

**BREAST CANCER RADIOTHERAPY  
AND HEART DISEASE**

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# **Breast Cancer Radiotherapy and Heart Disease**

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## **Abstract**

### **Introduction**

Some past breast cancer radiotherapy regimens led to an increased risk of death from heart disease. Although heart dose from breast cancer radiotherapy has generally reduced over the past few decades, there may still be some cardiac risk. Estimation of future risk for women irradiated today requires both measurement of their cardiac dose and dose-response relationships, which depend on cardiac dosimetry of past regimens, in conjunction with long-term follow-up data.

### **Methods**

Virtual simulation and computed tomography 3-dimensional treatment planning on a representative patient were used to estimate mean heart and coronary artery doses for women irradiated since 1950 in 71 randomised trials in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview. Patient-to-patient variability in cardiac dose was assessed.

Heart and coronary artery doses were also calculated for breast cancer radiotherapy regimens used since the 1950s in Sweden.

Cardiac doses from contemporary (year 2006) radiotherapy were assessed for 55 patients who received tangential breast cancer irradiation at a large UK radiotherapy centre. The maximum heart distance (i.e. the maximum distance between the anterior cardiac contour and the posterior tangential field edges) was measured for the left-sided patients, and its value as a predictor of cardiac doses assessed.

### **Results**

Mean heart dose for women irradiated in the EBCTCG trials varied from <1 to 18 Gray, and mean coronary artery dose from <1 to 57 Gray. Patient-to-patient variability was moderate.

Mean heart dose for women irradiated in Sweden since the 1950s varied from <1 to 24 Gray, and mean coronary artery dose from <1 to 46 Gray.

Heart dose from tangential irradiation has reduced over the past four decades. However, mean heart dose for left-sided patients irradiated in 2006 was 2 Gray and around half of them still received >20 Gray to parts of the heart and left anterior descending coronary artery. For these patients, maximum heart distance was a reliable predictor of cardiac doses. For the other patients, mean heart dose varied little and was usually less than 2 Gray.

### **Conclusions**

Cardiac doses from breast cancer radiotherapy can be estimated reliably and are now available for use in deriving dose-response relationships in the EBCTCG data and in a Scandinavian case-control study. Cardiac dose has reduced over the past four decades. Therefore the cardiac risk is also likely to have reduced. Nevertheless, for some patients, parts of the heart still receive >20 Gray in the year 2006.

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## Abbreviations

BED	biologically effective dose
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
IMC	internal mammary chain
RT	radiotherapy
Gy	Gray
LV	left ventricular
SSD	source to skin distance
Sv	Sievert
LAD	left anterior descending
MHD	maximum heart distance
NS	not specified
Co-60	cobalt-60
ICD	International Classification of Diseases
MI	myocardial infarction
CT	computed tomography
3D	3-dimensional
2D	2-dimensional
DVH	dose volume histogram
RCA	right coronary artery
CCA or Circ	circumflex coronary artery
SCF	supraclavicular fossa
CV	coefficient of variation
SD	standard deviation
SE	standard error
RACE	Radiation Associated Cardiac Events
ICRU	International Commission on Radiation Units
IMRT	intensity modulated radiotherapy
RMSPR	square root of the mean value of the squares of the prediction errors
SEER	Surveillance, Epidemiology and End-Results cancer registry

# **1. Introduction**

Adjuvant radiotherapy has been given to many women with breast cancer for more than 50 years and it is currently recommended for a substantial proportion of such women. Overviews of the trials of radiotherapy for breast cancer have shown that radiotherapy reduces the risk of local recurrence and improves mortality from breast cancer in most categories of women. The most recent overview from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) included individual patient data from 45,000 women in 86 randomised trials. Provisional results from this overview show that radiotherapy after breast conserving surgery reduced the 5 year local recurrence by 15.7% and the 15 year breast cancer mortality by 4.2% and that postmastectomy radiotherapy for node-positive disease reduced the 5 year local recurrence by 19.3% and the 20 year breast cancer mortality by 6.3%. Some previous breast cancer radiotherapy regimens, however, involved some unwanted irradiation of normal tissues, including the heart, and the EBCTCG overview has shown that the beneficial effect of the radiotherapy was reduced by an increase in mortality from non-breast cancer causes. When causes of death other than breast cancer were considered, the 20 year mortality was 29.2% among women randomised to radiotherapy compared with 27.1% among women randomised to no radiotherapy (Fig. 1). Detailed analysis revealed that the single largest cause of non-breast cancer death was heart disease. In these trials there was a 27% excess of death from heart disease which was highly statistically significant, representing 128 excess deaths. Indeed, the absolute number of radiation-induced cardiac deaths was four times greater than deaths from radiation-induced second cancer.

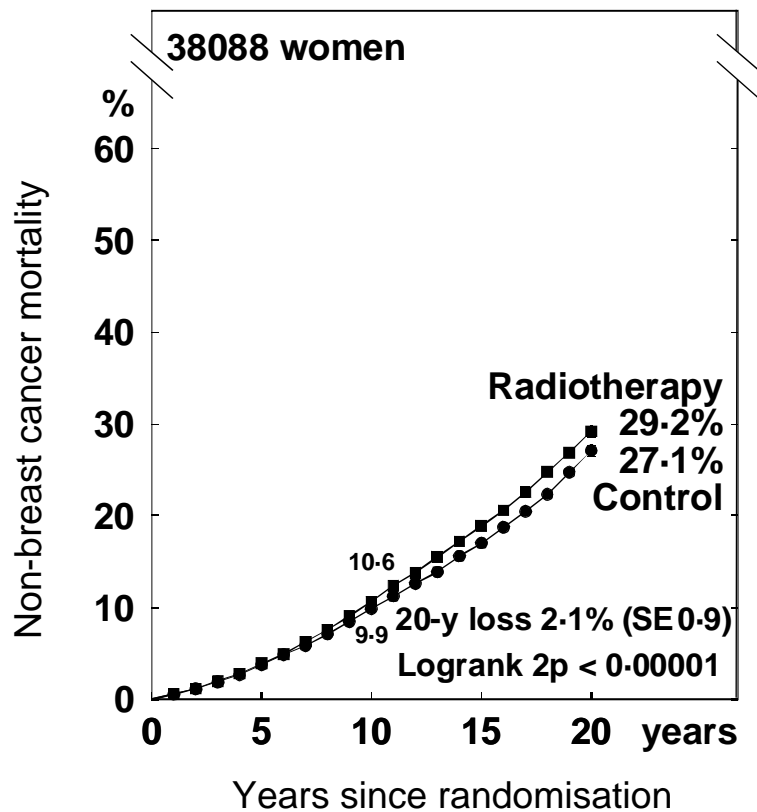


Fig. 1. Non-breast cancer mortality in 38,000 women with early breast cancer in 71 randomised trials either of radiotherapy versus not or of radiotherapy versus surgery [1].

### Observational studies in women with breast cancer

The excess mortality from heart disease seen in the EBCTCG overview has been confirmed by a number of observational studies in populations of women irradiated for breast cancer. In addition, a few studies have investigated incident heart disease after breast cancer radiotherapy. In observational studies where the women receiving radiation have not been selected at random, comparison of irradiated and unirradiated women may well give misleading answers [2]. However, regimens used to treat left-sided cancers usually deliver a higher cardiac radiation dose than those used to treat right-sided cancers. Until very recently the laterality of the tumour was not taken into account in deciding whether to give breast cancer

radiotherapy and, for those women who were given radiotherapy, it did not influence the technique used. Therefore, a comparison of heart disease mortality rates between women irradiated for left-sided breast cancer and women irradiated for right-sided breast cancer using non-randomised population-based data can provide unbiased information on the extent to which the risk of heart disease has been increased as a result of the radiotherapy [2]. Observational and randomised studies that provided insight into these risks and were published before 2005 are summarised in **Chapter 2** ‘Cardiac risks of breast cancer radiotherapy: A contemporary view’. Studies published since then, which add additional information, are summarised below.

The risk of cardiac mortality after breast cancer radiotherapy was investigated in around 21,000 women diagnosed with breast cancer between 1971 and 1988 and registered on the Thames Cancer Registry database [3]. The median follow-up was 18.5 years and around half of the women received radiotherapy. When irradiated women with left-sided breast cancer were compared with irradiated women with right-sided breast cancer, the left- versus right- hazard ratios at 15+ years were 1.25 (95% CI 1.05, 1.49) for cardiovascular mortality and 1.23 (95% CI 0.95, 1.60) for ischaemic heart disease mortality.

Incident heart disease after breast cancer radiotherapy has been investigated in four observational studies published since 2005. Two studies were based on the United States SEER and Medicare databases. In the first, Patt [4] identified around 16,000 patients irradiated for breast cancer between 1986 and 1993. Cardiac morbidity was assessed using discharge diagnosis information. The hazard ratios in patients irradiated for left-sided versus right-sided breast cancer were 1.06 (95% CI 0.99, 1.14) for any cardiac event and 1.05 (95% CI 0.94, 1.16) for

ischaemic heart disease. In the second SEER study, Doyle [5] studied the incidence of MI in around 50,000 elderly ( $\geq 65$  years) women diagnosed with breast cancer between 1992 and 2000. Among the 20,000 women who received radiotherapy, the ratio of myocardial infarction in women irradiated for left-sided versus right-sided cancer was 0.99 (95% CI 0.87, 1.11). Neither of these studies found any significant excess risk of cardiac morbidity in women irradiated for left-sided versus right-sided cancers, but in both studies, the follow-up was only around 10 years and therefore the full extent of any cardiac risk in these women may not yet be apparent.

Two studies published since 2005 have shown an excess of incident myocardial disease in women irradiated for left-sided versus right-sided breast cancers. In the first, Harris [6] studied 961 patients irradiated for breast cancer at the University of Pennsylvania between 1977 and 1994 and followed up for a median of 12 years. The ratio of incident myocardial infarction in women irradiated for left-sided versus right-sided breast cancers, was 3.1 (95% CI 1.5, 6.5) based on 39 events. In addition, patients who received left-sided irradiation were more likely to develop chest pain than those who received right-sided irradiation; the left-sided versus right-sided ratio of incident chest pain was 2.1 (95% CI 1.5, 2.9). The second study was a case-cohort study of women irradiated for breast cancer in Ontario, Canada between 1982 and 1988 [7]. The study included detailed information on the sites irradiated and the radiotherapy fields used and showed that the risk of myocardial infarction was related to the use of anterior internal mammary chain (IMC) radiotherapy, left breast radiotherapy and the size of the left breast boost field. These findings suggested that the use of radiotherapy regimens or fields that delivered high heart doses increased the risk of myocardial infarction relative to regimens that delivered lower heart doses.

These studies are consistent with the previously published data. They suggest that some previous breast cancer radiotherapy regimens increased the subsequent risk of heart disease, and that the main risk occurs at least 10 years after radiotherapy. The risks of both incident and fatal radiation-induced heart disease were usually higher in women irradiated for left-sided breast cancer than in women irradiated for right-sided cancer, suggesting that the risk of cardiac toxicity is related to the radiation dose received by the heart.

### **Myocardial imaging**

Since the main cardiac risks of radiotherapy occur at least 10 years after irradiation [8, Appendix A1 of this thesis], the risks of recent regimens cannot be assessed directly until around 10 years from now. Several studies have, however, shown that early damage to the heart can be detected using myocardial perfusion imaging within 6 months to a few years after irradiation. Studies of myocardial perfusion imaging that were published before 2005 are summarised in Chapter 2 ‘Cardiac risks of breast cancer radiotherapy: A contemporary view’. Updated data from one prospective myocardial perfusion imaging study and new data from two retrospective studies have been published since 2005 and are summarised below. All the studies are summarised in Table 1.

#### **Prospective studies of myocardial perfusion imaging**

The largest prospective myocardial perfusion imaging study of 114 patients irradiated for left-sided breast cancer [10-12] has been updated twice - firstly by Marks [13] and secondly by Prosnitz [21]. Marks [13] reported that two years after radiotherapy, 42% of patients had developed new perfusion defects. The study

Table 1. Studies of cardiac perfusion imaging in breast cancer patients who have been given radiotherapy (based on Seddon *et al.*, 2002 and updated)

Study	Study design	Patient population	Number of patients	Follow-up from RT to imaging (years) mean/median	RT techniques	Year of RT	Heart in RT field	Abnormal myocardial perfusion imaging	Anterior perfusion defect	Normal LV function in patients with defects
Sweden Gyenes <i>et al.</i> [9]	Prospective	Left-sided RT (3 patients received epirubicin)	12	1.1	Direct electrons and photons (n=8) or tangential opposed photons (n=4)	1993-1994	12/12 (required for study)	6/12 (50%)	6/6	6/6
U.S.A. Yu <i>et al.</i> [10] Lind <i>et al.</i> [11] Hardenbergh <i>et al.</i> [12] Marks <i>et al.</i> [13]*	Prospective	Left-sided RT	114	0.5, 1, 1.5 and 2	Tangential opposed megavoltage photons. 53 patients had partly wide tangent fields with cardiac shielding	1998-2001	49/114	11/26 (42%) in patients followed for 2 years	Most defects anterior	44/49 patients with LV irradiated had normal ejection fraction
Sweden Gyenes <i>et al.</i> [14]	Retrospective	Left-sided RT	20	18.4	Co-60 tangential opposed pair or direct electron field	1971-1976	NS	5/20 (25%)	5/5	5/5
		Control (no RT or right-sided RT)	17	19				0/17 (0%)	-	-
Sweden Gustavsson <i>et al.</i> [15]	Retrospective	Left-sided RT	34		Direct orthovoltage to chest wall; direct electron field to internal mammary nodes; direct 6 MV fields to supraclavicular fossa and axilla	1978-1983	All irradiated likely to have received some dose to heart. Dose higher for left-sided RT	4/34 (12%)	1/4	
		Control (right-sided RT)	33	13 (3 groups combined)				2/33 (6%)	0/2	All patients had normal systolic LV function.
		Control (no RT)	23					0/23 (0%)	-	
U.S.A. Correa <i>et al.</i> [16]	Retrospective	Left-sided RT	46		Tangential pair to breast; electron boost to tumour bed. Some received internal mammary, supraclavicular or axillary RT	1977-1990	NS	27/46 (59%)	19/27 defects in left-sided patients in LAD coronary artery territory	NS
		Control (right-sided RT)	36	12 (both groups combined)				3/36 (8%)		
Denmark Højris <i>et al.</i> [17]	Retrospective	Left-sided RT	10		Direct electron field to chest wall and internal mammary nodes	1982-1990	NS	4/10 (40%)	0/4	-
		Control (no RT)	7	7.9 (both groups combined)				4/7 (57%)	1/4	NS
U.K. Seddon <i>et al.</i> [18]	Retrospective	Left-sided RT	24	6.7	Tangential opposed pair Co-60, 5 or 6 MV	1987-1995	24/24 (required for study)	17/24 (71%)	17/17	17/17
		Control (right-sided RT)	12	8.3			0/12	2/12 (17%)	1/2	2/2
France Cowen <i>et al.</i> [19]	Retrospective	Left-sided RT	17	4.6	Tangential opposed pair Co-60 or 4 MV. Mixed photon/electron field to internal mammary nodes and supraclavicular fossa	1987-1993	NS	0/17 (0%)	-	-
Bulgaria Tzonevska <i>et al.</i> [20]	Retrospective	Left-sided RT	46	NS	NS	NS	All left-sided had part of heart in field	11/46 (24%)	11/11 left-sided abnormalities in LAD coronary artery territory	11/11
		Control (right-sided RT)	10					0/10 (0%)		

Abbreviations: RT=radiotherapy; LV=left ventricular; NS=not specified; LAD=Left anterior descending; Co-60=Cobalt 60

\*Results of a further update of this study, Prosnitz *et al.* [21], are not included in the table since patients with abnormal scans at 0.5-2 years were preferentially selected for further follow-up.

confirmed that the greater the irradiated volume of the left ventricle, the higher the incidence of perfusion defects. The most recent update of this study by Prosnitz [21] provided detailed information on the natural history of the perfusion defects that occurred after irradiation. An earlier report of this study [11] had suggested that some myocardial perfusion defects may resolve without intervention. The updated data [21] included a subset of 44 patients who were scanned at 6 monthly intervals for at least 3 years after irradiation. In this subset, most of the perfusion defects that developed soon after irradiation did not resolve, and new defects continued to appear up to 6 years after radiotherapy. Further prospective data on such patients with serial measurements over several years would be useful to assess further the natural history of these changes in the long-term.

Myocardial perfusion imaging studies provide valuable insight into the possible mechanisms of radiation-induced heart disease. At present, however, none of the studies has followed women for long enough to know if the defects observed provide reliable surrogate markers for the long-term risk of radiation-induced heart disease in these patients.

### **Retrospective studies of myocardial perfusion imaging**

Retrospective myocardial imaging studies have assessed the prevalence of damage to the heart from radiotherapy that was carried out in previous decades. Several retrospective myocardial perfusion studies were published before 2005 (Table 1). Since then, two further studies have been published. Tzonevska [20] studied 46 patients who received left-sided breast cancer radiotherapy and 10 who received right-sided. Myocardial perfusion scanning showed perfusion defects in 11/46 left-sided patients but in none of the right-sided patients. Correa [16] assessed

cardiac damage at around 12 years after tangential breast cancer radiotherapy using cardiac stress testing and cardiac catheterisation. The prevalence and distribution of coronary artery disease was compared in 46 left-sided and 36 right-sided patients. A significantly higher prevalence of cardiac stress test abnormalities was found in women irradiated for left-sided (27 of 46; 59%) versus right-sided cancer (3 of 36; 8%). Thirteen of the left-sided patients required cardiac catheterisation, and in 11 of these 13 patients, the left anterior descending (LAD) coronary artery, which receives the highest radiation doses from left-tangential irradiation, was found to be stenosed. The percentage of defects that affected the LAD coronary artery was 80% (11/13). This is greater than would be expected in non-radiation-related coronary artery disease, where the percentages are typically around 40-50% LAD coronary artery, 30-40% right coronary artery and 15-20% circumflex coronary artery [14].

In summary, myocardial imaging studies show that radiation-related damage can be seen within 6 months after radiotherapy in many women irradiated for breast cancer during the 1990s. These areas of damage do not usually resolve spontaneously, indeed new areas of damage may appear up to 6 years after irradiation. Myocardial perfusion imaging suggests that radiotherapy causes damage to the microvasculature, particularly in parts of the heart that receive more than 25 Gy dose. Cardiac catheterisation suggests that radiation may also damage the large vessels, for example the LAD coronary artery.

The clinical importance of these changes is currently unclear. Very few of the patients studied prospectively developed left ventricular impairment. Longer follow-up of prospective studies will enable assessment of whether the microvascular and macrovascular damage seen shortly after radiotherapy

contributes to the later development of symptomatic heart disease and to radiation-induced cardiac mortality.

### **Studies that relate heart dose to cardiac toxicity**

Several previous studies have related cardiac radiation dose to subsequent risk of heart disease. Gagliardi [22,23] applied radiobiological modelling to clinical data on long-term cardiac mortality in two randomised trials including around 40 deaths from ischaemic heart disease. Marks [13] and Das [24] assessed the incidence of myocardial perfusion defects in around 70 women who received different heart doses from left-tangential radiotherapy and Wei [25] investigated the incidence of pericardial effusion in around 100 patients irradiated for oesophageal cancer. Carr [26], in a study of around 2,000 patients irradiated for peptic ulcer disease, found that fractionated radiotherapy of around 3 Gy mean heart dose gave rise to a significant excess of death from ischaemic heart disease. There was a positive relationship between dose to the heart and risk of death from ischaemic heart disease. In this study doses in the order of a few Gray gave rise to a 50% increase in risk of cardiac death. Such studies provide useful insight into the relationship between cardiac dose and the risk of subsequent radiation-induced heart disease.

An analysis of data from several large epidemiological studies of radiation-induced heart disease was performed by Schultz-Hector [27]. Mean heart doses in each patient group were corrected for fractionation using an alpha-beta ratio of 2. Despite differences in the cardiac dose distributions between the different studies, the authors showed that data on the relationship between heart dose and the risk of cardiac death from all groups of patients in these epidemiological studies were

consistent with each other. Other studies, however, provide conflicting information on the relationship between radiation dose and cardiac risk [2].

### **The pathology of radiation-induced heart disease**

There is variation in the types of radiation-induced heart disease investigated in different epidemiological studies. In the largest observational study to date, the risk of radiation-induced heart disease included death from myocardial infarction (ICD 410), other ischaemic heart disease (ICD 411-414) and other heart disease (ICD 390-8, 402, 404, 415-429) and the risk appeared to be concentrated in the period 10 or more years after radiotherapy [8, see Appendix A1 of this thesis].

Consideration of the pathological processes that may lead to the excess of cardiac events seen in epidemiological studies should improve understanding of which cardiac structures might, if damaged, contribute to radiation-induced heart disease, and would therefore help to determine which organs at risk should be considered in future studies. For example, if microvascular damage to the myocardial capillaries was largely responsible for radiation-induced heart disease, then whole heart dose should be the most valuable predictor of cardiac toxicity. In contrast, if macrovascular damage to one or more of the three main coronary arteries were responsible, then doses to the coronary arteries should be the most valuable predictors of toxicity.

Studies investigating the pathological processes responsible for radiation-induced heart disease include animal studies, human autopsy studies and case series of patients who received thoracic irradiation. These different study types describe three main syndromes of radiation-related heart disease 1) pericarditis, 2) myocardial fibrosis and 3) coronary artery disease. The relevance of each of these

three endpoints to the excess of cardiac events seen in epidemiological studies of patients irradiated for breast cancer is discussed below.

### **1. Pericarditis**

Radiation-induced pericardial disease in animals and humans consists of several clinical syndromes including acute pericarditis, pericardial effusion and constrictive pericarditis [28-36]. These syndromes were first described in patients treated for Hodgkin's disease in the 1960s and 70s, who received doses of more than 40 Gy to the anterior pericardium [37]. Since then, further studies have shown that the incidence of radiation-induced pericardial damage increases with increasing radiation dose to the heart: the risk is very low below 35 Gy and rises steeply to 50% at around 60 Gy [27,31,32]. The risk also increases with increasing volume of the heart irradiated. Hence the incidence of pericarditis after breast cancer radiotherapy is likely to be low for most regimens, due to the small volume of heart included in the radiation fields [27,31,32]. Clinical studies have shown that pericardial damage usually becomes manifest within 2 years of irradiation, and clears spontaneously in the majority of patients [32,33,38]. Therefore it is unlikely to be responsible for the excess of cardiac morbidity and mortality seen 10 or more years after breast cancer radiotherapy in epidemiological studies.

### **2. Myocardial fibrosis**

Animal studies have shown that radiotherapy damages the capillary network of the heart which, in turn, causes death of the cardiac myocytes and subsequent myocardial fibrosis [28,32,34,37,39,40,41].

In humans, several case series of patients irradiated for Hodgkin's disease have shown that cardiac doses of more than 30 Gy can cause sufficient myocardial

damage to reduce the left ventricular ejection fraction [34,38,42-45]. The incidence of these reductions in ejection fraction appears to increase with increasing dose and volume of the heart irradiated [31]. In its most severe form, radiation-induced myocardial damage can cause clinical cardiomyopathy and congestive cardiac failure [33].

Histologically, late myocardial damage is characterised by myocardial fibrosis. This has been demonstrated in several case series and autopsy studies of patients who received thoracic irradiation [29,34,35]. These studies suggest that the extent and severity of myocardial fibrosis after radiotherapy is dose-related and is greatest in patients who receive more than 30 Gy dose to the myocardium.

*The relevance of myocardial fibrosis to radiation-induced heart disease after breast cancer radiotherapy*

Breast cancer irradiation in previous decades has involved doses of between 20 and 50 Gy to parts of the heart in some patients [46,47]. Such doses may well have resulted in areas of focal myocardial fibrosis. For example, left-tangential radiotherapy has been commonly used to irradiate the breast or chest wall since the 1950s. It delivers between 20 and 50 Gy to part of the anterior myocardium in some patients (Fig. 2). Myocardial perfusion imaging studies have shown that these ‘high-dose regions’ have developed irreversible perfusion defects between 6 months and 2 years after irradiation in around 40% of patients who received left-tangential irradiation in the 1990s (Table 1). These defects represent areas of subclinical myocardial infarction. Death of such a small part of the myocardium would not be expected to cause immediate symptoms in otherwise healthy individuals. Indeed, most of the patients found to have myocardial perfusion defects after breast

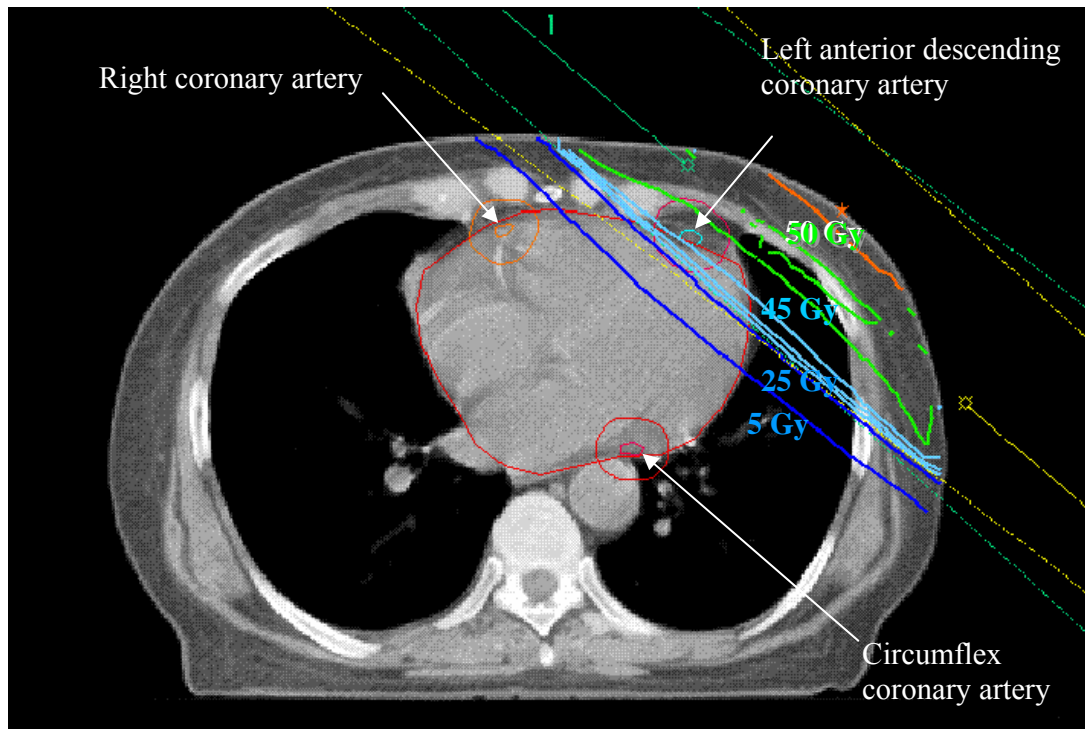


Fig. 2: Axial CT section showing the dose distribution from left cobalt-60 tangential pair irradiation, as used in the mid-1990s. Isodose lines correspond to dose in Gray. The heart is outlined in red. The three main coronary arteries are outlined and a 1 cm margin has been added to each.

cancer radiotherapy in these studies were asymptomatic and had normal left ventricular function on echocardiogram. However, as these patients age, many of them will develop age-related ischaemic heart disease. Small areas of pre-existing radiation-induced myocardial fibrosis may cause cardiac decompensation, myocardial infarction or heart failure sooner than would otherwise be expected. Thus irradiation of a small part of the heart, with consequent patches of myocardial fibrosis may well contribute to the excess in cardiac events seen in epidemiological studies of patients irradiated for breast cancer.

### **3. Coronary artery disease**

Non-radiation-related atherosclerosis is a slowly progressive disease, starting in childhood with the development of fatty streaks, and gradually advancing in middle and old age [48]. The speed of the development of atherosclerosis is affected by various risk factors such as smoking, diabetes mellitus and obesity.

Studies in both animals and humans show that atherosclerosis can also be caused by radiation. In several species of laboratory animal, irradiation of the heart has been found to cause atherosclerosis of the coronary arteries [27,31,49-51]. In humans, numerous case reports and autopsy studies have demonstrated premature atherosclerosis of large arteries after doses of around 30 Gy in young people with few risk factors for atherosclerosis apart from their history of radiotherapy [29,31,35,52-54]. The distribution and the histopathology of the coronary artery damage in these patients was similar to that normally seen in non-radiation-induced disease [31,34,41].

#### *Relevance of coronary artery disease to radiation-induced heart disease after breast cancer radiotherapy*

Human studies suggest that mean heart doses of around 30 Gy or more can cause atherosclerosis of the coronary arteries. Breast cancer radiotherapy in previous decades usually delivered between 1 and 20 Gy mean dose to the heart [47], which is lower than the cardiac doses in the above case reports. However, some radiotherapy regimens, for example left-tangential radiotherapy, delivered maximum doses of around 50 Gy to parts of the LAD coronary artery (Fig. 2) [46] which is a common site of myocardial infarction. Such doses may have been responsible for initiating atherosclerosis or for accelerating age-related

atherosclerosis, which may, in turn, have caused myocardial infarction or heart failure. Thus radiation-related atherosclerosis may well have contributed to the excess of cardiac events seen after breast cancer radiotherapy in epidemiological studies.

### **The effect of fractionation on radiation-induced heart disease**

Animal studies have been used to ascertain whether the risk of cardiac damage is fractionation-dependent and, if so, the value of the likely alpha-beta ratio for radiation-induced heart disease. Studies investigating the effects of different doses and fractionation schedules on the heart in rats [30,55] have shown that fractionation has a marked sparing effect on the heart. The calculated alpha-beta ratio for the late effect of symptomatic cardiac failure was between 1 and 3 Gy. It would therefore seem reasonable to use an alpha-beta ratio of 2 Gy for the calculation of biologically effective cardiac doses in humans. However, there are likely to be differences in the mechanisms responsible for death from heart disease many years after radiotherapy in humans and the mechanisms that caused heart failure 100 to 400 days after irradiation in rats. Therefore, although this alpha-beta ratio is the best estimate available at the present time, it should be applied with caution.

### **Which are the important cardiac organs at risk?**

Both animal and human studies suggest that irradiation of the heart can lead to later death and disability from heart disease through both microvascular damage to the myocardial capillaries and macrovascular damage to the large coronary arteries. Therefore the cardiac structures that may, when damaged, be responsible for the

excess of heart disease seen after radiotherapy in epidemiological studies are likely to be the whole myocardium and the three main coronary arteries. These structures have therefore been considered as the main ‘organs at risk’ in the following papers.

### **The need for dose-response relationships**

There is a pressing need amongst clinical oncologists for more information concerning the cardiac risks of radiotherapy. The benefits of breast cancer radiotherapy include moderate reductions in breast cancer mortality and substantial reductions in local recurrence, resulting in considerable improvements in breast cancer morbidity in many categories of women. There is substantial evidence that many of the radiotherapy regimens that were used in the past have resulted in an increased risk of heart disease and, in some instances, the increased cardiac mortality is known to have outweighed the reduction in breast cancer mortality. Radiotherapy regimens have changed in recent years, and cardiac doses are now usually lower than in the past. Despite this, the evidence that breast cancer radiotherapy has a net benefit in terms of survival for some of the groups of women who currently receive it is weak. Decisions relating to the selection of patients for radiotherapy and to the possible need for further improvements in breast radiotherapy planning involve balancing the risks and benefits of irradiation. At the moment, in the absence of reliable dose-response relationships, it is difficult to estimate the risk of heart disease for an individual patient. More precise knowledge of the cardiac risk of specific regimens would be relevant both to the development of treatment guidelines and to decisions regarding individual patients in the clinic and would enable identification of patients for whom the increased cost of advanced radiotherapy techniques is justified. Breast cancer is one of the commonest

indications for radiotherapy therefore any changes in breast radiotherapy practice may have considerable cost and workload implications.

### **Aims of the thesis**

The published literature raises a number of issues on which further research is needed, including: the shape of the dose-response relationships for radiation-induced heart disease (e.g. is there a threshold dose or is the relationship linear or linear-quadratic with no threshold?); the variation in risk with age at exposure, smoking status, prior heart disease and other factors; the tissues and structures most relevant to health detriment (e.g. the coronary arteries, or the whole myocardium?); and whether there are subpopulations of women who are unduly susceptible to radiation-induced heart disease.

The heart still receives some dose from many thoracic radiotherapy regimens used today. The future risk of these regimens cannot be assessed directly until at least 10 years after irradiation. Therefore indirect assessment using cardiac dose-response relationships is needed. The development of reliable dose-response relationships requires detailed cardiac dosimetry of radiotherapy regimens given to women for whom we have long-term follow-up information. The aim of this thesis is to provide cardiac dose estimates that can be used, along with disease rates from randomised and observational data, to develop reliable cardiac dose-response relationships. These relationships should facilitate assessment of the cardiac risks of current and future radiotherapy.

In **Chapter 3**, a methodology for the estimation of cardiac doses from previous radiotherapy regimens is presented. The methodology was used to estimate doses to the heart and to the three main coronary arteries for common breast cancer

radiotherapy regimens used worldwide between the 1950s and the 1990s, using a representative patient. Retrospective estimation of cardiac doses of patients in epidemiological studies is inevitably subject to several sources of variability. These sources were assessed, and variability in dose was quantified. The cardiac doses were applied to clinical outcome data for around 40,000 women irradiated in 71 EBCTCG trials of radiotherapy for early breast cancer and dose-response relationships were generated. These are presented in Appendix B1.

More precise characterisation of these dose-response relationships is planned using data from women irradiated in Sweden and Denmark for whom detailed clinical and radiotherapy information is available. **Chapter 4** summarises cardiac dose estimates for the radiotherapy regimens used in 358 women irradiated in Sweden since the 1950s. These doses are now available to apply to clinical outcome data on the risk of heart disease in these women. The combination of detailed dose estimates, along with detailed clinical data should provide reliable information on dose-response relationships for different types of heart disease. They should also enable assessment of how the radiation-induced cardiac risk might vary according to individual patient-related factors such as whether the woman was a smoker or had a history of previous heart disease and according to radiotherapy-related factors such as dose received by various cardiac structures.

Estimation of the cardiac risk of women irradiated today requires measurement of their cardiac dose, as well as dose-response relationships. Cardiac doses from contemporary breast cancer radiotherapy used in the year 2006, in a major UK radiotherapy centre, are presented in **Chapter 5**. These doses are likely to be similar to contemporary cardiac doses received from breast cancer radiotherapy in other geographical areas, both in the UK and worldwide. The doses are compared

with estimates of heart and coronary artery dose from radiotherapy techniques used in previous decades. Reductions in cardiac doses that have occurred over the past few decades are likely to have resulted in some reduction in the cardiac risks of today's radiotherapy, although some risk may remain.

The usefulness of cardiac dose-response relationships in clinical practice depends on the ability to measure heart doses for individual patients in the clinic today. The method of assessment of cardiac doses from breast cancer radiotherapy varies according to the resources available in individual cancer centres. In many centres in the UK and worldwide, 3-dimensional dose assessment is not yet possible. The strengths and limitations of a 2-dimensional method of estimating cardiac doses for these patients are presented in **Chapter 6**. This method should facilitate the estimation of cardiac doses for individual patients who receive left-tangential breast cancer radiotherapy in today's clinics, and thus enable prediction of their future cardiac risk.

