Breast Cancer Radiotherapy:
Exposure of the Heart and Lungs

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For John, James, Clara & Peter

Abstract

Breast cancer radiotherapy can cause heart disease and lung cancer, with the risks increasing with the incidental radiation dose to the heart or lungs. To derive appropriate strategies for limiting the risks to future patients, detailed estimates of the radiation doses involved are required.

Radiation-induced heart disease

An atlas for cardiac substructure (segment) contouring on radiotherapy planning scans was developed. The atlas was used to estimate segment doses for 470 women irradiated in Denmark or Sweden during 1958-2001 who had developed ischaemic heart disease with known segment location of cardiac injury, thus enabling an assessment as to which segments are sensitive to radiation.

Cardiac radiation doses were estimated for 771 women irradiated in the Netherlands during 1970 to 2009. The doses form the basis of three case-control studies characterising the relationship between cardiac dose and the risks of subsequent ischaemic heart disease, valvular heart disease and heart failure in young women (median age 50 years).

Radiation-induced lung cancer

Lung doses were estimated for ~40,000 women irradiated for breast cancer in 75 randomised trials. The doses were used to estimate the dose-response relationship for incident lung cancer. A systematic review of modern breast cancer regimens published worldwide during 2010-2015 was also performed. The modern typical doses found in these studies were combined with the estimated dose-response relationship to estimate absolute risks of lung cancer for women irradiated today.

Irradiation of the internal mammary chain

It has been recently shown that internal mammary chain irradiation improves survival but irradiating this region can expose the heart and lungs to several Gy radiation dose. To inform resource allocation, the percentage of women in one cancer centre who met current international criteria for IMC radiotherapy was investigated. Information on cardiovascular risk factors was also collected.

Finally, a phase II clinical trial proposal was developed aiming to investigate if proton beam therapy reduces acute cardiac injury compared to modern X-ray treatment.

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Contents

1 Introduction 19
1.1 Background 21
1.2 Radiation-induced heart disease 22
1.2.1 History 22
1.2.2 Dose constraints for the heart 25
1.2.3 Mechanism of injury 27
1.2.4 Imaging Studies 30
1.3 Radiation-induced lung cancer 32
1.4 Motivation for this thesis 34
1.4.1 Exposure of the heart and lungs is still an issue 34
1.4.2 Need for dose response relationships 35
1.4.3 Challenges 36
1.4.4 Lessons from the past are important for the future 37
1.5 Aims 38
1.6 References 41

2 A Cardiac contouring atlas for radiotherapy 51
2.1 Abstract 53
2.2 Introduction 55
2.3 Material and methods 56
2.3.1 Atlas development 56
2.3.2 Atlas description 60
2.3.3 Atlas evaluation 68
2.4 Results 69
2.5 Discussion 73
2.6 References 78

3 Cardiac structure doses in women irradiated for breast cancer in the past and their use in epidemiological studies 81
3.1 Abstract 83
3.2 Introduction 85
3.3 Methods and Materials 89
3.3.1 Regimens 89
3.3.2 Contouring 89
3.3.3 Selection of the “typical CT-scan” 94
3.3.4 Reconstruction and dose calculation 94
3.3.5 Inter-patient dose variation 96
3.4 Results 97
3.4.1 Tangential regimens 97
3.4.2 Anterior electron or orthovoltage regimens 104
3.4.3 Anterior megavoltage regimens 105
3.4.4 Cobalt chain regimens 105
3.4.5 Inter-patient variation 105
3.4.6 Correlations between cardiac segments 112
3.5 Discussion 112
3.6 References 118

4 Exposure of the heart, left ventricle and cardiac valves from breast cancer regimens used in the Netherlands 1970-2009. 123
4.1 Abstract 125
4.2 Introduction 127
4.3 Methods and materials 128
4.3.1 Regimens 128
4.3.2 Selection of a 'typical CT-dataset' 128
4.3.3 Contouring 129
4.3.4 Reconstruction and dose calculation 130
4.3.5 Estimation of cardiac doses 131
4.4 Results 138
4.4.1 Tangential fields 138
4.4.2 Megavoltage and mixed megavoltage/electron IMC fields 140
4.4.3 Orthovoltage or mixed orthovoltage/megavoltage IMC fields 142
4.4.4 Electron chest wall or IMC fields 143
4.4.5 Trends over time 144
4.4.6 Correlations between LV and whole heart doses 148
4.5 Discussion 148
4.6 References 152

5 Radiation dose-response for risk of myocardial infarction in breast cancer survivors 157
5.1 Abstract 159
5.2 Introduction 161
5.3 Methods 162
5.3.1 Cohort population 162
5.3.2 Case–control study 162
5.3.3 Data collection 163
5.3.4 Radiotherapy dosimetry 164
5.3.5 Statistical analyses 164
5.4 Results 167
5.4.1 Patient characteristics 167
5.4.2 Treatment-related risk factors 168
5.4.3 Cardiovascular risk factors 171
5.4.4 Radiation dose-response relationship 172
5.4.5 Whole heart dose-volume parameters 173
5.5 Discussion 177
5.6 Conclusion 180
5.7 References 181

6 Exposure of the lungs in breast cancer radiotherapy: a systematic review of lung doses published 2010-2015 185
6.1 Abstract 187
6.2 Introduction 189
6.3 Methods 190
6.3.1 Study identification 190
6.3.2 Data abstraction 194
6.3.3 Data analyses 194
6.4 Results 196

6.4.1 Tangential regimens 198
6.4.2 Regions irradiated 198
6.4.3 Technique and treatment position 201
6.4.4 Breathing adaptation 203
6.4.5 Other measures of lung dose 206
6.4.6 Dose calculation algorithm 210
6.5 Discussion 210
6.5.1 Methods to reduce lung exposure 210
6.5.2 Strengths and limitations 211
6.5.3 Absolute benefits and risks 212
6.6 Conclusions 213
6.7 References 214

7 International variation in criteria for internal mammary chain radiotherapy. 219
7.1 Abstract 221
7.2 Introduction 223
7.3 Methods 225
7.3.1 Internal mammary chain radiotherapy guidelines 225
7.3.2 Internal mammary chain clinical studies 226
7.3.3 Patients included, variables and information sources 226
7.3.4 Patient categorisation 229
7.4 Results 230
7.4.1 Internal mammary chain radiotherapy guidelines 230
7.4.2 Internal mammary chain clinical studies 230
7.4.3 Patients in UK centre 234
7.4.4 Percentage of patients meeting different IMC radiotherapy criteria 234
7.4.5 Cardiovascular risk factors in a single UK center 239
7.5 Discussion 239
7.6 Conclusions 242
7.7 References 243

8 Trial Concept: Protons for internal mammary chain irradiation 247
8.1 Rationale for a clinical trial 250
8.1.1 Proton beam therapy is coming soon to the UK 250
8.1.2 Cardiac radiation exposure may increase with IMC radiotherapy . 252
8.1.3 Clinical studies of proton beam therapy 254
8.1.4 Biomarkers for cardiac injury 255
8.2 Methods/Design 258
8.2.1 Interventions 259
8.2.2 Outcomes 261
8.2.3 Monitoring 261
8.2.4 Sample size considerations 263
8.3 Peer review 265
8.3.1 The need for a randomised study 267
8.3.2 Planning study and predictive modelling versus clinical study 268
8.3.3 The value of a feasibility study 268

8.3.4 Acute skin toxicity as a primary endpoint....269
8.3.5 Patient selection: risk factors versus complicated anatomy....269
8.3.6 CMR versus validated imaging tools....270
8.4 Where are we now?....270
8.5 References....272

9 General Summary and Clinical Implications....277
9.1 General Summary and Clinical Implications....279
9.2 Future research plans relating to studies in the thesis....290
9.3 References....292

10 Appendices....295

Appendices

Appendix A. Supplementary material to Chapter 2....A1
Appendix B. Supplementary material to Chapter 3....A7
Appendix C. Supplementary material to Chapter 4....A13
Appendix D. Supplementary material to Chapter 5....A19
Appendix E. Authored publications cited within thesis....A25

Figures

Figure 1-1. Ischaemic heart disease after breast cancer radiotherapy....26
Figure 1-2. Pathophysiological manifestations of radiation-induced heart disease for different radiosensitive structures within the heart....28

Figure 2-1. Diagram of 17-segment myocardial segmentation model....57
Figure 2-2. Identifying the atrioventricular and interventricular grooves....61
Figure 2-3. Axial radiotherapy CT planning image at the level of the left ventricle inferiorly showing contouring of the coronary arterial and left ventricular myocardial segments....63
Figure 2-4. Axial radiotherapy CT planning images showing contouring of the coronary arterial and left ventricular myocardial segments (slice thickness 3mm)....65
Figure 2-5. Coronary artery segmentation....67
Figure 2-6. Cardiac substructure contours by 6 observers on one CT-planning scan at the level of the left ventricle superiorly (a) and inferiorly (b)....71

Figure 3-1. Radiotherapy fields used to treat women with breast cancer in Sweden (1958 -2001) or Denmark (1978-2000)....87

Figure 3-2. Radiotherapy regimens used to treat women with breast cancer in Sweden (1958-2001) or Denmark (1978-2000). 88
Figure 3-3. Spatial distribution of cardiac dose from breast cancer tangential and direct electron radiotherapy regimens used to treat women with breast cancer in Sweden (1958 -2001) or Denmark (1978-2000). 99
Figure 3-4. Patient to patient variability in mean radiation dose to the whole heart and the left ventricular and coronary arterial segments in women receiving tangential or anterior electron regimens for breast cancer in Sweden (1958-2001) or Denmark (1978-2000)..... 107
Figure 3-5. D2cc (%) hotspot doses to the ventricular myocardium (right and left ventricles combined) in women receiving tangential or anterior electron regimens for breast cancer in Sweden (1958-2001) or Denmark (1978-2000)..... 108
Figure 3-6. D0.5cc (%) hotspot doses to the main coronary arteries (LMCA, LADCA, RCA and Cx combined) in women receiving tangential or anterior electron regimens for breast cancer in Sweden (1958-2001) or Denmark (1978-2000)..... 109
Figure 3-7. Correlations between mean radiation doses to the whole heart and different cardiac segments for women receiving tangential or anterior electron regimens for breast cancer in Sweden (1958-2001) or Denmark (1978-2000). 113

Figure 4-1. Radiotherapy fields used to treat women with breast cancer at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009. 132
Figure 4-2**.** Spatial distribution of radiation dose to the heart from typical left-breast cancer regimens used to target the breast or chest wall and IMC at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009. 141
Figure 4-3. Spatial distribution of radiation dose to the heart from a right-breast cancer regimen used to target the chest wall and IMC at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during the 1990s. 142
Figure 4-4. Whole heart radiation doses according to decade for women who underwent radiotherapy for breast cancer at the Netherlands cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009. 146
Figure 4-5. Correlations between whole heart and left ventricle mean radiation doses for women who underwent radiotherapy for breast cancer at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970- 2009, by laterality and IMC irradiation. 147

Figure 5-1. Survival after myocardial infarction diagnosis. Calculated using the Kaplan-Meier method..... 167
Figure 5-2. Modelled cumulative myocardial infarction rate for cases by categories of mean whole heart dose 171
Figure 5-3. Dose-response relationship between rate of myocardial infarction and mean whole heart dose (MWHD)..... 174

Figure 6-1. The process of study identification for the review 195
Figure 6-2. Mean ipsilateral lung dose (MLD_{ipsi}) from left or right tangential breast cancer radiotherapy according to country, gross national income per person in the country concerned, calendar year, and whether the radiotherapy plans were actually delivered or just planned. 199
Figure 6-3. Mean ipsilateral lung dose (MLD_{ipsi}) from left or right breast cancer radiotherapy according to regions irradiated. 200
Figure 6-4.Mean ipsilateral lung dose (MLD_{ipsi}) from left or right breast cancer radiotherapy according to regions irradiated and technique used. 202
Figure 6-5 Mean ipsilateral lung doses (MLD_{ipsi}) from left or right breast cancer radiotherapy with or without breathing adaptation according to regions irradiated and regimens used. 204
Figure 6-6. Percent volume of ipsilateral lung receiving 20 Gy or more (V20ipsi) from breast cancer radiation therapy according to region irradiated and technique used. 205
Figure 6-7. Percent volume of ipsilateral lung receiving 5 Gy or more (V5ipsi) from breast cancer radiation therapy according to regions irradiated and technique used. 207
Figure 6-8. Mean contralateral lung doses (MLD_{cont}) from breast cancer radiotherapy according to region irradiated and technique used. 208
Figure 6-9. Mean whole lung doses (MLD_{whole}) from breast cancer radiotherapy according to region irradiated and technique used. 209

Figure 7-1. Composition of study population with exclusion criteria 227
Figure 7-2 Flowchart for the selected clinical practice guidelines 233

Figure 8-1 Spread out Bragg Peak 251
Figure 8-2.T1-maps detected the location and extent of myocardial injury in acute myocarditis. 257
Figure 8-3. ProIMC Trial Design 262

Tables

Table 2-1. Left ventricular myocardial segmentation: use of traditional 17-segment model to derive five segments for the cardiac contouring atlas. 58
Table 2-2. Definition of the ten atlas coronary artery segments 59
Table 2-3. Variation in spatial measurements and doses from left breast cancer regimens for cardiac segments contoured by six observers on one CT-planning dataset. 70
Table 2-4. Variation in doses from right breast cancer regimens for cardiac segments contoured by six observers on one CT-planning scan. 72

Table 3-1. Radiotherapy regimens received by 470 women with breast cancer in Sweden (1958-2001) or Denmark (1978-2000) 90
Table 3-2. 'Typical CT dataset' selection 95

Table 3-3. Mean radiation therapy doses to myocardial structures from left-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000). 100
Table 3-4. Mean radiation therapy doses to coronary arterial structures from left-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000). 101
Table 3-5. Mean radiation therapy doses to myocardial structures from right-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000). 102
Table 3-6. Mean radiation therapy doses to coronary arterial structures from right-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000). 103
Table 3-7. Cardiac segments ordered according to dose received from left breast cancer radiotherapy regimens, comparison of order in typical CT scan with order in nine other scans. 110
Table 3-8. Cardiac segments ordered according to dose received from right breast cancer radiotherapy regimens, comparison of order in typical CT scan with order in four other scans. 111
Table 3-9. Comparison of doses in this study with previously published estimates for comparable regimens used in Sweden (1958-2001) or Denmark (1978-2000). 117

Table 4-1. Radiotherapy regimens and dose-fractionation schedules for 754 women with breast cancer at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009. 133
Table 4-2**.** Mean radiation doses to cardiac structures from breast cancer regimens used at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009. 139
Table 4-3**.** Whole heart and left ventricle radiation doses according to decade for 771 women selected as cases and controls for case-control studies of heart disease after treatment for breast cancer who underwent radiotherapy at the Netherlands Cancer Institute or the Erasmus MC Centre in the Netherlands during 1970-2009.* 145
Table 4-4. Comparison of doses per decade in this study with previously published doses per decade in the Netherlands during 1970-1986. 151

Table 5-1. Characteristics of myocardial infarction cases and matched controls. 166
Table 5-2. Associations between treatment characteristics and rate of myocardial infarction 169
Table 5-3. Mean and median mean whole heart dose, V5 and V25 by prescribed radiation field for all irradiated women (cases and controls). 169
Table 5-4. Associations between mean whole heart dose and rate of myocardial infarction, including adjusted rate ratios. 170
Table 5-5. Associations between mean whole heart dose and rate of myocardial infarction risk in irradiated cases and irradiated controls 170

Table 5-6. Associations between mean left ventricle dose and rate of myocardial infarction.....170
Table 5-7 Associations between patient-related risk factors and rate of myocardial infarction 172
Table 5-8. Excess rate ratios of myocardial infarction per Gray mean whole heart dose for subgroups.....175
Table 5-9. Associations between percentage of heart volume receiving ≥ 5-40 Gy and rate of myocardial infarction. 176

Table 6-1.Definitions of radiotherapy planning and delivery used in review 191
Table 6-2. Grouping of sub-categories used to create the types of "radiotherapy technique" shown in figures 3, 4 and 5.....193
Table 6-3. Studies reporting lung doses from breast cancer radiation therapy regimens and published during 2010 to 2015. 197

Table 7-1. List of electronic databases and websites searched for eligible guidelines*.....226
Table 7-2. Information sources used to abstract variables 228
Table 7-3. Patients irradiated for breast cancer in a UK centre fulfilling criteria for IMC radiotherapy in different countries.....231
Table 7-4. Patients irradiated for breast cancer in a UK centre fulfilling eligibility criteria for clinical studies of internal mammary chain radiotherapy. 232
Table 7-5. Patient and tumour variables among 305patients irradiated for invasive breast cancer in a UK centre during July-December 2014. 235
Table 7-6. Prevalence of cardiovascular risk factors among 155 women irradiated for breast cancer in a UK centre compared to women in the general UK population.....238

Table 8-1. Inclusion/Exclusion criteria 259
Table 8-2. Blood and cardiac magnetic resonance biomarkers for different mechanisms of cardiac injury 260
Table 8-3. Peer review of a clinical trial proposal of proton beam therapy for IMC irradiation in the U.K.....266

1 Introduction

1.1 Background

Breast cancer is the most prevalent cancer in most countries worldwide[1]. It is estimated that more than 1.68 million women were diagnosed with breast cancer in 2012[2]. There are now around 55,000 new cases every year in the U.K. and it is estimated that one in eight women will be diagnosed during their lifetime. Incidence rates have increased by 4% over the last decade but breast cancer mortality rates have decreased by 17%. Women diagnosed with breast cancer are surviving longer. Patients are presenting earlier or through screening programmes with more localised lesions. Cancer treatments are becoming more effective and life expectancy in the general population is improving. Around two-thirds of women are now surviving for twenty years or more. Considering the numbers of women affected by this disease and how many are surviving long-term it is becoming increasingly important to consider the late effects of treatment.

In the developed world the treatment for breast cancer is individualised for each woman diagnosed. Patient and tumour factors are considered before a multidisciplinary team approves a tailored treatment plan. For each treatment modality the benefits are weighed against the risks. The majority of patients are offered surgery to remove their primary macroscopic disease. Adjuvant treatments aiming to sterilise potential microscopic disease may also be offered. This may involve systemic treatment, which may include endocrine therapy, chemotherapy and targeted therapies such as anti-Her2 treatments. The majority of women diagnosed with early breast cancer are offered adjuvant radiotherapy[3].

This reduces breast cancer mortality after breast conserving surgery for women with node negative disease (rate ratio (RR) 0.83 (95% CI 0.73-0.95) and for women with node positive disease (RR 0.79 (95% CI 0.65-0.95). It also reduces breast cancer mortality for women after mastectomy with node positive disease (1-3 nodes: RR 0.80 (95% CI 0.67-0.95), > 3 nodes: RR 0.87 (95% CI 0.77-0.99))[4-5,AppendixE1]. The benefits of radiotherapy need to be balanced against the risks. It is known to increase the risks of heart disease and lung cancer, either of which may be fatal[6,7,Appendix E2]. To inform radiotherapy treatment decisions it is helpful to estimate the future absolute risks of radiation-induced heart disease and radiation-induced lung cancer for each woman irradiated. This requires measurement of their cardiac and lung doses and dose-response relationships. For those women predicted to be at high risk of developing late effects it is then important to consider ways in which these risks can be mitigated.

1.2 Radiation-induced heart disease

1.2.1 History

Radiotherapy may increase the risk of a broad spectrum of cardiac disease including ischaemic heart disease (IHD), heart failure, valvular heart disease (VHD), pericardial disease and conduction system abnormalities[8]. Before the 1950s, when low energy radiotherapy beams were used the heart was thought to be resistant to radiation[9]. Then in the 1950s megavoltage beams which penetrate deep into the body, were introduced which increased cardiac exposure and clinical cardiac effects[10]. In the 1960s and 1970s evidence emerged, mostly from studies of Hodgkin lymphoma survivors, but also from studies of breast cancer survivors, that radiotherapy may cause pericarditis or ischaemic heart disease

(IHD)[11,12]. Much more evidence came to light in the 1990s and 2000s that radiotherapy for breast cancer increases the risk of cardiac mortality. Two individual patient data meta-analyses found that breast cancer radiotherapy increased the risk of non-breast cancer death[13,14]. In 2005, a further meta-analysis by the Early Breast Cancer Trialists Collaborative Group, including individual patient data from 42,000 women in 78 randomised trials, reported an excess of non-breast-cancer deaths (RR (SE) 1.12 (0.04)) after breast cancer radiotherapy which was primarily attributable to excess cardiac deaths (RR (SE) 1.27 (0.07)) and lung cancer (RR(SE) 1.78 (0.22))[6].

Evidence for radiation-induced heart disease has also emerged from non-randomised studies. The heart is exposed to higher doses of radiation in left-sided breast radiotherapy than in right-sided breast radiotherapy[15]. In a number of observational studies excess cardiac *mortality* was observed in patients who received left-sided radiotherapy compared to right (RR 1.06-2.1)[16-24]. Variation in risk may have been due to differences in the populations studied, the radiotherapy regimens used or other cardiotoxic treatments used. The risk of radiation-related cardiac death increased according to time since diagnosis and decreased according to treatment era[19,21,23].

Excesses of *incident* heart disease have also been seen in studies of patients who received left-sided radiotherapy compared to right with most of the radiation-related risk due to IHD. In a large cohort study of 35,000 women in Denmark and Sweden who received breast cancer radiotherapy and were followed to 2006, the left-versus-right incidence ratio for IHD was 1.18 (95% CI 1.07-1.30, p=0.001)[24].

In another study of 961 women a higher rate of chest pain, coronary artery disease and myocardial infarction was reported for women who received left-sided radiotherapy versus right-sided radiotherapy ($p \leq 0.002$)[25]. There is some evidence that the left-versus-right heart disease risk is higher for women who also receive anthracycline-based chemotherapy[26].

