of an acute coronary event (i.e., a major coronary event or unstable angina) by assuming that for women younger than 50 years of age, those 50 to 59 years of age, those 60 to 69 years of age, and those 70 to 79 years of age, the rates of acute coronary events are 6 times, 5 times, 3 times, and 2 times the rates of death from ischemic heart disease, respectively.<sup>40</sup> The resulting baseline lifetime risk estimates are similar to recent estimates for the United States.<sup>41</sup>

For a 50-year-old woman with no preexisting cardiac risk factors, radiotherapy involving a mean dose to the heart of 3 Gy would increase her risk of death from ischemic heart disease before the age of 80 years from 1.9% to 2.4% (i.e., an absolute increase of about 0.5 percentage points), and it would increase her risk of having at least one acute coronary event from 4.5% to 5.4% (i.e., an absolute increase of about 0.9 percentage points) (Fig. 2). If her mean cardiac dose were 10 Gy, her absolute risk of death from ischemic heart disease would increase from 1.9% to 3.4% (1.5 percentage points), and her absolute risk of having at least one acute coronary event would increase from 4.5% to 7.7% (3.2 percentage points).

For women with one or more preexisting car-





**Figure 2. Cumulative Risks of Death from Ischemic Heart Disease and of at Least One Acute Coronary Event.**

In Panel A, rates of death from ischemic heart disease and from all causes in the underlying population were assumed to be equal to the most recent values available (mostly for the year 2010) for the 15 westernmost countries of the European Union (Table S11 in the Supplementary Appendix). In Panel B, the rates of acute coronary events in women in the underlying population who were younger than 50, 50 to 59, 60 to 69, and 70 to 79 years of age were assumed to be 6 times, 5 times, 3 times, and 2 times the rate of death from ischemic heart disease, respectively. In both panels, results are shown for a woman who was 50 years old at the time of breast-cancer diagnosis who received either no radiotherapy or radiotherapy with a mean dose to the heart of 3 Gy or 10 Gy. Results are shown for women with no cardiac risk factors and for those with one or more cardiac risk factors. In both panels, the distribution of cardiac risk factors in the population was assumed to be equal to that in the present study. Cumulative risks for other mean doses of radiation to the heart and for different ages at irradiation are provided in Tables S12 and S13 in the Supplementary Appendix. Acute coronary events are nonfatal or fatal major coronary events or unstable angina.

diac risk factors, both the baseline risks and the absolute increases in risk are higher. For example, radiotherapy involving a mean dose of radiation to the heart of 3 Gy in a 50-year-old woman with one or more cardiac risk factors would increase her risk of death from ischemic heart disease before the age of 80 years from 3.4% to 4.1% (an absolute increase of 0.7 percentage points), and it would increase her absolute risk of having an acute coronary event by the age of 80 years by 1.7 percentage points. A mean dose of 10 Gy to her heart would result in radiation-related risks that were considerably higher.

In conclusion, we found that incidental exposure of the heart to radiotherapy for breast cancer increased the rate of major coronary events by 7.4% per gray, with no apparent threshold. The percentage increase per unit increase in the mean dose of radiation to the heart was similar for women with and women without preexisting car-

diac risk factors, which indicates that the absolute increases in risk for a given dose to the heart were larger for women with preexisting cardiac risk factors. Therefore, clinicians may wish to consider cardiac dose and cardiac risk factors as well as tumor control when making decisions about the use of radiotherapy for breast cancer.

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## **Appendix G**

### **Contributions to and Planned Extensions of Studies in the Thesis**

The introductory chapters (1 to 3) are the work of DC alone. The studies presented in chapters 4 to 8 were all highly collaborative with contributions as described below. SD provided appropriate supervision throughout.

#### **Circulatory Mortality in the British Childhood Cancer Survivor Study (Chapter 4)**

- DC – Design of study, analysis and interpretation of data, composition of chapter
- SR – Assistance with (and programming for) statistical analyses
- MH and DW – Supply of data

Planned extensions:

- Analyses of non-fatal events within cohort
- Analyses of cardiovascular risk factors within cohort
- Extension of cohort to include 16,000 additional patients diagnosed 1992 to 2005

#### **Risk Factors for Valvular Heart Disease following Hodgkin Lymphoma (Chapter 5)**

- DC – Design of study, retrospective radiation dosimetry for cases and controls, analysis and interpretation of data, composition of the chapter
- MS – Co-ordination of data collection, assistance with (and programming for) statistical analyses
- YW – Programming for manipulation of DVH data from radiation dosimetry

Planned extensions:

- Extension of the cohort to provide a greater number of cases of VHD and controls
- Further case-control studies of ischaemic heart disease and cardiomyopathy/heart failure within the same cohort
- Development of methods of retrospective radiation dosimetry

#### **Cardiovascular Radiation Dosimetry and Predicted Excess Cardiac Mortality due to IFRT in the UK RAPID trial in Low-Risk, Early Stage Hodgkin Lymphoma (Chapter 6)**

- DC – Design of study, cardiovascular contouring and radiation dosimetry, analysis and interpretation of data, composition of chapter
- PD – Collection of RT data via RT quality assurance hub at Mount Vernon Hospital
- AB – Assistance with import of DICOM data into Eclipse and automation of EDQ2/NTCP calculations

Planned extensions:

- Cardiovascular dosimetry and risk modelling study within the proposed NCRI lymphoma CSG trial of IFRT vs. ISRT ('RADIO')

#### **A Clinical Tool for Estimating Mean Whole Heart Dose Radiation Dose from Involved Field Radiotherapy Including the Mediastinum (Chapter 7)**

- DC – Design of study, cardiovascular contouring, planning of radiation treatments, radiation dosimetry, analysis and interpretation of data, composition of chapter
- TF – Assistance with (and programming for) analysis of data and interpretation

Planned extensions:

- Use of CT data sets and results to further refine methods of retrospective cardiovascular radiation dosimetry for use in other studies (e.g. Dutch HL case-control studies)

Characterisation the Heart Using Cardiovascular Magnetic Resonance Imaging in Women Receiving Radiotherapy for Early Breast Cancer (Chapter 8)

- DC – Design of study, recruitment of participants, cardiovascular contouring and radiation dosimetry, analysis of strain rate imaging, data analysis and interpretation, composition of chapter
- VF (and colleagues from the University of Oxford Centre for Clinical Magnetic Resonance Research) – Cardiovascular assessments (including CMR scans), data collection, analysis of CMR results, supervision of analysis of strain rate imaging

Planned extensions:

- Extension of study to include women of higher cardiovascular risk
- Use of CMR to study radiation-related cardiac dysfunction in other cancer types

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