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# **2. Cardiac risks of breast cancer radiotherapy – a contemporary view**

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## Abstract

There has, for some time, been compelling evidence, both from randomised controlled trials and from observational studies, that some of the breast cancer radiotherapy regimens that have been used in the past have led to an increased risk of mortality from heart disease. There is also some evidence that the more recent regimens used in the United States are associated with lower risks than previous ones, but it is not clear whether current regimens are free from cardiac risk, especially in the light of recent evidence from the survivors of the bombings of Hiroshima and Nagasaki, in whom a clear relationship between the risk of mortality from heart disease and radiation dose has been observed for doses in the range 0-4 Gray.

Mortality from radiation-induced heart disease usually occurs at least a decade after irradiation. Symptomatic heart disease might have a much shorter induction period, but there is little information about it at present. Subclinical vascular abnormalities have been observed within months of irradiation, via myocardial perfusion imaging studies, but little is known about the relationship between these and later overt heart disease.

At present, there are few data relating heart dose and other specific characteristics of breast radiotherapy to cardiac outcome. Further information on these topics is needed in order to enable estimation of the cardiac risk that is likely to arise both from radiotherapy regimens in current use, and from those being considered for use in the future. Such knowledge would facilitate radiotherapy treatment planning and enable a reduction in cardiac risk while maintaining the known benefit in terms of breast cancer mortality.

**Key words:** *Breast cancer, cardiac toxicity, radiation-induced heart disease, radiotherapy.*

## **Introduction**

Case reports of coronary occlusion following thoracic radiotherapy appeared as early as the 1950s [1,2], and these were soon followed by a substantial body of evidence relating radiotherapy to heart disease in patients who had undergone mediastinal irradiation for Hodgkin's disease. Such individuals were generally treated with anteriorly weighted mantle radiotherapy and had at least 60% of their cardiac silhouette irradiated. The early studies usually consisted of case series and often focused on autopsy material, which enabled direct visualisation of myocardial or coronary artery damage. These studies provided evidence that radiation-related damage to the heart can include acute pericarditis, pericardial effusion, constrictive pericarditis, valvular dysfunction, conducting system dysfunction and myocardial fibrosis [3]. Radiation-induced coronary heart disease was also demonstrated in the early case series of patients with Hodgkin's disease. The occurrence of coronary artery stenoses in areas of expected high radiation dose in young patients with few risk factors for heart disease provided further evidence for the aetiological role of radiotherapy [4,5]. From 1990, epidemiological studies of large cohorts of Hodgkin's disease patients showed that, in terms of radiation-induced death, the most important endpoint was myocardial infarction (MI) [6,7], with mortality rates in the irradiated groups up to eight times higher than rates in the populations from which they were drawn. It was against this general background that the evidence relating radiotherapy for breast cancer to an increased risk of heart disease, started to accumulate.

Although it has been generally accepted since the mid-1960s that radiation doses of around 40 Gy or more can cause heart disease [8], it is only within recent years that evidence of an increased risk of radiation-induced heart disease at doses

below 5 Gy has arisen, (see McGale et al. for review [9]). The most important study to date has considered mortality in the survivors of the atomic bombings of Hiroshima and Nagasaki [10]. The individuals in this study received whole-body uniform doses in the range 0-4 Sievert (Sv). The radiation was mostly from gamma-rays but with a small neutron component, so that 1 Sv is approximately equal to 1 Gray (Gy) in this group. During 1968-97 the dose-response relationship for a wide group of non-cancer diseases was approximately linear, with direct evidence that the threshold dose was no higher than about 0.75 Sv. Careful statistical analysis showed that the increase could not be explained by misclassification of the cause of death, or by confounding with factors such as smoking [11], and the most likely explanation was a causal effect of radiation. Among the non-cancer diseases considered, the commonest specific cause of death was heart disease with 4477 deaths, and further analyses specifically of heart disease revealed a dose-response relationship that was highly statistically significant and appeared linear with no threshold, with each additional Sv of radiation increasing the mortality rate by a factor of 0.17 (90% confidence interval [CI] 0.08, 0.26) (Fig. 1).

The extent to which the risks of radiation-related heart disease seen in the atomic bomb survivors will apply to other populations is not yet clear. Nevertheless, the evidence of some increased risk at average cardiac doses below 5 Gy is currently mounting [9,12] and calls for careful thought about the likely risks of heart disease in irradiated breast cancer patients. This review summarises the evidence that is presently available.

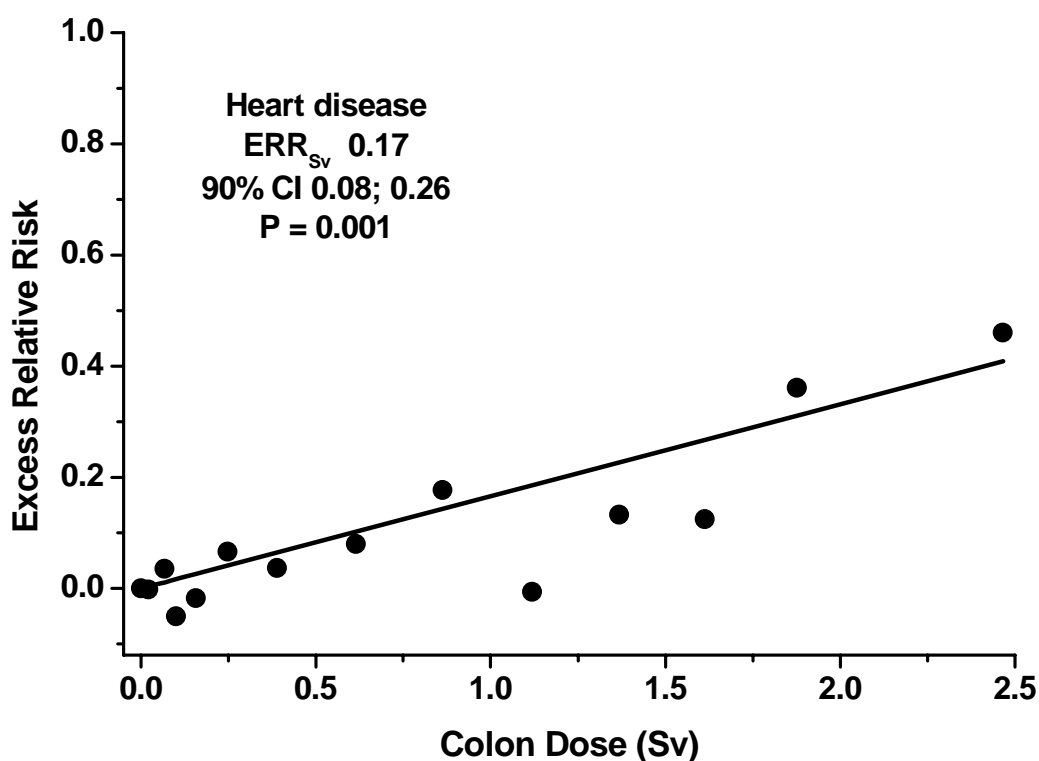


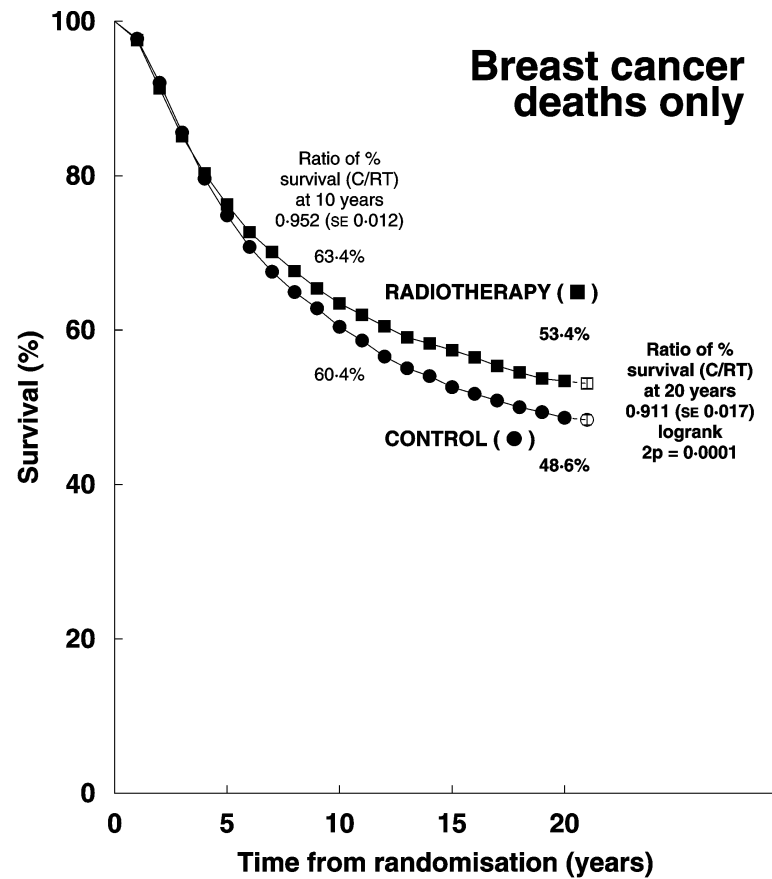
Fig. 1 - Risk of death from heart disease in the Life Span Study cohort of survivors of the atomic bombings of Hiroshima and Nagasaki. The graph shows the excess relative risk (ie the proportionate increase in risk) versus colon dose in Sievert (Sv). Doses to other organs were similar to the colon dose in this population. The radiation was mostly from gamma-rays with only a small neutron component, so 1 Sv  $\approx$  1 Gray (Gy).

### **Randomised controlled trials in patients with breast cancer**

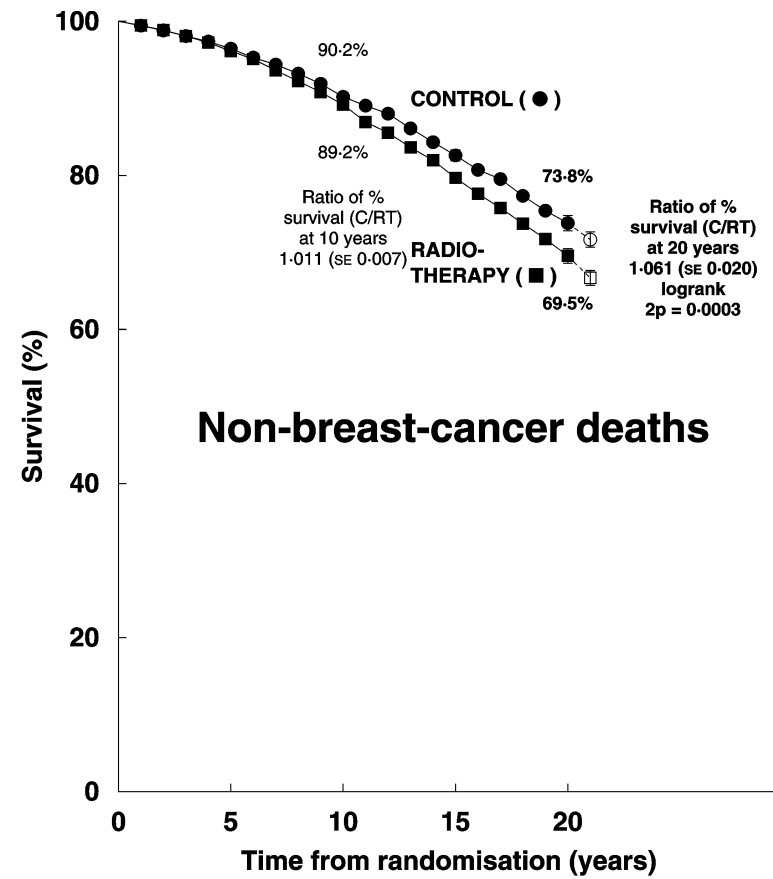
An overview [13] of the trials that started before 1975 comparing the survival of women given standard treatment (including surgery) plus radiotherapy to the survival of control women given only standard treatment found that overall survival was similar in the two groups during the first ten years after irradiation. In the period more than 10 years after irradiation, however, the irradiated women had

significantly poorer overall survival than the unirradiated control women. In an update of this overview, [14] it was demonstrated that the reason for the less favourable experience in the irradiated group was that there had been an excess of cardiac deaths.

A recent overview based on individual data from 40 randomised trials of radiotherapy for localised breast cancer that started before 1990 came from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [15] and included 20,000 randomised women. When all trials were considered together, regardless of radiotherapy regimen, there was a significant reduction in breast cancer mortality in irradiated patients and, in the absence of other causes of death, the 20 year survival of patients allocated radiotherapy would have been 53.4% compared with only 48.6% among controls (Fig. 2, left-hand panel). The beneficial effect of the radiotherapy was, however, counterbalanced by a higher mortality rate from causes of death other than breast cancer so that, when overall mortality was considered, there was an absolute improvement of only 1.2% in survival in the irradiated group at 20 years (37.1% in irradiated women versus 35.9% in controls, difference not statistically significant). Considering only causes of death other than breast cancer, the 20 year survival would have been only 69.5% among those allocated radiotherapy compared to 73.8% among the controls (Fig. 2, right-hand panel). Detailed analysis found no good evidence that the proportional increase in the mortality rate from causes other than breast cancer was materially influenced by the age of the women or the extent of the breast cancer when diagnosed [15]. The increased mortality in the irradiated group was chiefly due to a 30% increase in cardiovascular deaths in the period more than 10 years after randomisation.



Death rate and absolute difference in annual mortality / 1000					
	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years ≥20
Radiotherapy	53.7	37.6	20.9	15.2	7.2
Control	56.6	44.3	28.6	15.4	5.8
Difference	2.9 (SE 1.6)	6.7 (SE 1.8)	7.8 (SE 1.9)	0.1 (SE 1.9)	-1.4 (SE 1.9)



Deaths / 1000 woman-years and absolute difference in annual mortality / 1000					
	Years 0-4	Years 5-9	Years 10-14	Years 15-19	Years ≥20
Radiotherapy	291/38.9	327/22.5	261/11.8	176/6.5	103/2.4
Control	244/34.4	239/18.4	157/9.6	114/5.2	60/2.1
Difference	-0.4 (SE 0.6)	-1.6 (SE 1.2)	-5.7 (SE 1.9)	-5.2 (SE 2.9)	-14.4 (SE 5.5)

Fig. 2 - Absolute effects of radiotherapy on cause-specific survival in the EBCTCG overview [15].

None of the overviews to date has included any dosimetry. However, it has been noted that cardiac mortality in irradiated patients appeared to be greatest in trials with the highest expected cardiac doses [14]. Breast radiotherapy planning has improved over time, with recent regimens delivering lower radiation doses to the heart [16], raising the possibility that cardiac risks may be lower for more modern regimens than for older ones. However, the EBCTCG overview [15] did not find that the increased mortality from causes other than breast cancer in irradiated patients differed according to the type of radiotherapy or the date the trial started.

The above discussion refers to cardiac mortality. Two randomised controlled trials including 960 and 3083 patients [17,18] reported morbidity from ischaemic heart disease. Neither study found a significant excess of myocardial infarction in irradiated patients after 20 and 10 years follow-up respectively, however the numbers of events were only 58 and 95 respectively.

### **Observational studies in patients with breast cancer**

Outside the setting of a randomised clinical trial, the decision as to whether or not to irradiate a woman with breast cancer will usually be influenced by a number of factors related to her likely prognosis. Therefore, a simple comparison of subsequent mortality in irradiated and unirradiated women may be misleading in the investigation of the effects of radiotherapy, including the investigation of the risk of radiation-related heart disease. However, in the absence of radiotherapy, the laterality of the primary tumour is unlikely to be related to the woman's prognosis [19] and, until recently, it would not have been likely to be related to the decision as to whether to give radiotherapy. Radiation dose to the heart is usually higher in left-sided than in right-sided breast cancer [20,21]. Therefore, observational studies comparing heart disease rates in women with left-sided and right-sided primary

tumours may provide an unbiased assessment of the difference in cardiac risk resulting from the difference in cardiac dose between the two sides, and the findings of such studies can usefully supplement the results of the randomised controlled trials.

Rates of fatal MI or death from cardiovascular disease have been studied in three such populations. A study of the Swedish nationwide cancer registry including 55,000 women diagnosed with breast cancer during 1970-1985 showed a significantly increased risk of death from MI among patients with cancer of the left breast compared to patients with cancer of the right breast [22]; and an analysis of updated Swedish data, including 90,000 women diagnosed during 1970-1996, found that the mortality ratio, left-sided versus right-sided, for all cardiovascular disease, was 1.04 (95% CI 1.00, 1.09) [23]. The increase was concentrated in the period more than 10 years after diagnosis, in agreement with the findings of the randomised controlled trials and, during this period, the mortality ratio, left-sided versus right-sided, was 1.10 (95% CI 1.03, 1.18) for deaths from all cardiovascular disease and 1.13 (95% CI 1.03, 1.25) for deaths from ischaemic heart disease. There was no significant variation in the cardiac risk according to calendar year of diagnosis of the original breast cancer. The Swedish cancer registry does not record information as to whether or not a woman received radiotherapy, so these estimates refer to all women with breast cancer, regardless of whether they had radiotherapy. Estimates of the use of radiotherapy in Sweden during the 1970s and early 1980s indicate that approximately 30% of patients with breast cancer received breast radiotherapy as part of their initial treatment. Therefore, the increase in the risk of cardiovascular disease associated with radiotherapy is likely to be considerably higher than the mortality ratios reported in this study.

Unlike the nationwide Swedish cancer registry, the Surveillance, Epidemiology and End-Results (SEER) cancer registries in the United States do record whether or not an individual was treated with radiotherapy. An analysis of SEER data on 206,000 women diagnosed with breast cancer during 1973-1992 and followed until the end of 1994 found that the mortality ratio, left-sided versus right-sided, for MI after adjuvant radiotherapy was 1.17 (95% CI 1.01, 1.36). In contrast, there was no such difference for women who had not been irradiated [24]. Two analyses of updated data from the SEER cancer registries have recently been completed [25,26]. One of these was based on 300,000 women diagnosed with breast cancer during 1973-2001 and followed to the beginning of 2002 [25]. Thirty seven per cent of the women had been irradiated. The analysis demonstrated that without radiotherapy, the mortality ratios, left-sided versus right-sided, did not differ significantly from unity for breast cancer, cardiovascular disease, or all other known causes. With radiotherapy, they did not differ significantly from unity for breast cancer, or for all known causes excluding breast cancer and cardiovascular disease. In contrast, for cardiovascular disease the mortality ratio, left-sided versus right-sided, with radiotherapy was 1.16 (95% CI 1.08, 1.24; 2p=0.00004). This study demonstrated very clearly the increasing cardiac risk with increasing time since diagnosis: during time-periods <5, 5-9, 10-14 and 15+ years since diagnosis the mortality ratios, left-sided versus right-sided, with radiotherapy were 1.04 (0.93-1.15), 1.10 (0.97-1.25), 1.37 (1.14-1.64) and 1.53 (1.25-1.86) respectively (2p for trend: 0.0001). In both analyses there was some evidence of a reduced hazard for women diagnosed more recently. Inevitably, however, full information on the possible long-term risk associated with modern radiotherapy regimens is not yet available.

A smaller population-based Canadian study including 3006 women irradiated for breast cancer during 1982-1987 [27] found that the mortality ratio, left-sided versus right-sided was 2.10 (95% CI 1.11, 3.95).

The incidence of non-fatal cardiac events after adjuvant radiotherapy has been reported in two single-institution observational studies [28,29]. The studies included 2,128 and 684 patients respectively, all of whom had undergone breast-conserving surgery. Neither study found a significant difference between the event ratios, left-sided versus right-sided. However, median length of follow-up was only 10.2 years in one study and 9 years in the other. Therefore, any long-term cardiac risk in these populations may not yet be apparent.

### **Myocardial imaging**

The mechanism by which radiation causes heart disease is at present unknown but, as coronary artery disease is the commonest form of heart disease, it seems likely that it acts, at least in part, either by causing or by promoting coronary atherosclerosis. In all the populations of irradiated women where an increased mortality from heart disease has been observed, the risk is concentrated in the period more than 10 years after irradiation. Nevertheless, the initiation of damage must have taken place at the time of the radiotherapy and so additional information may be gained by studying vascular abnormalities and cardiac function in asymptomatic patients during the first few years after radiotherapy. A temporary reduction in left ventricular ejection fraction has been demonstrated in some patients immediately after radiotherapy; however, this returned to normal within 2-6 months [30,31].

Vascular damage can be assessed by myocardial perfusion scintigraphy which is a sensitive and specific technique for the detection of cardiac perfusion abnormalities [32]. A perfusion defect may result from the blockage of a coronary artery or from microvascular damage to an area of myocardium. Defects may be irreversible or reversible, with irreversible defects representing infarcted myocardium and reversible defects representing ischaemic myocardium. A partly reversible defect represents a mixture of the above (with part of the myocardium infarcted and part, ischaemic). The ability to visualise myocardial perfusion enables the extent of cardiac vascular damage to be assessed and gives some insight into the preclinical manifestations of radiation-related damage.

Nine studies (Table 1) have investigated the incidence or prevalence of cardiac perfusion defects after breast radiotherapy. These were mostly single institution with small patient numbers. Prospective and retrospective studies have been considered separately since follow-up times are different (between 6 months and 2 years for prospective and 4.6 years to 19 years for retrospective), and because they involve different endpoints (incidence and prevalence respectively).

### **Prospective studies**

In four prospective studies, cardiac perfusion imaging was performed immediately before, and at intervals after, left breast radiotherapy during the 1990s (see Table 1, upper half). The advantage of this approach is that the development of new lesions within such a short time period (6 months to 2 years) would be unusual in the absence of radiotherapy. Therefore any new abnormality on the post-radiotherapy scan seems likely to be treatment-related. A large proportion of patients (37-70%) developed new perfusion defects within 2 years of radiotherapy, suggesting that an

Table 1. Studies of cardiac perfusion imaging in breast cancer patients who have been given radiotherapy (based on Seddon *et al.* [40] and updated)

Study	Study design	Patient population	Number of patients	Follow-up from RT to imaging (years) mean/median	RT techniques	Year of RT	Heart in RT field	Abnormal myocardial perfusion imaging	Anterior perfusion defect	Normal LV function in patients with defects
U.S.A.; Yu <i>et al.</i> [33]	Prospective	Left-sided RT (50 patients also had doxorubicin)	83	0.5, 1, 1.5 and 2	Tangential opposed pair. 33 patients had partly wide tangential fields	1998-2001	Some patients	31/83 (37%)	Some defects anterior	NS
Sweden, U.S.A.; Lind <i>et al.</i> [34]	Prospective	Left-sided RT	69	0.5, 1 and 1.5	Tangential opposed pair. 25 patients had superior internal mammary nodes included in partly wide tangential fields	NS (recent)	NS	Increase in LAD coronary artery defects at 6 months; no increase in left circumflex or right coronary artery defects		NS
Sweden; Gyenes <i>et al.</i> [35]	Prospective	Left-sided RT (3 patients received epirubicin)	12	1.1	Direct electrons and photons (n=8) or tangential opposed photons (n=4)	1993-1994	12/12 (required for study)	6/12 (50%)	6/6	6/6
U.S.A.; Hardenbergh <i>et al.</i> [36]	Prospective	Left-sided RT and doxorubicin Left-sided RT, no chemotherapy	10 10	0.5 0.5	Tangential opposed megavoltage photons. Five patients had partly wide tangent fields with cardiac shielding	Late 1990s	7/10 10/10	7/10 (70%) 5/10 (50%)	NS NS	19/20 of all patients in study
Sweden; Gyenes <i>et al.</i> [37]	Retrospective	Left-sided RT Control (no RT or right-sided RT)	20 17	18.4 19	Co-60 tangential opposed pair or direct electron field	1971-1976	NS	5/20 (25%) 0/17	5/5 -	5/5 -
Sweden; Gustavsson <i>et al.</i> [38]	Retrospective	Left-sided RT Control (right-sided RT) Control (no RT)	34 33 23	13 (3 groups combined)	Direct orthovoltage to chest wall; direct electron field to internal mammary nodes; direct 6 MV fields to supraclavicular fossa and axilla	1978-1983	All irradiated likely to have received some dose to heart; dose higher for left-sided RT	4/34 (12%) 2/33 (6%) 0/23	1/4 0/2 -	All patients had normal systolic LV function.
Denmark; Højris <i>et al.</i> [39]	Retrospective	Left-sided RT Control (no RT)	10 7	7.9 (both groups combined)	Direct electron field to chest wall and internal mammary nodes	1982-1990	NS	4/10 (40%) 4/7 (57%)	0/4 1/4	NS
U.K.; Seddon <i>et al.</i> [40]	Retrospective	Left-sided RT Control (right-sided RT)	24 12	6.7 8.3	Tangential opposed pair Co-60, 5 or 6 MV	1987-1995	24/24 (required for study) 0/12	17/24 (71%) 2/12 (17%)	17/17 1/2	17/17 2/2
France; Cowen <i>et al.</i> [41]	Retrospective	Left-sided radiotherapy	17	4.6	Tangential opposed pair Co-60 or 4 MV; mixed photon/electron field to internal mammary nodes and supraclavicular fossa	1987-1993	NS	0/17	-	-

Abbreviations: RT=radiotherapy; NS=not specified; LAD=Left anterior descending; LV=Left ventricular; Co-60=Cobalt 60

appreciable number develop new areas of infarcted or ischaemic myocardium. The formation of atherosclerotic plaque in the context of non-radiation-induced heart disease usually occurs over a period of several years [42]. Thus development of visible scintigraphic defects suggesting infarction or ischaemia so early after radiotherapy treatment is surprising. It is possible that irradiation accelerates atherosclerosis that had already commenced prior to radiotherapy but was not extensive enough to cause detectable abnormalities. Another possibility is that visible perfusion defects may represent radiation-induced microvascular damage to the myocardium [35]. Interestingly, one study [34] suggested that some defects may resolve without intervention. In this study the presence of defects in the left anterior descending (LAD) coronary artery was assessed at 6, 12 and 18 months in 16 patients after radiotherapy. An excess of defects was identified at 6 months which tended to decrease slightly over the following 12 months, raising the possibility that a proportion of vascular abnormalities may resolve spontaneously. However, additional data on patients with serial measurements over several years would be needed to confirm this.

### **Studies that relate some measure of radiotherapy dose to defect formation**

The greater the radiation dose and volume of heart irradiated, the higher the expected risk of myocardial perfusion abnormalities. Correlation between vascular damage and radiation dose can be assessed in three ways. Firstly, by comparing the incidence of perfusion defects in patients with and without left ventricular inclusion in the radiotherapy field. Secondly, by assessing the location of defects relative to areas of expected high dose within the heart; and, thirdly, by using computerised tomography (CT) based 3-dimensional (3D) heart dose estimation and fusing this with the myocardial perfusion image. These approaches are described below.

*i) Assessment of inclusion of the heart in the radiotherapy field*

Patients who had inclusion of the left ventricle in the radiation field tended to receive a higher dose to the heart than patients without inclusion. Therefore some evidence for the aetiological role of radiotherapy can be derived from comparing the incidence of myocardial perfusion defects in these two groups of patients. Left ventricular inclusion was assessed in two prospective studies. In the first, it was a requirement for study group entry [35]; 6/12 (50%) of these patients developed new perfusion abnormalities. A later study [36] reported that 12/17 (71%) patients who had part of the left ventricle in the radiotherapy field developed new perfusion defects in comparison to 0/3 patients without left ventricular inclusion. Although firm conclusions cannot be drawn from such small numbers, the available data suggest that irradiation of part of the left ventricle to around 25 Gy or above contributes to the development of vascular abnormalities.

*ii) Matching location of defects with expected areas of high dose*

Dose to the heart from chest wall or internal mammary nodal radiotherapy is usually highest in the anterior portion of the heart [43]. Therefore if scintigraphic defects were radiation-induced, this region would be expected to contain a higher proportion of defects relative to other regions of the heart. In the study by Gyenes et al. [35], the perfusion abnormalities in all six patients who developed new defects were located anteriorly and were compatible with radiation-induced damage.

*iii) Fusion of CT planning with myocardial perfusion images*

The relationship between radiation dose and perfusion abnormalities has been characterised more precisely by two studies that used 3D CT planning to estimate

dose to different regions of the heart for each patient. The CT images were then fused with myocardial perfusion images. One study reported that reduction in perfusion was greatest in areas of the heart that received the highest doses [36]. In the other study, damage in the specific regions of the major coronary arteries was assessed in 69 patients [34]. Radiotherapy was delivered using a tangential opposed pair to the left breast which would be expected to deliver a high dose to the LAD coronary artery but not to the left circumflex and right coronary arteries. New perfusion defects in the LAD coronary artery were identified at 6 months and the severity of these was correlated with the volume of left ventricle that received more than 25 Gy. There were no perfusion changes in the left circumflex and right coronary arteries.

In summary, studies that relate myocardial perfusion abnormalities with some measure of radiation exposure of the heart suggest firstly that defects tend to occur more frequently in patients known to have received more than 50% of tumour dose to part of the heart and secondly that they tend to be located preferentially in areas of expected high dose. These findings suggest that radiation may have a direct effect on the microvasculature, coronary arteries, or both and that the magnitude of this effect may be dose-dependent. The possible effect of radiotherapy on the LAD coronary artery is of particular concern since it is located anteriorly, in an area of expected high dose from chest wall or breast radiotherapy [43].

### **Retrospective studies**

Retrospective studies enable estimation of the prevalence of vascular defects in irradiated patients. They also enable assessment of damage in patients who were treated with radiotherapy techniques used between 10 and 30 years ago, whereas

prospective studies have addressed more recent regimens. In order to assess the contribution of radiotherapy to the development of defects, the prevalence of such abnormalities needs to be compared with that in an equivalent unirradiated group, or with a patient group who received lower doses of cardiac radiation. Four of the five reported studies compared patients irradiated for left-sided breast cancer with unirradiated patients or patients irradiated for right-sided breast cancer (with lower average heart doses). Prevalence also depends on patient age and the presence of other cardiac risk factors such as smoking and hypercholesterolaemia.

Reversible, irreversible and mixed defects were reported. There was appreciable variability in the prevalence of perfusion abnormalities of between 0% and 71% for patients who received left-sided irradiation and between 0% and 57% for controls (Table 1, lower half). This can largely be explained by the differing follow-up times, variation in risk factors for cardiovascular disease and in radiation dose to the heart. A study of particular interest was Seddon et al. [40]. All 24 patients in the study group received some left ventricular irradiation. In this group a high prevalence of defects (71%) was demonstrated; this was significantly increased relative to 12 controls who received right-sided radiotherapy (17%). Perfusion defects were located anteriorly, and 16/17 corresponded to the area of heart that is likely to have received the highest radiation dose.

### **Underestimation of the effect**

Patients who had suffered cardiac events were excluded from all these studies, both prospective and retrospective, and those with initial positive scintigraphy were excluded from the prospective studies. Therefore, the most severely affected patients are not represented. Such studies report patients with 'silent' vascular

damage and therefore reported rates are likely to underestimate the true incidence of vascular disease after breast radiotherapy. This complicates extrapolation from these studies to what may happen in the general irradiated breast cancer population.

### **Clinical importance**

In summary, both irreversible and reversible myocardial perfusion defects have been demonstrated in irradiated patients. Retrospective studies enable assessment of long-term changes; the disadvantage of such studies is that the patients' pre-treatment cardiovascular status is not known. It may therefore be more difficult to assess whether radiotherapy is causative in any cardiovascular damage. Prospective studies enable comparison of the coronary vasculature before and after radiotherapy. Available studies suggest that radiotherapy may result in early damage. The clinical importance of these abnormalities is uncertain - only one reported patient with perfusion defects demonstrated impairment of left ventricular systolic function. However, the natural history of radiation-induced vascular damage is not well understood and such abnormalities may progress to overt heart disease in future years.

### **Dose and dose-response relationships**

As the interval between radiation exposure and any resulting increase in symptomatic heart disease is usually 10 years or more [12,23], it will take at least this length of time before the risk associated with newly introduced radiotherapy techniques can be assessed directly. At the present time the shape of the dose-response relationship for heart disease after radiotherapy is subject to substantial uncertainty. Measurement of radiation dose to the heart for women receiving radiotherapy, in combination with information on the risks of heart disease in the

populations for which follow-up data are already available (either in the randomised trials or in the observational studies), may help to clarify the dose-response relationship. This may then be useful in predicting future risk from current radiotherapy regimens for which follow-up data are not yet available.

### **Cardiac doses from breast radiotherapy**

Many of the patients in the studies where increased mortality from heart disease has been demonstrated were irradiated in the 1950s to 1970s. At that time, target volumes tended to be extensive. For example, the medial tangent of breast or chest wall irradiation often extended across the midline and internal mammary nodal irradiation was frequently employed [44-46]. Several studies have used 3D CT planning techniques to estimate the heart dose from breast and internal mammary nodal radiotherapy with such techniques [43,47,48]. Comparison of heart dose from breast radiotherapy techniques in the published literature is hindered by the lack of comparable quantitative dose estimates, as a variety of different measures of heart dose have been reported. Such studies suggest that the highest heart doses result from the use of a left direct anterior internal mammary field with a megavoltage beam (Fig. 3), which delivers approximately 21 Gy mean heart dose, if the prescribed dose is 50 Gy [47]. Janjan et al. [43] estimated that this technique delivered doses of between 25 and 50 Gy maximum to the coronary arteries, with the LAD and right coronary arteries receiving the highest doses.

Improvements in breast radiotherapy planning have led to a general reduction in dose to the heart. This was illustrated by a comparison of doses to the heart and coronary arteries in two groups of patients irradiated for breast cancer

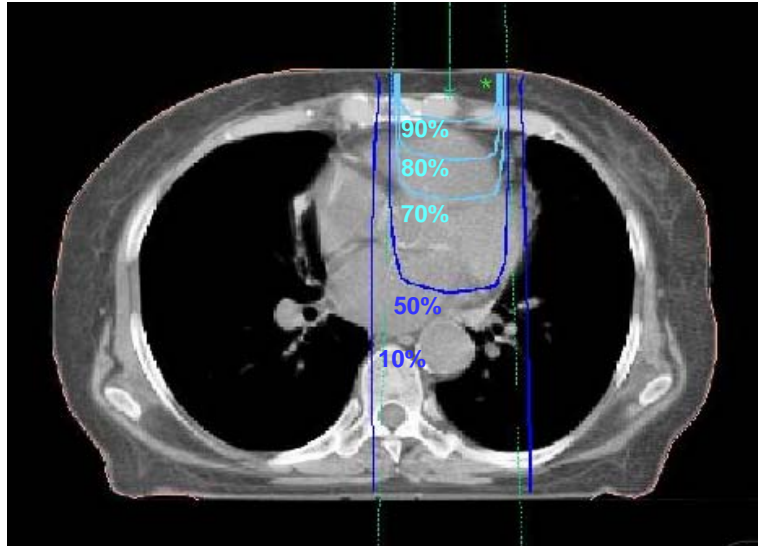


Fig. 3 Axial CT section showing the dose distribution from a left cobalt-60 direct anterior internal mammary field. Isodose lines correspond to percentages of given dose.

during 1957-1984 and 1988-1989 [16]. Dose to the heart and to the circumflex and right coronary arteries was lower in the group treated more recently. However, dose to the LAD coronary artery was high in both groups.