While there is good evidence that breast cancer radiotherapy can cause IHD, evidence that it can cause heart failure is conflicting. Radiotherapy is known to cause impaired myocardial function in Hodgkin lymphoma survivors[27]. A study by van Nimwegen et al derived quantitative estimates of heart failure risk in Hodgkin lymphoma survivors following radiotherapy with or without anthracyclines[28]. For breast cancer survivors, however, only a few studies have shown an increased risk of heart failure after radiotherapy,[7,29,,Appendix E5]. Other studies show no increased risk[24,25].

Similarly valvular heart disease has been well studied in Hodgkin lymphoma survivors[30,31] but not in breast cancer. Radiation exposure of the cardiac valves has been shown to increase the risk of VHD, especially at doses above 30 Gy[32]. In breast cancer one cohort study reported the left-versus-right ratio of valvular heart disease in 35,000 women irradiated during 1976-2006 was 1.54 (95% CI 1.11 to 2.13)[24]. This study also reported an increased incidence of pericarditis after breast cancer radiotherapy for left versus right-sided irradiation (RR 1.61 (95% CI 1.06-2.43)).

1.2.2 Dose constraints for the heart

Knowledge of radiation tolerance of the cardiac structures may help oncologists to maximise the therapeutic dose to the target regions while minimising the risk of radiation-induced heart disease. In 1991, the “Emami paper” provided a review of the literature addressing normal tissue tolerance. For radiation-induced heart disease the review reported that myocardial ischaemia may occur but pericarditis was chosen as the only end-point due to its prevalence and clinical importance at the time[33]. It stated that the 5 year risk of pericarditis was 5% if either the entire heart was irradiated to 40 Gray or if two-thirds was irradiated to 45 Gy or if one third was irradiated to 60 Gy. Twenty years after the "Emami paper", in 2010, an updated review of the literature addressing normal tissue tolerance was published by “The Quantitative Analysis of Normal Tissue Effects in the Clinic” (QUANTEC)[34]. This report described three clinical endpoints for radiation-induced heart disease: pericarditis, cardiac mortality from IHD and decreased myocardial perfusion. QUANTEC reported the risk of pericardial effusion was 13% with a $V30Gy_{pericardium}$ <46% (or mean pericardial dose <26 Gy). These constraints were derived from a study of pericarditis in patients irradiated for oesophageal cancer[35]. For cardiac mortality a V25Gy heart <10% (in 2 Gy per fraction) was predicted to be associated with a < 1% risk 15 years after radiotherapy. This estimate comes from a dose-response curve derived based on 17 excess deaths from myocardial infarction in patients who underwent radiotherapy in two randomised trials[36,37]. These trials were carried out in the late 1960s and 1970s. Data were used to model cardiac risks using the relative seriality normal tissue complication probability model[38,39].

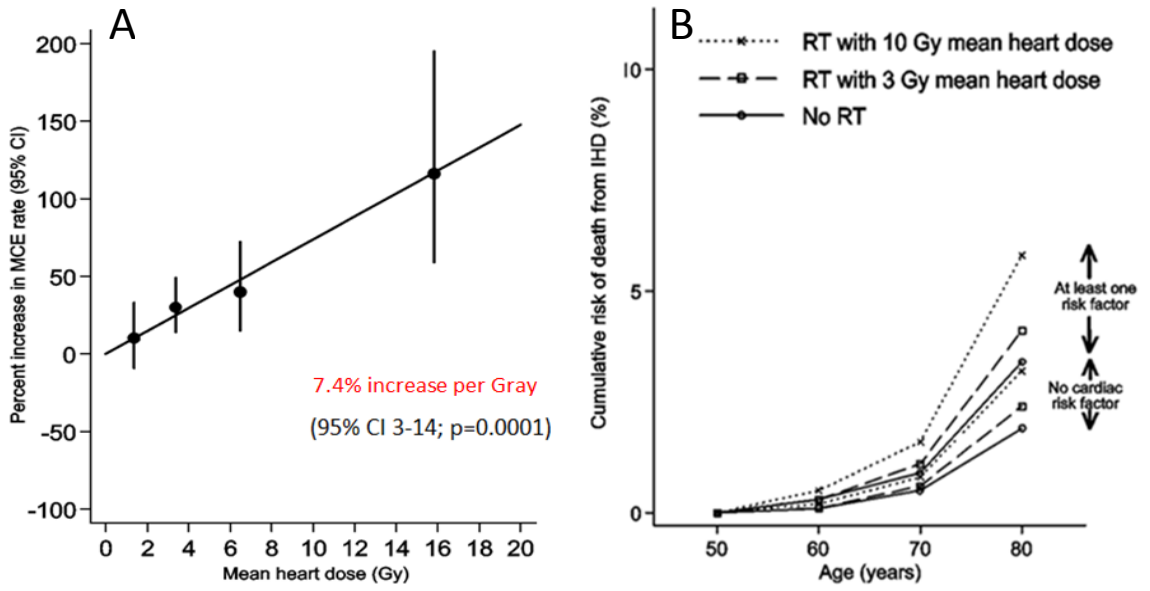


Figure 1-1. Ischaemic heart disease after breast cancer radiotherapy.

A. Rate of major coronary events according to mean radiation dose to the heart, as compared with the estimated rate with no radiation exposure to the heart.
B. Cumulative risks of death from ischaemic heart disease[40].
Reproduced with permission from Darby et al, 2013. Copyright Massachusetts Medical Society.

Since QUANTEC, a case-control study reported that the risk of major coronary events in patients irradiated for breast cancer increased approximately linearly by 7.4% per Gray mean radiation dose to the whole heart (95% CI 2.9-14.5; p<0.001) (fig. 1a)[40]. This dose-response relationship, which was based on around a 1,000 events, allows oncologists to assess the risk of both incident and fatal IHD using an individual woman's mean whole heart dose and information on cardiovascular risk factors (fig. 1b) The risk was present in the first ten years following diagnosis and the absolute risk was higher for women with cardiovascular risk factors. No threshold dose was observed for the development of IHD.

Since the Darby 2013 study, three other dose response relationships for IHD have been published. First, a case control study of patients with Hodgkin lymphoma by van Nimwegen et al reported a linear dose-response relationship for radiation-induced incident coronary heart disease and the risk per Gy was also 7.4%. This study included 325 cases. Second, van den Bogaard reported a relative increase per Gy in the first decade after breast cancer radiotherapy[42] (based on 30 acute coronary events) similar to Darby et al and third, an individual patient data meta-analysis of ~40,000 women in 75 randomised trials estimated the risk of heart disease death per Gy which was also consistent with these studies[7].

1.2.3 Mechanism of injury

Different mechanisms of injury result in different types of radiation-induced heart disease. Radiation-induced myocardial damage may result from microvascular or macrovascular injury (Fig. 2)[43,44]. Experimental evidence suggests that endothelial cells, which line the vasculature, are the primary target[43]. These cells are multifunctional. They provide a selectively permeable barrier, control vascular permeability, vascular tone and blood flow, and regulate immune, inflammatory and coagulation responses[45]. Endothelial cell injury leads to cytokine activation, acute inflammation and vascular permeability. There is dose-dependent elevation of pro-inflammatory cytokines, growth factors and adhesion molecules[46-50]. Endothelial cell activation and proliferation occurs followed by microvascular thrombosis and capillary loss. Endothelial cell injury also causes impairment of platelet adhesion, coagulation, fibrinolysis and vascular tone[51,52]. These

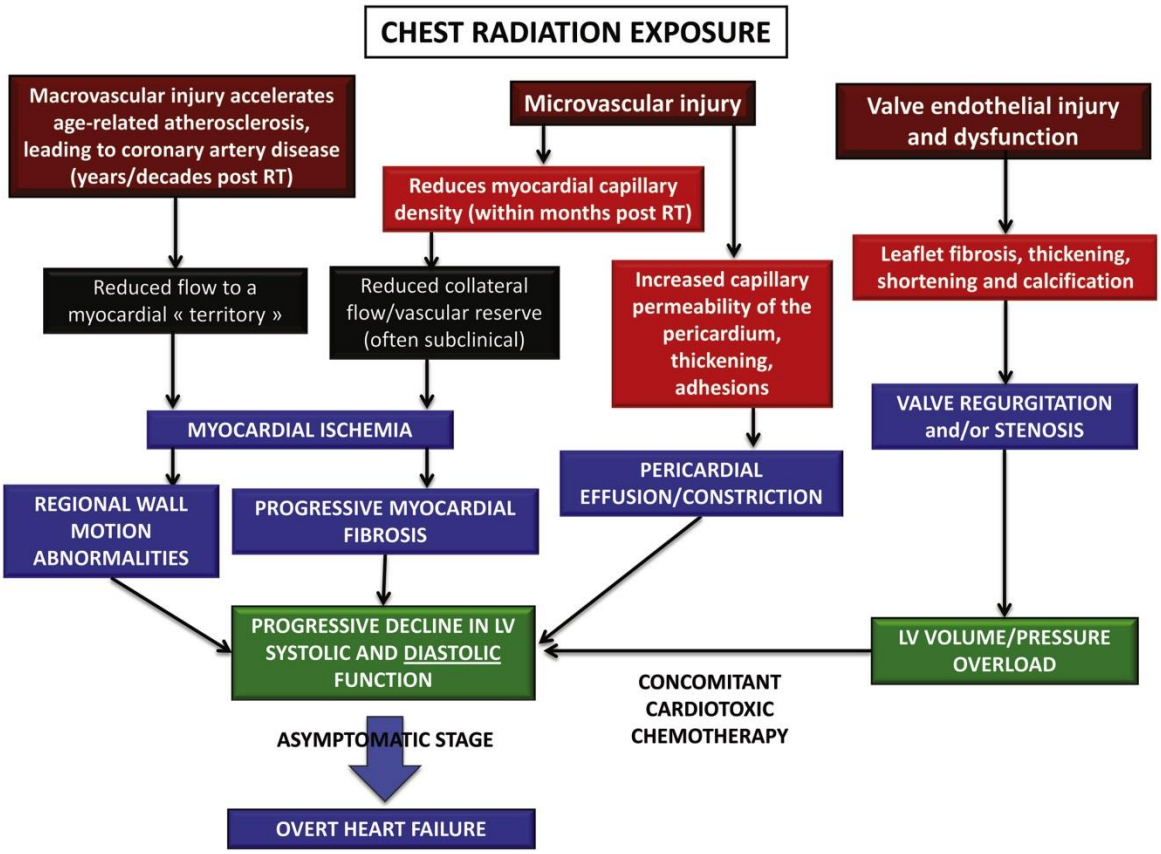


Figure 1-2. Pathophysiological manifestations of radiation-induced heart disease for different radiosensitive structures within the heart.

LV: left ventricle; RT: radiotherapy.
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mechanisms may lead to myocardial ischaemia and cell death[53]. Oxidative stress also plays a role, which may be initiated by either inflammatory processes or reduced tissue perfusion and hypoxia[54,55]. Fibrosis ensues and contributes to myocardial dysfunction, primarily diastolic dysfunction[53]. Transforming growth factor- β1 has been implicated as a master switch for fibrosis[56]. It increases pro-collagen mRNA, the precursor of collagen production. Collagen bands separate and replace myocytes. Fibrosis leads to myocardial dysfunction which may result in congestive heart failure. Extensive fibrosis may lead to a restrictive

cardiomyopathy. This is in contrast to anthracycline-related cardiomyopathy which is usually a dilated cardiomyopathy which occurs as a result of direct injury to myocytes.

Although microvascular injury is a major determinant of radiation-induced myocardial damage, myocardial ischemia may also result from occlusion of the coronary arteries. Endothelial cell injury leads to migration of monocytes into the intima of the coronary arteries. These are activated into macrophages which ingest lipid and form fatty streaks triggering atherosclerosis. A study on ApoE-/- mice suggested radiation-induced coronary atherosclerotic plaques are more likely to become unstable and rupture[57]. Patients may present with chest pain resulting from angina or myocardial infarction or they may present atypically without chest pain as radiation may have damaged the autonomic nervous system innervating the heart[58].

Acute inflammation of the pericardium may occur characterised by a protein-rich exudate which may manifest clinically as a pericardial effusion. This may progress to fibrin and collagen deposition leading to chronic constrictive pericarditis[43,53]. The mechanisms of injury for radiation-related VHD and conduction system abnormalities are less well understood. Radiation-related VHD is characterised by fibrosis and calcification. The cardiac valves are covered in endocardial cells, which may represent a target of irradiation[58]. The incidence of aortic and mitral valve disease is higher than for the pulmonary or tricuspid valvular disease possibly due to exposure of the left-sided valves to higher levels of haemodynamic stress[59]. VHD may manifest as valvular stenosis or

regurgitation or a combination of both but valvular stenosis has been observed most commonly after radiotherapy[60,61].

1.2.4 Imaging Studies

Cardiac single-photon emission computed tomography (SPECT) has been used to investigate myocardial perfusion and wall motion[62]. This involves injection of a radioactive tracer. Areas of decreased perfusion can be identified by a decrease in radioactive counts. A number of prospective studies of women who received left breast/chest wall radiotherapy who underwent SPECT before radiotherapy and at intervals after radiotherapy have observed early perfusion defects in the apical and anterolateral segments of the left ventricle, which were the segments closest to or included in the radiotherapy field.[63-66]. These studies did not assess spatial associations between dose and subsequent injury. There was correlation between the left ventricular volume within the radiotherapy fields and the per cent of patients with perfusion defects[64,66-67]. In two studies where the heart was excluded from the radiation fields, there were no perfusion defects[68,69].

Doppler echocardiography has also been used to investigate myocardial perfusion and wall motion. Strain rate imaging quantifies deformation properties of the myocardium. Strain is a measure of the relative length change of the myocardium. Strain rate is the speed at which the myocardial length changes. Studies have shown strain rate imaging can detect subclinical abnormalities in cardiac function after breast cancer radiotherapy and have related left ventricular segment doses to left ventricular segment injury[70-72]. The first study by Erven et al included 20 patients who received left-sided breast radiotherapy (mean left

ventricle dose: 6.7 Gy +/- 6 Gy, mean LV V_{30Gy} 5.2 +/- 11.5%) who had echocardiography before, after and 2 months post radiotherapy. This revealed dose-related regional decreases in myocardial function (strain) in segments that received > 3 Gy, 2 months after radiotherapy. Longitudinal peak systolic strain and strain rate were significantly reduced compared to baseline in the LV apical segments[71]. A subsequent study included 51 patients who received left-sided breast radiotherapy (mean LV dose 9 +/- 4 Gy, mean LV V_{30Gy} 8 +/- 7%) and had echocardiography before, after, and 8 and 14 months after radiotherapy[72]. All of the patients had anthracyclines, 22% had trastuzumab and 94% had IMC irradiation. No measurable difference in left ventricular ejection fraction (LVEF) from baseline was demonstrated. This was expected, as LVEF, a global parameter, cannot detect early subtle regional alterations in myocardial function[73]. A significant decrease in strain and strain rate compared to baseline was observed up to 14 months after radiotherapy, most marked in the anterior wall of the left ventricle, which received the highest dose (25 +/- 14 Gy).

Cardiac magnetic resonance (CMR) may be used to investigate myocardial dysfunction. It has been used to study the cardiac effects of radiotherapy in Hodgkin lymphoma and oesophageal carcinoma[74,75] . Unlike SPECT, CMR does not involve exposure to ionising radiation. It offers a higher spatial resolution and is less operator dependent or affected by body habitus than echocardiography. CMR is advantageous as it may detect multiple abnormalities including perfusion defects, inflammation, fibrosis, valvular disease, and myocardial infarction. CMR may include cine imaging for morphology and global function, tagged cine imaging for strain and strain rate, T1-mapping for myocarditis, T2-weighted

imaging for oedema, adenosine stress and rest perfusion imaging for perfusion defects and late gadolinium enhancement for fibrosis.

Two angiography studies have compared the incidence and distribution of coronary artery disease after left-sided versus right-sided radiotherapy[76,77]. In the US, a cohort study identified 14 women who had coronary angiogram after breast cancer radiotherapy[76]. Thirteen of these patients had received left breast radiotherapy, and most stenoses were identified in the left anterior descending coronary artery, which usually receives the highest radiation doses. A Swedish breast cancer cohort study identified 123 women who received breast cancer radiotherapy during 1970 to 2003 and subsequently had a coronary angiogram[77]. Again, most stenoses were located in areas of expected high radiation exposure. Neither of these studies provided individual coronary arterial segment doses. In Hodgkin lymphoma one study of 12 patients provided individual segment doses and showed stenosis mainly occurred in segments that received 20 Gy[78].

1.3 Radiation-induced lung cancer

Exposure of the lungs in breast cancer radiotherapy is unavoidable and epidemiological studies have shown that this may increase the risk of subsequent primary lung cancer[7,19,23,79,80,81,82,83, Appendix E2]. The risk only appears 10 years or more after radiotherapy[7,19,Appendix E2]. In an individual patient data meta-analysis of 40,000 women in 75 randomised trials there was no significant excess of lung cancer in the first decade after breast cancer radiotherapy but the rate ratio was 2.10 (95% CI 1.48 to 2.98) therafter[7,Appendix E2]. Both secondary lung cancer incidence[79] and mortality rates[19,23] appear to be decreasing over time. Several

studies have investigated the relationship between radiation dose and the development of lung cancer [7,80,81,84,85, Appendix E2]. These report estimates of excess rate ratio per gray (ERR/Gy) for lung cancer that range from 9% to 20% per Gy and there is no evidence that the dose-response relationship departs from linearity. Lung cancer mortality rates in the general population for long-term smokers are ~20 times greater than those in nonsmokers[86]. Therefore, for a given relative increased risk of lung cancer from breast cancer radiotherapy the absolute risk is likely to be much greater for smokers than for nonsmokers. A number of studies have attempted to investigate the radiation dose response relationship for lung cancer separately for smokers and nonsmokers but the number of cancers in never smokers is likely to be unreliable[7, Appendic E2]. As expected the relative risk of lung cancer appears to be greater in the ipsilateral lung than the contralateral lung because the ipsilateral lung usually receives a higher radiation dose than the contralateral lung[19,79,84] In one study of women irradiated during 1983-92, the lung cancer mortality ratio, ipsilateral versus contralateral was 3.87, 20 years after exposure[19].

Several studies suggest that the risk increases with mean dose to the whole lungs. It remains unclear, however, whether the increased risk of lung cancer after breast cancer radiotherapy is caused by exposing a small volume of lung to high doses of radiation or of exposing a large volume of lung to low doses of radiation. There is some evidence that even low doses of radiation may cause lung cancer. Carr et al found an increased risk of lung cancer in patients who received radiotherapy to the stomach for peptic ulcer disease[87]. There is concern that advanced techniques such as inverse-planned intensity-modulated

radiotherapy which may expose a large volume of the lung to low doses of radiation may increase the incidence of subsequent lung cancer[88].

1.4 Motivation for this thesis

1.4.1 Exposure of the heart and lungs is still an issue

Most of the evidence that links breast cancer radiotherapy with heart disease and lung cancer is based on studies of women treated in previous decades with outdated techniques who received higher heart and lung doses than those that are received today. Cardiac-sparing techniques are now being widely implemented which incorporate the use of multi-leaf collimators which shield the heart and lungs and breathing adaptation which involves the patient taking a deep breath during treatment drawing the heart backwards and downwards away from the treatment fields[89,90]. A number of contemporary studies suggest modern regimens pose a much-reduced risk of radiation-induced heart disease[22,91-93] due to improvements in radiotherapy techniques and in some cases, reduction in the prescribed radiation doses[94-96]. Certainly, on a population-based level the risk of radiation-related heart disease from breast cancer radiotherapy appears to have decreased substantially. Nonetheless, the potentially fatal late effects of concern are still likely to be relevant for subgroups of women irradiated today. Irradiating the lungs remains unavoidable for women receiving either left-sided or right-sided radiotherapy regardless of whether the regional lymph nodes are irradiated. Irradiating the heart is also still an issue for many women. A systematic review of the worldwide evidence of heart doses from breast cancer radiotherapy during 2003- 2013 has shown that the heart received on average around 5Gy in left-sided and 3Gy in right-sided radiotherapy[97,Appendix E3].

Heart and lung exposure may increase in future years as internal mammary chain (IMC) radiotherapy is more frequently used. Practice is currently changing since two recently published randomised control trials showed a survival advantage for women who received regional nodal irradiation compared to those who did not[98,99]. For women randomised to receive regional nodal radiotherapy, the IMC was included as part of the target. These trials do not isolate the benefit of IMC irradiation versus supraclavicular/ axillary nodal irradiation but they provide indirect support for including the IMC. A recent Danish cohort study provides direct support for IMC irradiation in which right-sided node-positive patients received regional nodal irradiation including IMC irradiation and left-sided node-positive patients received regional nodal irradiation without IMC irradiation[100]. Based on these data it is likely that more women will be offered IMC radiotherapy in the future. The IMC region is in close proximity to the anterior surface of the heart and cardiac and lung exposure increases when this region is irradiated to a therapeutic dose.

1.4.2 Need for dose response relationships

To assess the risks for women today, we need dose response relationships. These depend on cardiac and lung dosimetry of past regimens, in conjunction with long-term follow-up data. Despite there being an abundance of clinical and epidemiology studies on radiation-induced heart disease both the "Emami paper" and QUANTEC highlighted the paucity of data reporting rates of heart disease and dose-volume parameters and that there is a need for further research to investigate for quantitative dose and/or volume dependence for most cardiac

endpoints[33,34]. Since QUANTEC, Darby et al and other investigators have provided a dose-response relationship for fatal and incident ischaemic heart disease but more work is needed to further develop dose-response relationships for all types of radiation-related heart disease so that useful tools may be developed for predicting risks for women irradiated today[40,41,42].

When evaluating cardiac exposure oncologists generally focus on doses to the whole heart. It is uncertain whether particular cardiac substructures are more sensitive to radiotherapy induced damage than others and should, if possible be avoided in radiotherapy treatment planning. To date no dose-response relationships have been developed for specific cardiac substructure injury. Investigating such relationships may improve understanding of the causal pathways of radiation-induced heart disease which remain incompletely understood. The magnitude of risk from lower radiation doses is also uncertain and little is known about how risks are influenced by interactions between systemic therapies and radiotherapy. This information may inform radiotherapy planning.

1.4.3 Challenges

Radiation-induced heart disease or lung cancer may not become apparent for years after treatment. Developing dose-response relationships for such late effects presents a challenge. At present, in order to study effects occurring many decades after treatment, it is necessary to consider patients who received radiotherapy in the 1970s, 80s and 90s. CT-based dosimetry was not performed during this period and information on individual patient anatomy is unavailable.

Whether studying established cohorts or women enrolled in past randomised trials a method is required to estimate radiation doses retrospectively for the women treated in this era. A 'typical CT-scan" may be used for this purpose, on which regimens received in the past may be reconstructed on a modern radiotherapy treatment planning system. An important source of uncertainty to consider when using this method is the inter-patient variation in dose due to differences in anatomy[15]. Other sources of uncertainty also need to be considered including contouring error[101,102], dose calculation algorithm error[103], set-up error[104,105], and error secondary to cardiac and respiratory motion during treatment[106-108]. Despite these limitations, a “typical CT-scan" has previously enabled the derivation of a linear dose-response relationship (Darby 2013) for radiation-related IHD (expressed as a percentage increase in IHD rate per Gy mean whole heart dose). This was based on doses estimated retrospectively from radiotherapy charts[3] and has recently been validated in two independent studies[41,42] .

1.4.4 Lessons from the past are important for the future

Historical data may hold important clues about radiation-induced heart disease and radiation-induced lung cancer, clues that may not be provided by future prospective or retrospective studies of contemporary breast radiotherapy. Radiation-related heart disease can take many years to develop. Studying women who received their radiotherapy in previous decades provides an opportunity to assess 20 year risks. The level of cardiac and lung exposure was much higher in past decades than it is today and studies of women irradiated in the past are more likely to yield enough events for the development of dose-

response relationships than contemporary studies. A variety of beam arrangements and energies were used in the past which resulted in substantial cardiac exposure and the dose distribution through the heart was different for individual women. This heterogeneity provides opportunity for the development of dose response relationships for individual cardiac substructures which receive different levels of doses depending on the regimen received.

1.5 Aims

This thesis provides cardiac and lung dosimetry, including cardiac substructure dosimetry, which is related to long-term clinical outcome data. This will allow the consequences of radiation exposure of the heart and lungs to be characterised in terms of increased risk of late effects many years later. This will help to better inform patients during consent and will also inform management decisions. This work may also contribute to the formulation of evidence-based limits on cardiac and lung exposure from breast cancer radiotherapy which will aid radiotherapy planning.

Chapter 2 and 3 form the dosimetry base for a cross-sectional study of cardiac segment injury after breast cancer radiotherapy[Appendix E4]. This study investigates the effect of radiation on specific cardiac segments. Cardiac segment doses are applied to cardiac outcome data for 456 women treated in Scandinavia who developed a major coronary event after breast cancer radiotherapy. Contouring the cardiac segments is challenging as the heart is a complex anatomical organ, the heart chambers usually appear homogenous and it is difficult to visualise the coronary arteries. To generate reliable and reproducible retrospective dosimetry it

was first important to clearly define the cardiac segment contours of interest. **Chapter 2** presents a validated atlas for contouring the cardiac substructures on non-contrast radiotherapy planning scans[109]. **Chapter 3** presents a methodology for estimating cardiac segment doses from radiotherapy regimens used before the era of 3D CT-planning. The distribution of radiotherapy dose within the heart is described for regimens used in Sweden and Denmark during 1958-2001.The effect of inter-patient differences in anatomy on radiation doses to cardiac segments was quantified. How retrospectively estimated cardiac segment doses may be used to assess associations between dose and segment injury was explored.

Chapter 4 describes radiation doses to the whole heart, left ventricle and cardiac valves from 44 breast cancer regimens used in the Netherlands during 1970 to 2009. In a cohort study of 14,645 women with breast cancer in the Netherlands women who received IMC radiotherapy during the 1970s and 80s had significant excesses of myocardial infarction, valvular heart disease and heart failure compared with other similar women who did not receive IMC radiotherapy[Appendix E5]. From this cohort three nested case-control studies of myocardial infarction, heart failure and valvular heart disease after breast cancer are in progress. Within these case-control studies the cardiac doses estimated are being related to cardiac outcome data. They aim to validate previously reported dose-response relationships for radiation-induced MI and to investigate new dose-response relationships for radiation-induced HF and VHD. The first of these case-control studies is described in **Chapter 5.** This is a study of MI after breast cancer, which

includes younger women than previous reports (median age 50 years at breast cancer diagnosis).

Chapter 6 presents a systematic review of lung doses from breast cancer radiotherapy regimens published during 2010-2015[110]. This describes how lung exposure varies according to country, anatomical regions irradiated, technique, treatment position and the use of breathing adaptation. This work contributes to a study which estimated the risk of lung cancer after breast cancer radiotherapy for women irradiated today[Appendix E2]. Information on lung doses from previous randomised trials was combined with lung cancer incidence rate ratios for the women in the trials. The excess RRs/Gy were applied to the modern doses from the systematic review and modern population-wide death rates to predict risks in both smokers and non-smokers.

The recent data that has emerged supporting internal mammary chain irradiation is influencing national treatment guidelines. A recent consensus statement published by the Royal College of Radiologists, U.K. recommended that IMC radiotherapy should be considered in patients at high risk of recurrence with a primary lesion invading the chest wall or skin or ≥4 axillary macrometastases and in patients at intermediate risk of recurrence with 1-3 axillary macrometastases and central/medial disease, who have been recommended loco-regional irradiation based on risk factors (including age and tumour biology)[111]. **Chapter 7** investigates international variation in radiotherapy IMC guidelines and the percentage of women in a typical 6-month period in a single cancer centre that would be considered for IMC radiotherapy based on the Royal College of Radiologists' consensus (2016). This may inform resource allocation in UK radiotherapy departments. The number of women with risk factors for heart and

lung disease prior to radiotherapy was determined, whose risks from IMC radiotherapy may be higher than in women without pre-existing cardiovascular risk factors.

The RCR consensus statement proposes a mean heart dose constraint of < 6 Gy and an ipsilateral lung V17Gy <35%[111]. To ensure these constraints are met it is sometimes necessary to consider an advanced photon technique such as tangential volumetric arc therapy, with breathing adaptation, if this is available. A systematic review of heart doses in breast cancer radiotherapy delivered worldwide has shown that proton beam therapy delivered the lowest average mean heart dose (average mean heart dose 2.6 Gy) compared to other techniques[97, Appendix D3]. Proton beam therapy (PBT) achieves a sharp distal dose gradient enabling avoidance of normal tissues and so may increase the therapeutic index by maintaining the benefits of radiotherapy while minimising the risks. **Chapter 8** describes a randomised phase II trial proposal which aims to show that for women undergoing IMC irradiation the extent of acute myocarditis is less with proton beam therapy than it is with modern photon therapy with breathing adaptation. Such a trial may direct the need for a future phase III clinical trial investigating if protons can mitigate the potential for increased late cardiotoxicity when the IMC is irradiated.

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2 A Cardiac contouring atlas for radiotherapy

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2.1 Abstract

Background and Purpose

The heart is a complex anatomical organ and contouring the cardiac substructures is challenging. This study presents a reproducible method for contouring left ventricular and coronary arterial segments on radiotherapy CT-planning scans.

Material and Methods

Segments were defined from cardiology models and agreed by two cardiologists. Reference atlas contours were delineated and written guidelines prepared. Six radiation oncologists tested the atlas. Spatial variation was assessed using the DICE similarity coefficient (DSC) and the directed Hausdorff average distance ($\vec{d}_{H,avg}$). The effect of spatial variation on doses was assessed using six different breast cancer regimens.

Results

The atlas enabled contouring of 15 cardiac segments. Inter-observer contour overlap (mean DSC) was 0.60-0.73 for five left ventricular segments and 0.10-0.53 for ten coronary arterial segments. Inter-observer contour separation (mean $\vec{d}_{H,avg}$) was 1.5-2.2 mm for left ventricular segments and 1.3-5.1 mm for coronary artery segments. This spatial variation resulted in <1 Gy dose variation for most regimens and segments, but 1.2-21.8 Gy variation for segments close to a field edge.

Conclusions

This cardiac atlas enables reproducible contouring of segments of the left ventricle and main coronary arteries to facilitate future studies relating cardiac radiation doses to clinical outcomes.

2.2 Introduction

Radiotherapy increases cure rates in breast cancer, Hodgkin lymphoma, oesophageal cancer and lung cancer. However, in each of these cancers, radiotherapy may involve some cardiac exposure, thereby increasing the risk of several different heart diseases. Oncologists need to know the relationships between cardiac doses and various types of heart disease so they can estimate radiation-related risks for patients. A number of studies have derived dose-response relationships estimating the risk of various cardiac outcomes in terms of whole heart doses. One study of women irradiated for breast cancer, based on around 1000 events, showed that the risk of major coronary events increased by 7.4 % per Gy mean heart dose[1]. Several smaller studies related whole heart dose to cardiac death, valvular heart disease, decreased myocardial function and pericardial disease[2,3].

Whole heart dose may not be the best predictor of all types of radiation-related heart disease. Some studies have investigated the relationship between doses to particular cardiac substructures and subsequent damage to those structures. In Hodgkin lymphoma, one study related valve doses to subsequent valvular heart disease and another related coronary artery doses to subsequent coronary artery stenosis[4,5]. In breast cancer, two studies have related coronary artery doses to subsequent coronary artery stenosis[6,7] and further studies have related whole left ventricle dose to subsequent subclinical left ventricular abnormalities[8,9]. But the relationships between doses to different left ventricular or coronary artery

segments and subsequent injury of these segments have not yet been investigated.

The heart is a complex anatomical organ made up of muscle, arteries and valves and it can be difficult to contour cardiac substructures reproducibly. In 2010, the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) Report highlighted the need for guidelines to reduce inter-observer variation in cardiac contouring[2]. In 2011 investigators at the University of Michigan developed a cardiac atlas describing contouring of the cardiac chambers, coronary arteries, conduction system and valves[10]. We now present an atlas for contouring different segments of the coronary arteries and the left ventricle on radiotherapy planning CT scans.

2.3 Material and methods

2.3.1 Atlas development

Information was sought from (1) anatomy[11] and cardiac imaging[12] textbooks (2) IMAIOS e-anatomy[13] (3) key articles describing cardiac segmentation models or normal cardiac anatomy[14-19] and (4) the echocardiogram and angiogram reports of 500 women included as cases in a population-based study of women who had a major coronary event after breast cancer radiotherapy[1]. These reports verified that the segments in the atlas matched those described by cardiologists regarding the location of damage so that segment doses may be directly related to location of injury in future dose-response relationships. These four sources were used to define five left ventricular segments (Fig. 1, Table 1) and ten

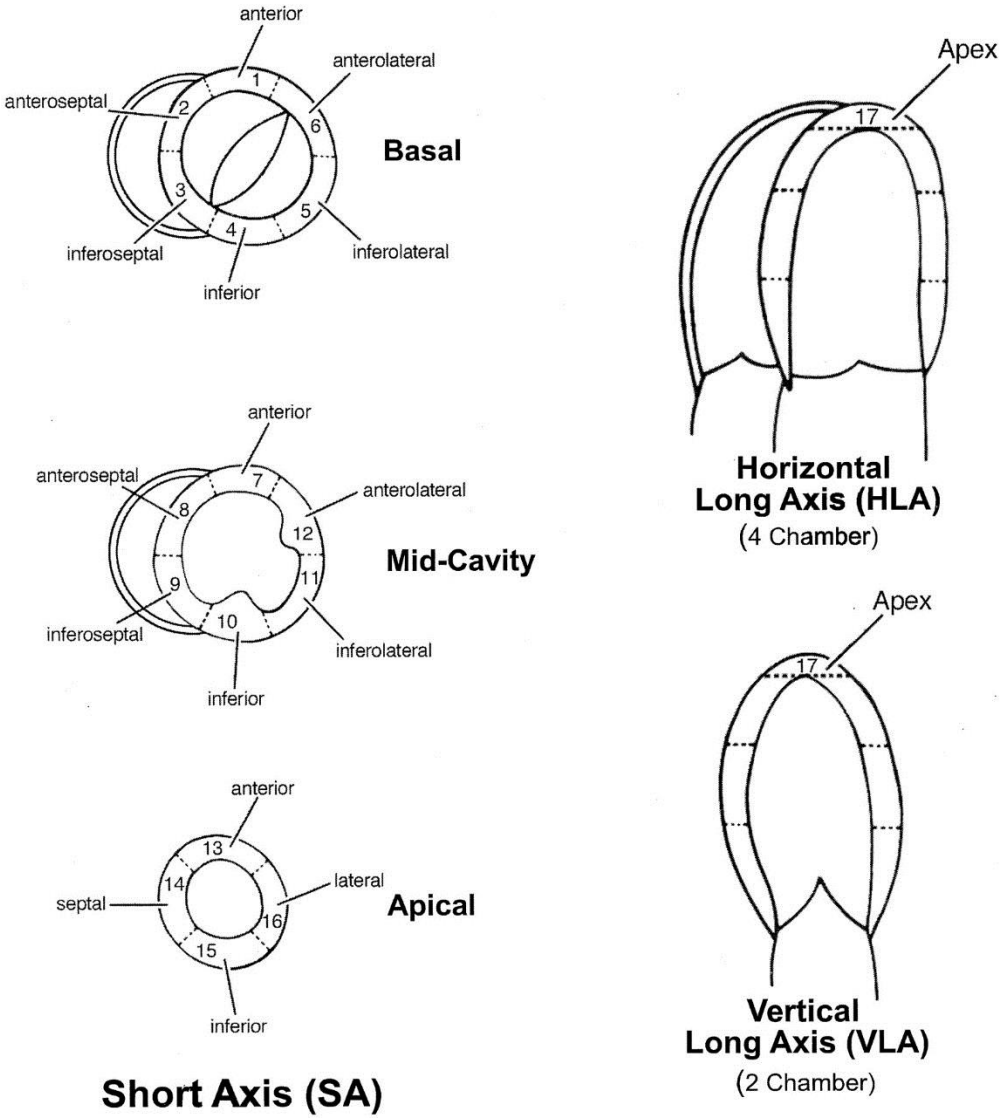


Figure 2-0-1. Diagram of 17-segment myocardial segmentation model

Diagram of vertical long-axis (VLA, approximating the 2-chamber view), horizontal long-axis (HLA, approximating the 4-chamber view), and short-axis (SA) planes showing the name, location, and anatomic landmarks for selection of the basal (tips of the mitral valve leaflets), mid-cavity (papillary muscles), and apical (beyond papillary muscles but before cavity ends) short-axis slices for the recommended 17-segment system. All imaging modalities should use these same landmarks, when available, for slice detection.

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Table 2-1. Left ventricular myocardial segmentation: use of traditional 17-segment model to derive five segments for the cardiac contouring atlas.

Present study	17-Segment Model [13,14]	
Segment name	Segment number*	Segment name
Anterior	1	Basal anterior
	7	Mid anterior
Lateral	5	Basal inferolateral
	6	Basal anterolateral
	11	Mid inferolateral
	12	Mid anterolateral
Apical	13	Apical anterior
	14	Apical septal
	15	Apical inferior
	16	Apical lateral
	17	Apex
Septal	2	Basal anteroseptal
	3	Basal inferoseptal
	8	Mid anteroseptal
	9	Mid inferoseptal
Inferior	4	Basal inferior
	10	Mid inferior

*The traditional 17-segment model divides the left ventricle into basal, mid and apical thirds. Segment numbers relate to the position of the segments, extending from the base to the apex.

Table 2-2. Definition of the ten atlas coronary artery segments

Atlas coronary artery segments	Definition[16,17]
Left main coronary artery	From the left lateral ascending aorta running between the left atrium and the pulmonary artery to the bifurcation into left anterior descending and circumflex coronary arteries (~ 1.5 cm in length).
Left anterior descending coronary artery	
Proximal	The proximal 1/5th of the vessel, from the end of the left main coronary artery passing anteriorly behind the pulmonary artery.
Mid	The mid 2/5th of the vessel descending anterolaterally in the anterior interventricular groove.
Distal	The distal 2/5th of the vessel running in the interventricular groove and extending to the apex.
Circumflex coronary artery	
Proximal	From the end of the left main coronary artery running in the left atrioventricular groove for 2cm in length.
Distal	From the end of the circumflex proximal running along the left atrioventricular groove posteriorly extending to the crux of the heart.
Right coronary artery	
Proximal	From the anterior aspect of the ascending aorta descending in the right atrioventricular groove to one-half the distance to the acute heart border*.
Mid	From the end of right coronary artery proximal to the acute heart border*.
Distal	From the acute heart border* running medially along the right atrioventricular groove posteriorly to the crux of the heart.
Posterior descending	From the crux of the heart to the apex running in the posterior interventricular groove to the tip of the apex.

*The acute heart border is the horizontal heart border extending from the lower right edge of the heart to the apex formed mainly by the right ventricle.

coronary artery segments (Table 2). We ensured that each contour definition was reproducibly identifiable on non-contrast radiotherapy CT-planning scans and large enough to allow accurate dose calculation.

Selection of an atlas CT set

Ten radiotherapy CT-planning scans were randomly selected from women irradiated for left-sided breast cancer at Odense University Hospital in the year 2010.The treatment position was supine with both arms above the head. CT scan slice thickness was 3 mm and intravenous contrast was not used. All segments were contoured by a radiation oncologist (FD) on the ten scans using Varian Eclipse^{TM} Treatment Planning System version 10.0.39, Varian Medical Systems, Palo Alto, USA. This was a contouring training exercise to ensure the guidelines would be applicable to patients with differing anatomy. Two cardiologists (KR and SM) reviewed, and made minor modifications, to the contours. The CT dataset most representative of typical anatomy, with minimal motion artefact, was selected as the atlas CT scan. Written guidelines for consistent contouring were jointly developed by two oncologists (FD and CT) and two cardiologists (KR, SM).

2.3.2 Atlas description

The right and left atrioventricular grooves on the surface of the heart

Identification of the grooves that divide the heart into four chambers can help when contouring cardiac segments. The atrioventricular grooves form a continuous sulcus separating the atria from the ventricles (Fig. 2a-b).

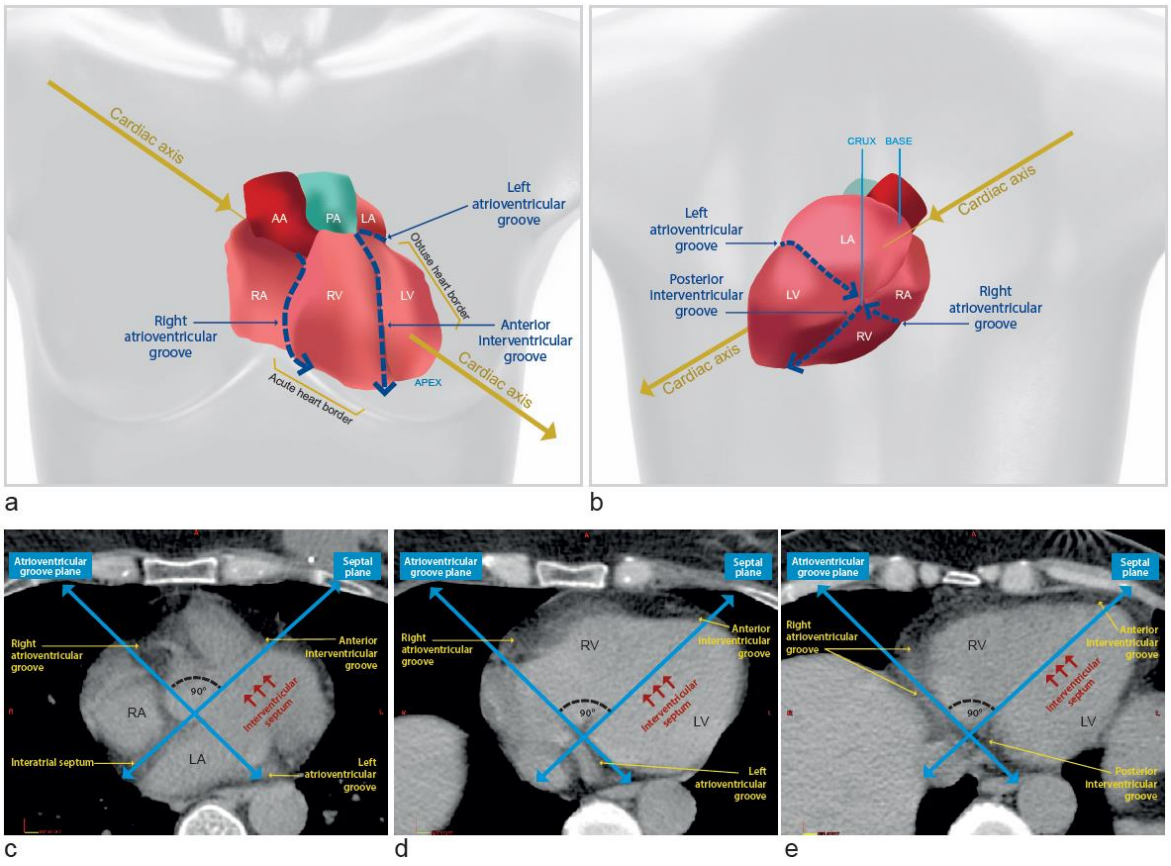


Figure 2-2. Identifying the atrioventricular and interventricular grooves.

a-b) Anterior (a) and posterior (b) view of the whole heart illustrating the cardiac axis, the cardiac chambers, and the atrioventricular and interventricular grooves. The cardiac axis projects through the center of the base of the heart (the left atrium) towards the cardiac apex. The acute heart border is the horizontal heart border extending from the lower right edge of the heart to the apex, which is formed mainly by the right ventricle. The obtuse heart border separates the sterno-costal and left surfaces of the heart extending from the left atrium to the cardiac apex.

c-e) Axial CT images at the level of the inter-atrial septum (c), the proximal inter-ventricular septum (d) and the distal inter-ventricular septum (e). The atrial and ventricular septa define the septal plane. The plane defined by the atrioventricular groove plane is usually perpendicular to the septal plane. [11-12] The septal plane may be marked with a line through the fat space between the right and left atria proximally, using the ruler tool on the treatment planning system. This represents the location of the interatrial septum which is usually clearly visible on CT (c). Scrolling down to the level of the ventricles this line overlies the interventricular septum and points just medial to the cardiac apex (d, e). Once the interventricular septum is located, the anterior and posterior interventricular grooves may be identified as they correspond to the anterior and posterior limits of the interventricular septum (d, e). The plane corresponding to the atrioventricular groove is approximately at right angles to the septal plane. The right and left atrioventricular grooves are usually identifiable since they are filled with fat (c-e).