Internal mammary irradiation is now no longer routinely recommended in the UK [49] but still continues to be used, particularly in continental Europe [50] and is being investigated by EORTC in a randomised controlled trial [51]. If it is necessary, the use of an electron field or mixed oblique photon and electron field can result in lower heart doses. The estimated mean heart doses from two such techniques from the late 1990s were 6.4-8.1 and 3.3-3.7 Gy for left-sided and right-sided radiotherapy respectively [20].

The dose received by the heart from a left-tangential opposed pair has also reduced over the past 20 years. The mean irradiated heart volume included in the radiotherapy field (as defined by the 50% isodose) of a left-tangential pair

determined using 3D CT dose planning, was around 25% for patients irradiated in the 1970s and 1980s compared to 6% for patients irradiated during 1994-1995 [52]. However, despite improved planning techniques, 6% of patients treated in the mid-1990s still had over 15% of the heart volume included in the radiotherapy field [52].

Even where the heart is not included in the radiation field, it is likely to receive scatter dose of around 1-2 Gy. At present there is no direct evidence of whether this will result in any long-term cardiac risk. However, the studies of the survivors of the atomic bombings of Hiroshima and Nagasaki suggest that even doses of this magnitude may increase the death rate from heart disease by 20-30% [10].

### **Dose-response modelling**

Detailed dose calculations were not performed prospectively or related to cardiac outcome in most of the randomised trials included in the EBCTCG overview [15] and, to date, none of the observational studies of women irradiated for breast cancer has attempted to use retrospective dosimetry calculations to determine the dose-response relationship for cardiac risk. Retrospective dosimetry can be informative, and has been used to obtain an empirical estimate of the dose-response relationship for cardiac mortality in one randomised trial from Stockholm [17,53]. In this study, radiation doses to the heart were estimated using 3D techniques applied to current CT scans for 960 patients who had previously been randomised either to radiotherapy or to the same other treatment but without the addition of radiotherapy. Patients with the highest estimated dose to the heart were those treated with left-tangential opposed cobalt-60 fields. This group experienced an increased mortality rate from cardiovascular disease relative to unirradiated controls (relative

hazard=2.0, 95% CI 1.0, 3.9). No such increase was seen among patients treated with techniques that delivered lower doses to the heart.

An alternative approach to obtaining insight into the dose-response relationship for cardiac risk is to use models that draw on the radiobiological theory of cell kill. The relative seriality model is one such approach, which assumes homogenous radiosensitivity and represents an organ in terms of 'functional subunits'. The organisation of these subunits in series and parallel is described by the 'relative seriality' parameter,  $s$ . The value of  $s$  is high for organs with predominantly serial architecture, such as oesophagus and spinal cord and low for predominantly 'parallel' organs such as lung [54]. The model has been used in conjunction with clinical data on long-term cardiac mortality from the Stockholm and Oslo randomised trials, and an estimated threshold dose of 20 Gy for death from ischaemic heart disease was obtained [21]. This value is, however, at odds with the observed linear dose-response relationship for mortality from heart disease for doses in the range 0-4 Gy in the survivors of the atomic bombings of Hiroshima and Nagasaki [10]. It is also at odds with observed increases in coronary heart disease mortality seen in peptic ulcer patients who received <4 Gy fractionated radiation to the heart [12]. The explanation for these discrepancies is not yet understood.

### **Concluding remarks**

The potential benefits of radiation therapy in terms of reducing local tumour recurrence and breast cancer mortality are now well established [15,55]. However, its long-term hazards of cancer [25,56] and heart disease are potentially considerable. Both randomised controlled trials and observational studies suggest that, at least as regards the excess mortality from past radiotherapy regimens, the

risk of heart disease outweighs the risk of second cancer. The time-course of the cardiac mortality risk is revealed clearly in the SEER data [25], which suggest that it is unimportant in the first ten years after radiotherapy, and therefore of little relevance either to breast cancer patients with poor prognosis or to elderly patients whose life-expectancy ignoring the risk of death from breast cancer is unlikely to exceed about 10 years. However, younger women with good prognosis may well have an excellent chance of surviving for more than 10 years after their breast cancer diagnosis, especially those diagnosed at an early stage through screening, so that the possible cardiac risks in the second, third, and even fourth decades after diagnosis need to be considered. For those receiving adjuvant chemotherapy containing anthracyclines their possible cardiac toxicity [57] is, of course, an additional concern. Symptomatic radiation-induced heart disease may occur considerably earlier than fatal heart disease, but as yet there is little data either on its time-course or on the magnitude of the risk, nor is it yet understood whether there is any relationship between the subclinical vascular abnormalities that have been observed within months of irradiation, via myocardial perfusion imaging studies, and later overt heart disease. The randomised trials have shown that, for some past breast radiotherapy regimens, the long-term fatal hazards of radiotherapy may even have outweighed its beneficial effect [15]. Since then, improvements in radiotherapy planning have resulted in a general reduction in heart doses. However, for some patients part of the heart may still be included in the radiotherapy field and, where this does occur, the highest doses are likely to be to the anterior heart, particularly the LAD coronary artery, which is one of the typical sites of origin for ischaemic heart disease. Even where the heart is completely outside the radiotherapy field, it is still likely to receive some radiation dose from scatter. The

detrimental effect of radiation doses in the range 0-5 Gy on mortality from heart disease has been demonstrated in a number of populations [9,10]. Therefore, even in this scenario, the risk of mortality from heart disease may not be completely avoided.

At present, there are few data relating heart dose and other specific characteristics of breast radiotherapy to cardiac outcome. Further information on these topics is needed in order to enable estimation of cardiac risk that is likely to arise both from radiotherapy regimens in current use, and from those being considered for use in the future. Such knowledge would facilitate radiotherapy treatment planning and enable a reduction in cardiac risk while maintaining the known benefit in terms of breast cancer mortality.

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# **3. Cardiac exposures in breast cancer radiotherapy: 1950s-1990s**

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## **Abstract**

### **Purpose**

To estimate doses to the heart and coronary arteries from common breast cancer radiotherapy regimens used worldwide from the 1950s to the 1990s.

### **Methods and materials**

Virtual simulation and computed tomography planning were used to reconstruct megavoltage and electron regimens. Manual planning was used for orthovoltage and brachytherapy regimens. Several sources of variability associated with the dose estimates were assessed.

### **Results**

Breast or chest wall radiotherapy resulted in whole heart doses of 0.9-14 Gy for left-sided and of 0.4-6 Gy for right-sided irradiation. Internal mammary chain radiotherapy delivered heart doses of 3-17 Gy and 2-10 Gy for left- and right-sided irradiation respectively. For most regimens, dose to the left anterior descending coronary artery was higher than heart dose. Scar boost, supraclavicular fossa and axillary radiotherapy delivered mean cardiac doses of  $\leq 3$  Gy. The greatest source of variability in estimating dose from a given regimen was patient anatomy.

### **Conclusion**

For most techniques, the highest radiation doses were received by the anterior part of the heart and by the left anterior descending coronary artery, which is a common site of atherosclerosis causing myocardial infarction. Irradiation of these structures may have contributed to the excess risk of death from heart disease seen after some past breast cancer radiotherapy regimens.

**Key words:** *Breast radiotherapy, heart disease, long-term effects.*

## Introduction

The majority of women treated for early breast cancer undergo primary surgery. This is often followed by adjuvant radiotherapy which reduces breast cancer mortality after breast-conserving surgery and after mastectomy in node-positive disease [1]. Long-term follow-up of these women has, however, revealed that some past regimens led to an increased risk of death from heart disease, particularly ten or more years after irradiation, presumably due to some unwanted irradiation of cardiac structures.

Dose-response curves for radiation-induced cardiac mortality have been produced using a radiobiological model, called the relative seriality model, in conjunction with data on long-term cardiac mortality from two randomised trials of radiotherapy in which deaths from ischaemic heart disease were reported in irradiated and unirradiated patients by breast cancer laterality [2,3]. These dose-response curves were, however, based on few cardiac deaths and are therefore subject to considerable uncertainty. They were used by Pierce *et al.* [4] to estimate normal tissue complication probabilities of cardiac mortality for seven post-mastectomy radiotherapy techniques, but the authors cautioned that “*until additional clinical data are available to validate predictive models, normal tissue complication probability estimates are best used for relative comparison between techniques rather than for absolute risk assessment.*”

The estimation of the cardiac risk of today’s breast cancer radiotherapy requires the development of reliable dose-response relationships, which in turn require detailed cardiac dosimetry of past regimens given to women for whom we have long-term follow-up. At present, few heart dosimetry data from breast cancer radiotherapy are available. Furthermore, it is unknown which quantitative measures

of heart dose or volume are most relevant to subsequent heart disease risk [2]. Studies have used a variety of heart dose specifications including absorbed dose [5,6], biologically effective dose (BED) [7], and ‘cumulative radiation effect’ (an estimate of biological radiation dose [8]). Published data recording percentage volume of the heart irradiated to various doses are limited. Such information may, however, be important in assessing radiation-related heart disease, since percentage volume of the heart irradiated to a certain ‘threshold’ dose may predict cardiac death better than, say, mean heart dose or BED. Information is also needed concerning the effect of irradiating different cardiac structures, especially the coronary arteries. Coronary artery dose has been reported for several techniques, but only for left-sided irradiation [5,6] whereas most studies report only mean dose to the whole heart.

In this study a methodology has been developed to estimate cardiac doses. We present dose estimates for the whole heart and for the three main coronary arteries for techniques that were commonly used in the past (1950s-1990s). Information on heart disease rates in randomised trials of breast cancer radiotherapy [1] and in observational studies [9] can be used in combination with these doses to derive dose-response relationships. These should enable prediction of the likely cardiac risk of current and future breast cancer radiotherapy regimens and facilitate the development of treatment guidelines. In addition, for individual patients (eg. those whose heart is included the radiation beam), it should allow assessment of cardiac risk based on their radiotherapy plan, thus identifying women for whom complex planning techniques may be justified in order to reduce cardiac dose.

## **Methods and materials**

### **General method**

A technique based upon virtual simulation and computed tomography (CT)-based 3-dimensional treatment planning has been used to reconstruct radiotherapy regimens used in previous decades for treating the breast, chest wall and/or locoregional lymph nodes. Dose distributions were calculated using a treatment planning system (Helax TMS version 6.1B, Nucletron Ltd, Veenendaal, the Netherlands) which is accurate to within  $\pm 2\%$  for dose and  $\pm 2$  mm for position in most situations, as shown by phantom measurements [10,11].

Approximately 40 consecutive CT planning scans of female patients, on the database of a UK radiotherapy department, were reviewed. The patients were supine, with a T-bar arm rest, similar to positions used for breast cancer radiotherapy in previous decades. From the forty, one representative patient of average weight and height was chosen for the detailed calculations.

The CT data were transferred to a virtual simulation software package (Exomio release 2.0, MedCom GmbH, Darmstadt, Germany). The 3-dimensional patient surface contours were defined by automated density gradient tracking. The heart and coronary arteries were contoured by a radiation oncologist and reviewed by a radiologist. The cranial limit of the heart included the right atrium and excluded the pulmonary trunk, ascending aorta and superior vena cava. The lowest contour of the heart was the caudal myocardial border. The scans were not contrast-enhanced. Therefore, on some images, the coronary arteries were not visible and their location was inferred using visible, reliable landmarks: the anterior interventricular, left atrioventricular and right atrioventricular grooves. Due to the

short length of the left main coronary artery, its contour was included with that of the left anterior descending (LAD) coronary artery.

Field borders, beam arrangements and machine parameters for each radiotherapy regimen were defined using virtual simulation with emphasis on the surface reconstruction function. Fig. 1 illustrates the use of virtual simulation to reconstruct a left internal mammary chain (IMC) field.

The treatment parameters and patient and organ at risk outlines were exported to the computerised treatment planning system and dose distributions were calculated. The algorithms employed for the photon beams were the pencil beam model [12,13] and the collapsed cone superposition convolution algorithm [13-15]. The former was used for all regimens and the latter for a selection of cases where tissue inhomogeneities were substantial. Agreement between algorithms for calculated heart doses was within 1% for most regimens and within 2% for all regimens.

For each regimen, cardiac dose volume histograms (DVHs) were generated. From these, estimates of mean and maximum dose and percentage volume irradiated to different doses were obtained for the heart and for the LAD and right and circumflex coronary arteries.

Cardiac dose distributions for several 250 kV regimens and iridium wire implants were also derived. This involved generating scaled hard-copies of appropriate CT slices on which isodose distributions for 250 kV x-rays or iridium wire implants were superimposed. Manual planning techniques incorporating lung correction were employed to generate cardiac dose distributions. The physical density of lung was taken to be  $0.25 \text{ g cm}^{-3}$ .

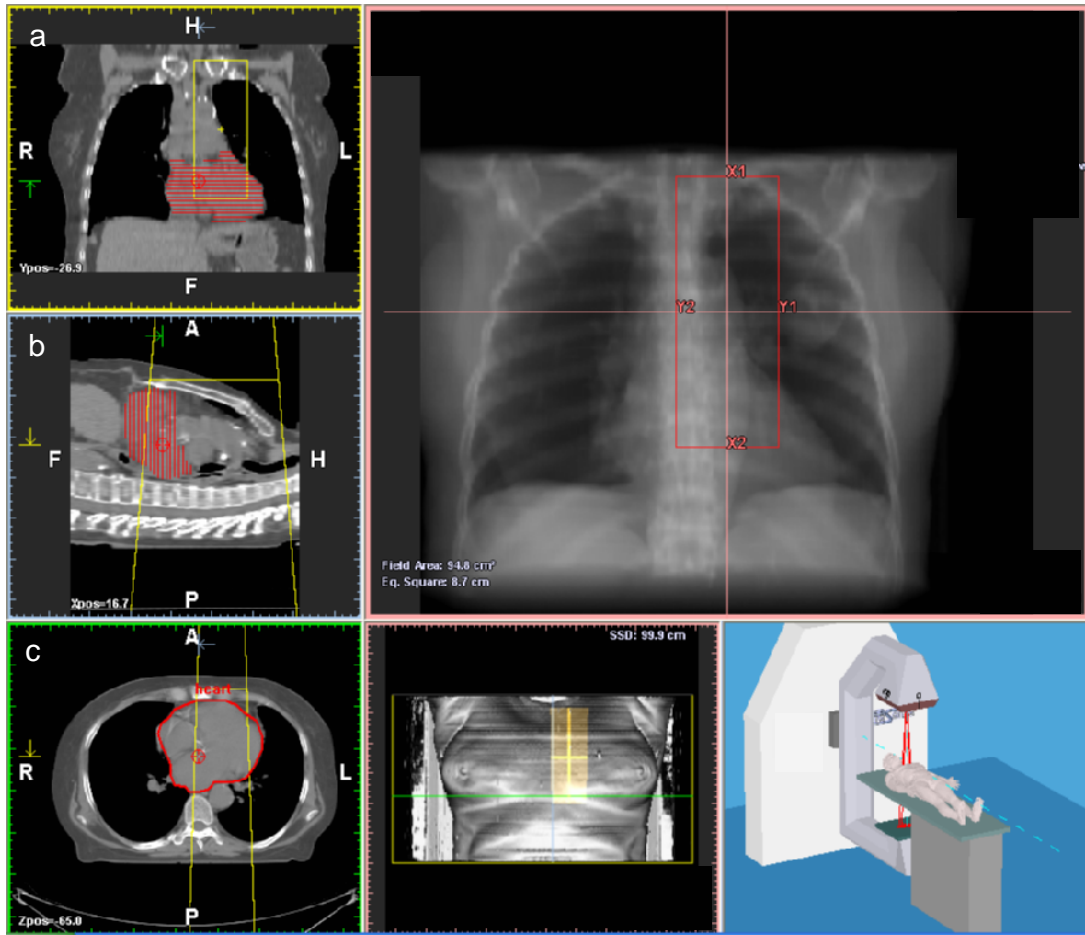


Fig. 1. Virtual simulation of a photon left direct internal mammary field. CT images are shown on the left in boxes a, b and c (a=coronal, b=sagittal, c=transverse). The edges of the radiation field are shown in yellow and the heart is outlined in red. The beam's eye view (top right) shows the position of the field (red) relative to the underlying heart and bony thorax. The surface reconstruction image (bottom middle) shows the light field in yellow.

For orthovoltage treatments, axial CT slices of the superior, middle and inferior levels of heart were used. For single direct fields, an applied dose was assumed. For tangential pair radiotherapy, the use of tissue-equivalent bolus between the two applicators was assumed. The proportion of each cardiac structure

included within each isodose line was calculated and used to plot DVHs. These were typically based on three CT slices per radiotherapy plan. For the heart, there were approximately 150 dose-points per CT slice, whereas for the three coronary arteries, their small volumes meant that only one dose-point per slice was used.

For all regimens, BEDs were calculated using the linear-quadratic model. Estimated alpha-beta ratios for radiation-related heart disease are between 1 and 3 Gy [16,17]. For these calculations, an alpha-beta ratio of 2 Gy was used. For orthovoltage radiotherapy, a correction factor of 1.1 was used to account for the enhanced biological effectiveness of low energy irradiation [7].

The reconstructed brachytherapy treatments were typical of those used as a boost to the tumour bed after breast-conserving surgery and external beam radiotherapy. The likely position of a surgical scar was marked using virtual simulation. Mid-plane cross-sectional isodoses of a standard two-plane five-wire iridium implant were superimposed on scaled hard-copies of three sagittal CT sections: one at the expected centre of the implant, one 2 cm medial and one 2 cm lateral to this point. The iridium wires were 6 cm long and positioned 1.5 cm apart and 1.5 cm beneath the skin.

### **Specific techniques reconstructed**

Radiotherapy details for over 60 trials of radiotherapy for early breast cancer (1950s to 1990s) were collated using trial publications and protocols, textbooks [18-21] and discussions with radiotherapists who had worked in various countries from 1950 onwards. Using this information, radiotherapy techniques commonly used to treat the chest wall, breast and associated lymphatics were reconstructed. Descriptions of target volumes, clinical definition of field borders, field arrangements and beam

energies are shown in Table 1 and illustrated by Fig. 2. Focus-to-skin distance was 100 cm for all fields; wedges and compensators were not used. Tangential pair beams were 180° opposed.

### **Variation in patient anatomy**

Two techniques were reconstructed on consecutive contemporary (2006) breast cancer patients on the CT planning database. These patients were angled on a breast-board, unlike the representative patient who was positioned flat. This difference means there are small systematic differences in doses between these patients and the representative patient. Interpatient variability however, should be comparable. Direct anterior left and right IMC fields and left-tangential irradiation were reconstructed on 20 consecutive patients. Right-tangential irradiation was reconstructed on 5 consecutive patients since little interpatient variation in heart dose was expected for this regimen.

## **Results**

### **Dose estimates for the representative patient**

Mean doses to the coronary arteries and maximum dose, mean dose and mean BED to the heart for the representative patient are summarised in Table 2. Webtables 1 to 8 (see end of this Chapter) give further details including percent volume of each structure irradiated to various doses, mean BED and maximum dose.

### **Heart dose from chest wall or breast irradiation**

For breast or chest wall radiotherapy (Fig. 2, panels a,b,c), mean heart dose varied between 0.9 and 14 Gy for left-sided and between 0.4 and 6 Gy for right-sided

Table 1. Radiotherapy techniques reconstructed for cardiac dose estimations\*

Target	Field arrangement	Definition of field borders	Beam energy	Comments
Chest wall/breast (a, b)	Tangential pair [18-20]	Superior—sternal notch Inferior—1 cm below inframammary fold Medial—midline or matched to internal mammary chain field Lateral—midaxillary line	6 MV Co-60 250 kV	Tissue equivalent bolus between applicators for 250 kv
Chest wall (c)	Direct anterior [19, 22]	Superior—inferior border of supraclavicular fossa field Inferior—xyphoid-sternal junction Medial—midline Lateral—midaxillary line	10 MeV electrons	
Chest wall and internal mammary nodes (d)	Tangential pair [19]	Superior—sternal notch Inferior—1 cm below inframammary fold Medial—1 cm to contralateral side of midline Lateral—midaxillary line	6 MV Co-60	Medial tangential beam angled 10° downwards
Chest wall and internal mammary nodes McWhirter fields (e)	Tangential pair [23]	Superior—sternal notch Inferior—1 cm below inframammary fold Medial—sternal border on contralateral side Lateral—midaxillary line	250 kV	Tissue equivalent bolus between applicators
Internal mammary nodes (f)	Direct anterior [18, 20, 24]	Superior—sternal notch Inferior—xyphoid-sternal junction Medial—midline Lateral—6 cm from medial border	6 MV Co-60 250 kV	Usual size: 17 × 6 cm
Internal mammary nodes (similar to f)	Direct anterior [19]	Superior—sternal notch Inferior—xyphoid-sternal junction Medial—1 cm contralateral to midline Lateral—7 cm from medial border	10 MeV electrons	Usual size: 17 × 7 cm
Mastectomy scar boost	Direct anterior [25, 26]	5 × 14 cm strip covering the approximate position of mastectomy scar	Co-60 10 MeV electrons 250 kV	Placement of field approximate
	Brachytherapy [27, 28]	Two plane, five-wire iridium implant	Iridium-192	
Supraclavicular fossa (g)	Direct anterior [18, 19]	Superior—cricothyroid groove Inferior—middle of second costal cartilage Medial—1 cm to contralateral side of midline Lateral—crosses acromioclavicular joint	6 MV Co-60	Usual size: 10 × 16 cm. Beam tilted 15° laterally
Posterior axilla (h)	Direct posterior [19]	Superior—spine of scapula Inferior—inferior border of supraclavicular fossa field Medial—follows the lateral wall of bony thorax Lateral—bisects the humeral head	6 MV Co-60	Lead used to shape medial border

\*Regimens a-h are illustrated in Fig. 2.

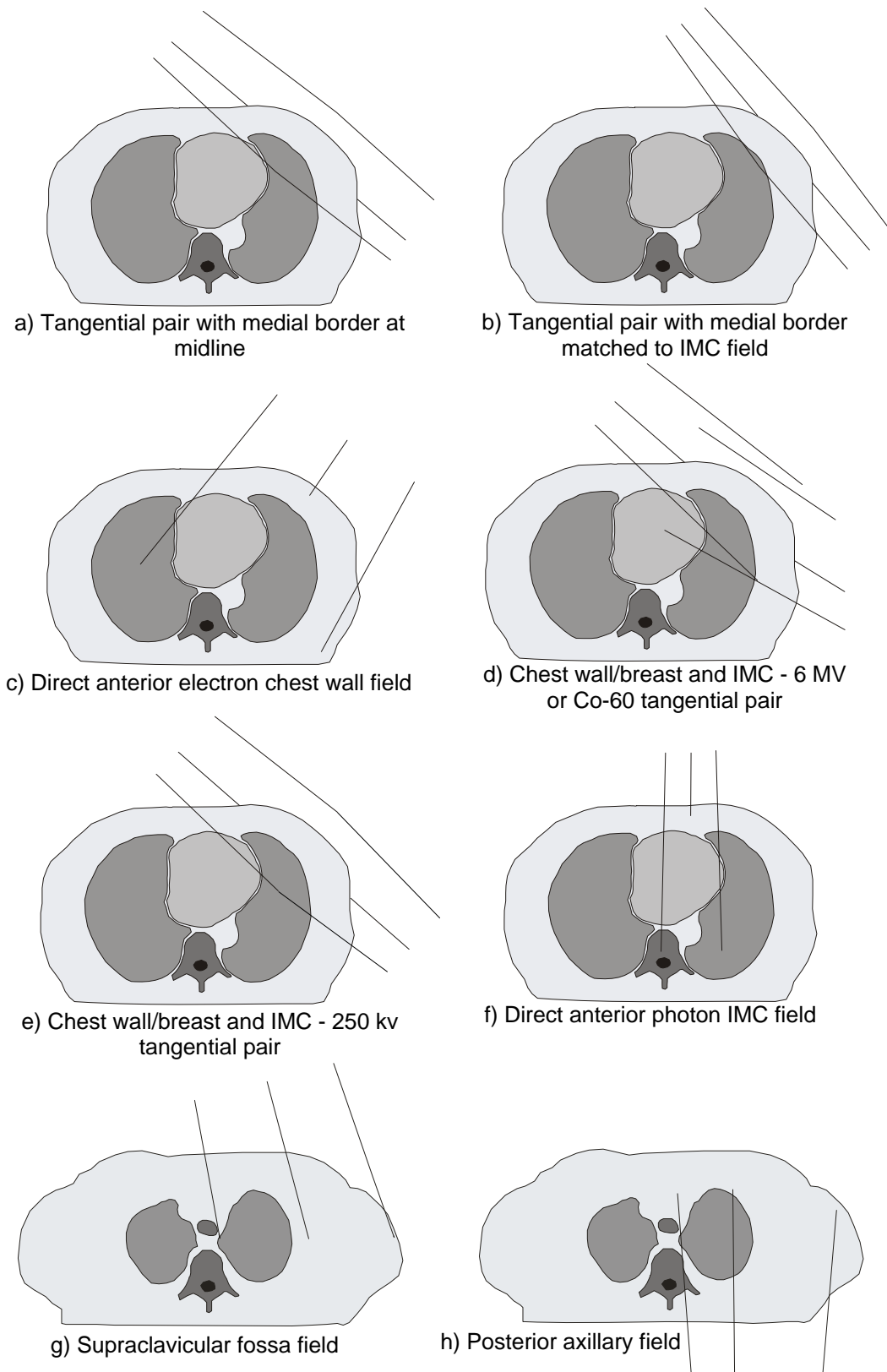


Fig. 2. Radiotherapy techniques reconstructed for cardiac dose estimations.

See Table 1 for further details, including definitions of field borders.

*Abbreviation:* IMC = internal mammary chain

Table 2. Heart and coronary artery doses from breast radiotherapy regimens\*

Target	Field arrangement	Beam energy	Typical dose and fractionation	Heart						LAD		RCA		CCA	
				Mean dose (Gy)		Maximum dose (Gy)		Mean BED (Gy <sub>2</sub> ) <sup>†</sup>		Mean dose (Gy)		Mean dose (Gy)		Mean dose (Gy)	
				Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Chest wall/breast a)	Tangential pair <sup>‡</sup>	6 MV	50 Gy in 25	4.7	1.5	49.2	4.8	7.0	1.9	21.9	1.4	2.0	2.4	2.8	1.0
		Co-60	50 Gy in 25	4.7	1.2	48.1	7.2	7.0	1.5	21.8	0.9	1.7	2.3	2.7	0.6
		250 kV <sup>§</sup>	42 Gy in 20	14	6	60	19	25	8	51	3	11	13	8	3
Chest wall/breast medial border matched to internal mammary field b)	Tangential pair <sup>‡</sup>	6 MV	50 Gy in 25	0.9	0.9	13.1	1.6	1.2	1.1	1.8	0.9	0.7	1.1	0.8	0.8
		Co-60	50 Gy in 25	1.0	0.4	10.7	1.0	1.2	0.6	2.1	0.3	0.6	0.6	0.8	<0.1
		250 kV <sup>§</sup>	42 Gy in 20	5	1	32	5	8	1	15	1	2	4	4	1
Chest wall c)	Direct anterior	10 MeV electrons	50 Gy in 25	2.8	1.5	27.8	20.0	3.6	1.9	10.3	0.6	1.7	4.8	0.9	0.4
Chest wall and internal mammary nodes (d, e)	Tangential pair <sup>‡</sup>	6 MV	50 Gy in 25	13.5	2.4	50.3	44.1	21.7	3.0	32.0	1.7	9.9	8.1	6.7	1.2
		Co-60	50 Gy in 25	13.3	2.3	49.4	43.0	21.0	2.9	31.8	1.3	9.1	8.7	6.9	0.8
		250 kV <sup>§</sup>	36 Gy in 20	14	9	48	41	26	13	46	6	11	26	9	5

Abbreviations: LAD=Left anterior descending coronary artery; RCA=Right coronary artery; CCA=Circumflex coronary artery; BED = biologically effective dose

\*Regimens a-h are illustrated by Fig. 2

<sup>†</sup>=BED calculated using  $\alpha/\beta$  ratio of 2

<sup>‡</sup>=Arm elevated on T-bar rest

<sup>§</sup>=Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place

Table 2 (continued). Heart and coronary artery doses from breast radiotherapy regimens\*

Target	Field arrangement	Beam energy	Typical dose and fractionation	Heart						LAD		RCA		CCA	
				Mean dose (Gy)		Maximum dose (Gy)		Mean BED (Gy <sub>2</sub> ) <sup>†</sup>		Mean dose (Gy)		Mean dose (Gy)		Mean dose (Gy)	
				Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Internal mammary nodes f)	Direct anterior	6 MV	50 Gy in 25	16.7	10.5	48.4	47.6	27.8	17.4	25.1	1.6	6.2	21.0	15.5	1.4
		Co-60	50 Gy in 25	15.0	9.3	44.1	43.6	23.4	14.6	22.7	1.2	6.5	20.5	13.5	1.2
		10 MeV electrons	50 Gy in 25	2.7	2.3	44.8	40.2	3.7	3.1	6.4	0.4	4.6	10.3	0.8	0.2
		250 kV <sup>§</sup>	50 Gy in 25	10	5	39	37	15	8	20	1	6	24	9	2
Mastectomy scar boost	Direct anterior	Co-60	10 Gy in 5	0.9	0.2	8.1	6.8	1.2	0.3	3.1	0.1	0.2	0.2	1.2	0.1
		10 MeV electrons	10 Gy in 5	0.3	0.2	5.1	2.9	0.4	0.3	1.3	<0.1	0.1	0.3	0.1	<0.1
		250 kV <sup>§</sup>	10 Gy in 5	1	1	6	5	1	1	2	<1	<1	<1	1	<1
	Brachytherapy	Iridium-192 <sup>§</sup>	20 Gy	1	–	7	–	2	–	2	–	<1	–	<1	–
Supraclavicular fossa g)	Direct anterior	6 MV	50 Gy in 25	0.8	–	1.4	–	1.1	–	1.0	–	0.8	–	0.8	–
		Co-60	50 Gy in 25	0.4	–	1.3	–	0.6	–	0.5	–	0.2	–	0.4	–
Posterior axilla h)	Direct posterior	6 MV	50 Gy in 25	0.5	–	0.8	–	0.8	–	0.6	–	0.4	–	0.5	–
		Co-60	50 Gy in 25	0.3	–	0.7	–	0.5	–	0.5	–	0.0	–	0.3	–

Abbreviations: LAD=Left anterior descending coronary artery; RCA=Right coronary artery; CCA=Circumflex coronary artery; BED = biologically effective dose

\*Regimens a-h are illustrated by Fig. 2

<sup>†</sup>=BED calculated using  $\alpha/\beta$  ratio of 2

<sup>‡</sup>=Arm elevated on T-bar rest

<sup>§</sup>=Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place

radiotherapy (Table 2). The largest doses resulted from orthovoltage (250 kV) irradiation. For example, for standard left-tangential radiotherapy (Fig. 2, panel a), mean heart doses were 4.7 Gy for megavoltage and 14 Gy for orthovoltage irradiation. This is partly explained by lateral scatter and partly by the depth-dose characteristics of an orthovoltage beam. In order to deliver 42 Gy at the mid-plane point on the central axis, a given dose of approximately 42 Gy multiplied by 1.8 is needed from each tangential 250 kV beam. The resulting dose distribution within the breast/chest wall and within normal tissue nearby is inhomogeneous, with hot-spots of up to 125% of tumour dose (53 Gy) within the heart for left-sided radiotherapy.

Where tangential beams were matched to a direct IMC field (Fig. 2, panel b), the medial tangential border was 6 cm from midline. The heart was therefore several centimetres from the posterior field edges and received low radiation doses from tangential beams: mean heart dose was 0.9-5 Gy for left-sided and 0.4-1 Gy for right-sided irradiation.

For wide-tangential radiotherapy (Fig. 2, panels d, e), the medial border was 1 cm contralateral to midline. Hence relatively large heart volumes were irradiated: 10 Gy or more was received by 44.8-53% and 3.0-29% of the heart for left- and right-sided irradiation respectively (Webtables 1 and 5), and mean heart doses were 13.3-14 Gy and 2.3-9 Gy for left- and right-sided irradiation.

For irradiation of the left breast or chest wall (Fig. 2, panels a,c), the part of the heart receiving the highest doses was the anterior surface of the left ventricle. The maximum heart dose was between 48.1 and 60 Gy for left-tangential irradiation (Fig. 2, panel a, Fig. 3) and 27.8 Gy for left electron irradiation (Fig. 2, panel c).

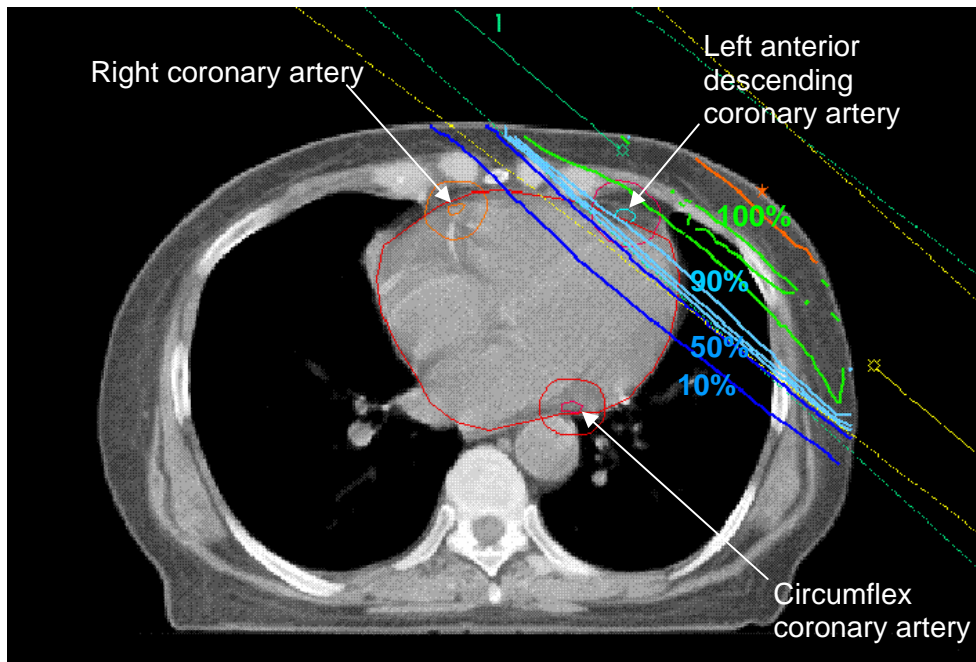


Fig. 3. Axial CT section showing the dose distribution from left Co-60 tangential pair radiotherapy. Isodose lines correspond to percentages of given dose. The three coronary arteries are outlined and a 1 cm margin has been added to each.