Abbreviations: PA: pulmonary artery, AA: ascending aorta, RA: right atrium, LA: left atrium, LV: left ventricle, RV: right ventricle.

The right atrioventricular groove begins anteriorly and superiorly, behind the ascending aorta. It then descends on the anterior surface of the heart and continues around the acute heart border (Fig. 2a). The left atrioventricular groove originates with the right atrioventricular groove superiorly behind the aorta. The first part is obscured by the aorta and the pulmonary artery. It then curves around the obtuse border of the heart to connect with the other end of the right atrioventricular groove at the crux of the heart, which is the point on the posterior surface of the heart where the four chambers of the heart intersect forming a cross (Fig. 2b).

The anterior and posterior interventricular grooves on the heart surface

The interventricular grooves are surface depressions on the myocardium and lie over the interventricular septum. The anterior interventricular groove descends on the anterior surface of the heart between the left and right ventricles to the apex. It is near, and almost parallel to, the obtuse heart border (Fig. 2a). The posterior interventricular groove starts at the crux of the heart and runs along the inferior surface of the heart, which itself runs horizontally along the diaphragm, sloping down and forwards towards the apex (Fig. 2b)[10-12].

The atrioventricular and interventricular grooves on axial CT scan

On CT it can be difficult to identify the interventricular septum, as the ventricles usually appear homogenous. It is useful to mark out two pre-defined planes: the septal plane, and the atrioventricular groove plane. These divide the heart approximately into the four chambers, and define the limits of the left ventricle (Fig. 2c-e).

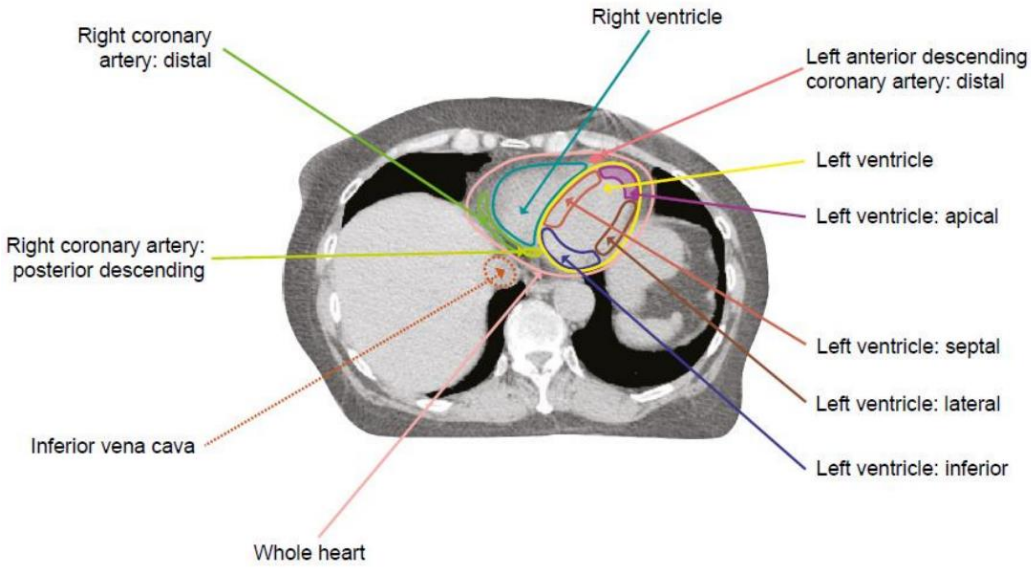
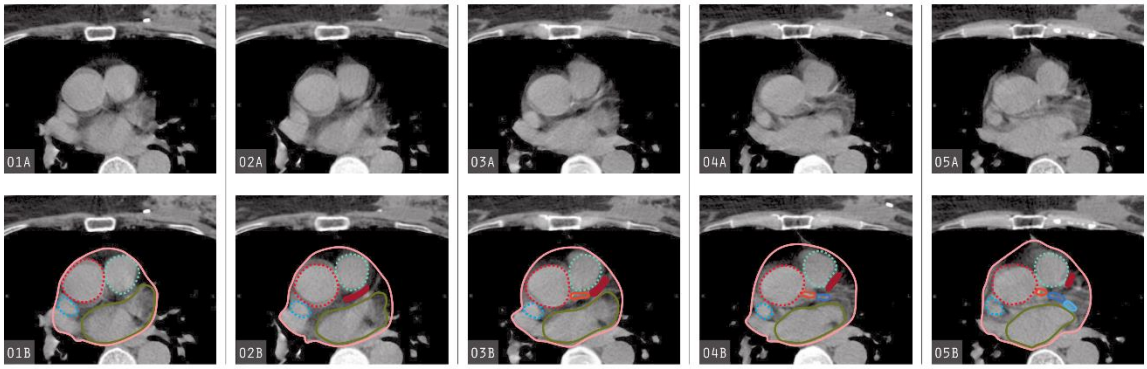
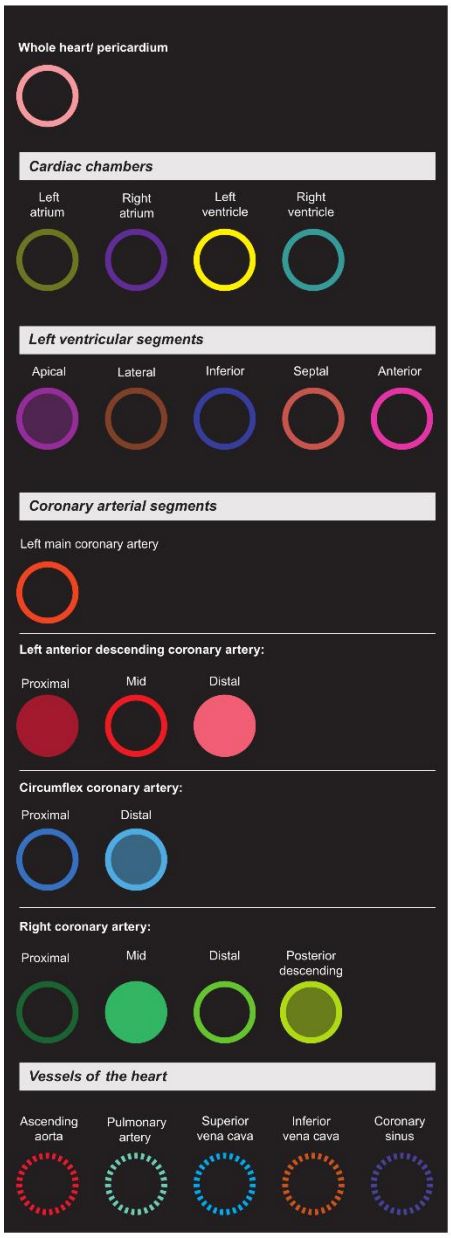


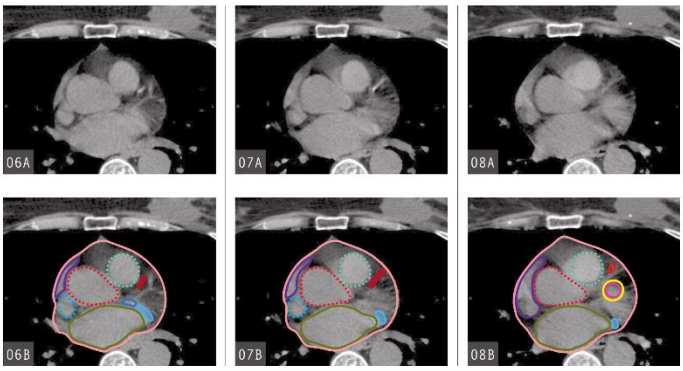
Figure 2-3. Axial radiotherapy CT planning image at the level of the left ventricle inferiorly showing contouring of the coronary arterial and left ventricular myocardial segments.

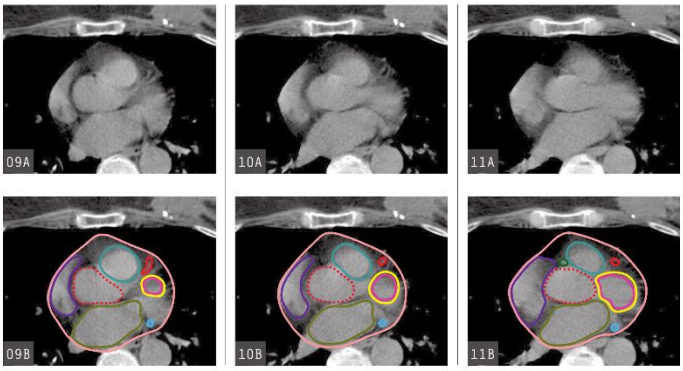
Left ventricular segmentation

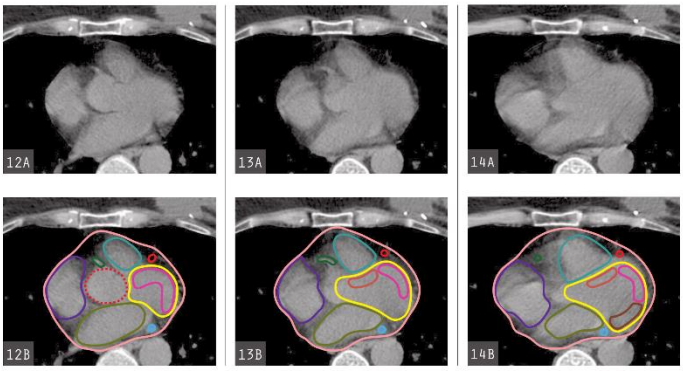
The apical segment comprises the lowermost extent (the distal third) of the left ventricle. The attachment of the right ventricular wall to the left ventricle separates the septum from the apical, anterior and inferior free walls. The inferior segment extends from the mitral valve superiorly to join the apex inferiorly. The lateral and anterior segments form the lateral and superior walls of the ventricle respectively and extend inferiorly to meet the apex (Table 1, Figs. 1,3-4)[13,14]. The average septal wall thickness in females is 1.1 cm for end-systole and 0.8 cm for end-diastole and the average posterior wall thickness is 1.4 cm for end-systole


01A
02A
03A
04A
05A
01B
02B
03B
04B
05B


Whole heart/ pericardium
Cardiac chambers
Left atrium
Right atrium
Left ventricle
Right ventricle
Left ventricular segments
Apical
Lateral
Inferior
Septal
Anterior
Coronary arterial segments
Left main coronary artery
Left anterior descending coronary artery:
Proximal
Mid
Distal
Circumflex coronary artery:
Proximal
Distal
Right coronary artery:
Proximal
Mid
Distal
Posterior descending
Vessels of the heart
Ascending aorta
Pulmonary artery
Superior vena cava
Inferior vena cava
Coronary sinus


06A
07A
08A
06B
07B
08B


09A
10A
11A
09B
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11B


12A
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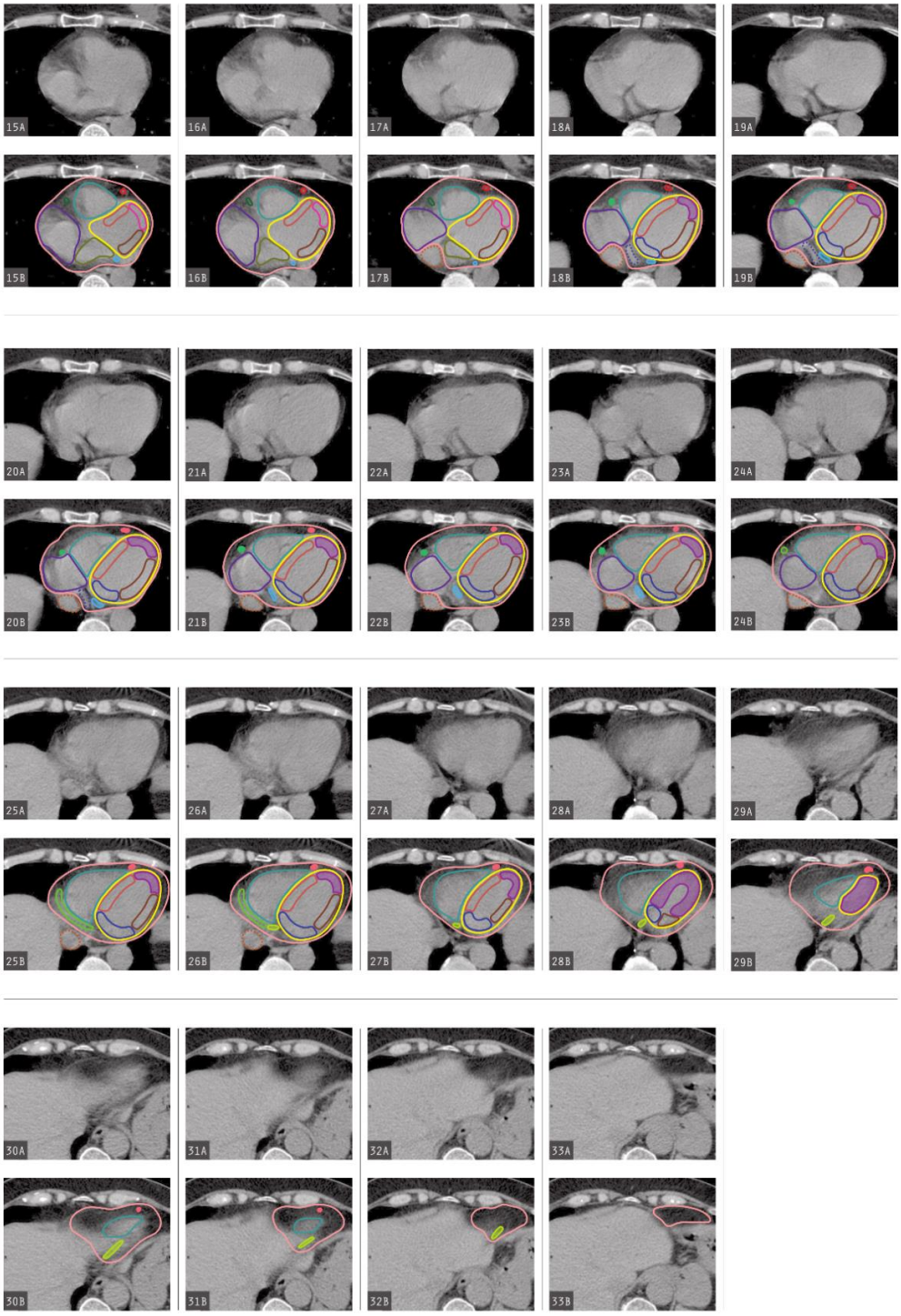


Figure 2-4. Axial radiotherapy CT planning images showing contouring of the coronary arterial and left ventricular myocardial segments (slice thickness 3mm).

Magnified axial radiotherapy CT planning images showing contouring of the coronary arterial and left ventricular myocardial segments (slice thickness 3mm) available at: http://www.thegreenjournal.com/article/S0167-8140(17)30030-0/addons

and 0.8 cm for end-diastole[15]. In the atlas, we set the thickness of the left ventricular wall as 1 cm throughout.

Coronary arterial segmentation

The left main coronary artery (LMCA) arises above the left aortic valve cusp and the right coronary artery (RCA) above the right cusp anteriorly. The levels at which these coronary arteries appear to originate may vary because patients may be scanned in different positions, or because the orientation of the cardiac axis may vary from patient to patient. Both these factors affect the orientation of the aorta relative to the axial CT slice. For nine of the ten CT scans in our study the RCA originated 4-6 axial CT slices (12-18 mm) inferior to the LMCA. For the remaining scan, the RCA originated on the same slice as the LMCA.

The coronary arteries run in the atrioventricular and interventricular grooves. The LMCA passes between the pulmonary artery and left atrium and branches into the circumflex coronary artery (Cx) and the left anterior descending coronary artery (LADCA). The LADCA descends in the anterior inter-ventricular groove to the apex of the heart. The Cx descends around the left side of the heart in the left atrioventricular groove to the posterior surface as far as the crux. The RCA travels in the right atrioventricular groove and continues inferiorly around the acute heart border to the posterior surface towards the crux. The posterior descending artery (which usually originates from the RCA) runs from the crux of the heart in the posterior inter-ventricular groove towards the apex (Table 2, Figs. 3-5)[16-18].

The diameter of each main coronary vessel decreases from proximal to distal. An angiography study of 90 women showed that the average coronary arterial luminal diameter was 3.2 mm[19]. In our atlas each coronary artery was contoured

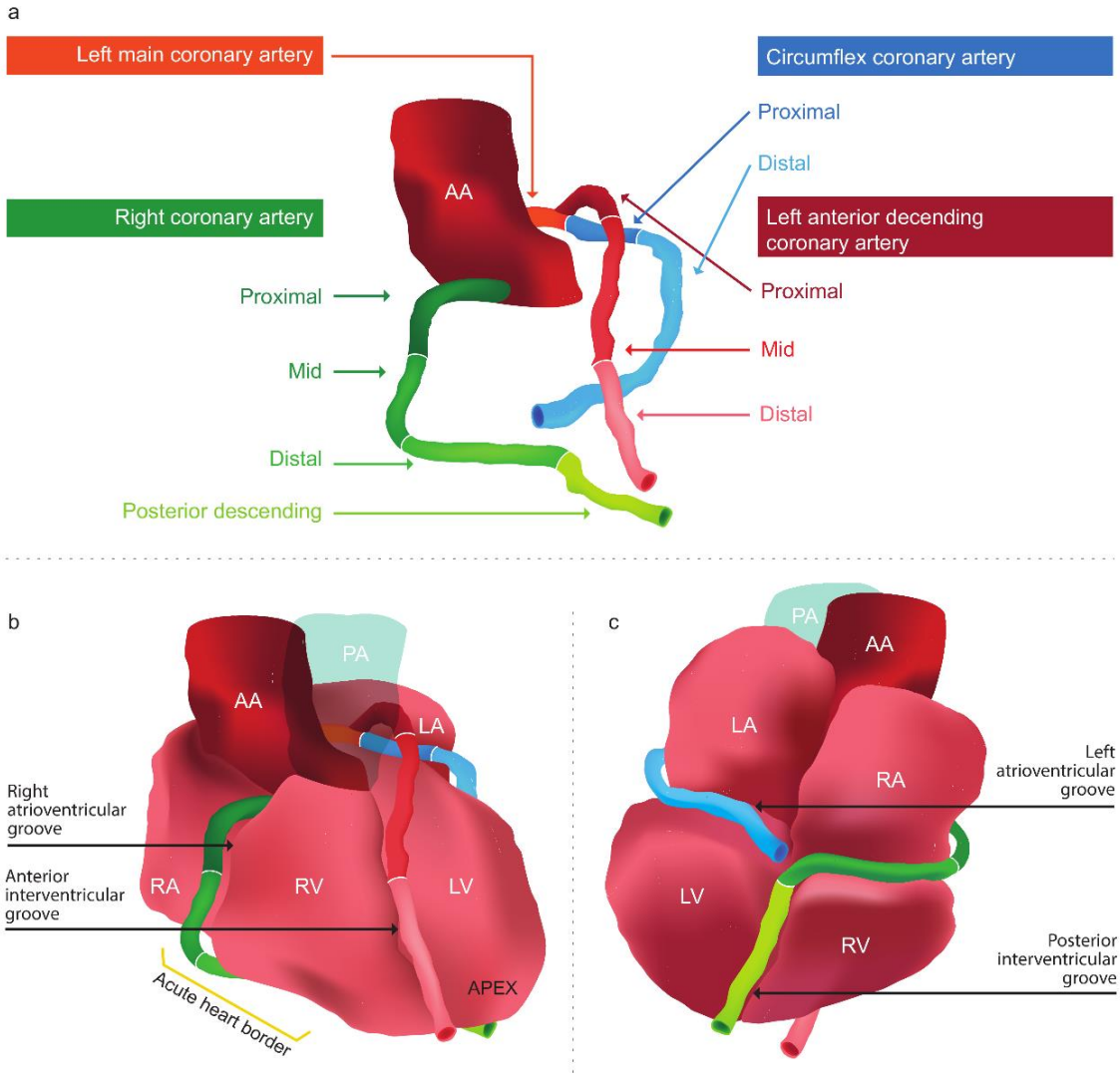


Figure 2-5. Coronary artery segmentation

3D representation of the segments of the three main coronary arteries in relation to the atrial and ventricular chambers, ascending aorta and pulmonary artery.
Abbreviations: PA: pulmonary artery, AA: ascending aorta, RA: right atrium, LA: left atrium, LV: left ventricle, RV: right ventricle.

with 4 mm diameter throughout its entire length. The vessels were not tapered because of uncertainties in dose estimation for very small segments in CT planning.