### Heart dose from IMC irradiation

The IMC is located anteriorly, in the intercostal spaces, close to the heart. Therefore IMC radiotherapy generally led to higher mean heart doses than irradiation of other targets, particularly for left-sided treatment. IMC radiotherapy, using either direct anterior (Fig. 2, panel f) or wide-tangential fields (Fig. 2, panels d,e), delivered 2.7-16.7 Gy mean heart dose for left-sided and 2.3-10.5 Gy for right-sided radiotherapy (Table 2), with the highest doses resulting from left direct anterior 6 MV irradiation (Fig. 4, panel b). The heart volume irradiated was also considerable, particularly for direct anterior photon fields which delivered  $\geq 10$  Gy to around 40% and 20% of the heart for left- and right-sided fields respectively. In contrast, direct electron IMC

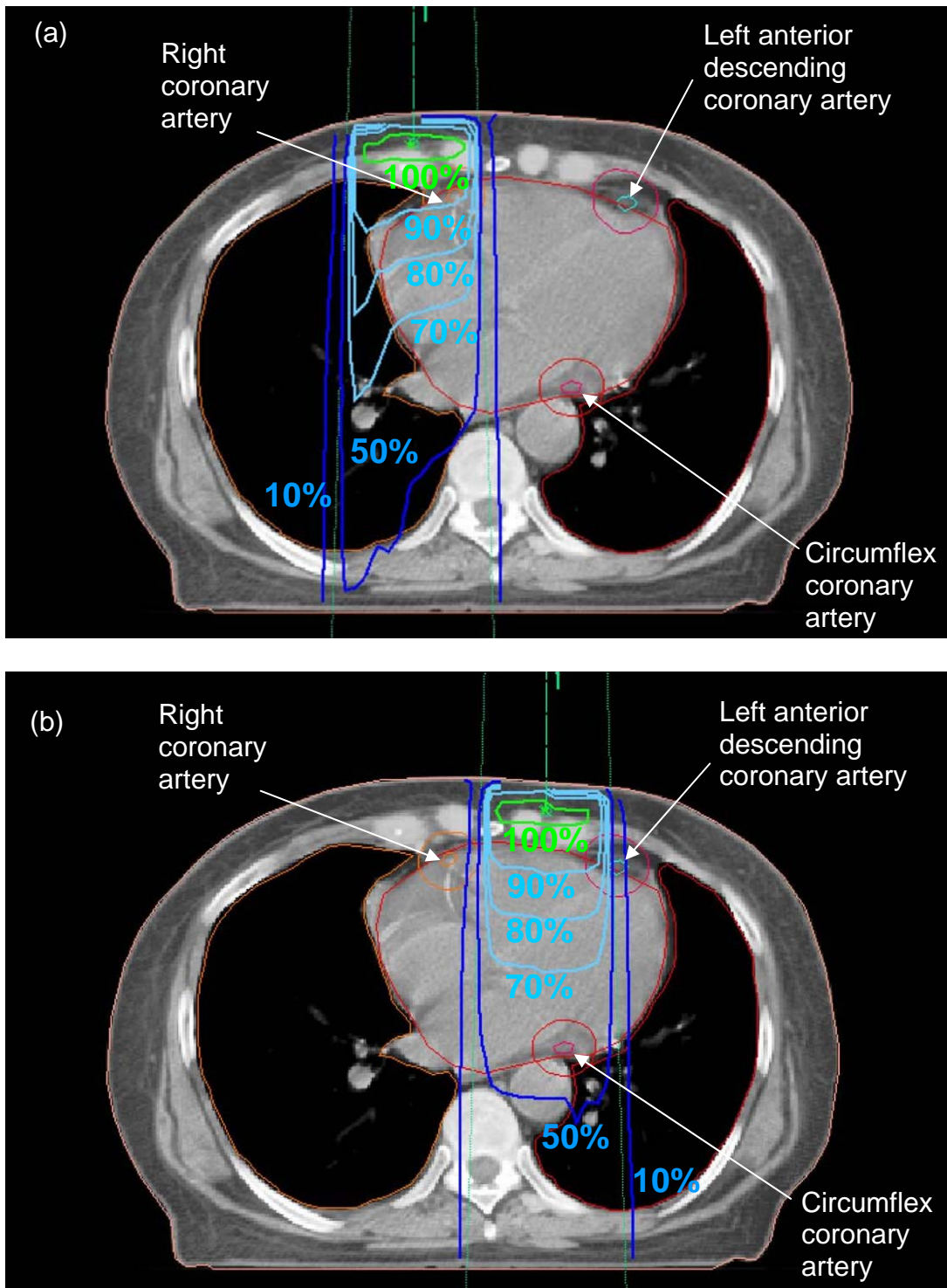


Fig. 4. Axial CT sections showing dose distributions from (a) right and (b) left 6 MV direct anterior internal mammary fields. Isodose lines correspond to percentages of given dose. The three coronary arteries are outlined and a 1 cm margin has been added to each.

irradiation resulted in lower mean heart doses of around 2 Gy and lower heart volumes of around 7% receiving  $\geq 10$  Gy (for both left- and right-sided radiotherapy), due to the rapid decrease in dose beyond the 90% isodose.

Direct anterior megavoltage IMC radiotherapy (Fig. 2, panel f, Fig. 4) resulted in irradiation of different parts of the heart for left- and right-sided treatment. For a right-sided field, doses of around 35 Gy were received by the right atrium, whereas for a left-sided field, similar doses were received by the left ventricle.

Where direct anterior IMC (Fig. 2, panel f) and matched tangential irradiation (Fig. 2, panel b) were used together, most of the total heart dose originated from the IMC field. For example, if 50 Gy was delivered to the chest wall and IMC using 6 MV beams, the IMC field would contribute 16.7 Gy, and the chest wall fields, 0.9 Gy heart dose giving a total mean heart dose of 17.6 Gy (Table 2).

### **Heart dose from scar boost irradiation**

Mean heart dose from boost irradiation of the surgical scar was  $\leq 1.0$  Gy for both left- and right-sided radiotherapy (Table 2). Left-sided photon beams delivered around 1 Gy mean heart dose whereas the left electron beam delivered only 0.3 Gy due to the rapid decrease in depth-dose. Iridium wire implants were used in previous decades to deliver doses of around 20 Gy boost to the scar [27,28]. The localised deposition of dose from these implants meant that only a few percent of tumour dose (around 1 Gy) was received by the heart for left-sided irradiation.

Heart dose from boost radiotherapy was small relative to dose from chest wall or breast radiotherapy due to the low given dose. For example, a patient who

received 50 Gy megavoltage tangential left chest wall radiotherapy, followed by 10 Gy electron scar boost would receive a total of 5.0 Gy mean heart dose: 4.7 Gy from chest wall and 0.3 Gy from boost irradiation (Table 2).

An important determinant of heart dose from boost radiotherapy is scar position relative to the heart, which is likely to vary from patient to patient. The doses presented here illustrate the relative magnitude of cardiac doses from different boost techniques and are useful for comparison between techniques. However, doses may vary substantially between individual patients, depending on boost position. The magnitude of this uncertainty is assessed below under the heading 'Variability in boost position'.

### **Heart dose from supraclavicular and axillary irradiation**

Supraclavicular fossa (SCF) and axillary fields were distant from the heart, which received scattered radiation alone. Mean dose was 0.3-0.8 Gy for left-sided fields. Right-sided SCF and axillary fields are even further from the heart. Therefore cardiac doses are likely to be lower.

### **Coronary artery doses**

The radiation dose received by each cardiac structure is mainly determined by its location relative to the treatment field(s). The LAD coronary artery on the anterior aspect of the heart is near the left breast and left IMC and, for all techniques used to treat these targets, LAD dose exceeded heart dose. For example, left megavoltage tangential irradiation delivered around 5 Gy mean heart dose compared with 20 Gy mean LAD dose (Table 2) and part of the LAD received >50 Gy (Fig. 3, Webtable 2). The LAD was in the penumbra of the left direct photon IMC field (Fig. 4,

bottom panel) and received around 20 Gy mean dose, whereas for the right-sided field (Fig. 4, top panel), it received <2 Gy mean dose from scattered irradiation.

The right coronary artery is located anteriorly, to the right of midline. For most techniques, it was excluded from the radiation field. For direct anterior IMC irradiation, it was included in the right-sided IMC field, but not in the left (Fig. 4): mean dose was 10.3-24 Gy for right-sided and 4.6-6.5 Gy for left-sided irradiation (Table 2).

The circumflex coronary artery is located in the posterior myocardium and generally received lower doses than either the LAD or right coronary arteries. Mean circumflex dose from tangential radiotherapy was between <0.1 and 8 Gy. Doses of <1 Gy were delivered by direct electron chest wall and scar boost irradiation.

### **Combinations of different regimens**

If a woman was treated with more than one regimen e.g. direct IMC and matched tangential breast fields or tangential breast plus boost radiotherapy, mean doses from each regimen may be added to calculate the total mean dose to each cardiac structure. For full dosimetric information including percentage volume of each structure irradiated to different doses or BED for combinations of different regimens, the described methodology can be used to reconstruct different regimens on the same dose-plan.

### **Patient-to-patient variability in heart dose**

The doses in Table 2 and Webtables 1-8 are estimates for a representative patient of average weight and build. The dose received by any individual patient will vary from these, depending on her individual characteristics including breast size, extent of breast surgery and sternal length and on the circumstances of her radiotherapy,

for example the linear accelerator used. These sources of variability would, in most cases, apply to any method of estimating cardiac dose retrospectively. The magnitude of their likely effect on cardiac dose is described below.

### **Variation in patient anatomy**

For tangential pair and direct IMC irradiation reconstructed on consecutive patients on the CT planning database, mean heart dose varied between 1 and 2 Gy (coefficient of variation, mean divided by standard deviation, (CV)=11%) for right-sided and between 2 and 4 Gy (CV=30%) for left-sided tangential pair radiotherapy and from 5 to 15 Gy (CV=21%) for right-sided and from 20 to 29 Gy (CV=11%) for left-sided IMC radiotherapy (Fig. 5). Thus, for each regimen, there was some interpatient variability in heart dose, but there was also substantial variation between different regimens.

### **The presence of breast tissue**

All doses in Table 2 and Webtables 1-8 are for a patient with breast tissue present. Irradiation using a direct electron field was usually performed after mastectomy, and tangential pair and external beam scar boost irradiation were employed after either mastectomy or breast-conserving surgery. These techniques were reconstructed on the representative patient with breast tissue on the irradiated side both included and excluded from the dose calculations. The decrease in mean heart dose caused by the presence of breast tissue was  $\leq 1.5\%$  and  $\leq 0.7$  Gy dose for all photon techniques (tangential pair and scar boost irradiation). For electron fields, the presence of breast tissue decreased mean heart dose by 2.7 Gy and 0.9 Gy for left and right electron chest wall fields respectively (Fig. 2, panel c) and by 0.2 Gy and 0.06 Gy for left and right electron scar boost irradiation.

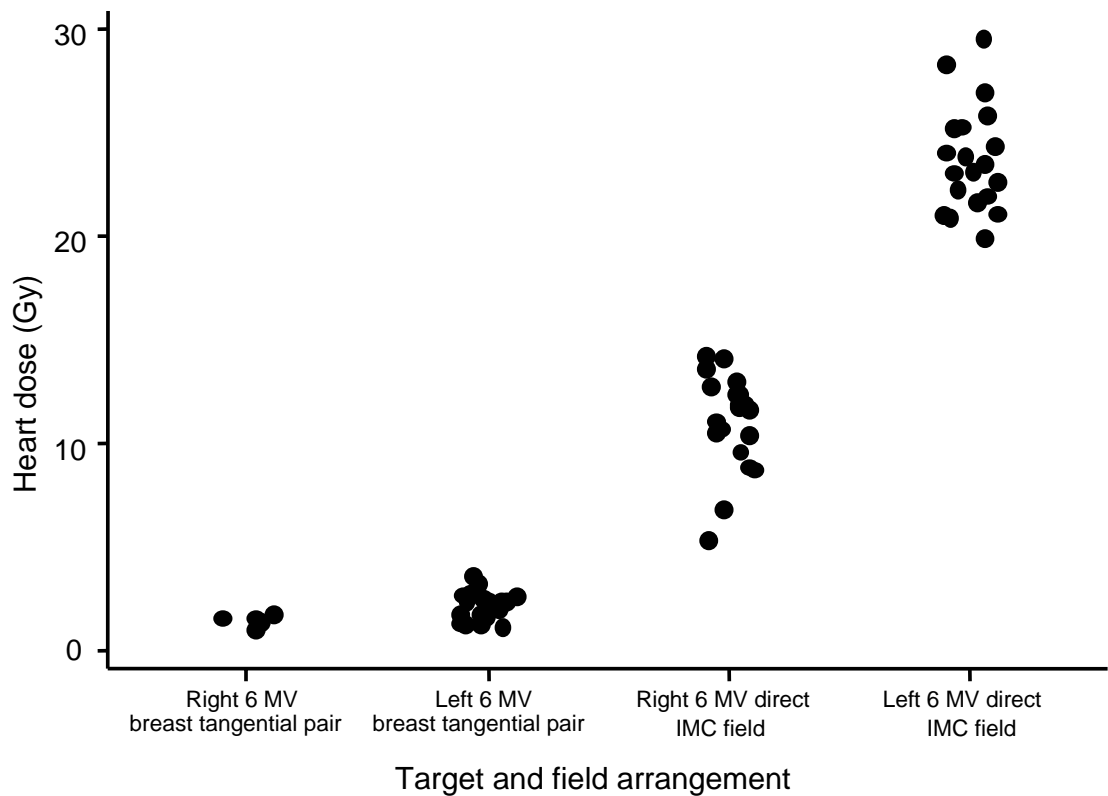


Fig. 5. Variability in mean heart dose received by patients taken from the computed tomography database of a radiotherapy centre in the UK, 2006. Left and right IMC and left-tangential irradiation were reconstructed on 20 consecutive patients. Right-tangential irradiation was reconstructed on 5 consecutive patients. Heart dose for each patient is represented by a black dot.

### Variation in patient position

Cardiac doses can be affected by patient treatment position. Factors likely to affect cardiac doses are those that change either thoracic (and therefore cardiac) position relative to radiation beams (e.g. thorax angled on a breast-board or flat on the bed) or those that influence field borders.

For our representative patient, thoracic position was similar to that used in previous decades for IMC, breast/chest wall and SCF radiotherapy. For axillary irradiation, some previous patients were treated prone, but this different position is unlikely to materially affect heart dose since axillary radiotherapy usually delivered scattered cardiac irradiation alone.

For tangential irradiation, ipsilateral arm position affects field borders [29]. Right breast/chest wall radiotherapy mostly involved only scattered cardiac dose. For left-tangential irradiation, the effect of change in arm position was studied using a camera-based contouring system (Osiris+, Qados, Sandhurst UK). Left-tangential 6 MV radiotherapy was reconstructed on a volunteer firstly with both arms above her head, supported by a T-bar arm rest and secondly with her ipsilateral arm abducted to 90°, and contralateral arm by her side. Heart dose was 2 Gy in the T-bar position and 3.4 Gy in the 90° arm position.

### **Difficulty identifying field borders**

Using the virtual simulator, precise identification of landmarks eg. sternal notch and xyphoid-sternal junction was subject to some uncertainty. The effect of this on mean heart dose was quantified by reconstructing tangential pair and direct IMC fields, firstly, with the field(s) in standard position, secondly, moved 1 cm superiorly and, thirdly, 1 cm inferiorly. Table 3 shows the difference in mean heart dose that resulted from such movements was usually <10% and always <20%.

### **Variability in boost position**

Cobalt-60 and iridium wire boosts were reconstructed, firstly centred on the nipple, secondly moved 2 cm superiorly and, thirdly, 2 cm inferiorly. Table 4 shows the resulting differences in mean heart dose. In reality, the position of the scar and, therefore, of the boost, may well vary more than  $\pm 2$  cm; therefore heart dose

Table 3. Mean heart dose for cobalt-60 breast radiotherapy regimens: effect of variability in field position on heart dose

Target	Field arrangement	Mean heart dose (Gy)					
		Field(s) in the standard position		Field(s) moved superiorly by 1 cm		Field(s) moved inferiorly by 1 cm	
		Left	Right	Left	Right	Left	Right
Chest wall/breast	Tangential pair	4.7	1.2	4.1	*	4.6	*
Chest wall and internal mammary chain	Tangential pair	13.3	2.3	12.1	*	13.2	*
Internal mammary chain	Direct anterior	15.0	9.3	12.6	8.4	17.1	10.4

\* Variability is likely to be minimal because dose is mainly from scattered irradiation

Table 4. Mean heart dose for left-sided scar boost radiotherapy: effect of variability in boost position on heart dose

Technique	Typical dose and fractionation	Mean heart dose (Gy)		
		Field or implant in the standard position	Field or implant moved superiorly by 2 cm	Field or implant moved inferiorly by 2 cm
Brachytherapy using iridium-192 wire implant	20 Gy	0.6	0.3	1
Direct anterior Co-60 beam	10 Gy in 5	0.9	0.3	1.8

measurements are subject to a high degree of uncertainty. In general, the further inferior the boost, the higher the heart dose. However, heart dose from boost irradiation is always low relative to other techniques due to the low given dose of between 10–20 Gy.

### **Use of different models of treatment unit**

For axillary and SCF irradiation, two different makes of linear accelerator with nominally the same energy (6 MV) were employed. These fields were chosen since they are usually distant from the heart, therefore heart dose is largely from scattered irradiation originating in the machine treatment head and may vary according to the machine used. Mean heart dose was between 0.8 and 1.4 Gy for supraclavicular and between 0.5 and 0.9 Gy for axillary fields. Thus the use of different radiotherapy machines made little difference to heart dose. In order to enable comparison between different regimens (Table 1), for each beam energy, data from only one machine was used.

### **Effect of changing source-to-skin distance (SSD) for cobalt-60 beams**

Direct IMC and tangential pair Cobalt-60 fields were set up using SSDs of 70 and 100 cm. This difference in SSD resulted in differences of only 0.2 Gy mean heart dose for IMC and 0.1 Gy for tangential pair irradiation.

## **Discussion**

We present dose estimates for breast cancer radiotherapy regimens that were in widespread use worldwide from the 1950s to the 1990s. There were considerable variations in cardiac doses according to regimen used. For example, 6 MV left

direct IMC radiotherapy delivered 17 Gy heart dose and 25 Gy LAD dose, whereas electron left IMC irradiation delivered 3 Gy heart dose and 6 Gy LAD dose, whilst still delivering therapeutic tumour dose. Such differences are likely to have resulted in wide variation in cardiac doses worldwide, over the past few decades, due to diversity in radiotherapy practice, which will be useful when deriving dose-response relationships. Our estimates include coronary artery and heart doses for a wide variety of different regimens and are consistent with the few published CT-based estimates (Table 5). Techniques available for comparison were: wide and standard left-tangential irradiation [30,22], and direct IMC irradiation [2,24]. Published estimates of irradiated heart volumes were usually consistent with our estimates to within  $\pm 3\%$  of volume and were never more than  $\pm 11\%$ .

### **Sources of variability for a given regimen**

The reconstruction of any radiotherapy regimen is inevitably subject to several sources of variability. This study has characterised the principal sources of dose variability for virtual simulation and CT planning of breast cancer radiotherapy. The major source of error in estimating cardiac doses for a given individual is likely to be variation in patient anatomy. Individual dose-plans and information on anatomy (e.g. patient outline) were rarely available before the 1980s. Therefore when estimating cardiac doses for groups of patients treated in early trials of radiotherapy for breast cancer, the use of dose estimates for a representative patient, of average weight and build, may give the best indication of cardiac doses received from particular regimens.

There was some uncertainty locating the three main coronary arteries since arterial contrast was not used for CT planning. However, these arteries were visible

Table 5. Comparison of measured and published cardiac dose estimates\*

Reference	Technique/field description	Beam energy	Laterality	Measure of dose/volume	Published estimate of volume	Present estimate of volume
Gyenes 1997 [30]	Wide-tangential pair to breast and internal mammary chain	Co-60	Left	Percentage volume of heart receiving >50% dose	25%	23%
	Tangential pair	6 MV	Left	Percentage volume of heart receiving >50% dose	5.7%	5.5%
Gagliardi 1996 [2]	Direct internal mammary chain field	Co-60	Left	Percentage volume of heart receiving >30% dose	55% <sup>‡</sup>	44%
	Direct internal mammary chain field	Co-60	Right	Percentage volume of heart receiving >46% dose	30% <sup>‡</sup>	27%

\*Janjan *et al.* [5] calculated point cardiac doses rather than mean doses as in the present study, so the results are not comparable and therefore we have omitted them from this comparison. Also Krueger *et al.* [6] reported heart and coronary artery doses from seven left-sided post-mastectomy regimens that were mostly used around the year 2000; they all differed from the regimens reconstructed in this study, which are largely historical.

<sup>‡</sup>Reported doses were estimated from published DVH graphs and converted from dose in equivalent 2 Gy fractions, and so there is a higher degree of uncertainty

on some CT slices, and their course tends to follow the interventricular and atrioventricular grooves which are identifiable on CT. In addition, the accuracy of CT-based estimates is limited by normal movement of the heart, lungs and thoracic cage. These movements will tend to change slightly the position of the heart relative to the radiation beams. However, the CT planning scan used for these reconstructions was acquired during several minutes (including many breathing cycles), and the original radiotherapy would also have been delivered over several minutes. Therefore the CT images are likely to illustrate the changing position of the heart relative to the treatment field(s) during the original radiotherapy, thus averaging the variation in dose caused by such changes.

For some regimens, heart dose is affected by patient position. Treatment position for tangential irradiation in the 1950s-1990s varied: in some regions the ipsilateral arm was elevated using a T-bar rest, in others it was abducted to 90°. For left-tangential radiotherapy, lowering the ipsilateral arm (from T-bar position to 90°) changed mean heart dose from 2.0 to 3.4 Gy in our volunteer, which represents a 70% increase. Similar systematic changes in heart dose have been reported for 11 other patients [29]. For our representative patient (T-bar position), 6 MV left-tangential irradiation delivered 4.7 Gy mean heart dose (Table 2). If she had been irradiated in the 90° arm position, her heart dose may have been around 8 Gy (assuming 70% dose increase for change from T-bar to 90° arm position). We speculate that mean LAD dose may have been more than 70% higher, since it is close to the radiation beams. The right and circumflex coronary arteries are distant from tangential beams and their doses are probably little affected by arm position. Our dose estimates for left-tangential irradiation are applicable to patients treated in

the T-bar position but are likely to systematically underestimate heart and LAD doses for patients irradiated with the ipsilateral arm lower, e.g. at 90°.

### **Irradiation of the LAD coronary artery**

For most breast cancer radiotherapy regimens, the anterior part of the heart including the LAD coronary artery received the highest radiation doses. Indeed LAD dose was generally higher than dose to the whole heart or the two other coronary arteries. The distribution of atherosclerosis in the general population is: 40-50% LAD, 30-40% right coronary artery and 15-20% circumflex coronary artery [31]. Therefore the highest radiation doses were received by the coronary artery that appears to be most prone to atherosclerosis. Blockage of the LAD by atherosclerosis can lead to left ventricular infarction. Hence, radiation-induced damage to this artery may contribute to the excess cardiac mortality seen after some past breast cancer radiotherapy regimens. Coronary arterial damage after radiotherapy has been assessed directly using myocardial perfusion imaging, which assesses myocardial ischaemia. Several studies have shown an excess of anterior cardiac perfusion defects in areas of expected high dose between 6 months and 20 years after radiotherapy for left breast cancer [31-34]. One study [35] revealed an increase in myocardial perfusion defects in the region supplied by the LAD six months after left-tangential pair radiotherapy, but not in the regions supplied by the other coronary arteries. It is unclear whether this damage leads to any clinical consequences or to the excess in death from heart disease seen after radiotherapy.

### **The need for a dose-response relationship**

In order to assess reliably the cardiac risks of current and future radiotherapy regimens, relationships between cardiac doses and subsequent cardiac morbidity

and mortality are needed. This study has quantified successfully cardiac doses and volumes irradiated for most common breast cancer radiotherapy regimens used between the 1950s and 1990s and has demonstrated a wide range of cardiac doses. These estimates were derived to enable the development of cardiac dose-response relationships using data in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) trials and data on other women for whom information on radiotherapy technique, tumour laterality, and outcome are available.

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**Contents of website material for:**

***Cardiac exposures in breast cancer radiotherapy: 1950s-1990s***

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	Dose from breast radiotherapy regimens	
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Doses are usually given to one decimal place. Doses for low energy regimens are rounded to the nearest whole number due to the uncertainties involved in manual planning.

Webtable 1. Whole heart dose from left-sided irradiation

Target	Field arrangement	Beam energy	Typical dose and fractionation	Mean dose (Gy)	Mean BED (Gy <sub>2</sub> )	Maximum dose (Gy)	% volume irradiated to different dose levels						
							2.5 Gy	5 Gy	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy
Chest wall/breast a)	Tangential pair	6 MV	50 Gy in 25	4.7	7.0	49.2	48.5	13.2	8.4	6.0	4.5	3.2	0.0
		Co-60	50 Gy in 25	4.7	7.0	48.1	41.2	17.3	9.8	6.5	4.8	3.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	14	25	60	97	83	52	19	10	6	4
Chest wall/breast medial border matched to internal mammary field b)	Tangential pair	6 MV	50 Gy in 25	0.9	1.2	13.1	5.5	0.2	0.1	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	1.0	1.2	10.7	5.6	0.9	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	5	8	32	71	42	17	3	1	0	0
Chest wall c)	Direct anterior	10 MeV electrons	50 Gy in 25	2.8	3.6	27.8	33.4	17.8	7.4	1.0	0.0	0.0	0.0
Chest wall and internal mammary nodes d) e)	Tangential pair	6 MV	50 Gy in 25	13.5	21.7	50.3	85.5	50.1	44.8	27.2	13.9	11.3	0.1
		Co-60	50 Gy in 25	13.3	21.0	49.4	80.5	55.8	45.4	26.4	14.4	10.0	0.0
		250 kV <sup>‡</sup>	36 Gy in 20	14	26	48	96	83	53	20	13	9	9
Internal mammary nodes f)	Direct anterior	6 MV	50 Gy in 25	16.7	27.8	48.4	82.5	51.7	47.2	42.4	31.4	10.1	0.0
		Co-60	50 Gy in 25	15.0	23.4	44.1	83.0	66.4	49.9	42.1	18.2	3.1	0.0
		10 MeV electrons	50 Gy in 25	2.7	3.7	44.8	25.3	13.0	6.9	3.1	1.3	0.3	0.0
		250 kV <sup>‡</sup>	50 Gy in 25	10	15	39	67	54	40	16	4	0	0
Mastectomy scar boost	Direct anterior	Co-60	10 Gy in 5	0.9	1.2	8.1	11.0	5.2	0.0	0.0	0.0	0.0	0.0
		10 MeV electrons	10 Gy in 5	0.3	0.4	5.1	1.4	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	10 Gy in 5	1	1	6	15	5	0	0	0	0	0
	Brachytherapy	Iridium-192 <sup>‡</sup>	20 Gy	1	2	7	7	0	0	0	0	0	0
Supraclavicular fossa g)	Direct anterior	6 MV	50 Gy in 25	0.8	1.1	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.4	0.6	1.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Posterior axilla h)	Direct posterior	6 MV	50 Gy in 25	0.5	0.8	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.3	0.5	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Regimens a-h are illustrated by Fig. 2.

<sup>‡</sup> Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place.

Webtable 2. Left anterior descending coronary artery dose from left-sided irradiation

Target	Field arrangement	Beam energy	Typical dose and fractionation	Mean dose (Gy)	Mean BED (Gy <sub>2</sub> )	Maximum dose (Gy)	% volume irradiated to different dose levels						
							2.5 Gy	5 Gy	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy
Chest wall/breast a)	Tangential pair	6 MV	50 Gy in 25	21.9	39.8	51.5	90.3	60.9	52.4	45.5	38.6	33.5	7.6
		Co-60	50 Gy in 25	21.8	39.2	51.2	86.7	65.6	54.5	46.0	39.1	31.0	4.2
		250 kV <sup>‡</sup>	42 Gy in 20	51	130	56	100	100	100	100	100	86	61
Chest wall/breast medial border matched to internal mammary field b)	Tangential pair	6 MV	50 Gy in 25	1.8	2.1	8.5	35.8	1.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	2.1	2.5	11.9	36.9	7.3	0.4	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	15	22	17	100	100	92	0	0	0	0
Chest wall c)	Direct anterior	10 MeV electrons	50 Gy in 25	10.3	14.3	38.2	81.0	63.2	42.9	16.8	4.6	0.0	0.0
Chest wall and internal mammary nodes d) e)	Tangential pair	6 MV	50 Gy in 25	32.0	59.5	52.1	0.3	87.4	80.5	73.1	55.6	51.1	15.6
		Co-60	50 Gy in 25	31.8	58.2	52.0	0.1	92.7	83.8	73.1	55.6	48.1	10.0
		250 kV <sup>‡</sup>	36 Gy in 20	46	109	50	100	100	100	100	100	82	33
Internal mammary nodes f)	Direct anterior	6 MV	50 Gy in 25	25.1	44.2	47.9	83.5	70.9	66.9	61.5	60.6	20.6	0.0
		Co-60	50 Gy in 25	22.7	37.2	42.9	97.8	83.3	69.8	60.8	53.2	4.0	0.0
		10 MeV electrons	50 Gy in 25	6.4	7.9	27.3	90.7	58.1	16.9	3.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	50 Gy in 25	20	32	24	96	93	85	71	0	0	0
Mastectomy scar boost	Direct anterior	Co-60	10 Gy in 5	3.1	5.0	8.0	45.9	36.8	0.0	0.0	0.0	0.0	0.0
		10 MeV electrons	10 Gy in 5	1.3	1.7	5.7	18.4	1.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	10 Gy in 5	2	3	6	25	18	0	0	0	0	0
	Brachytherapy	Iridium-192 <sup>‡</sup>	20 Gy	2	6	11	32	9	0	0	0	0	0
Supraclavicular fossa g)	Direct anterior	6 MV	50 Gy in 25	1.0	1.2	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.5	0.8	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Posterior axilla h)	Direct posterior	6 MV	50 Gy in 25	0.6	0.9	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.5	0.8	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Regimens a-h are illustrated by Fig. 2.

<sup>‡</sup> Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place.

Webtable 3. Right coronary artery dose from left-sided irradiation

Target	Field arrangement	Beam energy	Typical dose and fractionation	Mean dose (Gy)	Mean BED (Gy <sub>2</sub> )	Maximum dose (Gy)	% volume irradiated to different dose levels						
							2.5 Gy	5 Gy	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy
Chest wall/breast a)	Tangential pair	6 MV	50 Gy in 25	2.0	2.3	3.3	45.6	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	1.7	2.0	3.1	23.6	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	11	15	11	100	100	55	0	0	0	0
Chest wall/breast medial border matched to internal mammary field b)	Tangential pair	6 MV	50 Gy in 25	0.7	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.6	0.9	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	2	3	3	7	0	0	0	0	0	0
Chest wall c)	Direct anterior	10 MeV electrons	50 Gy in 25	1.7	2.1	11.1	30.5	8.6	0.7	0.0	0.0	0.0	0.0
Chest wall and internal mammary nodes d) e)	Tangential pair	6 MV	50 Gy in 25	9.9	12.8	18.0	99.5	66.0	55.8	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	9.1	11.5	16.6	99.1	72.1	54.9	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	36 Gy in 20	11	15	12	100	100	78	0	0	0	0
Internal mammary nodes f)	Direct anterior	6 MV	50 Gy in 25	6.2	9.4	41.5	52.8	20.7	11.5	11.5	9.5	2.2	0.0
		Co-60	50 Gy in 25	6.5	9.4	37.4	64.5	28.7	14.6	12.6	6.3	0.0	0.0
		10 MeV electrons	50 Gy in 25	4.6	6.2	32.1	53.2	33.1	16.5	4.5	0.5	0.0	0.0
		250 kV <sup>‡</sup>	50 Gy in 25	6	7	7	86	73	0	0	0	0	0
Mastectomy scar boost	Direct anterior	Co-60	10 Gy in 5	0.2	0.2	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		10 MeV electrons	10 Gy in 5	0.1	0.2	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	10 Gy in 5	<1	1	3	9	0	0	0	0	0	0
	Brachytherapy	Iridium-192 <sup>‡</sup>	20 Gy	<1	<1	<1	0	0	0	0	0	0	0
Supraclavicular fossa g)	Direct anterior	6 MV	50 Gy in 25	0.8	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.2	0.5	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Posterior axilla h)	Direct posterior	6 MV	50 Gy in 25	0.4	0.5	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	<0.1	<0.1	<0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Regimens a-h are illustrated by Fig. 2.

<sup>‡</sup> Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place.

Webtable 4. Circumflex coronary artery dose from left-sided irradiation

Target	Field arrangement	Beam energy	Typical dose and fractionation	Mean dose (Gy)	Mean BED (Gy <sub>2</sub> )	Maximum dose (Gy)	% volume irradiated to different dose levels						
							2.5 Gy	5 Gy	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy
Chest wall/breast a)	Tangential pair	6 MV	50 Gy in 25	2.8	3.6	44.1	32.0	6.2	4.7	2.3	0.9	0.4	0.0
		Co-60	50 Gy in 25	2.7	3.5	39.4	23.6	8.5	5.3	2.4	0.8	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	8	11	10	100	76	30	0	0	0	0
Chest wall/breast medial border matched to internal mammary field b)	Tangential pair	6 MV	50 Gy in 25	0.8	1.1	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.8	1.1	2.3	0.3	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	4	5	6	100	31	0	0	0	0	0
Chest wall c)	Direct anterior	10 MeV electrons	50 Gy in 25	0.9	1.1	4.1	7.6	0.0	0.0	0.0	0.0	0.0	0.0
Chest wall and internal mammary nodes d) e)	Tangential pair	6 MV	50 Gy in 25	6.7	9.6	44.1	75.7	26.6	20.0	11.7	3.9	2.4	0.0
		Co-60	50 Gy in 25	6.9	9.6	41.4	67.7	34.7	23.0	10.0	3.3	0.3	0.0
		250 kV <sup>‡</sup>	36 Gy in 20	9	12	12	100	100	33	0	0	0	0
Internal mammary nodes f)	Direct anterior	6 MV	50 Gy in 25	15.5	24.6	37.7	70.0	49.5	49.5	45.4	23.2	0.0	0.0
		Co-60	50 Gy in 25	13.5	19.6	32.7	100.0	67.1	46.7	41.6	5.4	0.0	0.0
		10 MeV electrons	50 Gy in 25	0.8	1.1	5.2	11.2	0.6	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	50 Gy in 25	9	12	11	91	82	50	0	0	0	0
Mastectomy scar boost	Direct anterior	Co-60	10 Gy in 5	1.2	1.8	6.1	20.5	9.8	0.0	0.0	0.0	0.0	0.0
		10 MeV electrons	10 Gy in 5	0.1	0.2	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	10 Gy in 5	1	1	4	11	4	0	0	0	0	0
	Brachytherapy	Iridium-192 <sup>‡</sup>	20 Gy	<1	<1	1	0	0	0	0	0	0	0
Supraclavicular fossa g)	Direct anterior	6 MV	50 Gy in 25	0.8	1.1	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.4	0.7	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Posterior axilla h)	Direct posterior	6 MV	50 Gy in 25	0.5	0.8	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.3	0.5	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Regimens a-h are illustrated by Fig. 2.

<sup>‡</sup> Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place.

Webtable 5. Whole heart dose from right-sided irradiation

Target	Field arrangement	Beam energy	Typical dose and fractionation	Mean dose (Gy)	Mean BED (Gy <sub>2</sub> )	Maximum dose (Gy)	% volume irradiated to different dose levels						
							2.5 Gy	5 Gy	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy
Chest wall/breast a)	Tangential pair	6 MV	50 Gy in 25	1.5	1.9	4.8	17.5	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	1.2	1.5	7.2	11.4	0.6	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	6	8	19	79	46	19	0	0	0	0
Chest wall/breast medial border matched to internal mammary field b)	Tangential pair	6 MV	50 Gy in 25	0.9	1.1	1.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.4	0.6	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	1	1	5	13	0	0	0	0	0	0
Chest wall c)	Direct anterior	10 MeV electrons	50 Gy in 25	1.5	1.9	20.0	16.4	7.7	2.7	0.0	0.0	0.0	0.0
Chest wall and internal mammary nodes d) e)	Tangential pair	6 MV	50 Gy in 25	2.4	3.0	44.1	32.1	5.8	3.0	0.9	0.3	0.1	0.0
		Co-60	50 Gy in 25	2.3	2.9	43.0	25.3	8.7	3.7	1.1	0.4	0.1	0.0
		250 kV <sup>‡</sup>	36 Gy in 20	9	13	41	90	63	29	7	4	1	1
Internal mammary nodes f)	Direct anterior	6 MV	50 Gy in 25	10.5	17.4	47.6	50.8	31.3	28.7	24.3	20.5	6.1	0.0
		Co-60	50 Gy in 25	9.3	14.6	43.6	47.2	36.1	29.6	23.5	12.6	1.6	0.0
		10 MeV electrons	50 Gy in 25	2.3	3.1	40.2	24.4	13.9	6.7	2.0	0.4	0.0	0.0
		250 kV <sup>‡</sup>	50 Gy in 25	5	8	37	45	30	21	8	1	0	0
Mastectomy scar boost	Direct anterior	Co-60	10 Gy in 5	0.2	0.3	6.8	1.7	0.2	0.0	0.0	0.0	0.0	0.0
		10 MeV electrons	10 Gy in 5	0.2	0.3	2.9	0.1	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	10 Gy in 5	1	1	5	9	1	0	0	0	0	0

Regimens a-h are illustrated by Fig. 2.

<sup>‡</sup> Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place.

Webtable 6. Left anterior descending coronary artery dose from right-sided irradiation

Target	Field arrangement	Beam energy	Typical dose and fractionation	Mean dose (Gy)	Mean BED (Gy <sub>2</sub> )	Maximum dose (Gy)	% volume irradiated to different dose levels						
							2.5 Gy	5 Gy	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy
Chest wall/breast a)	Tangential pair	6 MV	50 Gy in 25	1.4	1.6	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.9	1.2	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	3	4	4	100	0	0	0	0	0	0
Chest wall/breast medial border matched to internal mammary field b)	Tangential pair	6 MV	50 Gy in 25	0.9	1.1	1.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.3	0.5	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	1	1	1	0	0	0	0	0	0	0
Chest wall c)	Direct anterior	10 MeV electrons	50 Gy in 25	0.6	0.9	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Chest wall and internal mammary nodes d) e)	Tangential pair	6 MV	50 Gy in 25	1.7	2.0	2.6	11.4	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	1.3	1.6	2.3	2.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	36 Gy in 20	6	7	7	100	93	0	0	0	0	0
Internal mammary nodes f)	Direct anterior	6 MV	50 Gy in 25	1.6	2.0	16.1	18.9	3.4	1.2	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	1.2	1.5	16.7	12.7	3.4	1.2	0.0	0.0	0.0	0.0
		10 MeV electrons	50 Gy in 25	0.4	0.7	4.0	3.6	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	50 Gy in 25	1	1	2	0	0	0	0	0	0	0
Mastectomy scar boost	Direct anterior	Co-60	10 Gy in 5	0.1	0.1	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		10 MeV electrons	10 Gy in 5	0.0	0.1	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	10 Gy in 5	<1	<1	1	0	0	0	0	0	0	0

Regimens a-h are illustrated by Fig. 2.

<sup>‡</sup> Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place.

Webtable 7. Right coronary artery dose from right-sided irradiation

Target	Field arrangement	Beam energy	Typical dose and fractionation	Mean dose (Gy)	Mean BED (Gy <sub>2</sub> )	Maximum dose (Gy)	% volume irradiated to different dose levels						
							2.5 Gy	5 Gy	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy
Chest wall/breast a)	Tangential pair	6 MV	50 Gy in 25	2.4	2.8	6.1	66.1	1.3	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	2.3	2.7	8.7	51.4	5.4	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	13	19	14	100	100	100	0	0	0	0
Chest wall/breast medial border matched to internal mammary field b)	Tangential pair	6 MV	50 Gy in 25	1.1	1.4	1.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.6	0.9	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	4	5	4	88	30	0	0	0	0	0
Chest wall c)	Direct anterior	10 MeV electrons	50 Gy in 25	4.8	6.1	25.8	59.1	34.6	15.9	2.7	0.0	0.0	0.0
Chest wall and internal mammary nodes d) e)	Tangential pair	6 MV	50 Gy in 25	8.1	11.7	50.2	83.3	37.1	26.5	12.0	4.7	2.5	0.2
		Co-60	50 Gy in 25	8.7	12.6	49.7	78.3	47.4	29.8	13.6	5.4	2.3	0.2
		250 kV <sup>‡</sup>	36 Gy in 20	26	51	41	100	100	100	55	38	20	2
Internal mammary nodes f)	Direct anterior	6 MV	50 Gy in 25	21.0	37.8	49.2	79.6	56.6	51.1	45.5	45.3	30.1	0.0
		Co-60	50 Gy in 25	20.5	34.3	45.2	97.1	82.6	56.1	45.5	41.3	15.6	0.0
		10 MeV electrons	50 Gy in 25	10.3	15.2	44.8	71.3	56.0	37.3	20.3	9.7	2.2	0.0
		250 kV <sup>‡</sup>	50 Gy in 25	24	42	34	96	93	85	70	37	0	0
Mastectomy scar boost	Direct anterior	Co-60	10 Gy in 5	0.2	0.3	1.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		10 MeV electrons	10 Gy in 5	0.3	0.4	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	10 Gy in 5	<1	1	4	10	1	0	0	0	0	0

Regimens a-h are illustrated by Fig. 2.

<sup>‡</sup> Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place.

Webtable 8. Circumflex coronary artery dose from right-sided irradiation

Target	Field arrangement	Beam energy	Typical dose and fractionation	Mean dose (Gy)	Mean BED (Gy <sub>2</sub> )	Maximum dose (Gy)	% volume irradiated to different dose levels						
							2.5 Gy	5 Gy	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy
Chest wall/breast a)	Tangential pair	6 MV	50 Gy in 25	1.0	1.3	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.6	0.9	1.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	3	4	6	56	11	0	0	0	0	0
Chest wall/breast medial border matched to internal mammary field b)	Tangential pair	6 MV	50 Gy in 25	0.8	1.0	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	<0.1	<0.1	<0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	42 Gy in 20	1	1	1	0	0	0	0	0	0	0
Chest wall c)	Direct anterior	10 MeV electrons	50 Gy in 25	0.4	0.7	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Chest wall and internal mammary nodes d) e)	Tangential pair	6 MV	50 Gy in 25	1.2	1.5	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	0.8	1.1	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	36 Gy in 20	5	6	7	93	46	0	0	0	0	0
Internal mammary nodes f)	Direct anterior	6 MV	50 Gy in 25	1.4	1.7	2.4	5.0	0.0	0.0	0.0	0.0	0.0	0.0
		Co-60	50 Gy in 25	1.2	1.5	4.4	8.7	0.0	0.0	0.0	0.0	0.0	0.0
		10 MeV electrons	50 Gy in 25	0.2	0.5	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	50 Gy in 25	2	2	2	0	0	0	0	0	0	0
Mastectomy scar boost	Direct anterior	Co-60	10 Gy in 5	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		10 MeV electrons	10 Gy in 5	<0.1	<0.1	<0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		250 kV <sup>‡</sup>	10 Gy in 5	<1	<1	1	0	0	0	0	0	0	0

Regimens a-h are illustrated by Fig. 2.

<sup>‡</sup> Doses for low energy regimens are given to the nearest Gray due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place.

# 4 Cardiac doses from Swedish breast cancer radiotherapy since the 1950s

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## **Abstract**

### **Background and purpose**

To estimate cardiac doses from breast cancer radiotherapy in Sweden from the 1950s to the 1990s. These doses will enable derivation of dose-response relationships for the risk of radiation-induced heart disease.

### **Materials and methods**

The Swedish nationwide cancer register was used to identify women irradiated for breast cancer in the Stockholm area. Virtual simulation, computed tomography planning, and manual planning were used to reconstruct radiotherapy regimens. Estimates of heart and coronary artery dose were derived for each woman.

### **Results**

Cardiac doses were assessed in 358 women. Mean heart dose varied from <0.1 to 23.6 Gy and mean left anterior descending coronary artery dose varied from 0.1 to 46.3 Gy. Mean cardiac doses averaged across women irradiated in each decade for left-sided and right-sided breast cancers respectively were 5.1 Gy and 1.8 Gy in the 1950s, 10.5 Gy and 4.7 Gy in the 1970s and 3.0 Gy and 1.9 Gy in the 1990s.

### **Conclusions**

Cardiac doses from Swedish breast cancer radiotherapy increased from the 1950s to the 1970s, and then reduced substantially in the 1980s and 90s. The wide range of doses observed should provide substantial statistical power for the estimation of dose-response relationships for radiation-induced heart disease.

**Key words:** *Breast radiotherapy, heart disease, long-term effects.*

## **Introduction**

Radiotherapy for breast cancer reduces breast cancer mortality in many categories of women [1]. However it can deliver some unwanted irradiation to the heart, and some previous breast cancer radiotherapy regimens led to an increased risk of death from heart disease particularly in the period more than 10 years after exposure [1-3].

Cardiac doses have generally reduced over the past few decades. However, most current breast cancer radiotherapy regimens still inevitably involve some dose to the heart [4-10]. The extent of any future cardiac risk from present regimens is uncertain but could be estimated indirectly using cardiac dose-response relationships.

Several previous studies report cardiac dose-response relationships for various endpoints. Gagliardi [11,12] used mathematical modelling in conjunction with clinical data on long-term cardiac mortality in two randomised trials including around 40 deaths from ischaemic heart disease. Marks [13] and Das [14] assessed the incidence of myocardial perfusion defects in around 70 women who received different heart doses from left-tangential radiotherapy and Wei [15] investigated the incidence of pericardial effusion in around 100 patients irradiated for oesophageal cancer.

A new study, based on over 1000 women who developed heart disease after breast cancer irradiation, and a similar number who did not develop heart disease, has been set up in Denmark and Sweden to provide additional information on dose-response relationships for the risk of heart disease following breast cancer radiotherapy [16]. These relationships will be estimated using a number of different measures of cardiac dose, including mean dose to the heart and to each of the three coronary arteries. We have previously developed a method for the estimation of

cardiac doses from breast cancer radiotherapy regimens that were used worldwide in previous decades [17]. In the current paper, we have applied this methodology to the radiotherapy charts of individual women irradiated in Sweden in the 1950s to 1990s and included in the new study to estimate the cardiac doses they received. These doses will enable derivation of dose-response relationships for the risk of radiation-induced heart disease.

## **Materials and methods**

### **Selection of women**

The Swedish nationwide cancer register [18] was used to identify women who received external beam radiotherapy for breast cancer since 1958 (when the register started), at ages <70 years. Women who received radiotherapy at Oncology Departments in the Stockholm area were included. Each woman's radiotherapy chart, often including a photograph of the treatment field(s), was copied. If available, her dose-plan was also copied. Local ethical permission for the study was obtained.

### **Dosimetry methods**

Details of all techniques that were used to irradiate the breast, chest wall or internal mammary chain (IMC) were documented (Table 1), based on information from the radiotherapy charts and, where possible, from discussions with local radiation oncologists and physicists. Cardiac doses from supraclavicular fossa and axillary fields were not included in the calculation as their contribution to mean heart dose has previously been estimated to be an order of magnitude lower than dose from breast, chest wall or IMC irradiation [17].

### *Set-up of typical radiotherapy techniques*

Cardiac dose was estimated on the basis of a technique based upon virtual simulation (Exomio release 2.0, MedCom GmbH, Darmstadt, Germany) and computed tomography (CT)-based 3-dimensional treatment planning (Helax TMS version 6.1B, Nucletron Ltd, Veenendaal, the Netherlands). Techniques were reconstructed on the CT planning scan of one ‘representative patient’ of average weight and height who had been selected from around 40 CT planning scans on the database of a UK radiotherapy department. The CT slice thickness was 5 mm. The patient was supine, with a T-bar arm rest, similar to the breast treatment position used in previous decades in Sweden.

The heart and coronary arteries were contoured by a radiation oncologist and reviewed by a radiologist. The cranial limit of the heart included the right atrium and excluded the pulmonary trunk, ascending aorta and superior vena cava. The lowest contour of the heart was the caudal myocardial border. Due to the short length of the left main coronary artery, its contour was included with that of the left anterior descending (LAD) coronary artery. For further details of the methods used, see Taylor [17].

The algorithm used for the dose calculations was the pencil beam [19,20]. Megavoltage beam modalities included 6 MV and cobalt-60, and electron beam energy was 10 MeV. Manual planning, with lung correction, was carried out for 250 keV beams and for the cobalt chain (see Appendix at the end of this Chapter).

### *Categorisation of radiotherapy charts*

Each woman’s radiotherapy chart was categorised according to technique and laterality. Each woman’s total dose and dose per fraction were noted for every technique she received.

### *Dose calculations*

For each technique, dose volume histograms (DVHs) were generated for the heart and for each of the three coronary arteries for left- and right-sided irradiation. DVHs were used to derive estimates of mean dose and biologically effective dose (BED). For mean BED estimates, each step of the DVH was corrected using the linear-quadratic model with an alpha-beta ratio of 2 Gy [21,22]. For orthovoltage radiotherapy, a correction factor of 1.1 was used to account for the enhanced biological effectiveness of low energy irradiation [23].

The tumour dose (Table 1) was derived by calculating the dose at the centre of the target (breast or chest wall) for tangential irradiation (Fig. 1a & 1e) and direct orthovoltage chest wall fields (Fig. 1b), and at the expected depth of the IMC for cobalt chain irradiation (Fig. 1i) and direct orthovoltage IMC irradiation (Fig. 1h). For direct or oblique electron or cobalt fields (Fig. 1c, d, f, g and j) tumour dose was assumed to be 90% of the applied dose.

Percentage of tumour dose received by the heart was the mean heart dose divided by the tumour dose. This was calculated for all regimens used to irradiate a single region e.g. tangential breast irradiation (Table 1).

In order to estimate changes in cardiac doses over calendar period, the mean organ dose averaged over all the patients in each decade was calculated for the heart and three coronary arteries (Table 2). Similarly, the mean tumour dose was calculated for each decade, taking into account all the anatomical regions irradiated.

Table 1. Doses to the heart and to each of the three coronary arteries from radiotherapy techniques used in Sweden in the 1950s to 1990s, ordered according to calendar year.

Target	Dose (Gy)*	Dose per fraction (Gy)	Field arrangement	Beam energy	No. patients	Approximate tumour dose (Gy)†	% tumour dose to heart‡		Heart		LAD		RCA		Circ		Heart	
							Left	Right	Mean dose (Gy)‡		Mean BED (Gy <sub>2</sub> )§		Mean dose (Gy)		Mean dose (Gy)		Mean dose (Gy)	
									Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
<b>1950s and 1960s radiotherapy</b>																		
Breast (a) §§	10.5	3.5	Tangential pair	170 keV**	7	6	33	17	2	1	3	1	7	<1	1	2	1	<1
Breast (a)	10.5	3.5	Tangential pair	170 keV**	1	6	–	–	6	4	–	–	16	1	4	13	5	1
Chest wall (b)	Field 1: 32 Field 2: 28 Fields 3,4: 20	4	Four direct fields	170 keV**		14												
Breast (a)	10.5	3.5	Tangential pair	170 keV**	1	6	–	–	7	4	–	–	16	1	4	12	5	1
Internal mammary chain (h)	28	4	Direct anterior	170 keV**		20												
Breast (a)	10.5	3.5	Tangential pair	170 keV**	2	6	–	–	3.5	2.2	–	–	9.5	0.2	3.3	7.6	1.3	<1
Internal mammary chain (g)	40	4	Two direct anterior fields	9-15 MeV electrons		36												
Breast (a)	10.5	3.5	Tangential pair	170 keV**	6	6	–	–	2	1	–	–	7	<1	1	2	1	<1
Internal mammary chain (i)	7	7	Cobalt chain (short)	Co-60**		28												
Breast (a)	10.5	3.5	Tangential pair	170 keV**	9	6	–	–	6	4	–	–	11	<1	2	8	3	1
Internal mammary chain (i)	7	7	Cobalt chain (long)	Co-60**		28												
Internal mammary chain (h)	28	4	Direct anterior	170 keV**	3	20	25	15	5	3	10	6	9	1	3	10	4	1
Internal mammary chain (g)	40	4	Two direct anterior fields	9-15 MeV electrons	20	36	4	3	1.5	1.2	2.4	1.9	2.5	0.2	2.3	5.6	0.3	<0.1
Chest wall (b)	Field 1: 32 Field 2: 28 Fields 3,4: 20	4	Four direct fields	170 keV**	9	14	29	21	4	3	11	6	9	1	3	11	4	1
Internal mammary chain (i)	7	7	Cobalt chain (short)	Co-60**	41	28	<1	<1	0.05	0.03	0.1	<0.1	0.3	0.09	0.2	0.1	0.08	0.01
Internal mammary chain (i)	7	7	Cobalt chain (long)	Co-60**	60	28	14	11	4.0	3.0	11	6	4.0	0.4	1.0	6.0	2	1.0
<b>1970s radiotherapy</b>																		
Chest wall (c)	32	4	Oblique anterior	Co-60	10	29	–	–	18.5	9.0	45.5	20.6	27.4	2.0	23.4	24.7	17.1	1.2
Bilateral internal mammary chain (j)	36	4	Oblique anterior, central	Co-60		35												
Bilateral internal mammary chain (j)	40	4	Direct anterior, central	Co-60	12	36	54	54	19.5	19.5	43.5	43.5	10.8	10.8	25.1	25.1	13.1	13.1
Chest wall & internal mammary chain (e)	45 breast/chest wall	2	Wide-tangential pair	Co-60	59	45	36	14	16.3	6.2	28.0	9.3	32.0	2.8	14.4	22.2	8.2	1.1
Chest wall (d)	48	1.8	Oblique anterior	10-15 MeV electrons	35	43	10	5	4.1	2.0	5.3	2.5	14.4	0.7	2.7	6.8	1.6	0.6
<b>1980s and 1990s radiotherapy</b>																		
Internal mammary chain (h)	44	2.2	Direct anterior	Co-60	1	40	33	20	13.2	8.2	21.7	13.5	20.0	1.0	5.8	18.0	11.9	1.1
Chest wall & internal mammary chain (f)	Chest wall field: 48 IMC field: 50.6	2.1 2.2	Oblique anterior chest wall Direct anterior IMC	10 MeV electrons Co-60	24	43 46	–	–	4.3	2.4	5.6	2.8	18.3	1.7	1.5	4.3	2.6	0.6
Chest wall/breast (a)	50 breast/chest wall	2	Tangential pair	Co-60	22	50	9	2	4.7	1.2	7.0	1.5	21.8	0.9	1.7	2.3	2.7	0.6
Chest wall/breast (a)	50 breast/chest wall	2	Tangential pair	6 MV	36	50	6	4	2.8	2.0	3.5	2.3	11.0	2.0	2.0	2.4	1.8	1.4

\* Applied dose i.e. dose at Dmax (maximum dose) where different from prescribed dose

† See methods for definition

‡ For some regimens, cardiac doses were different from those of the patients described in Fig. 2 since the tumour dose was not the same for every patient.

Abbreviations: LAD=left anterior descending; RCA=right coronary artery; Circ=circumflex coronary artery; BED=biologically effective dose.

§ BED calculated using  $\alpha/\beta$  ratio of 2

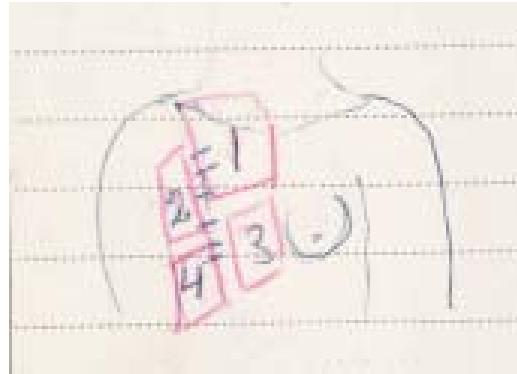
§§ (a), (b) etc refers to the illustrations in Fig. 1

\*\* Doses for hand planned regimens are rounded due to the uncertainties involved in manual planning. All other doses are given to 1 decimal place.

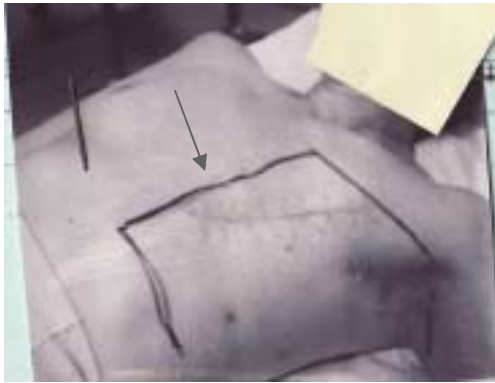
(a) Standard tangential pair



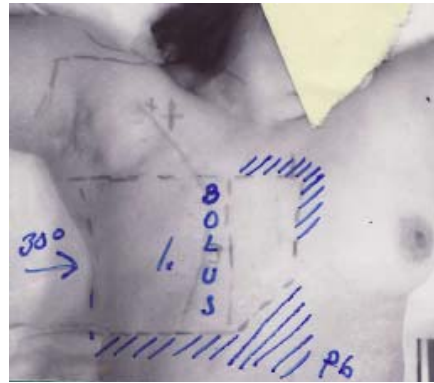
(b) Four orthovoltage fields



(c) Oblique cobalt chest wall field



(d) Oblique anterior electron chest wall field



(e) Wide-tangential pair

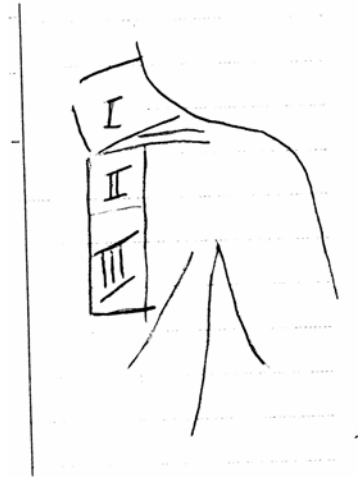


(f) Oblique electron chest wall and cobalt IMC

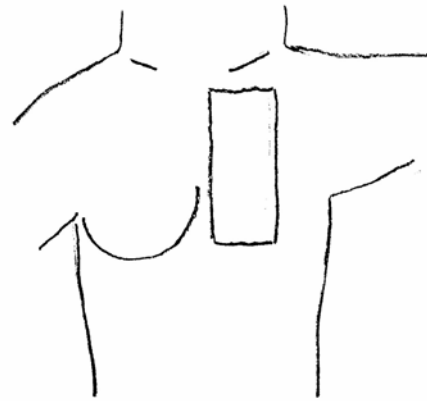


Fig. 1. Swedish radiotherapy techniques reconstructed for cardiac dose estimations  
(continued overleaf)

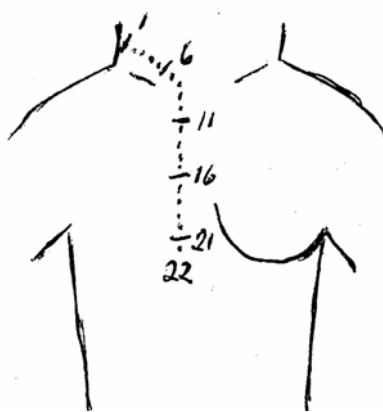
(g) Two anterior electron IMC fields



(h) Direct anterior IMC



(i) Cobalt chain



(j) Central cobalt IMC field

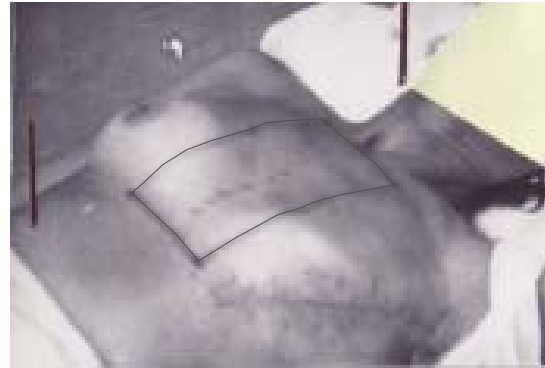


Fig. 1. (Continued) Swedish radiotherapy techniques reconstructed for cardiac dose estimations

## Results

Radiotherapy charts were abstracted for 358 women; 37 different regimens were used. For most techniques, heart dose was greater from left-sided than from right-sided irradiation. Mean heart dose for all women varied from  $<0.1$  to 23.6 Gy (Fig. 2a) and mean heart BED varied from  $<0.1$  to 45.5 Gy<sub>2</sub>. Coronary artery doses varied from 0.1 to 46.3 Gy for the LAD coronary artery (Fig. 2b), from 0.1 to 25.1 Gy for the right coronary artery and from  $<0.1$  to 17.2 Gy for the circumflex coronary artery.

Table 2. Cardiac doses for Swedish women identified using the Swedish nationwide cancer register and irradiated for breast cancer since 1958, based on individual radiotherapy charts

Decade of radiotherapy	Number of women	Tumour dose (Gy)	Average mean dose (standard deviation)									
			Heart BED* (Gy <sub>2</sub> )		Heart dose (Gy)		LAD dose (Gy)		RCA dose (Gy)		Circ dose (Gy)	
			Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
1958 & 59	25	19.1 (14.5)	3.6 <sup>†</sup> (2.9)	1.8 <sup>†</sup> (3.2)	5.1 (2.2)	1.8 (1.6)	10.2 (2.8)	0.6 (0.3)	2.7 (0.9)	4.2 (3.8)	2.7 (1.5)	0.8 (0.8)
1960s	148	30.4 (7.8)	8.1 (11.1)	4.7 (4.6)	4.6 (4.8)	2.1 (2.0)	7.3 (9.6)	0.5 (0.6)	3.8 (5.5)	6.6 (5.8)	2.9 (3.6)	0.6 (0.6)
1970s	93	41.3 (6.4)	14.9 (15.5)	6.4 (6.9)	10.5 (7.2)	4.7 (2.7)	22.2 (9.7)	1.7 (1.0)	10.1 (9.1)	14.7 (8.8)	6.9 (6.0)	0.9 (0.3)
1980s	65	47.2 (3.2)	10.7 (9.2)	3.5 (3.0)	7.0 (5.9)	2.7 (2.1)	21.6 (7.8)	1.7 (0.8)	4.3 (5.9)	7.0 (8.8)	3.9 (3.2)	0.8 (0.3)
1990s	27	48.6 (2.4)	3.6 (0.6)	2.3 (0.2)	3.0 (0.5)	1.9 (0.2)	12.0 (2.3)	1.6 (0.6)	1.9 (0.1)	3.4 (0.2)	1.9 (0.3)	1.1 (0.4)

\* BEDs were calculated for around 85% of women, it was not possible to calculate BEDs for the other 15% who received manually planned technique combinations

† BEDs are based on around 40% of the women irradiated in this decade

*Abbreviations:* BED=biologically effective dose; LAD=left anterior descending coronary artery; RCA=right coronary artery; Circ=circumflex coronary artery.

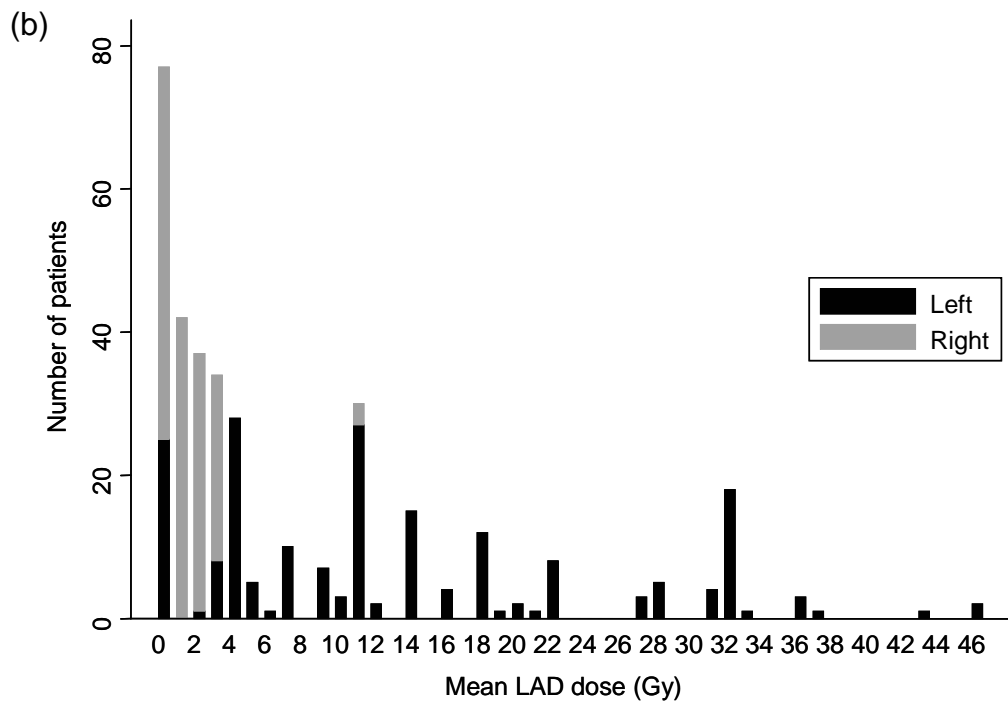
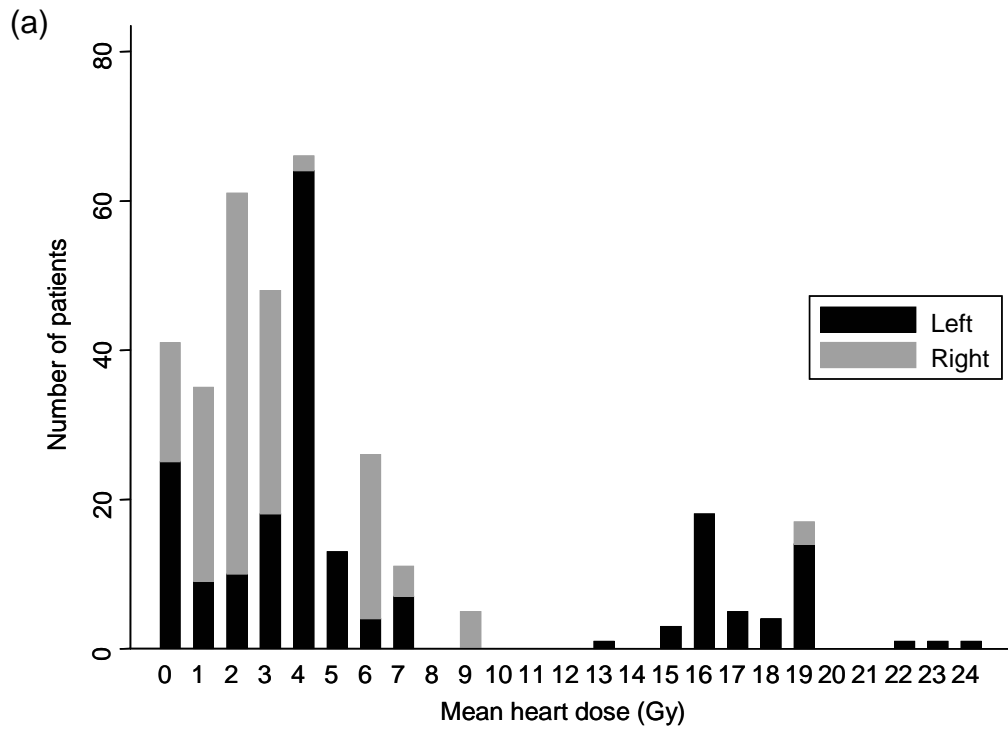


Fig. 2. Mean (a) heart and (b) left anterior descending (LAD) coronary artery doses in Swedish breast cancer patients irradiated since 1958. Dose for the left-sided patients is represented by black bars and dose for the right-sided patients, by grey bars.

### **Breast or chest wall irradiation**

In the 1950s and 60s, orthovoltage tangential breast irradiation was used prior to surgery (Fig. 1a). Mean heart doses were 2 Gy for left-sided irradiation ( $BED=3 \text{ Gy}_2$ ) and 1 Gy for right-sided irradiation ( $BED=1 \text{ Gy}_2$ ) (Table 1). Tumour dose for this technique was only about 6 Gy as the depth-dose characteristics of the orthovoltage beams meant that only around 30% of the applied dose from each beam was received at the centre of the breast.

In the 1970s and 1980s, wide-tangential irradiation using cobalt-60 beams was commonly used (Fig. 1e). The medial border for this technique was usually around 6 cm contralateral to midline, hence the heart was usually included in the fields. Mean heart doses were 16.3 Gy ( $BED=28.0 \text{ Gy}_2$ ) for left-sided irradiation and 6.2 Gy ( $BED=9.3 \text{ Gy}_2$ ) for right-sided irradiation.

Irradiation of the breast or chest wall in the late 1980s and in the 1990s was usually delivered using 6MV tangential beams, with the medial border on midline (Fig. 1a). The heart received mean radiation doses of 2.8 Gy ( $BED=3.5 \text{ Gy}_2$ ) for left-sided irradiation and 2.0 Gy ( $BED=2.3 \text{ Gy}_2$ ) for right-sided irradiation from this technique (Table 1). Tangential irradiation changed considerably between the 1950s and 1990s. The percentage tumour dose received by the heart was around 35% for left-sided and 15% for right-sided tangential irradiation in the 1950s, 60s and 70s. This reduced to 6% for left-sided and 4% for right-sided irradiation in the 1990s (Table 1).