2.3.3 Atlas evaluation

Six oncologists specialising in breast or thoracic radiotherapy (DC, OM, RJ, SV, FB, and CT) tested the atlas. They received the written guidelines, atlas images and the atlas CT-scan in DICOM-format. They then contoured the left ventricle, the five left ventricular segments and the ten coronary arterial segments.

Contouring variability was assessed using 3D Slicer version 4.4 and the extension Slicer RT software to compute concordance metrics[20]. The atlas contours were selected as the "reference" contours, to which all the observer contours were compared. First, to assess contour overlap, the Sørensen-Dice similarity coefficient (DSC = 2*Z*/(*X*+*Y*)) was measured, where *X* is the reference atlas contour, *Y* is the observer contour, and *Z* is the region shared between the contours. A value of 1.0 indicates perfect concordance, and a value of 0 indicates no concordance. Second, to assess the separation between the contour surfaces, the directed Hausdorff average distance ($\vec{d}_{H,avg}$) was measured. This is the distance from each point (x) on the reference contour (X) to its closest point (y) of the observer contour (Y) averaged over all points on the reference contour: $\vec{d}_{H,avg}(X,Y) = \frac{1}{|X|}\sum_{x\in X} \min_{y\in Y} d(x,y)$, where d is the distance between x and y and $|X|$ is the number of points on X [21]. The mean DSC and the mean $\vec{d}_{H,avg}$ refer to the arithmetic mean of the measurements recorded for each of the six observer contour/reference contour comparisons.

To assess the dosimetric consequences of variation in contouring, six breast cancer radiotherapy regimens were reconstructed (three techniques were reconstructed on the left and three on the right). These delivered 95% of the prescribed dose (50 Gy in 2 Gy fractions) to the breast PTV and 85% to the internal mammary and medial supraclavicular fossa nodal PTV. Left and right-sided regimens were reconstructed for: (1) conformal partially wide tangential technique (PWT), (2) conformal oblique parasternal photon technique (OPP) and (3) conventional mixed electron/photon direct parasternal technique (E–/MV)[22]. The analytical anisotropic algorithm (AAA) was used for dose calculations using the 0.1 cc calculation volume grid. For each of the six regimens, the mean dose to each cardiac segment was recorded.

2.4 Results

Contour overlap was greater for the left ventricular segments than for the coronary arterial segments (Table 3, Fig. 6). The mean DICE coefficient for the left ventricle was 0.91 and ranged between 0.60-0.73 for the left ventricular segments, indicating considerable overlap between the contours. The mean $\vec{d}_{H,avg}$ ranged from 1.5 to 2.2 mm. For the coronary arterial segments, the mean DICE coefficient was between 0.10 and 0.53. Despite poor overlap, the separation between the contours was not substantial as the $d_{H,\,avg}$ was only a few mm, ranging from 1.3 to 5.1 mm.

Table 2-3. Variation in spatial measurements and doses from left breast cancer regimens for cardiac segments contoured by six observers on one CT-planning dataset.

	Spatial variation Mean (SD), range of values			Dose variation (Gy), left-sided regimens Mean (SD), range of values		
Cardiac segments	DICE coefficient	Hausdorff average distance (mm)	Structure volume (cc)	PWT	OPP	E⁻/MV
Left ventricle	0.91, 0.89-0.94	1.3, 0.9-1.8	170.4, 149.8-181.6	6.7 (0.2), 6.4-7.0	8.2 (0.2), 7.9-8.6	15.6 (0.3), 15.0-15.9
LV: apical	0.69, 0.65-0.78	1.5, 1.0-1.8	19.8, 13.1-25.1	**22.3 (2.8), 18.8-26.4**	**21.0 (2.1), 18.6-24.1**	**9.9 (0.8), 9.1-10.9**
LV: lateral	0.73, 0.67-0.77	1.6, 1.2-2.5	22.1, 18.1-25.4	**3.4 (1.1), 2.0-4.6**	**6.3 (1.6), 4.3-7.9**	**8.5 (1.1), 7.2-9.7**
LV: inferior	0.65, 0.50-0.74	2.1, 1.6-2.7	13.0, 9.1-16.4	0.8 (0.1), 0.7-0.8	1.0 (0.0), 1.0-1.1	*17.6 (0.2), 17.3-17.9*
LV: septal	0.60, 0.45-0.76	2.2, 1.4-2.9	21.0, 15.6-29.4	**4.5 (0.8), 3.1-5.3**	**5.5 (1.7), 3.7-6.9**	*22.0 (0.3), 21.6-22.5*
LV: anterior	0.65, 0.60-0.78	1.6, 1.7-2.3	12.8, 7.3-23.0	**9.6 (4.1), 5.1-17.3**	**14.0 (3.9), 9.3-20.7**	**17.4 (1.3), 15.2-18.9**
LMCA	0.45, 0.09-0.76	1.4, 0.5-2.4	0.4, 0.2-0.6	1.5 (0.1), 1.1-1.2	1.3 (0.1), 1.1-1.3	*19.1 (0.4), 18.5-19.5*
LADCA proximal	0.53, 0.34-0.72	1.3, 0.5-2.2	1.1, 0.7-2.0	2.5 (0.5), 1.9-3.2	3.1 (0.6), 2.3-4.0	*22.2 (0.6), 21.3-23.0*
LADCA mid	0.39, 0.23-0.53	1.5, 0.7-2.1	0.8, 0.4-1.0	**25.1 (2.4), 22.1-28.5**	**27.0 (2.1), 23.7-29.1**	*28.1 (0.5), 27.4-28.9*
LADCA distal	0.23, 0.03-0.39	2.4, 1.2-4.6	0.6, 0.2-0.9	**35.8 (2.8), 33.5-40.0**	**32.0 (3.4), 28.0-37.8**	**21.8, (8.8), 12.1-33.9**
Cx proximal	0.25, 0.04-0.65	2.7, 0.7-4.5	0.4, 0.2-0.5	1.3 (0.1), 1.2-1.5	1.5 (0.1), 1.4-1.7	*19.8 (0.3), 19.5-20.3*
Cx distal	0.18, 0.06-0.31	3.4, 2.1-5.5	2.1, 0.7-4.5	0.9 (0.0), 0.9-1.0	1.1 (0.1), 1.1-1.3	**17.4 (0.4), 16.9-18.0**
RCA proximal	0.35, 0.00-0.46	3.1, 2.2-6.2	0.5, 0.2-0.9	1.7 (0.1), 1.5-1.7	1.4 (0.1), 1.3-1.4	3.0 (0.5), 2.1-3.4
RCA mid	0.22, 0.00-0.31	3.7, 1.8-10.7	0.3, 0.2-0.6	1.0 (0.1), 0.9-1.1	0.7 (0.0), 0.7-0.8	1.4 (0.1), 1.3-1.4
RCA distal	0.44, 0.30-0.55	1.9, 1.1-3.8	1.2, 1.1-1.5	0.6 (0.1), 0.5-0.7	0.5 (0.0), 0.5-0.5	1.6 (0.2), 1.3-1.9
RCA post desc	0.10, 0.00-0.26	5.1, 3.0-7.6	0.9, 0.5-1.4	0.8 (0.2), 0.6-1.0	0.9 (0.1), 0.7-1.0	**14.9 (2.0), 11.8-16.8**

Dose variation results are highlighted in bold for structures located near a high dose-gradient and in italics for structures located within the high-dose areas.

Definitions:

DICE coefficient : 2Z/(X+Y), where X is the reference atlas contour, Y is the observer contour, and Z is the region shared between the contours.The mean DICE coefficient refers to the arithmetic mean of the measurements recorded for each of the six observer contour/reference contour comparisons.

Hausdorff average distance : the distance from each point (x) on the reference contour (X) to its closest point (y) of the observer contour (Y) averaged over all points on the reference contour: $1/|X| \sum_{x \in X} \min_{y \in Y} d(x,y)$, where d is the distance between x and y and |X| is the number of points on X.The mean Hausdorff average distance refers to the average of the measurements recorded for each of the six observer contour/reference contour comparisons.

Abbreviations:

PWT: partially wide tangential technique; OPP: oblique parasternal photon technique; E⁻/MV: mixed electron/photon direct parasternal technique; LV: left ventricle, LMCA: left main coronary artery, LADCA: left anterior descending coronary artery, Cx: circumflex coronary artery; RCA: right coronary artery; post desc: posterior descending

Figure 2-6. Cardiac substructure contours by 6 observers on one CT-planning scan at the level of the left ventricle superiorly (a) and inferiorly (b).

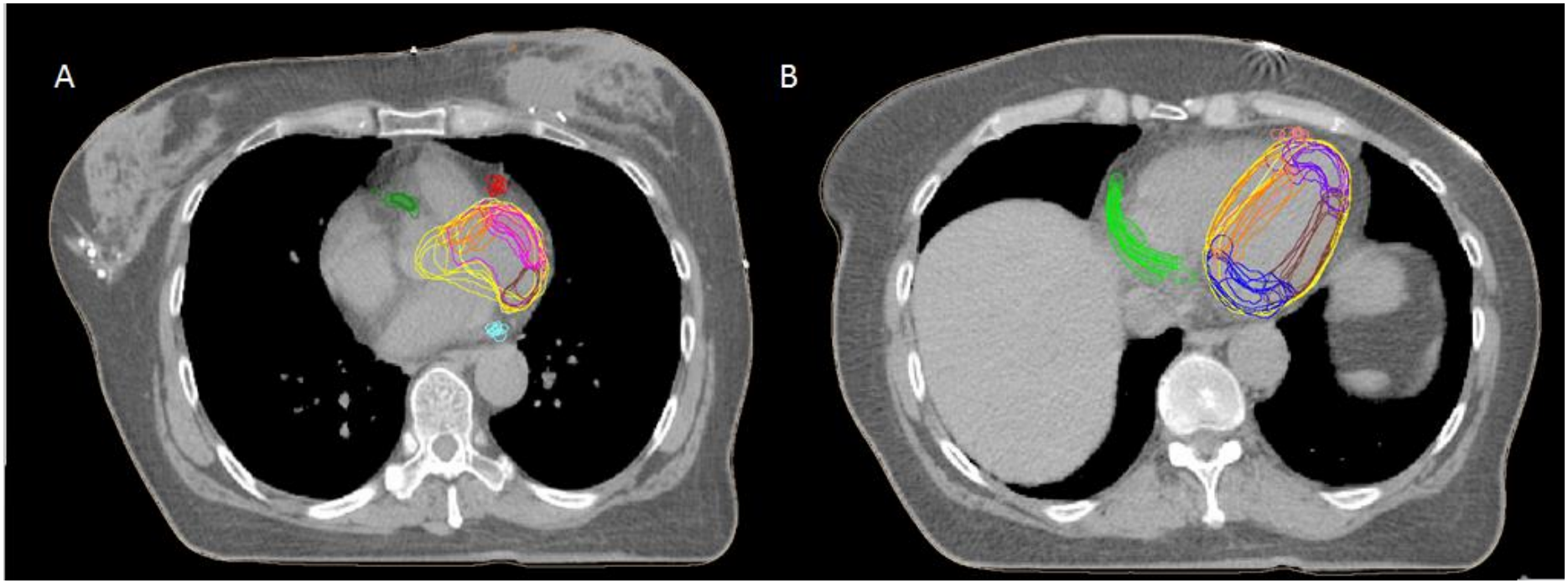


Table 2-4. Variation in doses from right breast cancer regimens for cardiac segments contoured by six observers on one CT-planning scan.

Cardiac segments	Dose variation (Gy), right-sided regimens Mean (SD), range		
	PWT	OPP	E⁻/MV
Left ventricle	0.3 (0.0), 0.3-0.3	0.2 (0.0), 0.2-0.2	0.7 (0.0), 0.7-0.7
LV: apical	0.2 (0.0), 0.2-0.2	0.1 (0.0), 0.1-0.1	0.5 (0.0), 0.5-0.5
LV: lateral	0.2 (0.0), 0.2-0.2	0.1 (0.0), 0.1-0.1	0.5 (0.0), 0.5-0.5
LV: inferior	0.3 (0.1), 0.3-0.4	0.3 (0.1), 0.2-0.3	0.9 (0.1), 0.8-1.0
LV: septal	0.5 (0.0), 0.4-0.5	0.4 (0.0), 0.4-0.5	0.9 (0.1), 0.8-1.0
LV: anterior	0.3 (0.0), 0.3-0.4	0.3 (0.0), 0.2-0.3	0.9 (0.1), 0.8-1.0
LMCA	0.8 (0.1), 0.7-6.8	0.8 (0.0), 0.8-0.8	1.9 (0.1), 1.8-2.0
LADCA proximal	0.6 (0.0),0.6-0.6	0.6 (0.1), 0.5-0.6	1.1 (0.1),1.0-1.2
LADCA mid	0.5 (0.0), 0.5-0.5	0.4 (0.0), 0.4-0.4	0.8 (0.0), 0.7-0.8
LADCA distal	0.2 (0.1), 0.1-0.3	0.1 (0.1), 0.1-0.2	0.6 (0.1), 0.5-0.6
Cx proximal	0.6 (0.0), 0.6-0.7	0.6 (0.1), 0.5-0.7	1.4 (0.1), 1.2-1.6
Cx distal	0.3 (0.0), 0.3-0.4	0.2 (0.1), 0.1-0.3	0.9 (0.1), 0.8-1.0
RCA proximal	2.3 (0.2), 1.9-2.5	2.5 (0.3), 2.1-2.8	**16.9 (3.6), 12.6-21.7**
RCA mid	**3.1 (1.3), 2.2-5.7**	**4.2 (2.5), 2.8-9.2**	**28.6 (3.7), 25.6-35.6**
RCA distal	1.4 (0.3), 1.0-1.8	1.7 (0.40), 1.2-2.1	**20.3(2.2), 18.1-23.6**
RCA post desc	0.4 (0.0),0.3-0.4	0.4 (0.1), 0.3-0.5	1.4 (0.4), 1.0-2.2

Dose variation results for structures located near the high dose-gradient are highlighted in bold.

Abbreviations: PWT: partially wide tangential technique; OPP: oblique parasternal photon technique; E⁻/MV: mixed electron/photon direct parasternal technique; LV: left ventricle; LMCA: left main coronary artery, LADCA: left anterior descending coronary artery, Cx: circumflex coronary artery, RCA: right coronary artery, post desc: posterior descending

Spatial variation in contouring resulted in differences to the doses received by each segment from the six radiotherapy regimens reconstructed. There were 96 regimen/segment combinations: 48 for left-sided regimens (Table 3) and 48 for right-sided regimens (Table 4). For 67 of the 96 regimen/segment combinations, the segments were not near the fields. Where this occurred, doses to most segments were <3 Gy, and the differences between the minimum and maximum doses for the observers were usually <1 Gy. For six regimen/segment combinations, the segment was in the high dose area, and not near any field borders (Table 3 italics). This occurred only for one regimen, left E—/MV radiotherapy, where the LV inferior, LV septal, LMCA, LADCA proximal, LADCA mid and the Cx proximal were in the radiation field for all observers. Segment doses were between 17.3 and 28.1 Gy for all observers, and the difference between the minimum and maximum doses was always less than 2 Gy. For the other 23 regimen/segment combinations, segments were on or near field borders (Table 3, Table 4 bold type), resulting in differences of between 2.2 and 21.8 Gy between the minimum and maximum estimated doses, with standard deviations between 0.4 and 8.8 Gy.

2.5 Discussion

In this study we present an atlas for contouring segments of the left ventricle and the coronary arterial tree on radiotherapy planning CT scans. This will facilitate consistent reporting of cardiac doses in radiotherapy research studies and in clinical trials so that radiation doses to these parts of the heart may be related to

clinical outcome data. Such dose-response relationships may help clinicians to assess the risks of damage to particular cardiac segments.

Spatial overlap averaged over the six observers was more than 60% for left ventricular segments but less than 50% for most coronary artery segments and the separation between the contours averaged over the six observers was larger for coronary artery segments (1.3-5.1 mm) than for left ventricle segments (1.5-2.2 mm). Poor overlap of the coronary arterial segment contours was expected because they are 1) difficult to outline reproducibly being long, narrow, irregularly shaped structures and 2) small in volume. As small contours cover a smaller area for a given CT area they are less likely to overlap. Assessing the effects of differences in contours on radiotherapy dose we found that dose variation was much greater for segments near a field edge than for other segments. Our findings are similar to those of Lorenzen[23] and Feng[10] who also reported inter-observer variability in contouring was much larger for cardiac structures that were near field edges than for other structures that were further away. Similar cardiac segment dose variation is likely to occur in modern regimens which also have steep dose gradients, such as proton therapy. For hypofractionated regimens, total target dose is lower so variation in absolute cardiac segment doses will be lower. Nevertheless, variation in EQD2 would be similar.

Our atlas aims to minimize dose variation from one source of uncertainty: differences in contouring. Other sources of uncertainty also need to be considered when estimating cardiac doses. Errors in set-up, dose-calculation algorithms, and intra-fraction motion secondary to breathing and the cardiac cycle

all contribute to dose uncertainty, even where individual CT scans are available. Where individual CT scans are not available and a representative patient is used for retrospective dose estimation, a further source of error in measurement of doses to small segments is variation in patient anatomy.

Our study has a number of strengths. First, the atlas was developed jointly between oncologists and cardiologists who agreed on the segments and instructions for contouring them. Second, six observers from three different countries contoured all the cardiac segments so a range of oncologists were represented. Third, the relevance of the segments to subsequent injury was confirmed by echocardiograms and angiograms from the cardiology records of 500 women. A number of models exist for segmenting the left ventricle. One such model includes 17 segments[14] which are subvolumes of the five main segments described in our atlas. Contouring 17 left ventricular segments reproducibly would be challenging and estimating doses to these subvolumes would only be useful after confirming that the cardiac outcome data, to which the doses will be related, describes those particular subvolumes**.** Fourth, estimated mean coronary artery segment doses are similar to maximum whole artery doses but they also give information on the spatial location of the high dose regions within the artery. In the future, oncologists may wish to avoid certain segments if they are shown to be more sensitive to radiation-related damage than others, or if there is evidence that injury to certain segments is associated with worse outcomes e.g. non-radiation induced LADCA proximal stenosis is associated with poorer outcomes than LADCA mid or distal stenosis[24]. Finally this atlas is based on a non-contrast CT planning scan and so is useful for contouring both on non-contrast scans,

which are routinely acquired for patients with breast cancer, and contrast-enhanced scans, which are routinely acquired for patients with Hodgkin lymphoma, lung and oesophageal cancer. Contrast may improve the accuracy of coronary artery identification, and the same definitions may be followed to identify segment limits. One study has shown that contrast helps to localize the main coronary arteries, but only for the proximal one third of the coronary arteries[25] and in the University of Michigan atlas, contrast made no difference to inter-observer variation in dose reporting[10].

Our study has some limitations. First, it was not possible to compare observer contours before and after access to the atlas. Oncologists are not trained in cardiac contouring so without the atlas the observers would not have been able to contour most segments. Second, the atlas is based on one CT-planning scan but anatomy differs between patients. For example for some women the LADCA proximal has a loop configuration so the atlas would not correctly identify the LADCA proximal position for them. Also, the location of the interventricular septum may vary. For example in the few patients with dilated cardiomyopathy, the interventricular septum may not be directly in line with the interatrial septum, so may not be correctly identified using the instructions in Fig.2.

This atlas provides surrogate definitions for contouring the coronary arterial and left ventricular segments on non-contrast CT-planning scans. There may be ways to improve how these segments are identified. First, contrast improves the ability to visualize the main coronary arteries but there are limitations as described above. Second, the use of respiratory and cardiac-gated images reduces blurring

due to respiratory motion and the dynamic cardiac cycle but this approach may not be practical if acquiring CT-planning scans on a large number of patients. Third, left ventricular segments may be easier to locate by fusing cardiac magnetic resonance scans to CT-planning scans but, as yet, there is no validated algorithm for this. Fourth, it may be possible to develop a tool for automatically delineating these structures in the future. Lastly, once radiotherapy commences, additional information from daily image guided radiotherapy may further improve the accuracy of the doses estimated to the cardiac structures.

This study provides an atlas enabling contouring of left ventricular and coronary arterial segments on radiotherapy CT-planning scans which may be applied to any radiotherapy that involves exposure of the heart. The use of consistent guidelines for segment contouring will facilitate future research studies investigating relationships between segment doses and cardiac outcomes.

Acknowledgements

Duane F, Aznar MC, Bartlett F, Cutter DJ, Darby SC, Jagsi R, Lorenzen EL, McArdle O, McGale P, Myerson S, Rahimi K, Vivekanandan S, Warren S, Taylor CW. A cardiac contouring atlas for radiotherapy. Radiother Oncol 2017;122(3):416-22.

I, F Duane had the original idea to produce the manuscript, designed the study, undertook collection and assembly of the data, the data analysis, the development of the tables and figures and drafted the first version of the manuscript. S Myerson and K Rahimi provided cardiology advice and contributed to the development of the atlas. E Lorenzen, S Warren and MC Aznar

provided medical physics advice. F Bartlett, D Cutter, R Jagsi, O McArdle, S Vivekanandan and C Taylor tested the atlas. All authors contributed to the development of the manuscript.

2.6 References

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3 Cardiac structure doses in women irradiated for breast cancer in the past and their use in epidemiological studies

3.1 Abstract

Background and Purpose

Incidental cardiac exposure during radiotherapy may cause heart disease years later. This study provides cardiac segment doses for women irradiated in the past who received a variety of regimens with different dose distributions to different segments. Such information is required for epidemiological studies investigating which cardiac segments should be preferentially avoided in radiotherapy.

Methods and Materials

Radiotherapy charts of 470 women who developed segment injury after breast cancer radiotherapy were examined and 41 regimens identified. Regimens were reconstructed on a "typical CT-scan". Doses were estimated for five left ventricle (LV) and ten coronary artery segments. Inter-patient dose variation was assessed in ten randomly selected CT-scans for left-sided regimens and in five for right-sided regimens.

Results

For the “typical CT-scan”, inter-regimen segment dose variation was substantial (range: LV segments <1-39 Gy, coronary artery segments <1-48 Gy). In 10 CT-scans, inter-patient segment dose variation was higher for segments near field borders (range: 3-47 Gy) than other segments (range: <2 Gy). LADCA segment doses were highly correlated with doses to the LV segments usually supplied by the LADCA. For individual regimens there was consistency in hotspot location and segment ranking of higher-versus-lower dose.

Conclusions

Segment-specific doses may be used to rank segments according to higher-versus-lower dose. The scope for developing quantitative dose-response relationships for cardiac segment injury based on radiotherapy charts is limited because different segment doses are often highly correlated and segment-specific dose uncertainties are not independent of each other.

3.2 Introduction

Breast cancer radiotherapy reduces breast cancer mortality[1,2] but may increase the risk of ischaemic heart disease (IHD)[3,4] by causing macrovascular coronary artery disease or microvascular myocardial disease[5]. The coronary arteries and myocardium have different structures and functions and may respond differently to radiation. In a recent case-control study of 963 women who developed IHD after breast cancer radiotherapy, the best available predictor of IHD was mean heart dose[3] and coronary artery doses were not significantly associated with the rate of IHD events after mean whole heart dose was taken into account. This may be because the coronary arteries and myocardium are equally sensitive to radiation. Alternatively, it may be an artefact due to strong correlations between doses to the coronary arteries and the myocardium in breast cancer radiotherapy and the greater uncertainties in estimated coronary artery doses compared with doses to the whole heart[6,7]. It remains unclear if using doses to a segment of the heart, e.g. a segment of a coronary artery, improves prediction of IHD risk from breast cancer radiotherapy.

Detailed information from angiogram and echocardiogram reports is available on the locations of injured cardiac segments for many women who received breast cancer radiotherapy in the past. However, few studies have related coronary artery or left ventricle (LV) segment radiation doses to detailed cardiology information[8,9]. As clinical cardiac disease often occurs years after exposure, such studies inevitably need to be carried out in patients treated before the era of CT-based radiotherapy planning. The question arises as to whether doses to

individual segments of the heart can be estimated for such patients and if they can how such estimates can appropriately be used.

This study describes the estimation of cardiac segment doses from breast cancer regimens used in women who subsequently developed segment damage. We describe inter-regimen variation in segment doses for 41 regimens and inter-patient variation in segment doses for 14 commonly-used regimens. We consider how these segment doses may be used to assess associations between dose and segment injury.

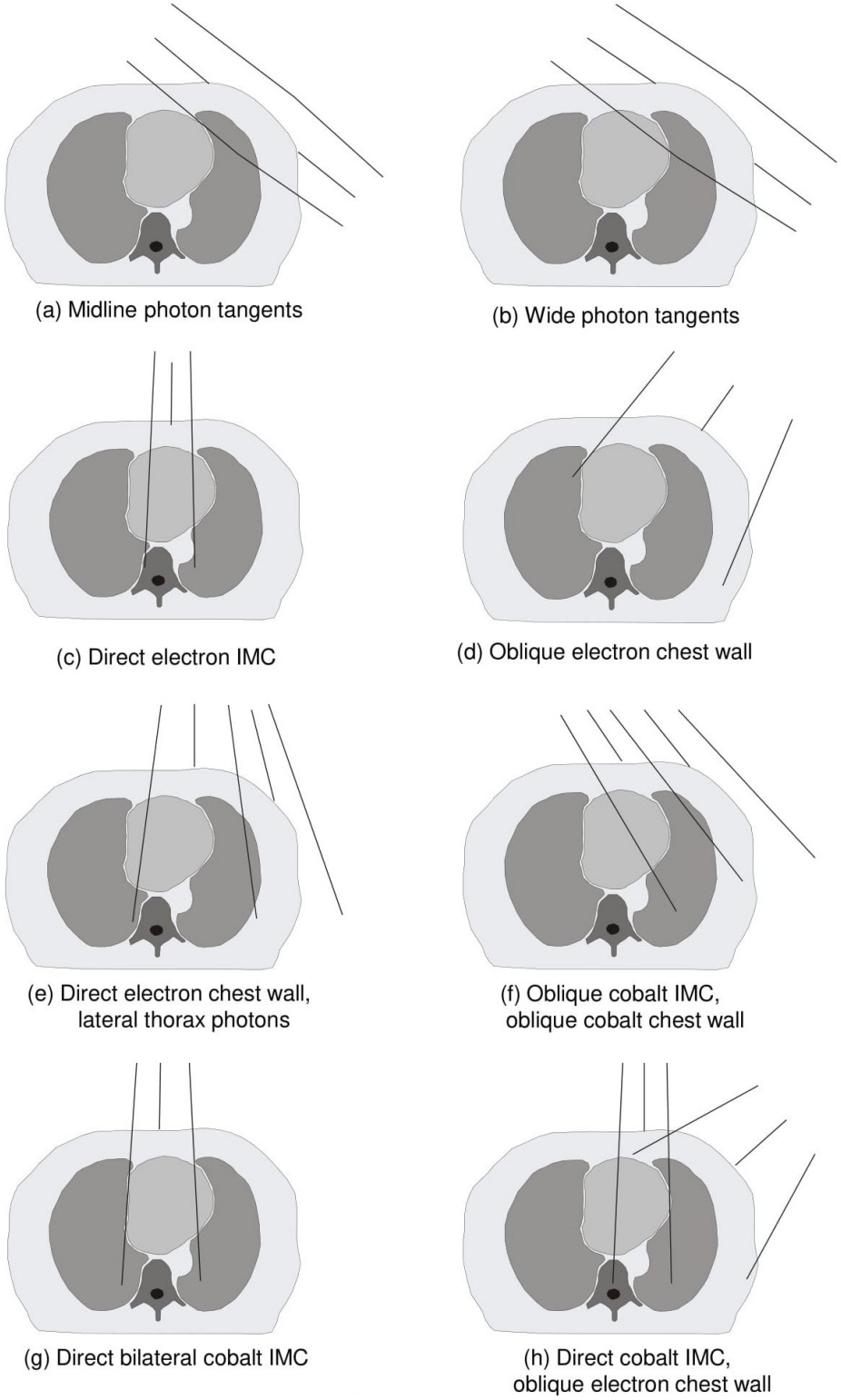
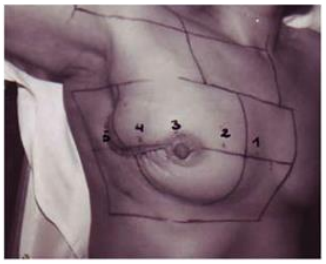
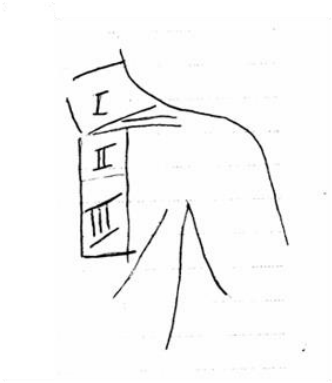


Figure 3-1. Radiotherapy fields used to treat women with breast cancer in Sweden (1958 -2001) or Denmark (1978-2000).

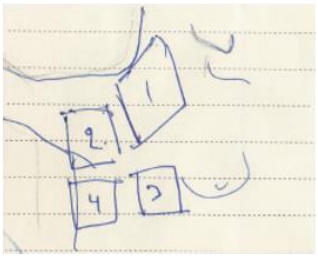
As is usual in radiotherapy planning the patient's right is on the reader's left. Adapted from Taylor 2007[15].



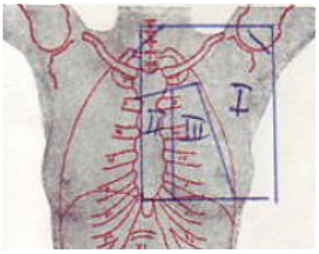
(i) Partially wide tangents



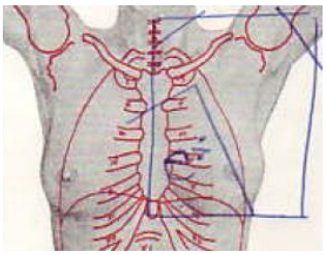
(j) Direct IMC (2-fields)



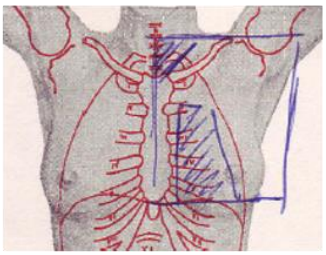
(k) Direct chest wall (4-fields)



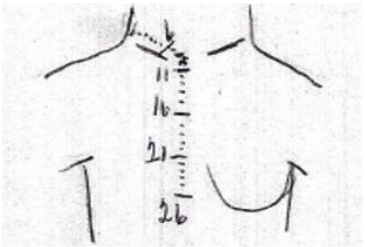
(l) Direct chest wall (2-field), lateral thorax, SCF, axilla



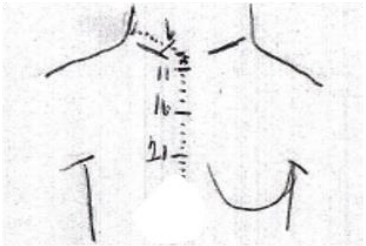
(m) Direct chest wall (1-field), lateral thorax, SCF, axilla



n) Direct chest wall (1-field), lateral thorax, SCF, axilla



(o) Long cobalt chain



(p) Short cobalt chain

Figure 3-2. Radiotherapy regimens used to treat women with breast cancer in Sweden (1958-2001) or Denmark (1978-2000).

3.3 Methods and Materials

3.3.1 Regimens

Regimens were identified from the radiotherapy charts of 470 women included in a population-based study of major coronary events with known location of segment injury after breast cancer radiotherapy[3,10]. The women were irradiated in Sweden during 1958-2001 or Denmark during 1978-2000. Radiotherapy charts included diagrams or photographs of the treatment fields, and sometimes dose-plans. Details on surgery, target definition, field borders, target dose, applied total dose, dose per fraction, beam energy and use of shielding, wedges and bolus were collected. Information was also collated from radiotherapy protocols.

3.3.2 Contouring

Ten radiotherapy CT-planning scans were randomly selected from women irradiated at Odense University Hospital, Denmark in the year 2010. The treatment position was supine, with both arms above the head. Scan slice thickness was 3 mm, and intravenous contrast was not used. The whole heart, the ventricles, and the left ventricle and coronary artery segments were contoured on all 10 scans using an atlas (Chapter 2)[11]. To simulate mastectomy the breast was contoured and assigned a CT-value for air. 1cm of tissue was retained above the pectoralis major muscle to account for residual subcutaneous tissue.

Table 3-1. Radiotherapy regimens received by 470 women with breast cancer in Sweden (1958-2001) or Denmark (1978-2000).

Country	Median year	Field arrangement	Number of women	Usual beam	Target(s)†	Dose (100%) Gy‡	Dose/ fraction	Field borders	Comments
Tangential (n=185)									
Sweden	1959	Tangents (a)§	9	170 kV	Breast	10.5||	3.5	Superior: 2nd costal cartilage Inferior: 1 cm below inframammary fold Medial: midline Lateral: mid-axillary line	Posterior border divergent Opposing symmetrical fields
	1975	Wide tangents (b)	42	Co^{60}	Breast or chest wall, IMC	36.0-65.0	1.4-2.5	Superior: 2nd costal cartilage Inferior: 1 cm below inframammary fold Medial: 6 cm from midline contra Lateral: mid-axillary line	Posterior border divergent Opposing symmetrical fields Collimator not angled Fixed SSD 80 cm
	1982	Tangents (a)	15	Co^{60}	Breast or chest wall	45.0-52.5	1.8-2.0	Superior: 2nd costal cartilage Inferior: 1 cm below inframammary fold Medial: midline Lateral: mid-axillary line	Posterior border divergent Opposing symmetrical fields Collimator not angled Fixed SSD 80 cm
	1990	Tangents (a) (1) ¶||	27	6 MV	Breast or chest wall	44.0-52.0	2.0	Superior: 2nd costal cartilage Inferior: 1 cm below inframammary fold Medial: midline Lateral: mid-axillary line	Posterior border divergent Opposing symmetrical fields Collimator not angled Isocentric technique
Denmark	1981	Wide Tangents (b) (2)	15	6 MV	Chest wall, IMC	38.9-50.0	1.9-2.0	Superior: 2nd costal cartilage Inferior: 1 cm below inframammary fold Medial: 3 cm from midline contra Lateral: mid-axillary line	Posterior border divergent Half beam blocked superiorly Fixed SSD 100 cm at centre of posterior field edge
	1982	Wide tangents (McWhirter) (b)	11	250 kV	Chest wall	25.4-36.0	1.7-2.5	Superior: 2nd costal cartilage Inferior: 1 cm below inframammary fold Medial: 2 cm from midline contra Lateral: mid-axillary line	Posterior border divergent Opposing symmetrical fields
	1994	Tangents (a) (3)	54	8 MV	Breast	47.5-52.0	1.9-2.2	Superior: 2nd costal cartilage Inferior: 1 cm below inframammary fold Medial: midline Lateral: mid-axillary line	Block defined posterior field border (tapered 1 cm around breast tissue inferiorly) Fixed SSD 100 cm along centre of posterior field edge
	1998	Partially wide tangents (i) (4)	12**	8 MV	Breast, IMC	46.0-54.0	1.8-2.0	Superior: 2nd costal cartilage Inferior: 1 cm below inframammary fold Medial: 3 cm from midline contra Lateral: mid-axillary line	Block defined posterior field border (tapered 1 cm around breast tissue below 5th rib) Half-beam-blocked superiorly Fixed SSD 100 cm at centre of posterior field edge

Table 3-1 continued

Country	Median year	Field arrangement †‡	Number of women	Usual beam	Target(s) §	Dose (100%) Gy ¶	Dose/ fraction	Field borders	Comments
Anterior electron or orthovoltage (n=155)									
Sweden	1960	Direct IMC (1-field) (c)	4	170 kV	IMC	14.0-28.0	3.5-4.0	Superior: suprasternal notch Inferior: xiphoid tip Medial: 1 cm from midline contra Lateral: 5 cm from midline	Gantry angle 0°
	1963	Direct IMC (2-fields) (c) (j) (5)	17	12 MeV	IMC	40.0	4.0-5.0	Superior: suprasternal notch Inferior: 14 cm from suprasternal notch Medial: midline Lateral: 4.5 cm from midline	Matching superior and inferior direct anterior beams Typical field size 4.5 cm x 7 cm†† SSD 100cm
	1963	Direct chest wall (4 fields) (k)	17	170 kV	IMC	20.0-35.0	3.5-4.0	Superior: suprasternal notch Inferior: xiphoid tip Medial: 1 cm from midline contra Lateral: 5 cm from midline	Gantry angle 0° 4 x matching direct anterior beams Only the two medial chest wall fields were reconstructed because the other fields were distant from the heart
	1974	Oblique chest wall (d) (6)	21	12 MeV	Chest wall, IMC	44.2-52.5	1.8-2.1	Superior: suprasternal notch Inferior: 1 cm below inframammary fold Medial: midline Lateral: midaxillary line	Gantry angle 35° towards contra side Central bolus (1 cm thick and 8 cm wide) Lower medial corner of the field was blocked Typical field size 14.5 cm x 17 cm†† Fixed SSD 120 cm
Denmark	1981	Direct chest wall Lateral thorax, SCF, axilla (n)	15	100 kV	Chest wall	33.0-48.0	2.0-3.0	*Chest wall field* Superior: suprasternal notch Inferior: xiphisternum joint Medial: midline Lateral: 1 cm medial to lateral lung border	Gantry angle 0° Typical field size 12 cm x 10 cm††
				8 MV	Lateral thorax, SCF, axilla	48.0-50.0	2.0-4.2	*Lat thorax, SCF, axilla field* Superior: inferior border C6 vertebra Inferolateral: inframammary fold or 3 cm below scar Inferomedial: 2nd rib Medial superior: 1 cm from midline contra Medial inferior: 1 cm medial to lateral lung Lateral: 3 cm lateral to humeral head	Gantry angle 15° towards ipsilateral side Chest wall block (lateral border 1 cm medial to lateral lung) 90% dose at half the AP diameter below humeral head Typical field size 14 cm x 24 cm†† Fixed SSD 100 cm
	1982	Direct chest wall Lateral thorax, SCF, axilla (e) (m) (7)	43‡‡	9 MeV	Chest wall	39.8-54.3	2.2-4.0	*Chest wall field* Superior: 2nd rib Inferior: lateral lung border at level of 7th rib Medial: 1 cm from midline contra Lateral: 1 cm medial to lateral lung border	Gantry angle 0° 92% of dose delivered at 3cm depth Fixed SSD 100 cm
				8 MV	Lateral thorax, SCF, axilla	40.9-54.7	2.1-4.2	*Lat thorax, SCF, axilla field* Superior: inferior border C6 vertebra Inferolateral: inframammary fold or 3 cm below scar Inferomedial: 2nd rib Medial superior: 1 cm from midline contra Medial inferior: 1 cm medial to lateral lung Lateral: 3 cm lateral to humeral head	Gantry angle 15° towards ipsilateral side Chest wall block (lateral border 1 cm medial to lateral lung) 90% dose at half the AP diameter below humeral head Typical field size 14 cm x 24 cm†† Fixed SSD 100 cm

Table 3-1 continued

Country	*Median year*	*Field arrangement* †‡	*Number of women*	*Usual beam*	*Target(s)* §	*Dose (100%) Gy* ¶	*Dose/ fraction*	*Field borders*	*Comments*
	1987	Direct IMC Direct chest wall Lateral thorax, SCF, axilla (l)	30§§	9 MeV	IMC	48.3-54.3	2.0-2.4	*IMC field* Superior: 1st costal cartilage Inferior: middle of 5th costal cartilage Medial: 1 cm from midline contra Lateral superior: 5 cm from midline Lateral inferior: 4 cm from midline	Gantry angle 0° 85% dose at depth of pleura plus 0.5 cm Fixed SSD 100cm
				6 MeV	Chest wall	48.0-54.3	2.0-2.4	*Chest wall field* Superior: 1st costal cartilage Inferior: inframammary fold or 3 cm below scar Medial: matching IMC field Lateral: 1 cm medial to lateral lung border	Gantry angle 0° 85% dose at depth of pleura minus 0.5 cm Fixed SSD 100 cm
				8 MV	Lateral thorax, SCF, axilla	48.0-55.9	2.1-2.4	*Lat thorax, SCF, axilla field* Superior: inferior border C6 vertebra Inferolateral: inframammary fold or 3 cm below scar Inferomedial: 2nd rib Medial superior: 1 cm from midline contra Medial inferior: 1 cm medial to lateral lung Lateral: 3 cm lateral to humeral head	Gantry angle 15° towards ipsilateral side Chest wall block (lateral border 1 cm medial to lateral lung) 90% dose at half the AP diameter below humeral head Typical field size 14 cm x 24 cm†† Fixed SSD 100 cm
	1991	Oblique chest wall (d)	8	12 MeV	Chest wall	51.6-54.0	2.2-2.4	Superior: suprasternal notch Inferior: 1 cm below inframammary fold Medial: midline Lateral: midaxillary line	Gantry angle 35° towards contra side Central bolus (1 cm thick x 8 cm wide) Lower medial corner blocked Typical field size 14.5 cm x 17 cm†† Fixed SSD 120 cm
Anterior megavoltage (n=56)									
Sweden	1969	Oblique IMC Oblique chest wall (f)	17	Co^{60}	IMC	36.0	4.0	*IMC field* Superior: suprasternal notch Inferior: xiphisternum Medial: 4.5 cm from midline contra Lateral: 4.5 cm from midline	Gantry angle 30° towards ipsilateral side SSD 80 cm
				Co^{60}	Chest wall	32.0-36.0	4.0	*Chest wall field* Superior: suprasternal notch Inferior: xiphisternum Medial: matched to IMC field Lateral: 2 cm from skin surface	Gantry angle 30° towards ipsilateral side SSD 80 cm
	1974	Direct bilateral IMC (g)	14	Co^{60}	IMC	36.0-42.0	3.0-4.0	Superior: suprasternal notch Inferior: xiphisternum Medial: 4.5 cm from midline contra Lateral: 4.5 cm from midline ipsilateral	Gantry angle 0° IMC field centred at midline Typical field size 9 cm x 21 cm†† SSD 80 cm
	1983	Direct IMC Oblique chest wall (h)	25	Co^{60}	IMC	49.5-52.3	2.0-2.8	*IMC field* Superior: suprasternal notch Inferior: xiphoid tip Medial: midline Lateral: 5.5 cm from midline contra	Gantry angle 0° Typical field size 5.5 cm x 15.5 cm†† SSD 80 cm
				9 MeV	Chest wall	47.3-48.5	1.9-2.6	*Chest wall field* Superior: suprasternal notch Inferior: xiphisternum Medial: matched to IMC field Lateral: mid-axillary line	Gantry angle 40° towards contra side Typical field size 9 cm x 21 cm†† SSD 100 cm

Table 3-1 continued

Country	Median year	Field arrangement †‡	Number of women	Usual beam	Target(s) §	Dose (100%) Gy ¶	Dose/ fraction	Field borders	Comments
Cobalt chain (n=74) ¶¶									
Sweden	1963	Cobalt chain long (o)	36	Co^{60}	IMC, SCF	7.0-9.0	3.5	Isocentre 2.5 cm from midline Inferior: 4th intercostal space	3.5 cm x 6 cm overlapping fields along the IMC
	1966	Cobalt chain short (p)	38	Co^{60}	IMC, SCF	7.0-9.0	3.5	Isocentre 2.5 cm from midline Inferior: 7 cm below 4th intercostal space	3.5 cm x 6 cm overlapping fields along the IMC

*Regimens are ordered as in Tables 3-6. Each technique listed accounts for two regimens, one for left-sided and one for right-sided cancers apart from one direct megavoltage technique (direct bilateral IMC) which was the same for left and right-sided cancers.