### **Internal mammary chain irradiation**

Cobalt chain radiotherapy (Fig. 1i) was used in Stockholm to irradiate the IMC in the 1960s [24,25], and was received by 116 of the 358 patients studied. Details of

the technique are given in the appendix. The ‘short cobalt chain’ irradiated only the superior part of the heart and delivered 0.05 Gy mean heart dose for left-sided and 0.03 Gy for right-sided irradiation. The ‘long cobalt chain’ included more of the heart volume, hence mean heart doses from this technique were greater: 4.0 Gy for left-sided and 3.0 Gy for right-sided irradiation. The relatively low heart doses were partly due to the short source to skin distance (6 cm) of the cobalt fields, which resulted in a rapid decrease in depth-dose, and partly to the low given dose of around 7 Gy per field. The fraction size was large (usually 7 Gy), thus mean heart BED from the long cobalt chain was 11 Gy<sub>2</sub> for left-sided and 6 Gy<sub>2</sub> for right-sided irradiation.

In the 1970s, some women received irradiation of both the left- and right-IMCs using a 8 cm wide, cobalt-60 field (Fig. 1j). The field was central and delivered the same cardiac doses for women with left- and right-sided tumours (Table 1). A field with similar borders was sometimes used in conjunction with an oblique cobalt-60 chest wall field. When this occurred, the gantry of both fields was angled around 20° to the contralateral side. For the irradiation of left-sided breast cancer, the gantry was angled to the right and much of the heart volume was included in the fields: mean heart dose was 18.5 Gy (BED=45.5 Gy<sub>2</sub>) and all three coronary arteries received >17 Gy (Table 1). For the irradiation of right-sided cancer, the gantry was angled to the left, and mean heart dose was lower at 9.0 Gy (BED=20.6 Gy<sub>2</sub>) (Table 1).

### **Coronary artery doses from radiotherapy regimens**

Of the cardiac structures considered, the LAD coronary artery received the highest radiation doses from most left-sided regimens due to its proximity to the left breast

and IMC (Table 1). The right coronary artery is close to the right breast and IMC and it received the highest doses from most right-sided regimens. The circumflex coronary artery is located posteriorly, distant from both breasts and IMCs. It received the lowest doses from most left- and right-sided regimens (Table 1).

## **Discussion**

More than thirty breast cancer radiotherapy regimens have been used in Stockholm since the 1950s, resulting in a wide range of doses to the heart and to the three coronary arteries. Cardiac doses from each regimen depended largely on technique, laterality, beam energy and tumour dose. They increased from the 1950s to the 1970s, and reduced substantially in the 1980s and 90s.

### **Strengths and limitations of the study**

This study included 358 women who were irradiated in Stockholm since 1958. Our sample contained 85 women, on average, per 10 year period. Therefore the breast cancer radiotherapy techniques that were commonly used during these time periods are likely to have been evaluated, and the changes in techniques that have occurred since the 1950s are likely to be accurately described. The few women for whom medical records were unavailable could not be included, therefore the proportions of women receiving different radiotherapy regimens in this study may be slightly different from those in the entire population of women irradiated for breast cancer in Stockholm since 1958.

Retrospective estimation of cardiac doses of individual patients in epidemiological studies is inevitably subject to several sources of variability. Those

that are relevant to the dosimetry methods used in this study have previously been described and quantified [17]. The greatest source of variability in cardiac dose estimation was found to be the effect of differing patient anatomy e.g. heart position, body fat and thoracic shape. Nevertheless, the difference in heart dose produced by anatomical variation was smaller than the difference produced by different regimens [17, 11]. CT-based 3-dimensional treatment planning for breast cancer patients was not routinely used clinically until the 1990s, thus in our study, dose distributions had to be reconstructed using CT data from a representative patient.

For a few regimens, the radiotherapy charts showed that there was interpatient variability in field size and field border position by a centimetre or two. These differences are likely to have resulted in small variations in cardiac doses for different patients who received the same regimen. In such cases, we constructed the most commonly used field sizes and borders. The effect of differences in field borders on heart dose has previously been assessed. Movement of commonly used breast cancer fields by 1 cm superiorly or inferiorly was found to result in differences to mean heart dose of between 1% and 16% of tumour dose [17].

The beam energy used for electron fields was originally chosen for each woman to achieve an even chest wall dose (Fig. 1d, f and g) and it varied from 9 to 15 MeV for the women studied. We used 10 MeV beams for the reconstruction of all electron fields, based on tissue thickness in our representative patient. The tailoring of electron radiotherapy for individual patients is likely to have reduced the effect of differing patient anatomy on both dose to the target (chest wall or IMC) and dose to the underlying heart since the higher energy beams were used for the patients with the thickest chest wall tissue.

### **Heart dose in different decades**

Swedish breast cancer radiotherapy changed in several ways between the 1950s and the 1990s due to clinical developments affecting target definition, and technological developments. Firstly, in the 1950s and 60s, orthovoltage and cobalt-60 beams were usually used whereas in the 1990s, megavoltage beams were used (Table 1). Secondly, the use of pre-operative breast radiotherapy reduced; in this study it was received by 26 of the 173 women irradiated in the 1950s and 60s, but in none of the women irradiated more recently. Thirdly, tumour dose and fractionation changed. Tumour dose increased from 19.1 Gy (standard deviation (SD) 14.5) on average in the 1950s to 48.6 Gy (SD 2.4) in the 1990s (Table 2), and dose per fraction reduced from 3.5-7.0 Gy in the 1950s, to around 2.0 Gy in the 1990s (Table 1). Fourthly, definition of the target changed. The target (chest wall, breast or IMC) in the 1970s usually included a larger volume of tissue compared to the earlier and later decades. These changes have affected the dose distribution in the target and in the heart. The average mean heart dose and BED per decade increased from the 1950s to the 1970s (Table 2). This was partly due to the increasing use of wide cobalt tangential irradiation, and partly due to an increase in the average tumour dose. In the 1980s and 1990s tumour dose continued to rise. Despite this, the average mean heart dose reduced to 3.0 Gy (SD 0.5) for left-sided and 1.9 Gy (SD 0.2) for right-sided irradiation in the 1990s. These dose reductions were mainly due to the increasing use of regimens that spared the heart e.g. tangential irradiation, with the medial border on midline (Table 1).

The peak of cardiac doses in the 1970s suggests that women irradiated in this decade may have experienced a relatively high risk of radiation-induced heart

disease. Indeed Rutqvist [26] showed that the risk of death from ischaemic heart disease in women who received left wide-tangential irradiation in the 1970s Stockholm radiotherapy trial was 3.2 times greater ( $p < 0.05$ ) than the risk in unirradiated controls. A study of the Swedish nationwide cancer registry [3] has shown that the ratio of death from heart disease in left- versus right-sided women diagnosed with breast cancer in the 1970s was 1.10 (95% confidence interval (CI) 1.03, 1.18) compared with 1.01 (95% CI 0.96, 1.07) for women diagnosed more recently. Only around a third of the women in this study received radiotherapy, therefore the left-right differences in risk in irradiated women will be greater than these. The reduction in risk since the 1970s may be due to the shorter follow-up period for women irradiated more recently but it is in line with what would be expected based on the reduction in cardiac doses.

Heart dose has continued to reduce over the past 10 years due to changes in target definition, treatment technique, technology and awareness of the potential problem of radiation-induced heart disease. For example, for the last ten years all left breast cancer patients irradiated at Karolinska University Hospital, Stockholm have been planned so that the calculated normal tissue complication probability for long-term cardiac mortality based on current models does not exceed 1% [8,11,12]. This constraint has particularly reduced the volume of heart that receives more than 20 Gy radiation dose. The corresponding mean heart doses for patients irradiated this year (2008) for stage I and II left breast cancer are thus 2.8 Gy and 3.3 Gy respectively (prescribed dose: 46 Gy, 2 Gy/fraction).

The current study has measured heart and coronary artery doses for radiotherapy regimens used in Sweden between the 1950s and the 1990s. LAD coronary artery doses may be particularly relevant since this artery is a common site

of atherosclerosis causing myocardial infarction. It receives a high dose from many left breast cancer radiotherapy regimens and may well contribute to radiation-induced heart disease. The combination of the wide range of coronary artery doses, as well as heart doses, with detailed information on morbidity and mortality from heart disease in the new Scandinavian study should provide solid clinical and dosimetric data for the development of reliable dose-response relationships for several cardiac endpoints and several cardiac structures [16]. These results should enable the prediction of future cardiac risk of current and future regimens which would be relevant to the development of treatment guidelines and to decisions regarding individual patients in the clinic.

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## **Appendix: Method for reconstruction of the cobalt chain**

The clinical features of the lower six fields of a typical cobalt chain are illustrated in Figure A1 (see also Fig. 1i). The chain consisted of several overlapping fields each measuring 6 cm long and 3.5 cm wide. The isocentre of each field was 2.5 cm ipsilateral to midline and 1 cm away from the isocentre of adjacent field(s). The inferior border was the 4<sup>th</sup> intercostal space. The chain of fields usually extended up to the sternal notch and, for most patients, further fields were added to irradiate the supraclavicular fossa. Source to skin distance (SSD) was 6 cm [24]. The total number of fields varied from 12 to 27. Each field was irradiated once and either one or two fields were irradiated per day.

For this study, the cobalt fields were reconstructed using virtual simulation and CT planning. The SSD of each field was 50 cm, since this was the minimum SSD modelled by Helax software. The six most inferior cobalt fields were reconstructed since these would be expected to deliver the highest heart doses (Fig. A1). The number of fields reconstructed was determined by the maximum number of fields that could be combined by Helax CT planning software (six). Fields above this level would be several centimetres away from the cardiac contour and therefore should contribute little to heart dose.

Dose distributions for each of the six fields were produced. These distributions were combined with 100% weighting for each beam. The algorithm employed was the pencil beam model.

Scaled hard copies of all CT slices which included cardiac structures were generated. The following adjustments were made to the dose distribution on each CT slice:

1. The calculated dose-plans were based on a SSD of 50 cm. The cobalt chain was usually delivered using a SSD of 6 cm. Correction was made for this difference using the F-formula [27].
2. Comparison of calculated beam profiles with published profiles of the beam used for cobalt chain irradiation at the Radiumhemmet, Stockholm [28] showed that the calculated profiles underestimated tissue dose by around 5% of dose at depths of more than 10 cm. Published profiles were used to correct the positions of the relevant isodose lines.
3. Divergence of the beam created at a SSD of 50 cm was less than that expected from a beam at a SSD of 6 cm. Published beam profiles [28] were used to correct beam divergence.

The percentage volume of the heart irradiated to different dose levels was estimated by measuring the proportion of the heart volume included within each isodose line on each CT slice.

Around half of the Swedish patients who had cobalt chain irradiation, received the ‘short cobalt chain’ described above. The other half received a cobalt chain that extended further inferiorly by around 7 cm, the ‘long cobalt chain’. For reconstruction of the ‘long cobalt chain’, the six fields were moved 7 cm inferiorly.

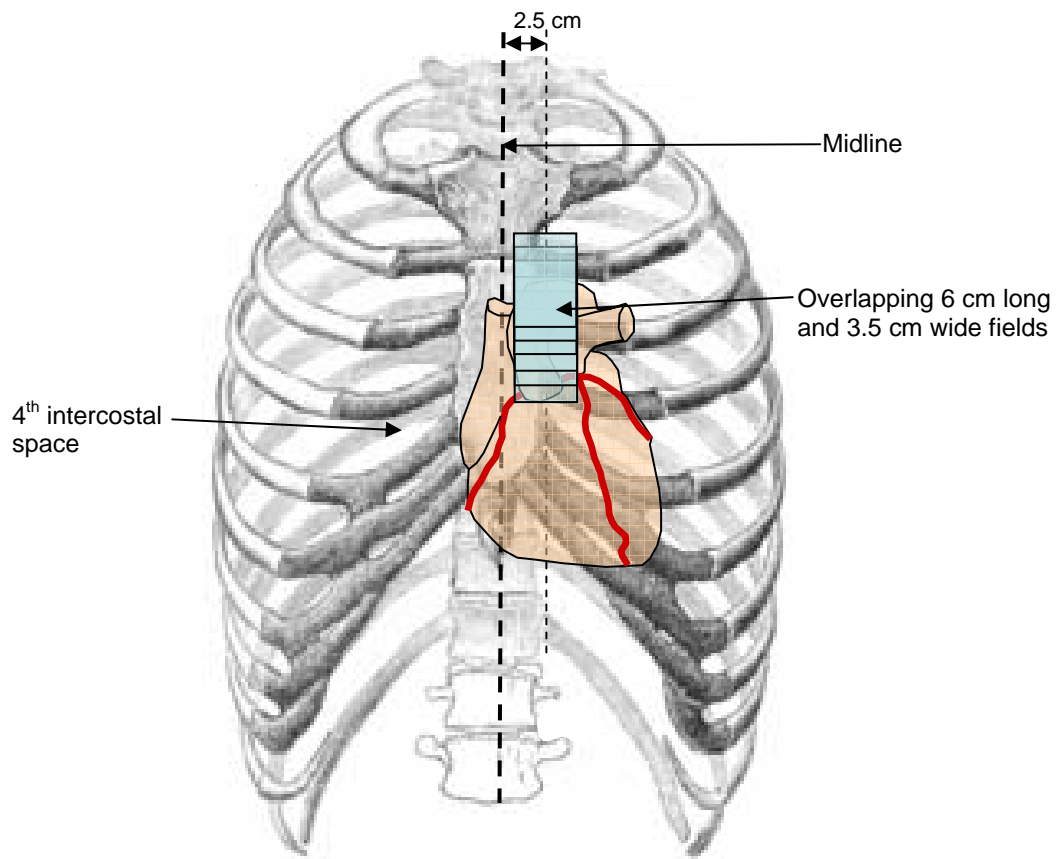


Fig. A1. Reconstruction of the inferior part of the short left cobalt chain

# 5. Cardiac dose from tangential breast cancer radiotherapy in the year 2006

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## **Abstract**

### **Purpose**

To quantify the radiation doses received by the heart and coronary arteries from contemporary tangential breast or chest wall radiotherapy.

### **Methods and materials**

Fifty consecutive patients with left-sided breast cancer and five consecutive patients with right-sided breast cancer treated at a large UK radiotherapy centre during the year 2006 were selected. All patients were irradiated using 6 or 8 MV tangential beams to the breast or chest wall. For each dose-plan, dose volume histograms for the heart and left anterior descending (LAD) coronary artery were calculated. For five of the left-sided and all five right-sided patients, dose volume histograms for the right and circumflex coronary arteries were also calculated. Detailed spatial assessment of dose to the LAD coronary artery was performed for three left-sided patients.

### **Results**

For the 50 patients given left-sided irradiation, the average mean dose was 2.3 Gy (standard deviation (SD) 0.7) to the heart and 7.6 Gy (SD 4.5) to the LAD coronary artery, with the distal LAD receiving the highest doses. The right and circumflex coronary arteries received around 2 Gy mean dose. Part of the heart received >20 Gy in 22 (44%) left-sided patients. For the 5 patients given right-sided irradiation, average mean doses to all cardiac structures were in the range 1.2 to 2 Gy.

## **Conclusions**

Heart dose from left-tangential radiotherapy has reduced considerably over the past 40 years but part of the heart still received over 20 Gy for around half of left-sided patients. Cardiac dose for right-sided patients was generally from scattered irradiation alone.

**Key words:** *Breast radiotherapy, heart disease, long-term effects, coronary artery, contemporary radiotherapy.*

## **Introduction**

Randomised trials that began in the 1950s to 1980s have shown that adjuvant radiotherapy for breast cancer can reduce breast cancer mortality in many categories of women [1]. However many of the regimens used in these trials involved some unwanted irradiation of the heart, leading to a 27% (95% confidence interval (CI) 13%, 41%) increase in mortality from heart disease and reducing the beneficial effect of the radiotherapy on overall survival [1]. Regimens used to treat left-sided breast cancers generally deliver higher cardiac radiation doses than those used to treat right-sided cancers and, until recently, similar proportions of women with left-sided and right-sided breast cancer in the general population have been irradiated. Therefore, observational studies comparing cardiac mortality rates between women irradiated for left-sided and women irradiated for right-sided breast cancer in the general population can also give an indication of the extent to which radiotherapy has increased cardiac risk. The largest such study [2,3] found that cardiac mortality was 16% higher in women with left-sided breast cancer compared to women with right-sided breast cancer (95% CI 8%, 24%) mainly due to the long-term effects of radiotherapy in the 1970s.

Radiotherapy guidelines have changed since the women in the above studies were treated. For example, irradiation of the internal mammary chain, which tended to result in the highest heart doses [4], is now much less frequently performed [5,6]. Radiotherapy techniques have also changed. In a comparison of older (1957-1984) orthovoltage and more recent (1988-1989) megavoltage irradiation of the breast or chest wall, the mean percentage volume of the heart receiving 5 Gy<sub>2</sub> biologically effective dose (BED) reduced from 87% for older (1957-1984) radiotherapy to 41% for more recent (1988-1989) radiotherapy [7].

In view of these reductions in cardiac exposure, the cardiac risks of breast radiotherapy are also likely to have reduced over the past few decades. However, as much of the radiation-induced cardiac death occurs more than a decade after treatment [8], the full risk of recent regimens cannot yet be assessed directly. Nevertheless, some indication of the likely risk can be gained by comparing heart and coronary artery doses for contemporary (2006) patients with doses received by patients irradiated with older regimens (pre-1980s) for which the risks are known.

We have used 3-dimensional computerised tomography (CT)-based dosimetry methods to estimate dose and volume irradiated for the heart and the three main coronary arteries in 55 breast cancer patients treated with tangential irradiation in the Yorkshire Cancer Centre, UK in 2006.

## **Methods and Materials**

Fifty consecutive patients with left-sided breast cancer and five consecutive patients with right-sided breast cancer who received adjuvant breast or chest wall radiotherapy at a large UK radiotherapy centre were selected from the CT planning database. Most patients (around 75%) had undergone breast conserving surgery and the rest had undergone mastectomy for stage I or II breast cancer followed by tangential pair irradiation in early 2006. The few women who received radiotherapy to the regional lymph nodes were excluded from the study.

All patients were positioned on a breast board with the sternum horizontal to the treatment couch and both arms above the head. The tangential field borders were determined clinically by the attending clinician and marked using radio-opaque wires. The medial border was 1 cm ipsilateral to the midline, the superior border was the sternal notch, the inferior border was 1 cm below the infra-mammary fold

and the lateral border was 1 cm outside the lateral palpable border of the breast (or the mid-axillary line for mastectomised patients). Patients were scanned using a wide-bore virtual simulator, with 5 mm slices, from the clavicle to the mid-abdomen. Two 180° opposed isocentric tangential fields were set up based on the clinically determined borders.

Each patient's radiotherapy was planned such that the dose distribution was optimised on the central slice and was normalised to the International Commission on Radiation Units (ICRU) reference point of the breast. CT data and treatment parameters were exported to a computerised treatment planning system (Theraplan Plus, Nucletron UK Ltd). Beam weights and wedge angles were optimised based on the dose distribution for the central axis plane. All patients were planned using 6 MV photons unless a wide separation between the tangential beams made it impossible to achieve ICRU 50 dose limits on the central slice, in which case 8 MV photons were used. Bolus was used only if there was skin involvement. Field borders were not modified to reduce or avoid cardiac irradiation and cardiac shielding was not used, in common with many other UK radiotherapy centres at the time. All patients were treated with a tumour dose of 40 Gy to the isocentre in 15 fractions, 5 days a week. The dose distributions were calculated, with full CT density information including lung correction, using the pencil beam algorithm [9,10].

The cardiac dose-distributions were calculated using the full 3-dimensional CT set. The patient surface was defined by automated density gradient tracking. The organs at risk that were assessed were the heart and coronary arteries. The heart and left anterior descending (LAD) coronary artery were outlined for all patients. In addition the right and circumflex coronary arteries were outlined for five

consecutive left-sided patients and for all five right-sided patients. The superior limit of the heart included the right and left atria and excluded the pulmonary trunk, ascending aorta and superior vena cava. The inferior limit of the heart was the caudal border of the myocardium. Due to its short length, the left main coronary artery was assessed with the LAD coronary artery. The CT scans were not contrast-enhanced. Therefore, on some CT images, it was not possible to visualise the coronary arteries directly and their location was inferred using visible, reliable, cardiac landmarks [11] as follows: the location of the LAD coronary artery was identified using the course of the anterior interventricular groove. The circumflex coronary artery was contoured from its branch point off the left main coronary artery and its course was identified using the left atrioventricular groove. The right coronary artery was contoured from its origin above the right cusp of the aortic valve. Its location was identified using the right atrioventricular groove. A radial margin of 1 cm was added to each coronary artery contour to allow for uncertainty in identification of arterial position, respiratory movement and for the beating movement of the heart. The contours were reviewed and modified, where appropriate, by one of the authors (radiologist JTS).

For each treatment plan, dose volume histograms (DVHs) for the heart and for the LAD coronary artery, with a 1 cm radial margin, were generated. For all 5 right-sided and for the first 5 consecutive left-sided patients, DVHs for the right and circumflex coronary arteries, with margin, were also generated. For each organ at risk, mean and maximum doses were assessed for each patient. For each of these quantities the average value over all assessed patients (referred to as ‘average mean’ or ‘average maximum’) was calculated together with its standard deviation (SD).

CT images of all left-sided patients who received more than 12 Gy (30% of tumour dose) mean radiation dose to the LAD coronary artery were assessed further in order to determine which part(s) of the artery received the highest doses. From these, the three CT scans with the least distortion due to movement of the heart were selected. Point dose to the centre of the LAD coronary artery contour was noted on each CT slice. The distances of these point doses from the origin of the LAD (i.e. the branch point of the left main coronary artery into LAD and circumflex coronary arteries) were noted. These doses and distances were used to create a 2-dimensional representation of dose to the LAD coronary artery for each of the three CT scans.

## **Results**

### **Mean dose to the heart and coronary arteries**

For left-sided patients, the heart was close to the tangential fields and the average mean heart dose was 2.3 Gy (SD 0.7) (Table 1a & Fig. 1a). In contrast, for the five patients who received right-sided irradiation, the heart was distant from the fields. It received scattered dose alone i.e. dose from radiation outside the radiotherapy beams (Fig. 1b) and the average mean heart dose was 1.5 Gy (SD 0.2) (Table 1a).

For left-sided radiotherapy, the anterior location of the LAD coronary artery in the interventricular groove meant that it was close to, or in, the fields for most patients (Fig. 1a) and it received 7.6 Gy (SD 4.5) average mean dose\*. For right-sided radiotherapy the LAD coronary artery was usually more than 7 cm from the fields and it received 1.6 Gy (SD 0.2) average mean dose from scattered irradiation (Table 1a & Fig. 1b). Thus the mean LAD coronary artery dose from

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\* All coronary artery doses are for the artery with a 1 cm radial margin

Table 1. Mean and maximum doses to the heart and three main coronary arteries from tangential pair radiotherapy

	Heart	LAD coronary artery	Right coronary artery	Circumflex coronary artery
a) Average mean dose <sup>†</sup> in Gy (standard deviation)				
Left-sided irradiation	2.3 (0.7) <sup>‡</sup>	7.6 (4.5) <sup>‡</sup>	2.0 (0.3)	1.8 (0.3)
Right-sided irradiation	1.5 (0.2)	1.6 (0.2)	2.0 (0.3)	1.2 (0.1)
b) Average maximum dose <sup>†</sup> in Gy (standard deviation)				
Left-sided irradiation	30.7 (10.8) <sup>‡</sup>	35.2 (8.8) <sup>‡</sup>	2.5 (0.3)	2.4 (0.4)
Right-sided irradiation	2.6 (0.3)	1.9 (0.2)	2.5 (0.4)	1.5 (0.2)

*Abbreviation:* LAD=left anterior descending

<sup>†</sup>i.e. the mean or maximum organ dose averaged over all the patients (50 or 5) for whom the assessment was carried out.

<sup>‡</sup>These values were based on 50 patients, whereas all others were based on 5 patients.

left-sided irradiation was around five times higher than the dose from right-sided irradiation. The right and circumflex coronary arteries were distant from both left- and right-sided tangential fields and received scattered dose alone (Table 1 & Fig. 1).

### **Cardiac structures that received more than 20 Gy**

For left-sided radiotherapy, the heart received scattered irradiation alone in 28 patients (56%). For the other 22 patients (44%), a small part of the heart was in the radiation fields, i.e. it received more than 20 Gy (Fig. 1a & Fig. 2). Of these 22 patients, 20 patients had 1-2% of the heart volume in the fields and the remaining 2 patients had >5% of the heart volume in the fields (Fig. 2).

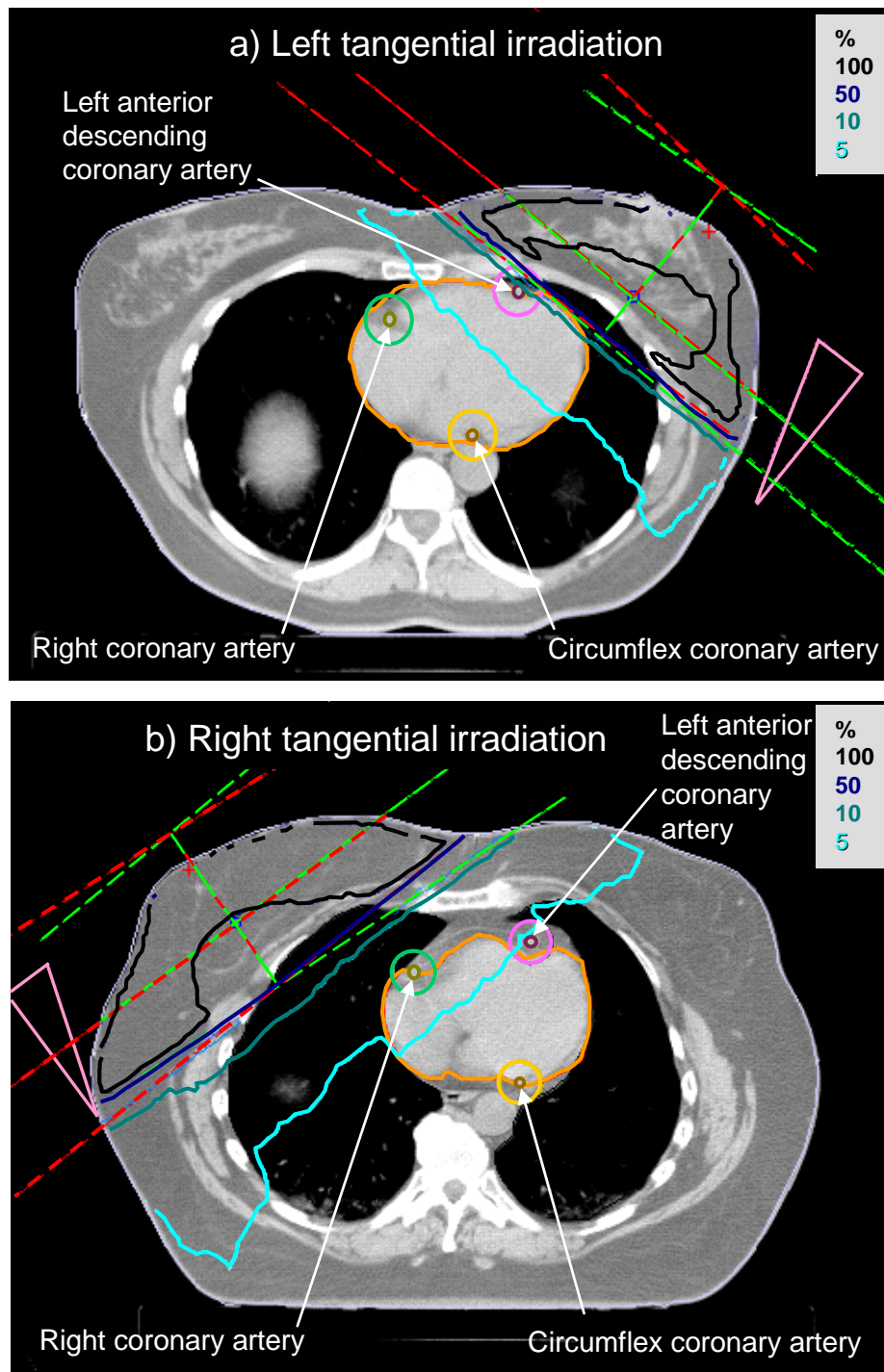


Fig. 1. Dose distribution from 6 MV tangential irradiation. The heart is outlined in orange. The coronary arteries are outlined and a radial margin of 1 cm has been added to each.

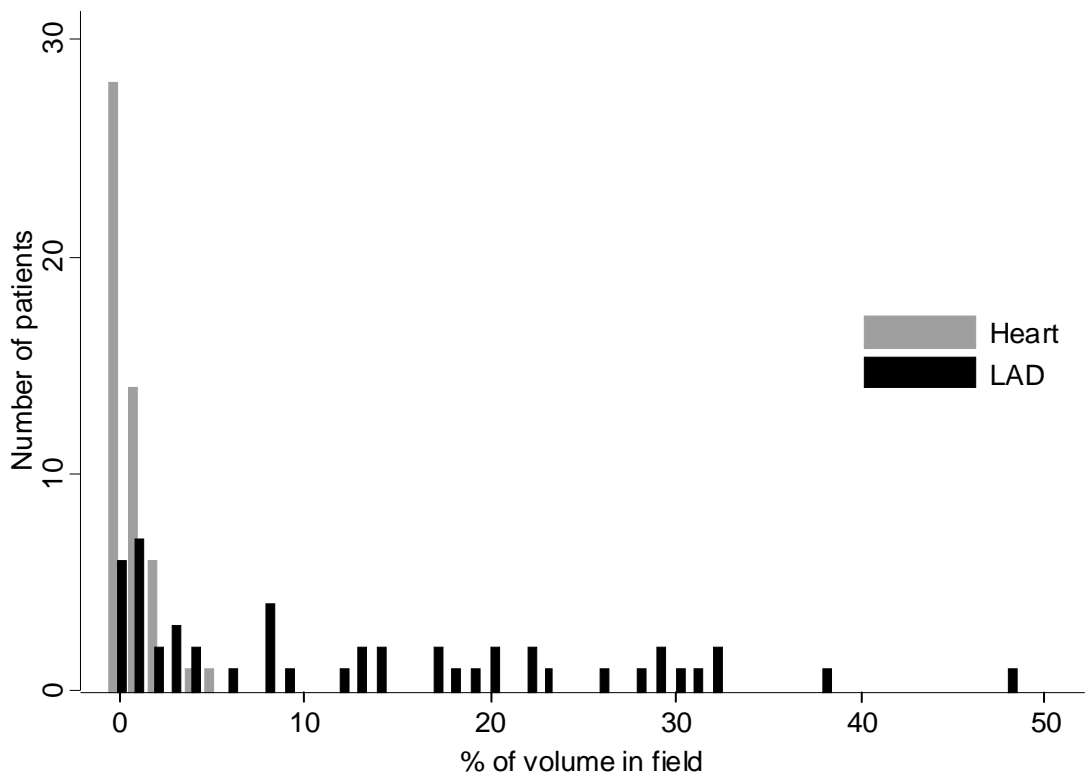


Fig. 2. Histogram of percentage volume of the heart and left anterior descending (LAD) coronary artery in the radiation fields (i.e. receiving >20 Gy) for 50 patients treated with left-tangential irradiation.

For left-sided radiotherapy, the cardiac structures that received the highest doses were the apex of the left ventricle and the LAD coronary artery (Fig. 1a). For some patients the LAD coronary artery radial margins were outside the volume of the heart. This meant that the LAD coronary artery contour was closer to the fields than the heart was and it therefore received higher doses than the heart. Average maximum point doses to the heart and LAD coronary artery for left-sided irradiation were 30.7 Gy (SD 10.8) and 35.2 Gy (SD 8.8) respectively (Table 1b).

The average volume of the LAD coronary artery included in the field was 13%. There was substantial patient-to-patient variability: for 26% of patients,

≤1% of the LAD volume was in the fields, while for 58% of patients 2-29% was included and for 16% of patients 30% or more of the volume was included in the fields (Fig. 2). Average maximum doses to the right and circumflex coronary arteries for left-sided irradiation and to all cardiac structures for right-sided irradiation were less than 3 Gy and ranged from 1.5 (SD 0.2) for the circumflex coronary artery to 2.6 (SD 0.3) for the heart (Table 1b).

### **Patient-to-patient variability in mean dose**

Of the cardiac organs considered, patient-to-patient variability in mean dose was greatest for LAD coronary artery dose from left-sided irradiation. The mean LAD dose for 50 left-sided patients varied from 2.4 to 21.2 Gy (SD 4.5) (Table 1 & Fig. 3). High LAD coronary artery dose was associated with high mean heart dose (Fig. 4), and the patient with the highest mean heart dose (4.4 Gy) also had the highest LAD dose (21.3 Gy) (Fig. 3).

Mean heart dose ranged from 1.4 to 4.4 Gy for left-sided irradiation (Fig. 3). There was little variability in mean dose to the right and circumflex coronary arteries from left-sided irradiation or in dose to any cardiac structure from right-sided irradiation (see Table 1a for standard deviations).

### **Dose to different parts of the LAD coronary artery**

Twelve patients who had left-sided radiotherapy received mean LAD coronary artery doses of >12 Gy (30% of tumour dose). The three patients whose CT scans demonstrated the least motion artefact, were studied in detail. The LAD coronary artery, measured from its origin at the bifurcation of the left main coronary artery, to the apex of the left ventricle, varied in length from 8.9 to 10.2 cm (Fig. 5).

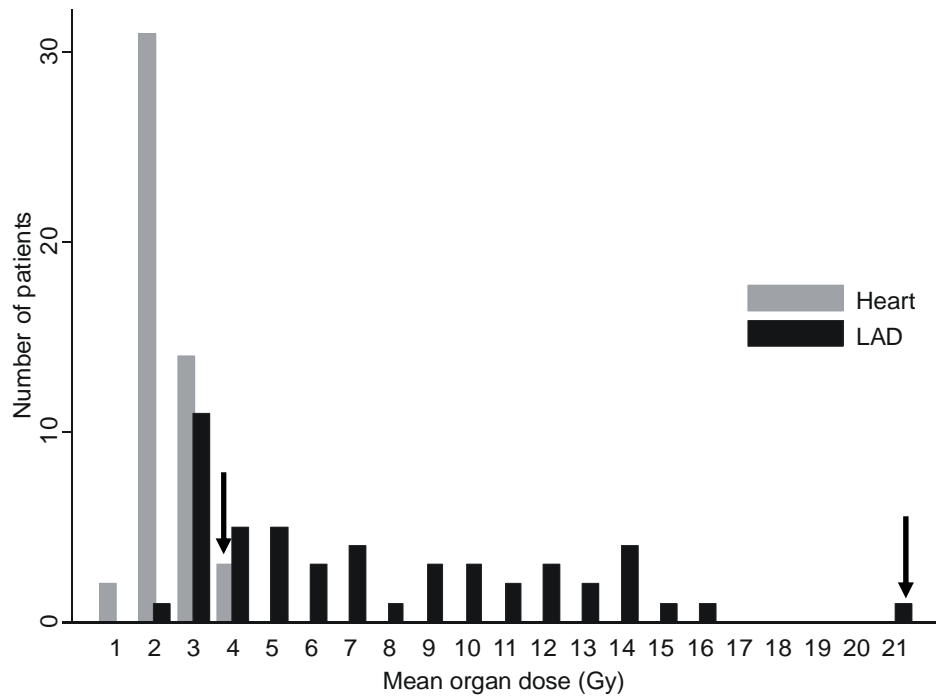


Fig. 3. Histogram of mean doses to the heart and left anterior descending (LAD) coronary artery for 50 patients treated with left-tangential irradiation. The patient who received the highest mean heart dose also received the highest mean LAD coronary artery dose and is marked with an arrow.

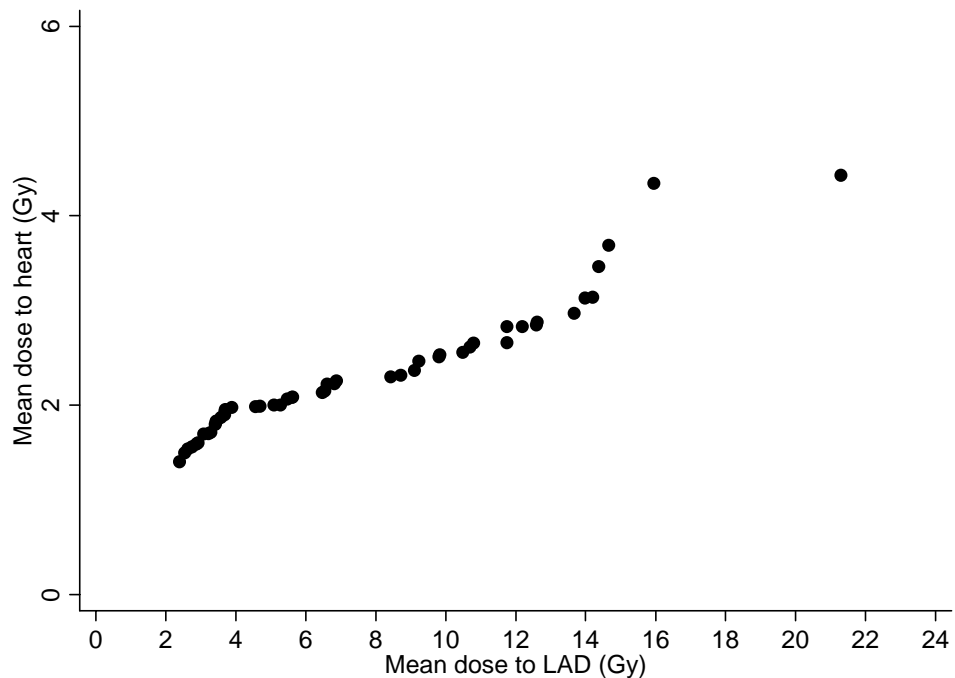


Fig. 4. Relationship between mean heart dose and mean left anterior descending (LAD) coronary artery dose for 50 patients treated with left-tangential radiotherapy.

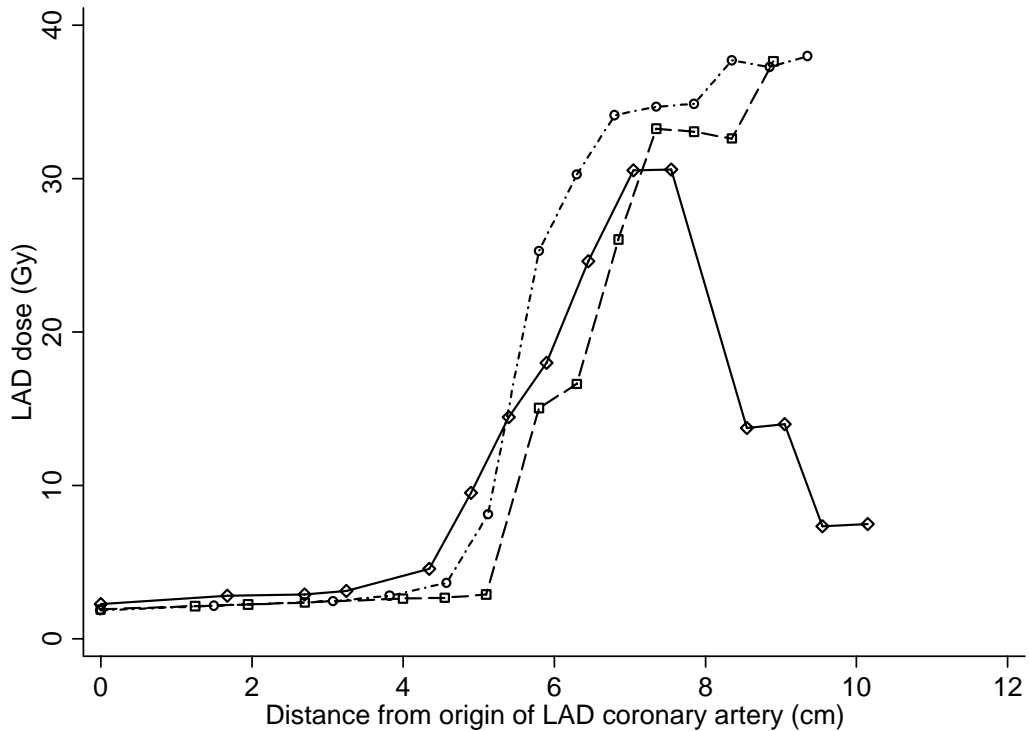


Fig. 5. Left anterior descending (LAD) coronary artery point doses on each CT slice versus distance from arterial origin for three left-sided patients with mean LAD coronary artery dose >12 Gy. For 2 patients the part of artery >7cm from the origin was in the fields (i.e. it received >20 Gy). For the third patient, the artery enters the fields at around 6 cm and leaves the fields at around 8 cm from the origin.

For all three patients, the proximal part of the artery (up to 4 cm from its origin) was outside the high dose region and received less than 4 Gy (10% of tumour dose). As the LAD coronary artery descended in the interventricular groove between the apices of the right and left ventricles, it extended anteriorly, into the tangential beams, and parts of the distal LAD received doses of more than 30 Gy (75% of tumour dose) (Fig. 5).

## **Discussion**

We have quantified dose to the heart and to the three main coronary arteries from adjuvant radiotherapy in 55 breast cancer patients irradiated in a major UK radiotherapy centre in the year 2006.

### **Strengths and limitations of the study**

Patients for this study were selected consecutively from the CT planning database of the radiotherapy centre. Their order on the database should be independent of any of the factors currently known to affect heart dose, for example, surgical procedure, patient anatomy and the availability of different treatment units. Given this method of selection our sample is likely to be representative of the population of women irradiated at the Yorkshire Cancer Centre in early 2006.

This study assessed heart dose from tangential fields alone and did not consider scar boost or nodal irradiation. For left- or right-sided electron scar boost irradiation, heart dose is generally less than 0.3 Gy. For left-sided axillary radiotherapy, heart dose is around 0.4 Gy, and less than this for right-sided axillary irradiation [4]. Thus for these women, any additional cardiac dose from boost or axillary radiotherapy would have been an order of magnitude lower than the dose from tangential radiotherapy.

Heart dose from left supraclavicular irradiation is also much lower than heart dose from tangential irradiation at around 0.6 Gy (for a given dose of 40 Gy) [4], and less than this for right supraclavicular irradiation. There is some geographical variation in its use, but generally the supraclavicular fossa is only irradiated in around 10% of adjuvant breast radiotherapy patients [12,13]. In contrast, for internal mammary radiotherapy the heart dose varies from around 2 Gy to 13 Gy depending

on technique and laterality [14,15] but is only received by around 1% of patients [12]. Our results do not apply to the small subset of patients who receive internal mammary irradiation.

For the detailed study of LAD coronary artery dose, in order to minimise length measurement errors in the LAD, three CT plans with little distortion due to cardiac movement were selected from twelve plans that delivered >12 Gy mean LAD coronary artery dose. Movement artefact is primarily affected by breathing. Therefore breathless or anxious patients were unlikely to be included in this sample of three patients, but otherwise it is likely to be representative of left-sided tangential patients who received >12 Gy to the LAD coronary artery.

The dose distributions were calculated by Theraplan software, which is accurate to within  $\pm 2\%$  for dose and  $\pm 2$  mm for position in most clinical situations as confirmed by phantom measurements [16,17]. For regions outside the beam edges the accuracy in terms of absolute dose per monitor unit is within the range 3% to 5% [17,18].

This retrospective study of 55 breast cancer patients has provided cardiac dose estimates for tangential radiotherapy in one centre in the UK. Patient-to-patient dose variability was considerable and was largely determined by differences in patient anatomy [4]. There is likely to be additional variation between radiotherapy centres in the UK and between different countries worldwide depending on factors such as tumour dose (which varies from around 32.5 to 50.0 Gy [12,19,20]) and geographical variation in the prevalence of obesity. In addition, in some radiotherapy centres where tangential field borders are customised, or where advanced radiotherapy planning techniques e.g. intensity modulated radiotherapy

(IMRT) are routinely used, heart doses are likely to be lower than those in this study.

### **Reduction in cardiac doses since the 1970s**

Comparisons of the doses presented in this paper with cardiac doses received from different left-tangential radiotherapy regimens used in the past are shown in Table 2. Tumour dose was 40 Gy for the regimen used in 2006 and 50 Gy for the quoted regimens used in the 1970s and 1990s, therefore results for both mean cardiac dose (Table 2a) and percentage of tumour dose delivered to cardiac structures (Table 2b) are shown. Dose estimates from 1970s and 1990s Swedish left-tangential regimens have been used for comparison with the current estimates since, for these regimens,

Table 2. Reduction in mean dose to cardiac structures from left-tangential radiotherapy 1970s-2006

Calendar period	Heart	LAD coronary artery	Right coronary artery	Circumflex coronary artery
a) Mean dose (Gy)				
1970s (Sweden) [4]	13.3	31.8	9.1	6.9
1990s (Sweden) [4]	4.7	21.9	2.0	2.8
2006 (UK)	2.3	7.6	2.0	1.8
b) Mean dose (% tumour dose)				
1970s (Sweden) [4]	26.6	63.6	18.2	13.8
1990s (Sweden) [4]	9.4	43.8	4.0	5.6
2006 (UK)	5.8	19.0	5.0	4.5

*Abbreviation:* LAD=left anterior descending

detailed information concerning both the field parameters and the time period of use have been published [4]. Similar regimens were used in other countries during these time periods so these Swedish cardiac doses are likely to be similar to cardiac doses received elsewhere [21,22]. There have been reductions in both mean heart dose from 13.3 Gy in the 1970s to 2.3 Gy in 2006 and mean percentage of tumour dose received by the heart from 26.6% in the 1970s to 5.8% in 2006 for left-tangential irradiation. Mean doses to all three coronary arteries have also reduced, particularly dose to the LAD coronary artery, which has decreased from 31.8 Gy to 7.6 Gy and from 63.6% to 19.0% of tumour dose. For right-tangential radiotherapy, heart dose has also reduced from 2.3 Gy in the 1970s to 1.5 Gy in 2006 [4]. LAD and circumflex coronary artery doses from right-sided radiotherapy have changed little since the 1970s, whereas right coronary artery dose has reduced from 8.7 Gy to 2.0 Gy [4]. The cardiac dose reductions since the 1970s are likely to be due to a number of different factors including: the shift of the medial field border from the contralateral to the ipsilateral side, the use of higher energy beams (6 or 8 MV rather than cobalt-60) and the use of CT data for radiotherapy planning. Similar changes have occurred in many different countries therefore cardiac dose reductions from tangential irradiation are likely to have occurred worldwide.

These dose reductions are likely to have resulted in widespread reductions in cardiac risk over the past 40 years. They probably account for the suggested risk reductions seen when women irradiated for left-sided and for right-sided breast cancer in the United States between 1973 and 2001 are compared [2,3]. In the future, further dose reductions are expected due to the increasing use of advanced radiotherapy techniques such as IMRT.

### **Pathogenesis of radiation-induced heart disease**

The aetiology of the excess cardiac mortality seen years after irradiation is not yet fully understood, and is currently being investigated in the SUPREMO trial of post-mastectomy radiotherapy. In particular it is not clear whether myocardial damage or coronary artery damage, or both, are responsible and whether the risk of radiation-induced heart disease is affected by the use of anthracyclines. Damage to the LAD coronary artery is a common cause of non-radiation-induced myocardial infarction (MI), and may also play a role in radiation-induced MI. Left-tangential irradiation tends to deliver a high mean radiation dose to this artery (around 8 Gy in this study) with parts of the artery receiving more than 20 Gy in some patients. The highest doses were received by the distal part of the LAD coronary artery, as also seen in a study by Krueger et al. (2004) [23]. The prognosis of non-radiation-induced atherosclerosis is worse for proximal than for distal LAD coronary artery disease [24,25]. If this were also true of radiation-related coronary artery disease, irradiation of the distal LAD coronary artery may be less detrimental than irradiation of the proximal part. However at present, the clinical consequences of the high doses received by the distal part of the LAD coronary artery are unknown.

### **The effect of scattered irradiation**

For both left- and right-sided radiotherapy, using either standard tangents or IMRT, most of the heart volume receives more than 1 Gy dose from scattered irradiation [26]. This low dose exposure of the whole heart may contribute to the cardiac damage that leads to excess cardiac mortality. Evidence for this is derived from study of the survivors of the atomic bombings of Hiroshima and Nagasaki, who received mean uniform single cardiac doses of 4 Gy or less [27]. There was a

significant excess of deaths from heart disease in this cohort with a linear relationship between dose and cardiac mortality. Excess mortality from heart disease has also been seen in patients who received para-aortic irradiation for testicular cancer, which resulted in around 1 Gy scattered irradiation to the heart [28]. These studies raise the possibility that doses of around 1 to 2 Gy received by the whole heart may contribute to radiation-induced cardiac damage.

## **Conclusions**

Around half of the patients irradiated with left-tangential radiotherapy received doses of 20 Gy or more to a small part of the anterior heart, which usually included the LAD coronary artery. Most of the heart volume, including the right and circumflex coronary arteries, received scattered irradiation alone and mean heart dose was around 2 Gy for left-sided irradiation. For right-sided irradiation, cardiac structures received 1.2 to 2 Gy mean dose. These doses are considerably lower than cardiac doses from the regimens which are now known to have caused excess cardiac mortality, hence their risk is likely to be lower. However the clinical implications of these doses are, as yet, unknown.

## **Acknowledgement**

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# **6. Estimating cardiac exposure from breast cancer radiotherapy in clinical practice**

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## **Abstract**

### **Purpose**

To assess the value of maximum heart distance (MHD) in predicting dose and biologically effective dose (BED) to the heart and the left anterior descending (LAD) coronary artery for left-tangential breast or chest wall irradiation.

### **Methods and materials**

Fifty consecutive breast cancer patients given adjuvant left-tangential irradiation at a large UK radiotherapy centre during 2006 were selected. For each patient the following were derived using 3-dimensional computed tomography (CT) planning: 1) mean dose and BED to the heart, 2) mean dose and BED to the LAD coronary artery, 3) MHD, 4) position of the CT slice showing the maximum area of irradiated heart relative to the mid-plane slice, and 5) sternal and contralateral breast thickness (measures of body fat).

### **Results**

There was a strong linear correlation between MHD and mean heart dose; for every 1 cm increase in MHD, the mean heart dose increased by 2.9% on average (95% confidence interval 2.5, 3.3). There was a strong linear-quadratic relationship between MHD and mean heart BED. Mean LAD coronary artery dose and BED were also correlated with MHD but the associations were weaker. These relationships were not affected by body fat. The mid-plane CT slice did not give a reliable assessment of cardiac irradiation.

## **Conclusions**

MHD is a reliable predictor of mean heart dose and BED and gives an approximate estimate of mean LAD coronary artery dose and BED. Doses predicted by the MHD could help assess the risk of radiation-induced cardiac toxicity where individual CT-based cardiac dosimetry is not possible.

**Key words:** *Maximum heart distance, breast cancer radiotherapy, long-term effects, coronary artery, contemporary radiotherapy.*

## **Introduction**

Breast cancer radiotherapy can increase the risk of death from heart disease [1,2]. The magnitude of the risk is largely determined by the cardiac radiation dose [2-6]. To date, useful measures of dose in the prediction of cardiac toxicity include mean heart dose and biologically effective heart dose (BED) [6,7]. Dose to the coronary arteries may also predict toxicity, particularly for the left anterior descending (LAD) coronary artery, which receives appreciable doses from left-breast radiotherapy. This artery commonly supplies a large myocardial territory. Hence, LAD coronary artery-related myocardial infarction tends to lead to more severe clinical outcomes than infarction related to the other major coronary arteries [8,9]. Several large ongoing studies [10,11] are currently investigating the relationships between various measures of dose (including mean dose and mean BED to the whole heart and to each of the three main coronary arteries) and subsequent risk of cardiac damage. The aim of such studies is to generate dose-response relationships to predict the radiation-related cardiac risk for future breast cancer patients.

Conventional adjuvant breast or chest wall radiotherapy usually involves tangential beams, which deliver around 2 Gy radiation dose to the heart and around 8 Gy to the LAD coronary artery for left-sided radiotherapy [12]. There is some patient-to-patient variability in these doses depending on factors such as the position of the heart and breast size. Mean doses for 50 patients treated in the UK with left-tangential irradiation in the year 2006 ranged from 1.4 to 4.4 Gy for the heart (standard deviation (SD) 0.7) and from 2.4 to 21.2 Gy for the LAD coronary artery (SD 4.5) [12]. In view of this variability, individual patient cardiac dose assessment is needed to identify patients who would receive high cardiac doses from standard left-tangential irradiation, for whom complex planning techniques such as intensity

modulated radiotherapy may be desirable. For right-tangential irradiation, the heart receives less dose. The average mean heart dose was 1.5 Gy for five right-sided patients irradiated in 2006; the standard deviation was 0.2 Gy, indicating that there was little variability in heart dose [12].

The current gold standard of cardiac dose assessment is 3-dimensional (3D) computed tomography (CT) planning. Organs at risk are contoured manually and cardiac doses are measured using the pencil beam or collapsed cone algorithms to generate dose volume histograms (DVHs). This enables accurate assessment of dose to different cardiac structures. At present there is substantial geographical variation in the availability of: 1) CT planning technology and 2) staff resources for cardiac contouring in breast cancer radiotherapy. In parts of the United States and Scandinavia, routine breast CT planning, including cardiac contouring, has been performed for several years [13]. In contrast, in some radiotherapy centres worldwide CT data are not yet available for breast radiotherapy planning, therefore direct 3D assessment of cardiac dose is not possible. In some other centres, the technology to CT-plan breast radiotherapy on multiple slices is available but the large number of breast cancer patients irradiated means that there are insufficient staff resources for cardiac contouring of every patient. For example, only 5 of the 34 UK centres that participated in the START trial (which closed in 2002) used CT facilities for breast radiotherapy planning [14]. In radiotherapy centres where routine 3D CT breast radiotherapy planning is not yet possible, assessment of cardiac doses needs to be carried out by other means.

The maximum heart distance (MHD) is the maximum distance between the anterior cardiac contour and the posterior tangential field edges (Fig. 1). It can be easily and cheaply measured on the beam's eye view on a virtual simulator [15] or

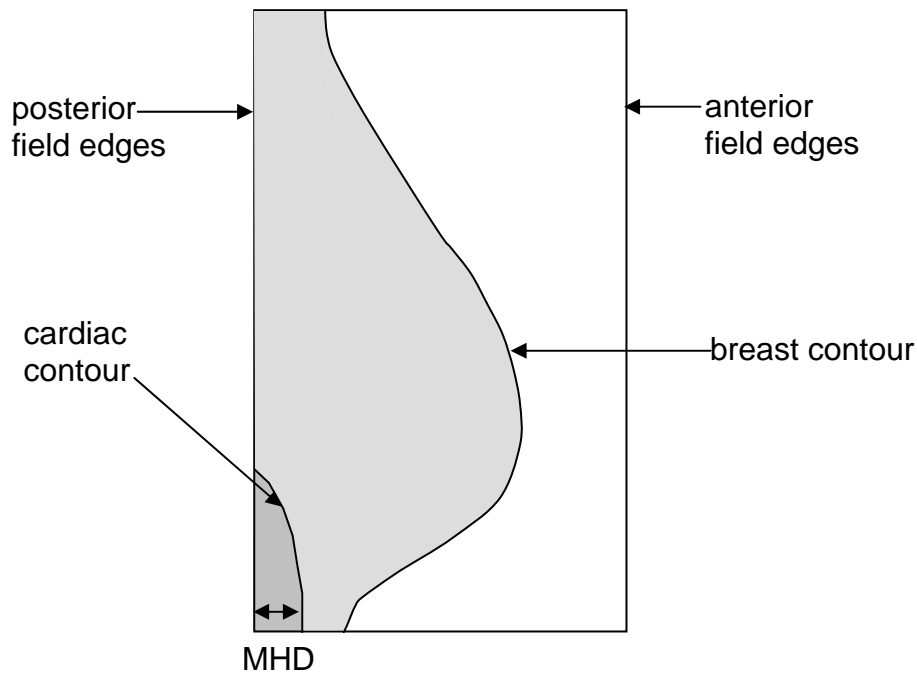


Fig. 1. The maximum heart distance (MHD) as seen on the beam's eye view. The MHD is the maximum distance between the anterior cardiac contour and the posterior tangential field edges.

on a conventional simulation film. If a patient's MHD could be used to predict her mean heart and LAD coronary artery dose or BED, then MHD could be used to help assess individual patient risk of subsequent radiation-induced heart disease in centres where routine 3D breast CT planning is not yet possible.

We investigated the relationship between MHD and the following measures of dose: mean heart dose, mean heart BED, mean LAD coronary artery dose and mean LAD coronary artery BED for 50 patients treated with left-tangential irradiation, to ascertain if MHD was a reliable predictor of cardiac doses in these women. In addition, we investigated whether the inclusion of two measures of body fat, as well as MHD, improved the prediction of cardiac dose.

## **Methods and Materials**

### **Study subjects**

Fifty consecutive women with left-sided breast cancer were selected from the Yorkshire Cancer Centre CT planning database. Most patients (around 75%) had undergone breast-conserving surgery and the remainder had undergone mastectomy. All had tangential pair irradiation in early 2006. The few women who received radiotherapy to the regional lymph nodes were excluded from the study. Scar boost irradiation was not considered, but heart dose from contemporary electron left-sided boost radiotherapy is generally  $<0.3$  Gy, which is an order of magnitude lower than dose from left-tangential irradiation [16]. All patients were treated with a tumour dose of 40 Gy in 15 fractions, 5 days per week. For a description of radiotherapy technique see Taylor et al. 2008 [12].

### **Dosimetric methods**

CT data and treatment parameters were exported to a computerised treatment planning system (Theraplan Plus, Nucletron UK Ltd). The patient surface, heart and LAD coronary artery were outlined (for details see Taylor et al. 2008 [12]). For each patient, DVHs for the heart and the LAD coronary artery were generated and mean dose to each was calculated. Mean BEDs for each patient were based on DVHs and were calculated using the linear-quadratic model. The available alpha-beta ratios for radiation-related heart disease are between 1 and 3 Gy [17,18]. In these calculations, we used an alpha-beta ratio of 2 Gy. The MHD (Fig. 1) was measured using axial CT slices.

For each patient, two additional measurements were performed on axial CT sections to assess the effect of patient body fat on cardiac doses as follows: 1) the

perpendicular distance between the rib cage and the nipple of the contralateral breast i.e. ‘breast thickness’ and 2) the perpendicular distance between the sternum and the skin surface anteriorly i.e. ‘sternal soft tissue thickness’ (Fig. 2).

For all 50 patients, optimisation of each patient’s original treatment plan had been performed using the mid-plane CT slice alone. The dosimetry for this study used the full CT set. For patients who had part of the heart volume included in the field, the position of the CT slice showing the maximal area of irradiated heart relative to the mid-plane slice was measured.

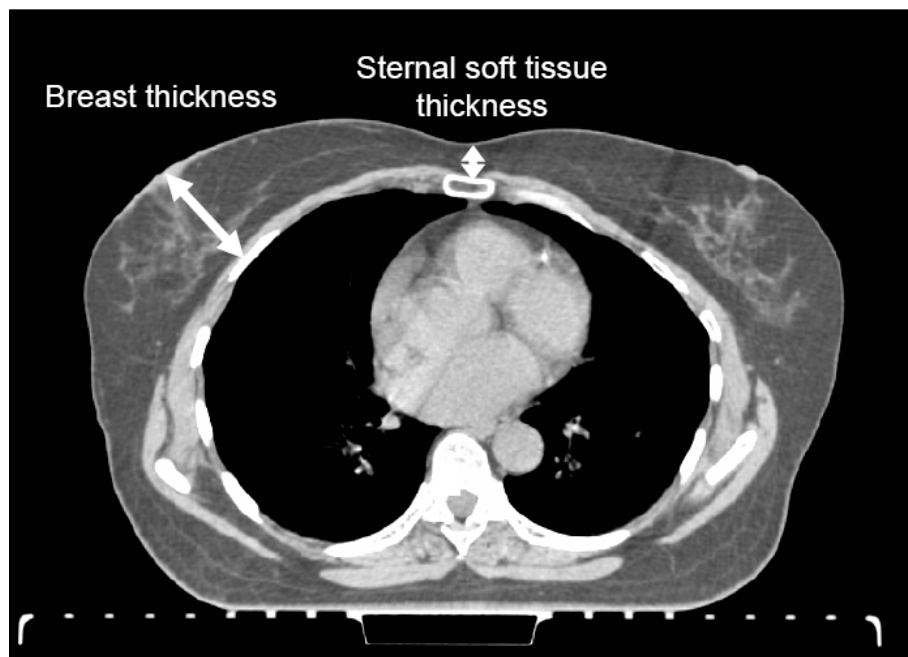


Fig. 2. Axial CT section showing two measures of body fat:

- (1) Breast thickness i.e. perpendicular distance between the rib cage and the nipple of the contralateral breast.
- (2) Sternal soft tissue thickness i.e. perpendicular distance between the sternum and the skin surface anteriorly.

## **Statistical methods**

The relationship between each measure of cardiac dose and MHD was characterised by fitting a series of regression models using the Stata statistical software (version 9.2; Stata Corporation, College Station, TX). Initially, MHD,  $MHD^2$  and  $MHD^3$  were all included as explanatory variables with cardiac dose as the dependent variable. First  $MHD^3$  and then  $MHD^2$  were discarded from the model if they were not significantly different from zero at  $p < 0.05$  using Student's t-test.  $R^2$  (i.e. the multiple correlation coefficient squared) was calculated to assess the percentage of the total variance in the mean doses explained by the final model.

The ability of MHD to predict cardiac dose for new women who had not been included in deriving the final model was assessed. This was done by fitting the final model to the data on all the women but one and then using the fitted model to predict heart dose for the excluded woman. For each model, the prediction error was calculated as the difference between the omitted woman's actual cardiac dose and her dose as predicted by the model. This procedure was repeated for each woman in the dataset. The average prediction error for each model was then assessed by calculating the square root of the mean value of the squares of the prediction errors (RMSPR). Finally, to assess whether incorporating the measures of body fat (breast thickness and sternal soft tissue thickness) into the models improved prediction, the RMSPR was re-calculated after including them in the regression models.

## **Results**

### **Maximum heart distance**

The MHD for the 50 patients assessed ranged from 0 to 2.28 cm (SD 0.52). For eight of the 50 patients, no part of the heart was included in the left-tangential fields

i.e. the MHD was 0. For 40 patients the MHD was between 0.1 and 2 cm, and for two patients the MHD was greater than 2 cm. The mean MHD for all 50 patients was 0.59 cm.

37 of the 50 patients received breast conserving surgery and their mean MHD was 0.61 cm; the other 13 patients received mastectomy and their mean MHD was 0.52 cm (difference in MHD not statistically significant).

### **Relationships between MHD and mean heart dose and BED**

There was a strong positive linear correlation between MHD and mean heart dose (Fig. 3a). MHD accounted for 81% of the variability in mean heart dose i.e.  $R^2$  was 81%. For every 1 cm increase in MHD, the mean heart dose increased by an average of 2.9% of tumour dose, (95% confidence interval (CI) 2.5, 3.3). When MHD was used to predict mean heart dose, the prediction was within 1.2% for 90% of patients and was always within 1.8% (Fig. 4a).

There was a strong positive linear-quadratic relationship between MHD and mean heart BED and  $R^2$  was 88% (Fig. 3b). When MHD was used to predict mean heart BED, the prediction was within 0.7 Gy<sub>2</sub> for 90% of patients and always within 1.4 Gy<sub>2</sub> (Fig. 4b).

### **Relationships between MHD and mean LAD coronary artery dose and BED**

Mean dose and mean BED to the LAD coronary artery were generally substantially higher than mean dose and mean BED to the heart. Mean LAD coronary artery dose was positively correlated with MHD and  $R^2$  was 60% (Fig. 3c). The relationships between LAD coronary artery doses and MHD demonstrated more scatter than those between mean heart doses and MHD. For every 1 cm

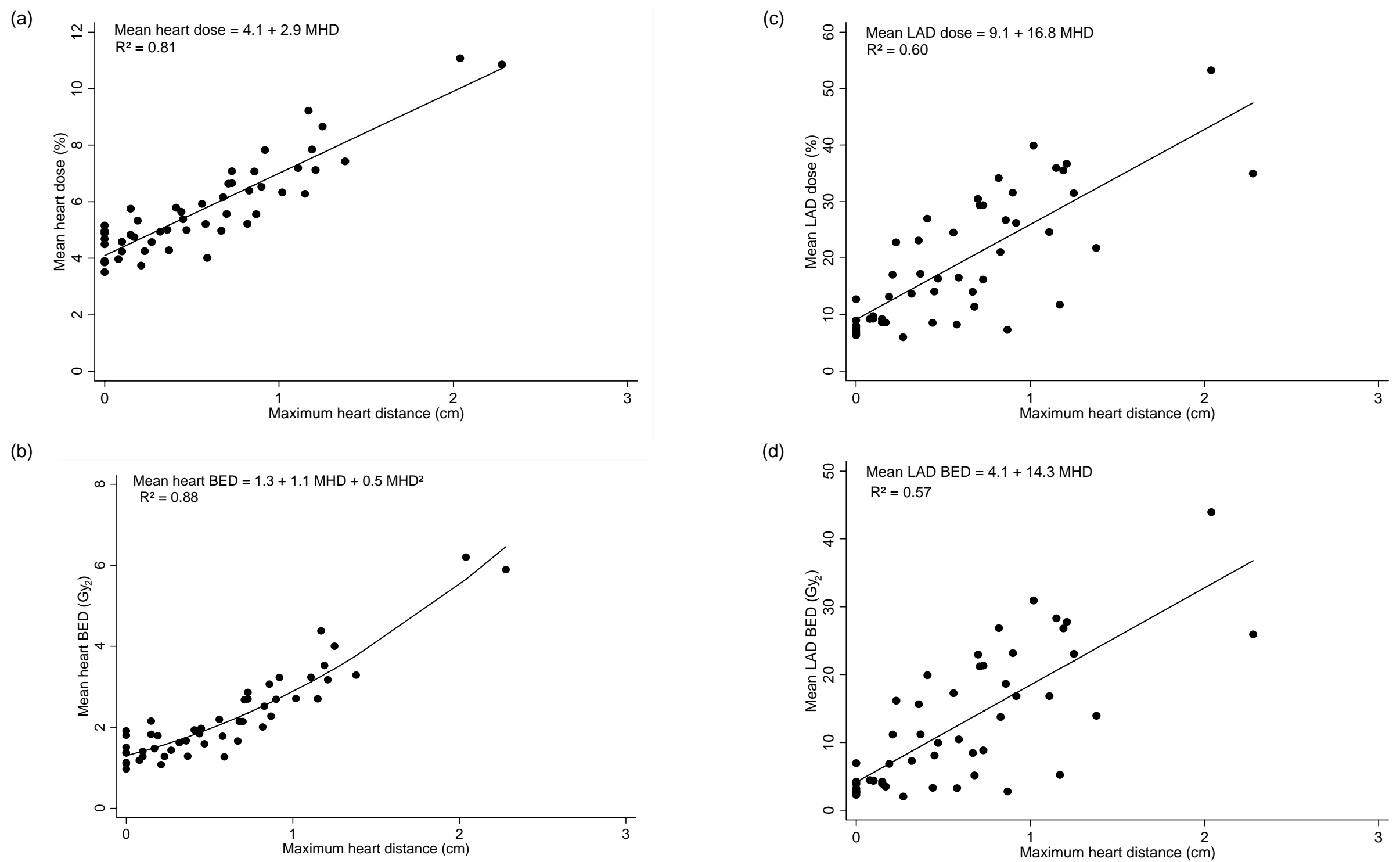


Fig. 3. Relationships between various measures of heart dose and maximum heart distance (MHD) for 50 breast cancer patients treated with left-tangential radiotherapy at a major UK radiotherapy centre in 2006.

*Abbreviations:* MHD=maximum heart distance; BED=biologically effective dose; LAD=left anterior descending; R2 is the multiple correlation coefficient squared for the line shown on each graph. It measures the percentage of the total variance in the dose measures explained by MHD in panels (a), (c) and (d) and between MHD and MHD2 in panel (b).