Information was collated from radiotherapy charts, radiotherapy protocols and from oncologists and physicists who had delivered them (see references (i)-(vi) below).

†Some regimens included separate fields to the SCF and/or axilla but as the doses to the whole heart and to all of the cardiac structures were less than 0.5 Gy, they were not reconstructed. Some regimens included separate field(s) to boost the surgical bed after breast conserving surgery but information was lacking on the location of the surgical bed and heart dose from these fields is likely to be ≤ 1.0 Gy (see Taylor 2007[vii]) so these boost fields were not reconstructed.

‡Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast/chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

§Regimens a-p are illustrated in Fig. 1-2.

¶Regimens 1-7 were reconstructed on 10 CT scans to study the effect of patient anatomy on segment doses (Figs. 4-6).

||One woman in the category received 36 Gy in 12 fractions.

**This includes 3 women irradiated in Sweden whose radiotherapy was similar to this Danish technique.

††Field size: width (cm) x length (cm).

‡‡This includes 7 women irradiated in Sweden whose radiotherapy was similar to this Danish technique.

§§This includes 3 Swedish women who received techniques similar to this Danish technique.

¶¶For description of cobalt chain see Taylor 2009[i].

Abbreviations: kV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, SSD: source-surface distance, AP: antero-postero, Co^{60}: cobalt 60.

References

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3.3.3 Selection of the “typical CT-scan”

The two most common left-sided regimens for the women in the study were identified and reconstructed on all 10 CT-scans. These were a midline tangential regimen (Fig. 1 (a), Table 1 (technique 3)) used after breast conserving surgery and a direct electron chest wall regimen (Fig. 1(e), Table 1 (technique 7)) used after mastectomy. Whole heart doses and cardiac substructure doses were collated as were whole heart volume, chest wall separation, sternal length and Haller index (ratio of height between the anterior spine and the posterior sternum to the transverse width of the chest). The scan with mean heart doses closest to average for both techniques and which was not atypical for any of the anatomical factors examined was selected as the “typical CT-scan” (Table 2).

3.3.4 Reconstruction and dose calculation

All identified regimens were reconstructed on this "typical CT-scan" using 3-dimensional treatment planning (Varian Eclipse^{TM} Treatment Planning System (TPS) version 10.0.39). Lines were drawn on the body surface to represent clinical landmarks used to plan 2-dimensional radiotherapy in previous decades. Field borders, gantry angles, and custom blocks[12] were guided by these clinical surface markings and by digitally-reconstructed radiographs. The dose calculation algorithms were: analytical anisotropic algorithm for photon plans, Monte Carlo for electron plans, and pencil beam for cobalt plans. If photon beam energies were unavailable they were created using mixed energy beams. Dose

Table 3-2. 'Typical CT dataset' selection

Scan No.	Mean heart dose (Gy)		Anatomical measurements			
	Left tangents, midline divergent [(a)(3)*]	Left direct chest wall electrons [(e) (7)*]	Sternal length (cm)	Heart volume (cc)	Chest wall separation (cm)†	Haller index‡
1	1.8	1.9	17.0	781.7	24.3	2.1
2	5.5	3.4	18.0	719.6	22.3	1.8
3	1.2	1.6	16.0	1010.5	21.6	1.9
4	3.7	1.9	19.0	901.7	20.0	2.6
5§	4.0	4.8	17.0	710.5	19.0	1.9
6	3.1	2.9	16.0	836.0	20.9	1.9
7	8.2	5.4	16.0	691.4	19.3	3.4
8	7.6	6.9	19.0	834.4	20.4	2.6
9	0.9	2.0	18.0	826.6	21.0	2.5
10	4.6	3.0	19.0	615.8	18.5	0.5
Correlation of anatomical measurements with mean heart dose estimates¶						
Regimen (a)			*r= -0.06, p=0.87*	*r= -0.37, p=0.27*	*r= -0.30, p=0.40*	*r= 0.52, p=0.13*
Regimen (e)			*r= 0.11, p=0.77*	*r= -0.39, p=0.27*	*r= -0.43, p=0.22*	*r= 0.32, p=0.34*

*Regimens (a) and (e) are illustrated in Fig. 1. For regimen (e) the doses reported here are from the direct electron chest wall beam only, not the the lateral photon chest wall field. These regimens are also numbered (3) and (7) in other tables and figures.

†Chest wall separation: the distance between the midline and the midaxillary line

‡Haller index: ratio of height between anterior spine and posterior sternum to the transverse width of the chest.

§Scan 5 was selected as the 'average CT dataset' because it was the scan with mean heart doses closest to average from both techniques a and e (which were the two most commonly identified left-sided regimens) and was not atypical for any of the anatomical factors examined.

¶The anatomical factors evaluated did not correlate with mean heart dose and no scan had consistently average readings for these measurements.

r= correlation coefficient testing the strength of correlation between mean heart dose and anatomical measurements

p= test for correlation equal to zero

was calculated using the 0.1 cm calculation volume grid for all except cobalt regimens, where the minimum grid was 0.25 cm. Dose-volume histograms (DVHs) were exported for each cardiac segment with dose-bins of 0.1%.

Orthovoltage regimens were reconstructed by manual planning. Field borders were defined using CT-based 3-dimensional virtual simulation. Ten axial CT images (CT slice spacing=1.2 cm) spanning the heart were printed and scaled-up to life-size. Isodose charts were superimposed onto each CT slice and used to map dose onto cardiac segments. The isodose shift method was used to correct for lung in the field(s) and stand-off at the body surface (isodose shift factor 0.8). The proportions of each cardiac segment included within isodose lines were calculated. DVHs were plotted and mean segment doses calculated.

For all regimens, DVHs were used to calculate mean doses in equivalent 2 Gy fractions (EQD2). EQD2 dose was separately calculated for each dose-bin in each DVH using $nd[(d+ \alpha/\beta)/(2+ \alpha/\beta)]$, where n=number of fractions, d=mean dose to the cardiac structure per fraction (Gy), and α/β=2 Gy[13,14].

3.3.5 Inter-patient dose variation

The effect of interpatient variability in anatomy on cardiac segment doses was investigated in 14 regimens (with different field arrangements) from the two most common technique categories. Eight of these 14 (four left-sided and four right-sided) were tangential regimens (Table 1 (techniques 1-4)) and six (three left-sided and three right-sided) were anterior electron regimens (table 1, techniques 5-7). Left-regimens were reconstructed on all ten CT-scans and right-regimens

on only five scans because interpatient variability in cardiac dose is usually lower from right-radiotherapy[15]. For each regimen differences between the highest and lowest mean doses (ranges) between individual CT scans for each cardiac segment were calculated. Differences between the highest and lowest hotspot doses (ranges) were also calculated including: D2cc (minimum dose covering the hottest 2.0 cc) of the ventricular myocardium (right ventricle (RV) and left ventricle (LV) combined) and D0.5cc (minimum dose covering the hottest 0.5 cc) of the main coronary arteries (left main coronary artery (LMCA), left anterior descending coronary artery (LADCA), right coronary artery (RCA) and circumflex coronary artery (Cx) combined).

3.4 Results

Forty-one regimens were identified from 470 radiotherapy charts. 20 regimens were for left breast cancer, 20 for right cancer and one regimen was the same for left and right cancers (Fig. 1-2, Table 1).

3.4.1 Tangential regimens

For left megavoltage tangential radiotherapy, cardiac doses were mainly determined by the position of the medial border and divergence of the posterior border (Table 3-4, Fig 3). For left *midline* megavoltage tangents mean doses were LV: 6.0-7.6 Gy and RV: 3.0-4.7 Gy (Table 3, Fig. 3a). For left *wide* megavoltage tangents with a divergent posterior field border both ventricles received ≥12.5 Gy but for *partially wide* tangents both ventricles received <6.1 Gy (Table 3, Fig 2b). For left megavoltage tangents, mean individual LV segment

doses varied substantially (range 0.6 - 38.8 Gy). The LV apex received the highest doses of ≥22.5 Gy. The anterior LV segment received ≥11.7 Gy from wide divergent and partially wide megavoltage tangents but ≤9.2 Gy from midline megavoltage tangents. The LV septal segment received ≥12.8 Gy from wide divergent megavoltage tangents but ≤5.3 Gy from partially wide and midline megavoltage tangents. The lateral and inferior segments were further from the fields and received ≤6.4 Gy from all left megavoltage tangents.

Mean doses to coronary artery segments in left megavoltage tangential radiotherapy varied from 0.4 to 48.0 Gy. For all megavoltage tangents the LADCA mid and distal segments received the highest doses of ≥32.8 Gy (Table 4, Fig. 3). The LADCA proximal received ≥18.9 Gy from wide divergent and partially wide megavoltage tangents and 8.6-11.0 Gy from midline megavoltage tangents. RCA and Cx segments were further from the fields and received 0.4-8.2 Gy.

For orthovoltage midline tangents, the prescribed dose was only 10.5 Gy and all cardiac segments received ≤9 Gy (Table 3-4). For McWhirter orthovoltage wide-tangential radiotherapy (36.0 Gy prescribed dose), whole LV and LADCA doses were similar to those for megavoltage wide tangents but RCA and Cx doses were higher due to scattered radiation from orthovoltage beams.

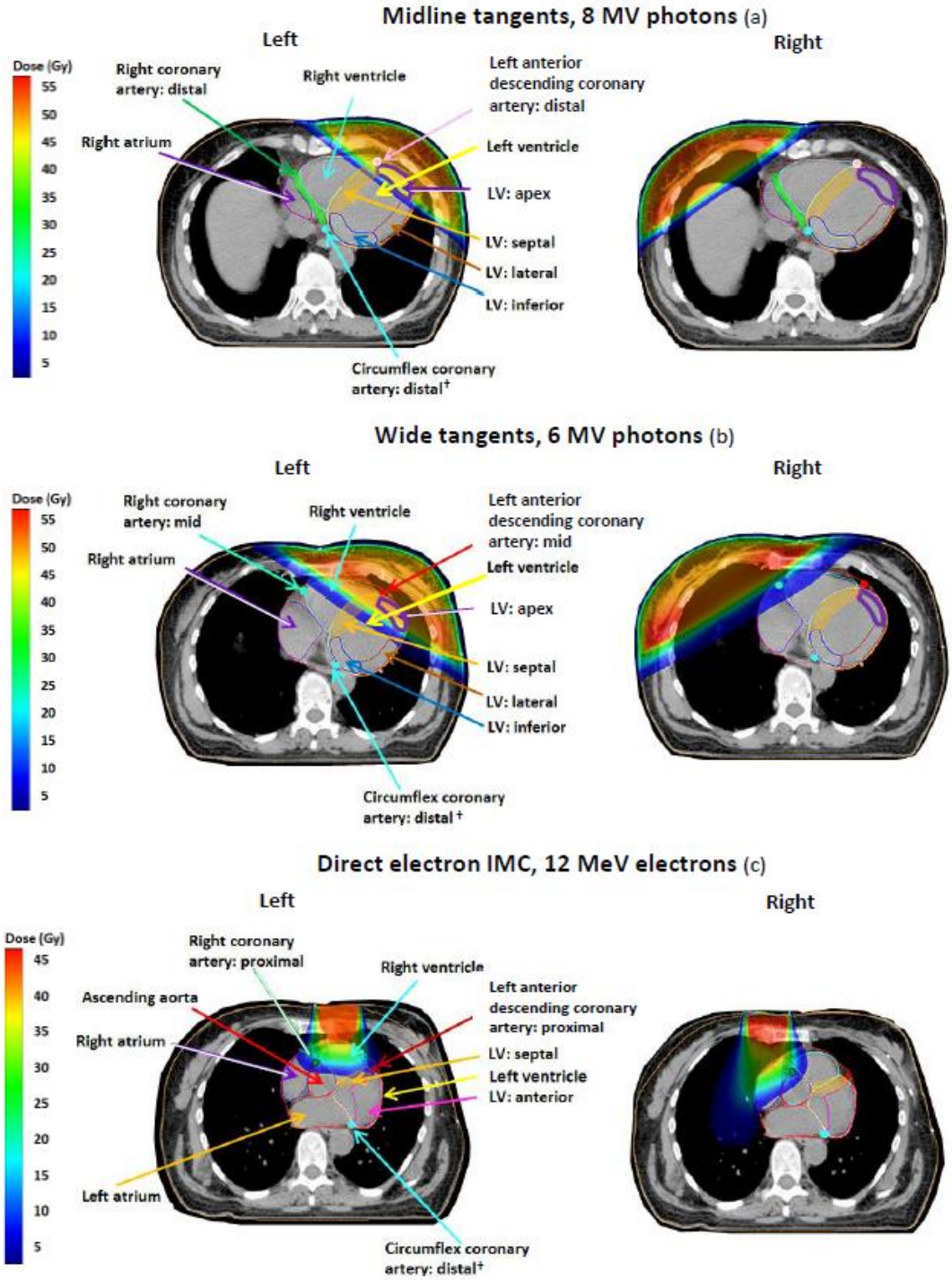


Figure 3-3. Spatial distribution of cardiac dose from breast cancer tangential and direct electron radiotherapy regimens used to treat women with breast cancer in Sweden (1958 -2001) or Denmark (1978-2000).

Left-regimens a-c illustrated in Fig. 1.
† The main circumflex coronary artery has only two segments, proximal and distal
Abbreviations: MV: megavoltage, MeV: mega electron-volts.

Table 3-3. Mean radiation therapy doses to myocardial structures from left-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000).

Radiotherapy regimen*						Mean cardiac doses (Gy)†							
	Median	Medial			Dose	Whole	Ventricles:		Left ventricular myocardial segments:				
Country	year	border	Field arrangement	Usual beam energy	(100%) Gy‡	heart	Left	Right	Apex	Lateral	Inferior	Septal	Anterior
Tangential													
Sweden	1959	Midline	Tangents, divergent (a)§	170 kV	10.5	2	3	3	8	3	1	3	3
	1975	6 cm contra	Wide tangents, divergent (b)	Co^{60}	45.0	11.3	13.6	18.3	35.7	6.4	2.0	16.3	18.8
	1982	Midline	Tangents, divergent (a)	Co^{60}	50.0	5.3	7.6	4.7	33.2	3.0	1.3	5.3	9.2
	1990	Midline	Tangents, divergent (a) (1)¶	6 MV	50.0	4.8	7.2	3.6	37.1	2.3	1.0	4.2	7.7
Denmark	1981	3 cm contra	Wide tangents, divergent (b) (2)	6 MV	40.7	9.1	12.5	13.0	38.8	5.7	1.3	12.8	18.2
	1982	2 cm contra	Wide tangents (McWhirter) (b)	250 kV	36.0	11	13	13	31	12	6	14	18
	1994	Midline	Tangents, block posteriorly (a) (3)	8 MV	48.0	4.0	6.0	3.0	31.2	2.0	0.6	3.3	7.6
	1998	3 cm contra	Partially wide tangents, block posteriorly (i) (4)	8 MV	48.0	4.9	5.9	6.1	22.5	2.6	0.7	4.7	11.7
Anterior electron or orthovoltage													
Sweden	1960	1 cm contra	Direct IMC (1-field) (c)	170 kV	28.0	9	7	11	5	5	7	13	7
	1963	Midline	Direct IMC (2-fields) (c) (j) (5)	12 MeV	40.0	3.7	0.8	8.3	0.5	0.4	0.4	2.1	1.5
	1963	1 cm contra	Direct chest wall (4 fields) (k)	170 kV	20.0	7	5	8	3	4	5	9	6
	1974	1 cm contra	Oblique chest wall (d) (6)	12 MeV	47.8	9.4	8.6	14.4	28.7	5.2	0.7	9.1	19.1
Denmark	1981	Midline	Direct chest wall (1-field)/lat thorax, SCF, axilla (n)	100 kV/8 MV	36.0/50.0	10	9	11	6	7	4	11	21
	1982	1 cm contra	Direct chest wall (1-field)/lat thorax,SCF, axilla (e) (m) (7)	9 MeV/8 MV	51.8/51.7	6.7	4.6	9.3	9.6	3.1	2.0	4.2	14.4
	1987	1 cm contra	Direct chest wall (2-fields)/lat thorax, SCF, axilla (l)	9 MeV/6 MeV/8 MV	54.0/50.0/54.0	5.4	3.2	8.5	4.0	3.3	2.4	3.1	5.0
	1991	Midline	Oblique chest wall (d)	12 MeV	51.8	10.2	9.4	15.6	31.2	5.6	0.8	9.8	20.7
Anterior megavoltage													
Sweden	1969	4.5 cm contra	Oblique IMC/oblique chest wall (f)	Co^{60}/Co^{60}	36.0/32.0	21.9	23.1	27.6	27.1	20.3	19.6	25.6	23.8
	1974	4.5 cm contra	Direct bilateral IMC (g)||	Co^{60}	40.0	21.7	12.8	30.0	1.8	4.4	21.1	24.1	5.8
	1983	Midline	Direct IMC/oblique chest wall (h)	Co^{60}/9 MeV	50.6/48.3	20.8	20.1	28.6	10.5	9.9	23.1	30.6	18.4
Cobalt chain **													
Sweden	1963	Midline	Cobalt chain long (overlapping fields) (o)	Co^{60}	7.0	4	6	4	6	2	2	4	6
	1966	Midline	Cobalt chain short (overlapping fields) (p)	Co^{60}	7.0	<1	<1	<1	<1	<1	<1	<1	<1

Highlighted tangential regimens are *wide* tangents, others are *midline* tangents. Highlighted anterior electron or orthovoltage regimens are *oblique* electron fields, others include *direct* fields.

*For further details on the radiotherapy regimens see Table 1.

†Mean cardiac doses estimated using manual planning i.e. orthovoltage and cobalt chain are given to nearest Gy.

‡Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast/chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

§Regimens a-p are illustrated in Fig. 1-2.

¶Regimens 1-7 were reconstructed on 10 CT scans to study the effect of patient anatomy on segment doses (Fig. 4-6).

||Cardiac doses are the same for left-sided and right-sided breast cancer as the same field was used for both.

**For description of cobalt chain see Taylor 2009[16].

Abbreviations: kV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, Co^{60}: cobalt 60

Table 3-4. Mean radiation therapy doses to coronary arterial structures from left-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000).

Radiotherapy regimen*						Mean coronary artery doses (Gy)†												
	Median	Medial		Usual beam	Dose	Left	Left anterior descending				Right					Circumflex		
Country	year	border	Field arrangement	energy	(100%) Gy‡	main	whole	prox	mid	dist	whole	prox	mid	dist	pd	whole	prox	dist
Tangential																		
Sweden	1959	Midline	Tangents, divergent (a)§	170 kV	10.5	1	8	6	9	9	2	2	1	1	2	1	2	1
	1975	6 cm contra	Wide tangents, divergent (b)	Co^{60}	45.0	3.8	35.7	28.3	39.6	38.8	5.7	7.7	8.2	2.0	4.9	1.8	3.0	1.6
	1982	Midline	Tangents, divergent (a)	Co^{60}	50.0	1.9	31.7	11.0	41.8	41.2	1.6	1.8	1.6	1.2	1.7	1.3	1.8	1.2
	1990	Midline	Tangents, divergent (a) (1)¶	6 MV	50.0	1.5	34.1	8.6	46.2	46.1	1.2	1.4	1.1	0.8	1.3	0.9	1.5	0.8
Denmark	1981	3 cm contra	Wide tangents, divergent (b) (2)	6 MV	40.7	1.8	36.2	25.2	41.8	40.4	2.4	2.3	2.2	1.3	3.5	1.1	1.7	1.0
	1982	2 cm contra	Wide tangents (McWhirter) (b)	250 kV	36.0	4	33	24	37	36	7	9	7	5	7	5	8	5
	1994	Midline	Tangents, block posteriorly (a) (3)	8 MV	48.0	1.1	33.1	8.9	46.0	43.4	0.8	1.0	0.7	0.4	0.9	0.6	1.1	0.5
	1998	3 cm contra	Partially wide tangents, block posteriorly (i) (4)	8 MV	48.0	2.0	33.7	18.9	48.0	32.8	1.8	2.7	2.6	0.6	1.2	0.7	1.7	0.6
Anterior electron or orthovoltage																		
Sweden	1960	1 cm contra	Direct IMC (1-field) (c)	170 kV	28.0	16	10	14	11	7	10	18	11	11	3	10	14	9
	1963	Midline	Direct IMC (2-fields) (c) (j) (5)	12 MeV	40.0	4.6	3.4	7.0	2.9	0.5	4.7	13.1	4.0	0.4	0.2	0.8	1.8	0.6
	1963	1 cm contra	Direct chest wall (4 fields) (k)	170 kV	20.0	12	7	10	8	5	7	13	8	8	2	7	10	6
	1974	1 cm contra	Oblique chest wall (d) (6)	12 MeV	47.8	8.3	34.4	30.2	36.3	36.3	6.0	9.4	11.5	1.0	1.4	1.4	4.9	0.9
Denmark	1981	Midline	Direct chest wall (1-field)/lat thorax, SCF, axilla (n)	100 kV/8 MV	36.0/50.0	21	14	28	19	1	8	18	11	3	1	11	21	9
	1982	1 cm contra	Direct chest wall (1-field)/lat thorax,SCF, axilla (e)(m)(7)	9 MeV/8 MV	51.8/51.7	4.1	30.2	35.4	46.2	8.7	6.5	11.3	10.9	2.6	0.8	2.9	3.8	2.7
	1987	1 cm contra	Direct chest wall (2-fields)/lat thorax, SCF, axilla (l)	9 MeV/6 MeV/8 MV	54.0/50.0/54.0	3.5	13.5	14.6	17.7	7.5	5.6	10.8	7.4	2.0	1.4	2.8	3.4	2.7
	1991	Midline	Oblique chest wall (d)	12 MeV	51.8	9.0	37.3	32.8	39.4	39.3	6.5	10.2	12.5	1.1	1.5	1.6	5.3	1.0
Anterior megavoltage																		
Sweden	1969	4.5 cm contra	Oblique IMC/oblique chest wall (f)	Co^{60}/Co^{60}	36.0/32.0	25.1	28.1	27.1	28.4	28.6	25.0	29.0	29.0	19.5	21.3	19.3	22.5	18.8
	1974	4.5 cm contra	Direct bilateral IMC (g) ||	Co^{60}	40.0	28.1	4.0	8.2	1.8	2.3	28.0	32.4	33.4	26.0	21.0	21.7	23.9	21.4
	1983	Midline	Direct IMC/oblique chest wall (h)	Co^{60}/9 MeV	50.6/48.3	36.1	31.8	36.4	29.3	28.0	12.2	22.7	2.5	17.9	8.5	27.8	33.4	26.8
Cobalt chain*																		
Sweden	1963	Midline	Cobalt chain long (overlapping fields) (o)	Co^{60}	7.0	7	6	8	7	4	4	7	2	2	2	2	2	2
	1966	Midline	Cobalt chain short (overlapping fields) (p)	Co^{60}	7.0	1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1

Highlighted tangential regimens are *wide* tangents, others are *midline* tangents. Highlighted anterior electron or orthovoltage regimens are *oblique* electron fields, others include *direct* fields.