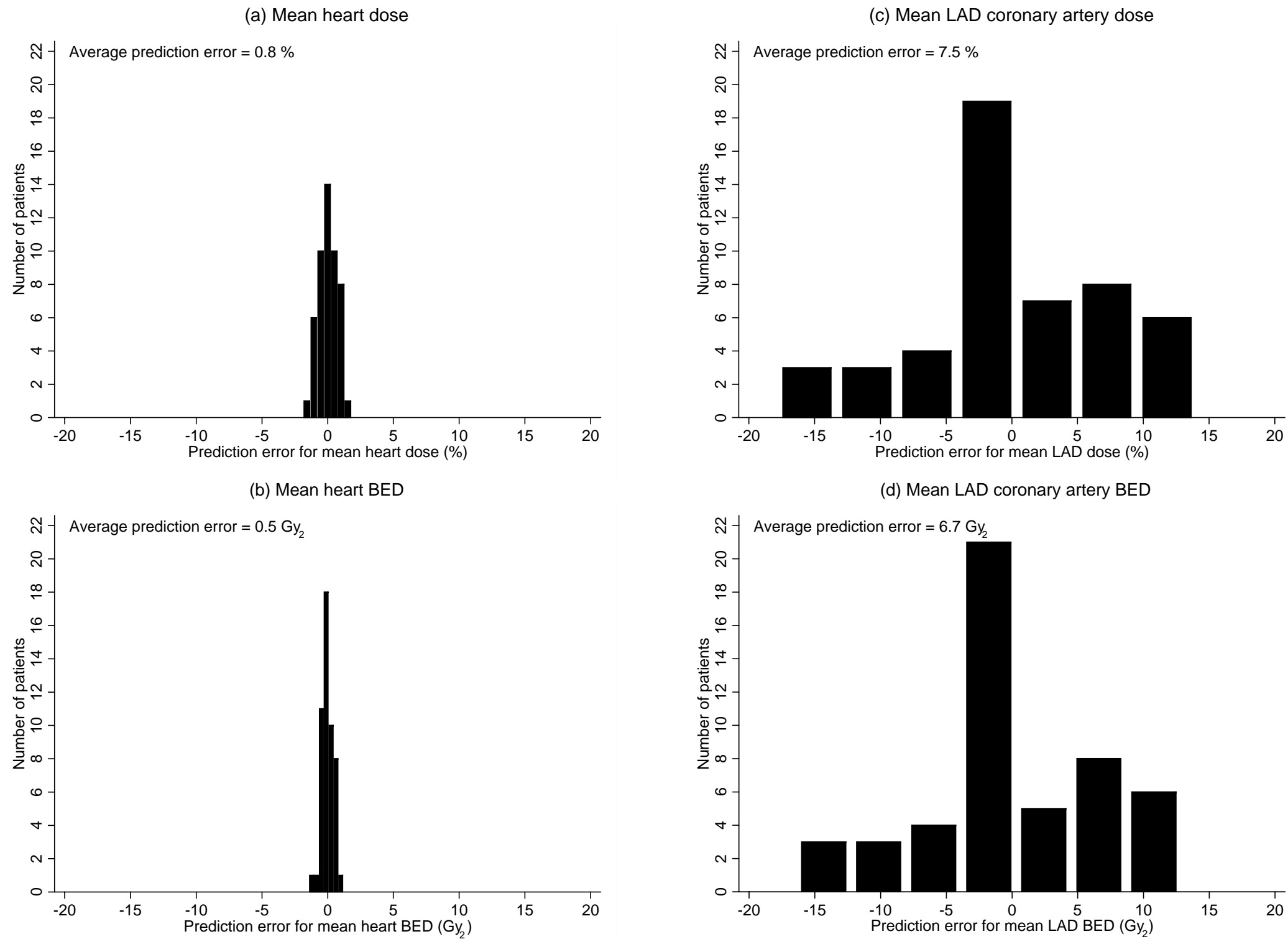


Fig. 4. Prediction error for the relationships between various measures of heart dose and maximum heart distance shown in Fig. 3. Each histogram summarises the differences between the cardiac doses received by a woman, and the value that would have been predicted for that woman based on information from the other 49 women. See statistical methods for definition of average prediction error. Abbreviations as for Fig. 3.

increase in MHD, the mean LAD coronary artery dose increased by an average of 16.8% (95% CI 12.8, 20.8). MHD predicted mean LAD coronary artery dose to within 4% of tumour dose for half of the patients and within the range -17% to 14% of tumour dose for all patients (Fig. 4c).

There was a positive linear correlation between MHD and mean LAD coronary artery BED and  $R^2$  was 57% (Fig. 3d). For every 1 cm increase in MHD, LAD coronary artery BED increased by an average of 14.3 Gy<sub>2</sub> (95% CI 10.7, 17.9). MHD predicted mean LAD coronary artery BED to within 3.5 Gy<sub>2</sub> for half of the patients and within the dose range -16.4 Gy<sub>2</sub> to 12.9 Gy<sub>2</sub> for all patients (Fig. 4d).

#### **Patient body fat and heart dose**

Sternal soft tissue thickness and contralateral breast thickness were positively correlated ( $R^2=58\%$ ) (data not shown). There was a moderate positive correlation between mean heart dose and contralateral breast thickness ( $R^2=30\%$ ). For every 1 cm increase in breast thickness, the mean heart dose rose by an average of 0.5% of tumour dose (95% CI 0.3, 0.7) (Fig. 5). There was also a positive correlation between mean heart dose and sternal soft tissue thickness ( $R^2=19\%$ ) (data not shown). These associations were much weaker than those between MHD and mean heart dose or BED.

The average prediction error when using MHD to predict mean heart dose using a linear relationship, as in Fig. 3a, was 0.8% (Table 1). When sternal soft tissue thickness was included in the regression model, as well as MHD, the average prediction error remained unchanged and when breast thickness was included, it

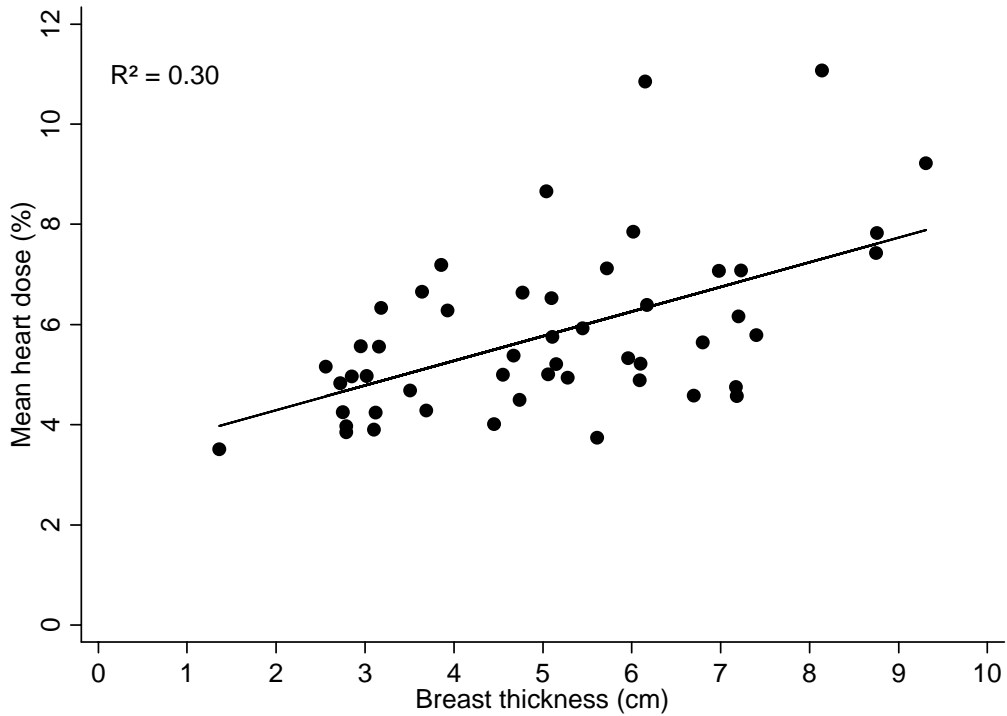


Fig. 5. Relationship between mean heart dose and breast thickness (perpendicular distance between the rib cage and the nipple of the contralateral breast) for 50 left-tangential breast cancer patients.  $R^2$  is the multiple correlation coefficient squared for the line shown on the graph.

decreased slightly to 0.7%. When both breast thickness and sternal soft tissue thickness were included, it remained at 0.7%. Thus adding both measures of body fat to the model for the relationship between mean heart dose and MHD made very little difference to the ability to predict mean heart dose. Similarly, the addition of breast thickness and sternal soft tissue thickness made little difference to the models for the relationships between mean heart BED and MHD and between mean LAD coronary artery dose/BED and MHD (Table 1). Thus the models shown in Fig. 3 can be applied to patients of different sizes within the size range studied.

Table 1. Typical prediction error for predicting various measures of cardiac dose (i) using just MHD as in Figs. 3 and 4 and (ii) to (iv) also including sternal soft tissue thickness and/or breast thickness in the model.

	Variables used to predict cardiac dose			
	(i) MHD	(ii) MHD and sternal soft tissue thickness	(iii) MHD and breast thickness	(iv) MHD and breast thickness and sternal soft tissue thickness
Measure of cardiac dose:				
Mean heart dose	0.8%	0.8%	0.7%	0.7%
Mean heart BED	0.5 Gy <sub>2</sub>	0.5 Gy <sub>2</sub>	0.4 Gy <sub>2</sub>	0.4 Gy <sub>2</sub>
Mean LAD coronary artery dose	7.5%	7.3%	7.6%	7.4%
Mean LAD coronary artery BED	6.7 Gy <sub>2</sub>	6.5 Gy <sub>2</sub>	6.8 Gy <sub>2</sub>	6.6 Gy <sub>2</sub>

*Abbreviations:* MHD=maximum heart distance; BED=biologically effective dose; LAD=left anterior descending.

### **Assessment of cardiac dose from the mid-plane slice**

For eight patients, the MHD was zero i.e. the cardiac contour was not included in the radiotherapy fields on any CT slice; mean heart dose for these patients was <5.2% of tumour dose. For the other 42 patients, part of the heart was included in the fields on at least one slice. The position of the slice showing the maximum area of irradiated heart (MHD) was determined by the location of the heart, whereas the position of the mid-plane slice was largely determined by breast position.

Fig. 6 shows the mid-plane CT slices (Figs. 6a & 6c) and the slices showing the maximum area of heart irradiated (Figs. 6b & 6d) for two typical patients. For patient 1, the mid-plane slice was 2.0 cm away from the slice showing the maximum area of irradiated heart; it showed the middle of the heart, including both cardiac ventricles (Fig. 6a). For patient 2, the mid-plane slice was 4.5 cm away from the slice showing the maximum area of irradiated heart; it showed the superior part of the heart and included the atria (Fig. 6c). Variation in the position of the mid-plane relative to the heart meant that the mid-plane slice showed different parts of the heart for different patients, therefore no consistent measure of cardiac irradiation could be derived from it. For neither patient was it possible to predict the extent of cardiac irradiation based on the mid-plane image.

For one of the 42 patients who had part of the heart included in the fields, the mid-plane CT slice was the slice that showed the maximum area of irradiated heart and it gave a good estimate of the extent of cardiac irradiation. For the other 41 patients, the position of the CT slice showing the maximum area of irradiated heart relative to the mid-plane slice varied from 0.5 cm superior to 7.0 cm inferior (Fig. 7). Thus, for the patients in this study, it was not possible to use the mid-plane to assess cardiac irradiation.

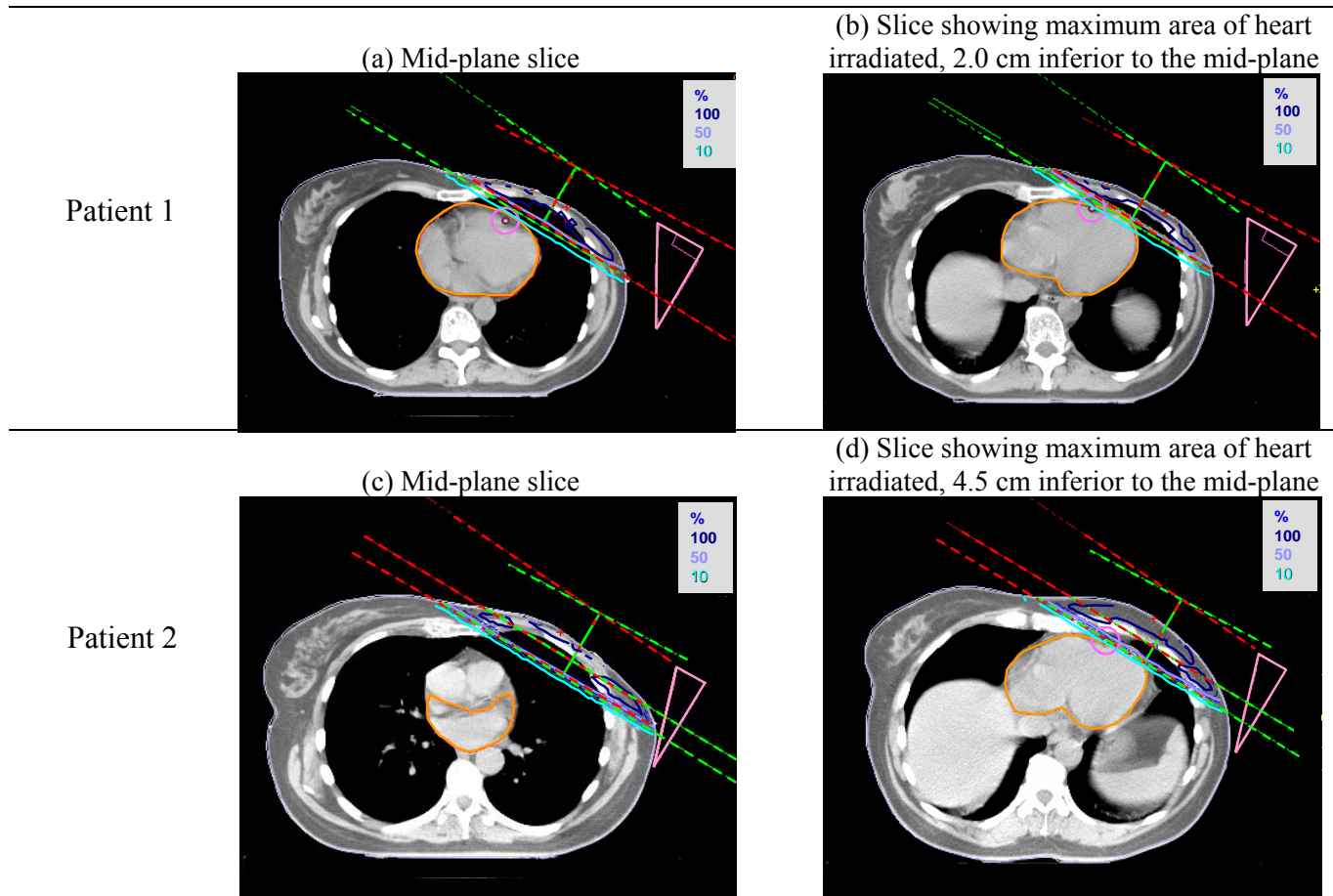


Fig. 6. Cardiac irradiation of two typical patients treated with left-tangential irradiation as seen on the mid-plane CT slice (a,c), and on the CT slice showing the maximum area of heart irradiated (b,d). The heart is outlined in orange and the left anterior descending coronary artery (with 1 cm radial margin) is outlined in pink. For patient 1, the slice showing the maximum area of heart irradiated was 2.0 cm inferior to the mid-plane slice. For patient 2, the slice showing the maximum area of heart irradiated was 4.5 cm inferior to the mid-plane slice.

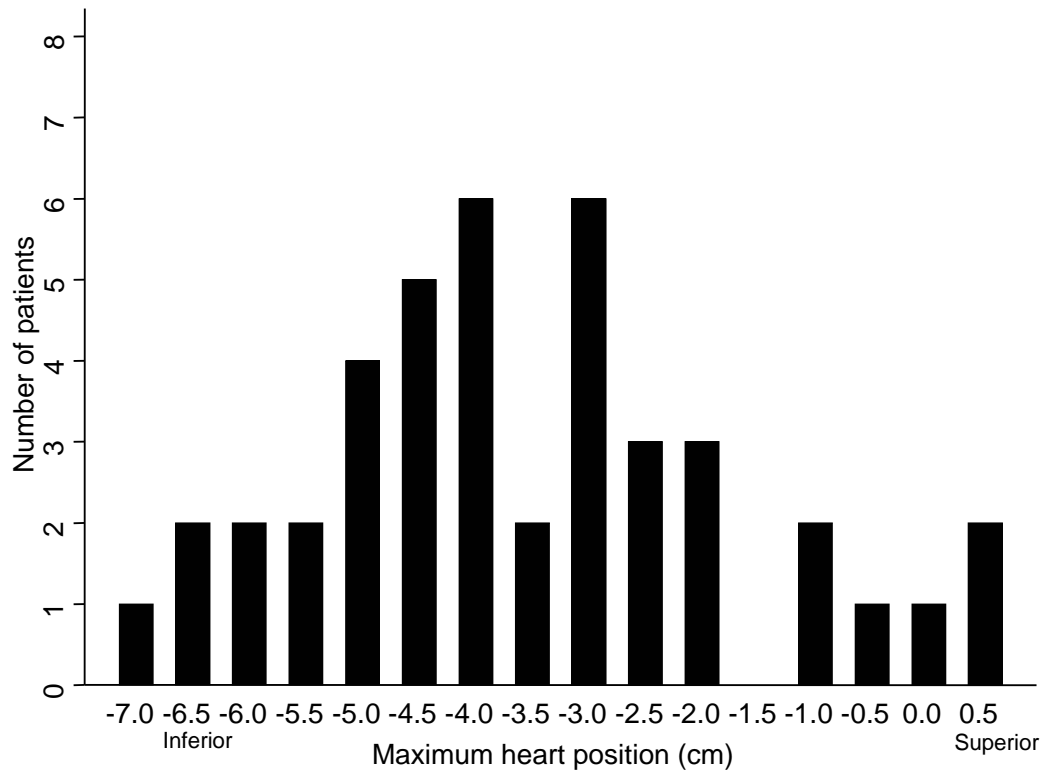


Fig. 7. Histogram of the position of the CT slice showing the maximum area of heart irradiated relative to the mid-plane slice for 42 of the 50 patients whose heart was included in left-tangential radiation fields. For the other 8 patients, the heart was not included in the fields.

## Discussion

### The use of MHD to predict heart dose

For the 50 patients assessed, MHD was a good predictor of both mean dose and mean BED to the whole heart from left-tangential irradiation. MHD predicted mean heart dose to within 1.2% of tumour dose for 90% of patients and to within 1.8% for all patients. It predicted mean heart BED to within 0.7 Gy<sub>2</sub> for 90% of patients and to within 1.4 Gy<sub>2</sub> for all patients.

Several studies have shown that the risk of radiation-induced death from heart disease is related to cardiac dose [6,7]. Therefore doses predicted by the MHD may be helpful in assessing the risk of radiation-induced cardiac mortality, thus enabling identification of patients who would receive high heart doses from standard tangential irradiation and for whom complex planning techniques may be desirable.

A strong correlation between MHD and normal tissue complication probability of cardiac mortality for left-tangential radiotherapy has previously been demonstrated using radiobiological modelling in 47 patients [19]. The complication probabilities were based on the relative seriality model which included several assumptions about the structure and function of the heart [20]. The data used to estimate the model parameters were from two randomised breast cancer trials of surgery alone versus surgery plus radiotherapy, which included only around 15 radiation-related cardiac deaths [5]. The authors therefore cautioned against relying on normal tissue complication probability estimates alone for the assessment of absolute cardiac risk and suggested that additional measures of dose should also be used [19]. Measurements such as mean dose and BED to the heart and to the LAD coronary artery may provide additional information in the assessment of cardiac toxicity.

A recent study investigated cardiovascular morbidity in 1601 Dutch breast cancer patients [21]. Patients irradiated for left-sided breast cancer had a significantly greater risk of developing cardiovascular disease than those irradiated for right-sided cancer; hazard ratio, left versus right, 1.38 (95% CI 1.05, 1.81). 778 women who received left-tangential irradiation were categorised according to their MHD. There was no statistically significant trend of increased cardiovascular risk

with greater MHD, but with only 139 events in left-sided patients, the study had limited power. Further clinical data may help to clarify the relationship between MHD and subsequent heart disease.

### **The use of MHD to predict LAD coronary artery dose**

MHD in these data gave an approximate estimate of mean LAD coronary artery dose and BED, although the correlations between LAD coronary artery doses and MHD were weaker than those between heart doses and MHD. This is likely to be due to the small volume of the artery, anatomical variation in its location, breathing artefacts on the CT scan and uncertainty in contouring.

The LAD coronary artery often receives more than 5 Gy mean dose from left-tangential radiotherapy [12] which may be a determining factor in radiation-induced cardiac disease. The relationships between LAD coronary artery doses and cardiac toxicity have not yet been characterised but are being investigated in ongoing studies [10,11].

### **Generalisability of this study**

This study was based on 50 patients treated with one radiotherapy technique in one centre. The models in Fig. 3 are now used to help guide breast radiotherapy planning in that centre, in which there are not yet sufficient resources for routine 3D cardiac dose assessments. Tangential radiotherapy is widely used worldwide for breast or chest wall irradiation. Therefore the results are likely to be widely applicable. The tangential technique used in our study was standard and was similar to that used in breast cancer radiotherapy worldwide [22,23]. For example, it was comparable to standard tangential irradiation as used in the START radiotherapy

trial which involved 34 centres in the UK [14]. MHD for a subset of 62 START trial patients ranged from 0.0 to 2.0 compared with 0.0 to 2.3 cm in our 50 patients. Patients in our study were treated with standard field borders and beam energies. Therefore these relationships should also be valid for left-tangential radiotherapy planning in other centres both in the UK and elsewhere where there are similar resource limitations, as long as patients are within the size range studied.

Patients for this study were selected consecutively from the CT planning database. Therefore the anatomical characteristics of this sample are likely to be representative of those in the Yorkshire breast cancer population. The relationships between MHD and cardiac doses (Fig. 3) and between mean heart dose and body fat (Fig. 5) are likely to be applicable to other patients within the size-range studied. However, occasionally patients are outside this size-range, for example patients with severe obesity or cachexia. In addition, in some populations, thoracic shape may differ from that in the UK. In such women, caution should be exercised if the relationships in Figures 3 and 5 are applied to them.

### **Current breast radiotherapy planning**

3D CT planning provides accurate and detailed estimates of cardiac doses. It would be desirable to have such information on irradiated breast cancer patients in all radiotherapy centres. However, in many centres in the UK and worldwide, this is not possible at the present time. The use of CT planning for breast cancer radiotherapy is likely to increase in the next decade, thus 3D dose assessment will be available for an increasing number of patients. Until then, in centres without resources for routine breast CT planning, cardiac dose needs to be assessed using 2D information. In some centres where CT planning technology is available, but

there are insufficient staff resources for contouring every patient, this method may be used to identify patients with high MHD measurements who may benefit from full cardiac contouring.

In several radiotherapy centres, cardiac dose assessment is currently carried out using the mid-plane slice. This study showed that, if the heart was included in the radiation fields, the mid-plane slice was usually distant from the slice showing the greatest area of heart irradiated and did not provide a reliable assessment of cardiac dose (Fig. 7). A similar finding was reported in the START radiotherapy trial quality assurance program [14] which assessed cardiac irradiation in 62 patients who received left-tangential radiotherapy. Two CT slices were obtained for each patient: one at the level of the maximum heart distance and one at the mid-plane. For >80% of patients, the mid-plane slice did not show the maximum area of heart irradiated, and for >50% of patients, it was  $\geq 2$  cm away from the slice showing the maximum area of heart irradiated. As in our study, the maximum heart distance slice was usually inferior to the mid-plane.

## **Conclusions**

Until resources for routine 3D CT cardiac dose assessment are available for breast cancer patients in all radiotherapy centres, 2D assessment can be used as an interim measure. For 50 patients treated with left-tangential irradiation, MHD was a good predictor of mean heart dose and BED and gave an approximate indication of dose and BED to the LAD coronary artery. In contrast, assessment of the mid-plane CT slice alone did not give an accurate indication of heart dose. The relationships between MHD and cardiac doses described here are currently being used to guide left-tangential radiotherapy planning in one large UK radiotherapy centre and may

also be useful in other centres where 3D cardiac dose assessment in breast cancer radiotherapy is not yet routinely available.

## **Acknowledgements**

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## **7. Discussion**

Breast cancer is the most common cancer in women with around a million new cases worldwide per year [1]. Early detection and improvements in local and systemic treatments have improved survival and in England and Wales, around 70% of women now survive for more than 10 years, and 60% survive for more than 20 years following breast cancer diagnosis [1]. Consequently, the harmful long-term effects of treatment are becoming increasingly important.

International treatment guidelines currently recommend the use of radiotherapy after breast conserving surgery for all women and after mastectomy for many women [2,3]. Around 20,000 such women are irradiated each year in the UK alone. Breast cancer radiotherapy has several late side-effects including lymphoedema, radiation-induced cancer and radiation-pneumonitis. The late effect that has caused the highest number of deaths in women irradiated for breast cancer is radiation-induced heart disease [4, see Appendix A2 of this thesis].

The general aim of this thesis was to enable assessment of the risk of radiation-induced heart disease for current and future breast cancer patients. This has been done, firstly by providing the dosimetry base for two epidemiological studies which aim to characterise dose-response relationships for heart disease [5,6], secondly by measuring cardiac doses received by contemporary breast cancer patients and thirdly by validating a simple method for measuring cardiac doses in radiotherapy centres where routine individual CT-based cardiac dose assessment is currently not possible.

**Chapters 1 and 2** summarise the relevant literature on radiation-induced heart disease. The risk of heart disease after radiotherapy has been demonstrated in several populations of women in randomised trials and observational studies. The main risk appears to occur at least 10 years after irradiation [7]. Therefore it will be

at least a decade before the risks of today's radiotherapy can be observed directly. The cardiac risks of current and future breast cancer radiotherapy can, however, be estimated using dose-response relationships, which require cardiac dosimetry of past regimens given to women for whom we have long-term follow-up. Previous dose-response relationships for radiation-induced heart disease are based on sparse clinical data. Gagliardi [8] was based on long-term cardiac mortality in two randomised trials of radiotherapy versus no radiotherapy in which deaths from ischaemic heart disease were reported in irradiated and unirradiated patients by breast cancer laterality; it included less than 20 excess deaths from ischaemic heart disease. Rutqvist [9] was based on one of the two trials analysed by Gagliardi [8], and included less than 10 excess deaths from ischaemic heart disease. Das [10] and Marks [11] assessed the incidence of myocardial perfusion defects in around 70 women who received different heart doses from left-tangential radiotherapy. Further clinical and dosimetric data are needed to provide reliable dose-response relationships, which will precisely assess the risks of current and future radiotherapy regimens.

A methodology for the estimation of detailed cardiac doses was developed and presented in **Chapter 3**. Virtual simulation, CT planning and manual planning were used to estimate doses to the heart, and to the left anterior descending (LAD), right and circumflex coronary arteries for common radiotherapy regimens used worldwide between the 1950s and the 1990s. Heart doses from these regimens varied from <1 Gy to 17 Gy and coronary artery doses varied from <1 Gy to 51 Gy. Sources of variability in heart dose, which inevitably occur in the retrospective reconstruction of radiotherapy regimens, were quantified. The major source of error

in the estimation of heart dose for a given individual was found to be variation in patient anatomy.

The cardiac doses in this study were combined with information on the subsequent risk of heart disease in around 40,000 women irradiated in 71 trials of radiotherapy in a recent update of the EBCTCG (Early Breast Cancer Trialists' Collaborative Group) overview [12]. The ratio of heart disease deaths in irradiated versus unirradiated patients increased according to mean cardiac radiation dose, and there was a significant association between mean heart dose and risk of death from heart disease. The risk of death from heart disease was 30% per 10 Gy mean dose to the heart [12].

The numbers of women in the EBCTCG data are insufficient to characterise the cardiac risk precisely, or to monitor whether risk is lower for patients treated more recently. Moreover, the trials were not designed to study heart disease, so detailed information on the radiotherapy used or the type of heart disease are not usually available. A further limitation is that women who were already unwell (including those with heart disease) were often excluded from the trials, so these data may under-estimate the absolute heart disease risk in the general population of breast cancer patients. Additional information on the risk of radiation-induced heart disease in non-randomised populations, e.g. women identified through cancer registries, is therefore needed.

Such additional information will be provided in a case-control study of women identified using the Swedish and Danish cancer registries [6]. In data from populations where the women receiving radiation have not been selected at random, comparison of disease rates in irradiated and unirradiated women may well give misleading answers [13]. However, regimens used to treat left-sided cancers

usually deliver a higher cardiac radiation dose than those used to treat right-sided cancers. Therefore, unbiased dose-response relationships could be derived by comparing the subsequent cardiac morbidity and mortality of irradiated women with left-sided and right-sided breast cancer, in conjunction with quantitative estimates of the cardiac dose. The Scandinavian case-control study is nested within a cohort study of 50,000 Scandinavian women irradiated for breast cancer and will include around 1500 women who developed or died from heart disease after breast cancer radiotherapy and a similar number of irradiated controls who did not develop heart disease. Detailed information is available on each woman's medical history prior to breast cancer irradiation, on her cardiac outcome, and on the radiotherapy she received. The study should enable precise characterisation of the dose-response relationships for radiation-induced heart disease. It will also examine the possible modifying effect on cardiac risk of factors such as smoking, obesity, pre-existing disease and chemotherapy.

**Chapter 4** forms the dosimetry base for the Swedish part of the case-control study. The methods developed in chapter 3 were used to estimate doses to the heart and to each of the three coronary arteries for radiotherapy regimens used in individual women (cases and controls) irradiated in Sweden. There was a wide range of doses of between <1 Gy and 24 Gy heart dose for women irradiated in Sweden since the 1950s. Cardiac doses varied according to decade of irradiation. Doses rose between the 1950s and the 1970s, and fell again in the 1980s and 1990s. This is consistent with the existing epidemiological data from Sweden [7], which suggests that the risk of death from heart disease was highest for women irradiated in the 1970s, and reduced for women irradiated more recently.

Breast cancer radiotherapy has changed over the past four decades. Internal mammary irradiation, which tends to deliver the highest heart doses, is less frequently performed [14,15] and radiotherapy techniques have changed from orthovoltage to megavoltage [16]. Estimation of the cardiac risk of today's radiotherapy involves combining dose estimates for today's patients with dose-response relationships for radiation-induced heart disease. **Chapter 5** used CT planning to estimate dose to the heart and coronary arteries for patients irradiated in a major radiotherapy centre in the UK in the year 2006. The study showed that cardiac doses from left- and right-tangential irradiation have reduced substantially since the 1970s. For example, left-tangential irradiation delivered around 13 Gy mean heart dose in the 1970s, and around 2 Gy in 2006, thus the risks from breast cancer radiotherapy are likely to have reduced. Nevertheless, these doses are higher than those shown to increase cardiac mortality in other populations [17,18]. Therefore there may still be some risk.

Chapter 5 also revealed that there was little patient-to-patient variability in these doses from right-tangential irradiation, but there was considerable variability from left-tangential irradiation. Mean doses for the 50 patients treated with left-tangential radiotherapy ranged from 1.4 to 4.4 Gy for the heart (standard deviation (SD) 0.7) and from 2.4 to 21.2 Gy for the LAD coronary artery (SD 4.5). In view of this variability, individual patient cardiac dose assessment is needed to identify patients who would receive high cardiac doses from standard left-tangential irradiation, for whom complex planning techniques such as intensity modulated radiotherapy may be desirable. CT planning with cardiac contouring is able to accurately assess cardiac doses, thus enabling calculation of cardiac risk for individual patients using dose-response relationships. In some radiotherapy centres,

this is routinely available for all breast cancer patients, but in many centres, it is not. Thus, the need for a practical method of estimating cardiac dose from left-tangential radiotherapy using 2D information was identified.

**Chapter 6** assessed a method of estimating mean dose and biologically effective dose (BED) to the heart and to the LAD coronary artery from left-tangential radiotherapy using the maximum heart distance (the maximum distance between the anterior cardiac contour and the posterior tangential field edges). This 2D information can be easily measured on the beam's eye view of a virtual simulator or on a conventional simulation film. The maximum heart distance was found to be a good predictor of mean heart dose and BED and gave an approximate indication of dose and BED to the LAD coronary artery for left-tangential patients whose heart was included in the fields. The use of this measure should enable clinicians in centres without the resources for routine CT-planning to estimate individual patient cardiac doses from left-tangential radiotherapy, and therefore to use dose-response relationships to estimate the risk of radiation-induced heart disease in these women.

The above dosimetry studies (Chapters 3-6) showed that both recent and historical breast cancer radiotherapy regimens tended to deliver the highest doses to the anterior part of the heart, including the LAD coronary artery. Indeed, tangential irradiation, which is commonly used today, delivers more than 20 Gy to around 13% of the volume of the artery. The LAD coronary artery is a common site of myocardial infarction, hence radiation-induced damage to this artery might well have contributed to the excess of radiation-induced heart disease seen after previous radiotherapy regimens. Indeed prospective myocardial perfusion imaging studies suggest that damage to the LAD coronary artery still occurs for 1990s radiotherapy

regimens [19,20]. It is unclear whether this damage leads to any clinical consequences or to the excess risk of death from heart disease seen in epidemiological studies.

### **Clinical implications**

There is a pressing need amongst clinical oncologists for more information concerning the cardiac risks of radiotherapy. An increasing number of women with breast cancer are likely to survive their cancer; therefore the long-term risks of radiotherapy are very relevant to them. Decisions relating to the selection of patients for radiotherapy and to the possible need for further improvements in breast radiotherapy planning involve balancing the risks and benefits of irradiation. Dose-response relationships should enable the quantification of cardiac risk of specific regimens which would be relevant to the development of treatment guidelines. It would also be relevant to decisions regarding individual patients in the clinic and would enable identification of patients for whom the increased cost of advanced radiotherapy techniques is justified. Furthermore, cardiac dose-response relationships should be relevant to patients who receive involved field thoracic radiotherapy for lymphoma, which delivers more than 10 Gy dose to the heart in some patients [21]. Quantification of the cardiac risks of lymphoma radiotherapy would have implications for lymphoma radiotherapy treatment planning and for cardiology follow-up of such patients irradiated in previous decades.

This thesis presents cardiac dose estimates from a wide range of international radiotherapy techniques used in the EBCTCG trials. These have been combined with cause of death information to develop the first dose-response relationship for radiation-induced heart disease based on substantial data [12]. This

relationship can be used to estimate the approximate relative risk of radiation-induced heart disease per unit heart dose for patients irradiated in the clinic today.

There are, however, several limitations to the EBCTCG dose-response relationship. The Scandinavian case-control study includes detailed clinical and dosimetric information and should provide more reliable dose-response relationships. Abstraction of information from the oncology notes of cases and controls is underway in both Sweden and Denmark. The radiotherapy regimens for the Swedish part of the study have been reconstructed (see Chapter 4) and dosimetry for the Danish part is underway. Consideration is being given to expanding the study to other countries. The study should generate reliable dose-response relationships which will enable accurate assessment of the risks of radiation-induced heart disease for current and future radiotherapy regimens. Such knowledge should facilitate radiotherapy treatment planning and enable a reduction in cardiac risk, while maintaining the known benefit in terms of breast cancer mortality.

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## **8. Conclusions**

1. Around 40,000 women irradiated in 71 randomised trials of radiotherapy in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview received more than forty radiotherapy regimens resulting in a wide range of cardiac doses. Mean heart dose varied from <1 Gy to 18 Gy and mean coronary artery doses varied from <1 Gy to 57 Gy.
2. Provisional analyses of the EBCTCG data show that the higher the radiation dose received by the heart, the greater the risk of death from heart disease. The increase in risk of death from heart disease was 30% per 10 Gy mean heart dose.
3. More than thirty breast cancer regimens have been used in Sweden since the 1950s, resulting in a wide range of cardiac doses from <1 Gy to 24 Gy for the heart and from <1 Gy to 46 Gy for the LAD coronary artery. These doses, along with information on cardiac outcome, should provide substantial statistical power for the estimation of dose-response relationships for radiation-induced heart disease in the case-control study.
4. Heart dose from both left- and right-tangential breast cancer irradiation has reduced over the past four decades. Mean heart dose from left-tangential irradiation reduced from about 13 Gy in the 1970s to 2 Gy in 2006. However, around half of left-sided patients irradiated in 2006 still received over 20 Gy to part of the heart. The LAD coronary artery, which is a common site of myocardial infarction, received around 8 Gy mean dose. These doses may well increase the risk of heart disease.
5. Maximum heart distance was a reliable predictor of mean heart dose and biologically effective heart dose from left-tangential radiotherapy. It may be used to help predict cardiac doses for individual patients.