*For further details on the radiotherapy regimens see Table 1.

†Mean cardiac doses estimated using manual planning i.e. orthovoltage and cobalt chain are given to nearest Gy.

‡Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast/chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

§Regimens a-p are illustrated in Fig. 1-2.

¶Regimens 1-7 were reconstructed on 10 CT scans to study the effect of patient anatomy on segment doses (Fig. 4-6).

||Cardiac doses are the same for left-sided and right-sided breast cancer as the same field was used for both.

**For description of cobalt chain see Taylor 2009[16].

Abbreviations: kV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, prox: proximal, dist: distal, pd: posterior descending, Co60: cobalt 60

Table 3-5. Mean radiation therapy doses to myocardial structures from right-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000).

Radiotherapy regimen*						Mean cardiac doses (Gy)†							
	Median	Medial			Dose	Whole	Ventricles:		Left ventricular myocardial segments:				
Country	year	border	Field arrangement	Usual beam energy	(100%) Gy‡	heart	Left	Right	Apex	Lateral	Inferior	Septal	Anterior
Tangential													
Sweden	1959	Midline	Tangents, divergent (a)§	170 kV	10.5	1§	1	1	1	<1	<1	1	1
	1975	6 cm contra	Wide tangents, divergent (b)	Co^{60}	45.0	3.9	1.4	6.5	1.3	0.9	1.1	2.0	1.4
	1982	Midline	Tangents, divergent (a)	Co^{60}	50.0	1.2	0.8	1.4	0.7	0.6	0.8	1.0	0.8
	1990	Midline	Tangents, divergent (a) (1)¶	6 MV	50.0	0.7	0.2	0.9	0.1	0.1	0.3	0.4	0.2
Denmark	1981	3 cm contra	Wide tangents, divergent (b) (2)	6 MV	40.7	1.2	0.5	1.8	0.4	0.1	0.5	1.0	0.4
	1982	2 cm contra	Wide tangents (McWhirter) (b)	250 kV	36.0	5	3	7	3	1	3	4	3
	1994	Midline	Tangents, block posteriorly (a) (3)	8 MV	48.0	0.4	0.1	0.5	0.1	0.1	0.2	0.2	0.1
	1998	3 cm contra	Partially wide tangents, block posteriorly (i) (4)	8 MV	48.0	0.8	0.2	1.1	0.1	0.1	0.3	0.4	0.2
Anterior electron or orthovoltage													
Sweden	1960	1 cm contra	Direct IMC (1-field) (c)	170 kV	28.0	7	1	6	1	1	5	5	1
	1963	Midline	Direct IMC (2-fields) (c) (j) (5)	12 MeV	40.0	3.1	0.2	2.6	0.1	0.1	0.3	0.4	0.2
	1963	1 cm contra	Direct chest wall (4 fields) (k)	170 kV	20.0	5	1	5	1	1	4	3	1
	1974	1 cm contra	Oblique chest wall (d) (6)	12 MeV	47.8	4.8	0.6	5.4	0.5	0.5	0.6	0.9	0.8
Denmark	1981	Midline	Direct chest wall (1-field)/lat thorax, SCF, axilla (n)	100 kV/8 MV	36.0/50.0	6	1	4	<1	1	2	2	1
	1982	1 cm contra	Direct chest wall (1-field)/lat thorax, SCF, axilla (e) (m) (7)	9 MeV/8 MV	51.8/51.7	3.1	0.4	3.2	0.2	0.3	0.6	0.5	0.4
	1987	1 cm contra	Direct chest wall (2-fields)/lat thorax, SCF, axilla (l)	9 MeV/6 MeV/8 MV	54.0/50.0/54.0	2.4	0.4	1.9	0.2	0.3	0.5	0.5	0.4
	1991	Midline	Oblique chest wall (d)	12 MeV	51.8	5.2	0.7	5.8	0.5	0.5	0.6	1	0.9
Anterior megavoltage													
Sweden	1969	4.5 cm contra	Oblique IMC/oblique chest wall (f)	Co^{60}/Co^{60}	36.0/32.0	11.6	1.8	19.9	0.8	0.9	2.0	3.9	1.2
	1974	4.5 cm contra	Direct bilateral IMC (g) ||	Co^{60}	40.0	21.7	12.8	30.0	1.8	4.4	21.1	24.1	5.8
	1983	Midline	Direct IMC/oblique chest wall (h)	Co^{60}/9 MeV	50.6/48.3	10.4	1.0	7.7	0.4	0.7	1.7	1.3	0.8
Cobalt chain*													
Sweden	1963	Midline	Cobalt chain long (overlapping fields) (o)	Co^{60}	7.0	3	1	2	<1	<1	2	2	1
	1966	Midline	Cobalt chain short (overlapping fields) (p)	Co^{60}	7.0	<1	<1	<1	<1	<1	<1	<1	<1

Highlighted tangential regimens are *wide* tangents, others are *midline* tangents. Highlighted anterior electron or orthovoltage regimens are *oblique* electron fields, others include *direct* fields.

*For further details on the radiotherapy regimens see Table 1.

†Mean cardiac doses estimated using manual planning i.e. orthovoltage and cobalt chain are given to nearest Gy.

‡Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast/chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

§Regimens a-p are illustrated in Fig. 1 and Supplementary Figs. 1-2.

¶Regimens 1-7 were reconstructed on 5 CT scans to study the effect of patient anatomy on segment doses (Fig. 4-6).

||Cardiac doses are the same for left-sided and right-sided breast cancer as the same field was used for both.

**For description of cobalt chain see Taylor 2009[(i)].

Abbreviations: kV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, Co^{60}: cobalt 60

(i) Taylor CW, Nisbet A, McGale P, et al. Cardiac doses from Swedish breast cancer radiotherapy since the 1950s. Radiother Oncol 2009;90:127-35.

Table 3-6. Mean radiation therapy doses to coronary arterial structures from right-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000).

Radiotherapy regimen*						Mean coronary artery doses (Gy)†												
	Median	Medial			Dose	left	left anterior descending				right					circumflex		
Country	year	border	Field arrangement	Usual beam energy	(100%) Gy‡	main	whole	prox	mid	dist	whole	prox	mid	dist	pd	whole	prox	dist
Tangential																		
Sweden	1959	Midline	Tangents, divergent (a)§	170 kV	10.5	1	1	1	1	1	2	2	3	3	1	1	1	<1
	1975	6 cm contra	Wide tangents, divergent (b)	Co^{60}	45.0	2.0	2.3	1.8	2.3	2.6	12.1	11.9	32.0	4.0	1.2	1.2	1.4	1.2
	1982	Midline	Tangents, divergent (a)	Co^{60}	50.0	1.1	0.9	0.9	0.9	0.8	1.8	2.1	3.2	1.2	0.7	0.8	0.9	0.8
	1990	Midline	Tangents, divergent (a) (1)¶	6 MV	50.0	0.5	0.3	0.2	0.3	0.3	1.3	1.6	2.5	0.9	0.4	0.3	0.3	0.3
Denmark	1981	3 cm contra	Wide tangents, divergent (b) (2)	6 MV	40.7	0.9	0.8	0.7	0.7	0.8	3.5	2.6	9.3	1.5	0.8	0.3	0.5	0.3
	1982	2 cm contra	Wide tangents (McWhirter) (b)	250 kV	36.0	4	4	4	4	4	8	10	11	13	4	3	4	3
	1994	Midline	Tangents, block posteriorly (a) (3)	8 MV	48.0	0.3	0.1	0.1	0.1	<0.1	1.0	1.2	2.1	0.6	0.2	0.2	0.2	0.2
	1998	3 cm contra	Partially wide tangents, block posteriorly (i) (4)	8 MV	48.0	0.6	0.2	0.3	0.2	0.2	2.1	2.4	5.0	1.0	0.3	0.3	0.3	0.3
Anterior electron or orthovoltage																		
Sweden	1960	1 cm contra	Direct IMC (1-field) (c)	170 kV	28.0	3	1	2	1	1	12	18	18	21	3	7	3	8
	1963	Midline	Direct IMC (2-fields) (c) (j) (5)	12 MeV	40.0	0.8	0.2	0.3	0.2	<0.1	12.5	21.6	25.7	1.2	0.2	0.4	0.6	0.4
	1963	1 cm contra	Direct chest wall (4 fields) (k)	170 kV	20.0	2	1	1	1	<1	9	13	13	15	2	5	2	5
	1974	1 cm contra	Oblique chest wall (d) (6)	12 MeV	47.8	1.0	1.5	2.3	1.5	0.7	12.4	15.0	26.3	2.6	0.6	0.7	0.7	0.6
Denmark	1981	Midline	Direct chest wall (1-field)/lat thorax, SCF, axilla (n)	100 kV/8 MV	36.0/50.0	4	1	2	1	<1	11	23	24	18	1	4	3	4
	1982	1 cm contra	Direct chest wall (1-field)/lat thorax, SCF, axilla (e)(m)(7)	9 MeV/8 MV	51.8/51.7	0.8	0.3	0.5	0.3	0.2	9.6	12.7	21.4	2.4	1.0	1.0	0.6	1.1
	1987	1 cm contra	Direct chest wall (2-fields)/lat thorax, SCF, axilla (l)	9 MeV/6 MeV/8 MV	54.0/50.0/54.0	0.8	0.4	0.6	0.4	0.2	8.2	12.8	17.1	2.2	0.5	0.8	0.6	0.8
	1991	Midline	Oblique chest wall (d)	12 MeV	51.8	1.0	1.6	2.5	1.6	0.7	13.4	21.1	28.5	2.8	0.6	0.7	0.8	0.7
Anterior megavoltage																		
Sweden	1969	4.5 cm contra	Oblique IMC/oblique chest wall (f)	Co^{60}/Co^{60}	36.0/32.0	4.2	1.2	1.4	1.1	1.1	18.5	28.2	29.5	17.6	3.8	2.2	1.7	2.3
	1974	4.5 cm contra	Direct bilateral IMC (g) ||	Co^{60}	40.0	28.1	4.0	8.2	1.8	2.3	28.0	32.4	33.4	26.0	21.0	21.7	23.9	21.4
	1983	Midline	Direct IMC/oblique chest wall (h)	Co^{60}/9 MeV	50.6/48.3	1.9	0.6	0.8	0.5	0.4	22.8	31.5	42.6	22.5	2.6	2.7	1.3	2.9
Cobalt chain*																		
Sweden	1963	Midline	Cobalt chain long (overlapping fields) (o)	Co^{60}	7.0	1	<1	1	1	<1	7	8	10	3	3	1	1	1
	1966	Midline	Cobalt chain short (overlapping fields) (p)	Co^{60}	7.0	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1

Highlighted tangential regimens are *wide* tangents, others are *midline* tangents. Highlighted anterior electron or orthovoltage regimens are *oblique* electron fields, others include *direct* fields.

*For further details on the radiotherapy regimens see Table 1.

†Mean cardiac doses estimated using manual planning i.e. orthovoltage and cobalt chain are given to nearest Gy.

‡Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast/chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

§Regimens a-p are illustrated in Figs. 1-2

¶Regimens 1-7 were reconstructed on 5 CT scans to study the effect of patient anatomy on segment doses (Fig. 4-6).

||Cardiac doses are the same for left-sided and right-sided breast cancer as the same field was used for both.

**For description of cobalt chain see Taylor 2009[(i)].

Abbreviations: kV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, prox: proximal, dist: distal, pd: posterior descending, Co^{60}: cobalt 60

(i) Taylor CW, Nisbet A, McGale P, et al. Cardiac doses from Swedish breast cancer radiotherapy since the 1950s. Radiother Oncol 2009;90:127-35.

For all right-tangential regimens, the RV received higher mean doses (0.5-7.0 Gy) than the LV (0.1-3.0 Gy) (Table 5, Fig. 3). Coronary artery segments all received ≤4 Gy apart from RCA segments, which received 0.3-32.0 Gy from right megavoltage wide tangents (Table 6, Fig 3).

3.4.2 Anterior electron or orthovoltage regimens

For anterior electron or orthovoltage radiotherapy, doses depended on field borders, beam energy and whether the beam was direct or oblique. For all regimens the RV received higher doses than the LV because it was closer to anterior fields (left regimens: RV 8.0-15.6 Gy, LV 0.8-9.4 Gy, right-regimens: RV 1.9-6.0 Gy, LV 0.2-1.0 Gy) (Table 3,5, Fig. 3). Left oblique beams were angled towards the LV, and gave higher LV doses (8.6 -9.4 Gy) than left direct beams (0.8-9.0 Gy). For left oblique beams, the LV apex received the highest doses (28.7-31.2 Gy). For left direct beams the anterior or septal LV segments received the highest doses (LV anterior 1.5-21.0 Gy, LV septal 2.1-13.0 Gy). Right anterior electron or orthovoltage regimens delivered ≤5.0 Gy to all LV segments (Table 5).

The coronary artery segments closest to the fields received the highest doses. For left-regimens these were the LADCA and RCA proximal and mid segments (2.9-46.2 Gy) (Table 4) and for right-regimens, the RCA proximal and mid segments (12.7-28.5 Gy) (Table 6).

3.4.3 Anterior megavoltage regimens

Five anterior megavoltage regimens were used: two for left-cancer, two for right-cancer and one regimen was the same in left and right-cancers. Most segments were in the radiotherapy fields and received >20 Gy (Fig.1f-h, Tables 3-6).

3.4.4 Cobalt chain regimens

Cobalt chain radiotherapy involved small, rectangular, overlapping cobalt fields in a vertical line along the internal mammary chain[16]. The short cobalt chain was above the level of the heart and all segments received <1 Gy (Tables 3-6). The long cobalt chain covered part of the heart and delivered <1-10 Gy to cardiac segments.

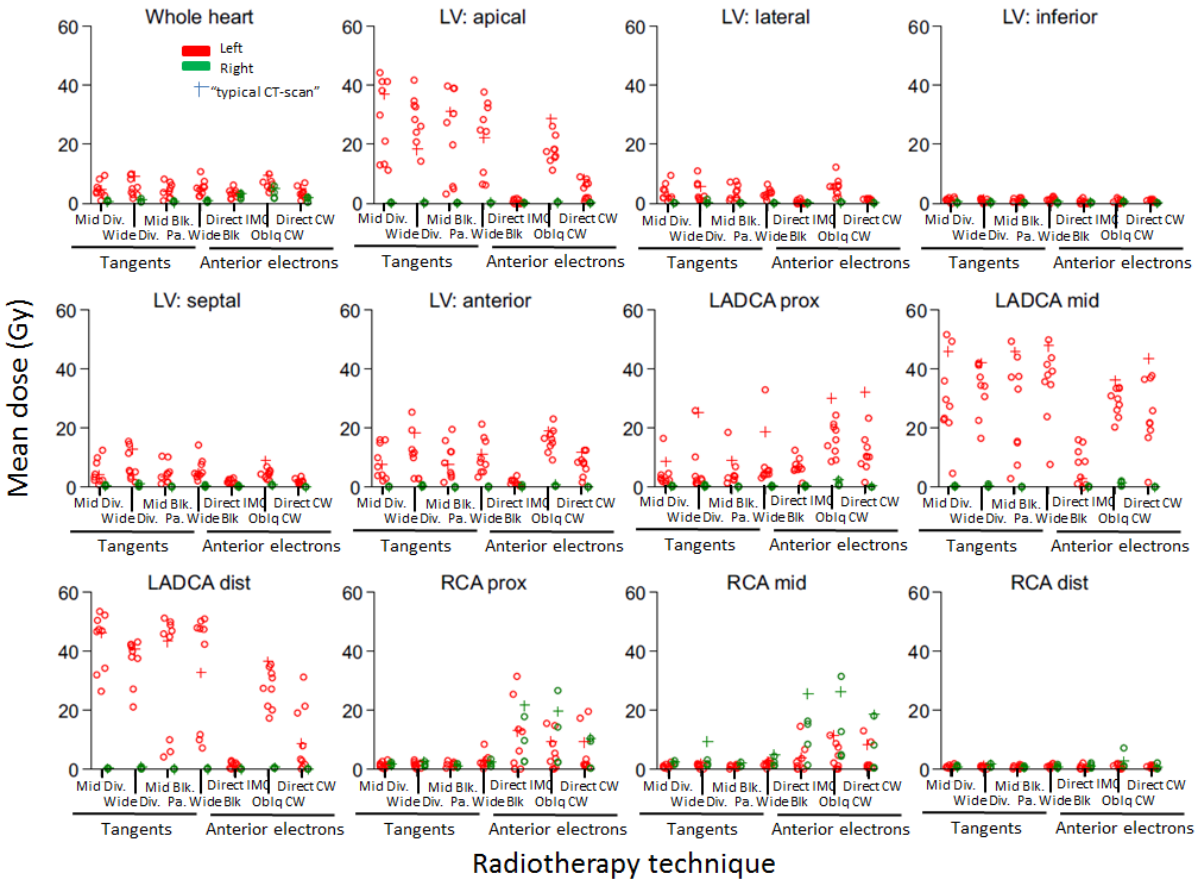
3.4.5 Inter-patient variation

Interpatient variability in mean doses ranged from <1 to 2 Gy for segments distant from the fields (Fig. 4). For segments near the fields it ranged from 3 to 47 Gy for left and 3 to 27 Gy for right-regimens.

For LV segments in left tangents, the LV apex, lateral, septal and anterior segments were near field edges, resulting in dose variability of 8 to 37 Gy (Figs. 2a,b and 3). For the LV inferior segment dose varied by <6 Gy. For left anterior electrons LV segment dose variability was <17 Gy. For right tangents and right anterior electrons LV segment dose variability was <1 Gy.

For coronary artery segments in left tangents dose variability for LADCA segments ranged from 14-47 Gy (Fig 2a,b and 3). For coronary arterial segments further from the fields dose variation was 1-11 Gy. For right tangents dose variability was <8 Gy. For left anterior electrons, the LADCA segments and the RCA proximal and mid segments were close to fields and for right anterior electrons the RCA proximal and mid segments were close to the fields. Dose variability for these segments ranged from 3-41 Gy. For arterial segments further from the fields dose variability was <6 Gy.

Hotspot doses were located in the LV apex, LV anterior and LADCA segments for most left-regimens and in the RV, RCA proximal and RCA mid segments for most right-regimens (Figs. 5-6). The order of segments according to higher-versus-lower dose was the same as that in the typical CT-scan for 91% of LV segment/regimen combinations, 91% of whole coronary artery/regimen combinations and 81% of coronary artery segment/regimen combinations (Tables 7-8).



Regimen definitions

Tangents
(1) Mid. Div: midline divergent, (50 Gy/25f)
(2) Wide Div: wide divergent, medial border 3cm contralateral, (41 Gy/22f)
(3) Mid. Blk: midline, blocked posterior border tapered inferiorly around breast (48 Gy/24f)
(4) Pa. Wide Blk.: partially wide, medial border 3cm contralateral, blocked posterior border tapered inferiorly below 5th rib (48 Gy/28f)

Anterior electron
(5) Direct IMC: direct IMC(40 Gy/10f)
(6) Oblq CW: oblique chest wall (48 Gy/26f)
(7) Direct CW: direct chest wall (52 Gy/24f)

Figure 3-4. Patient to patient variability in mean radiation dose to the whole heart and the left ventricular and coronary arterial segments in women receiving tangential or anterior electron regimens for breast cancer in Sweden (1958-2001) or Denmark (1978-2000).

For further details on regimens 1-7 see Table 1.

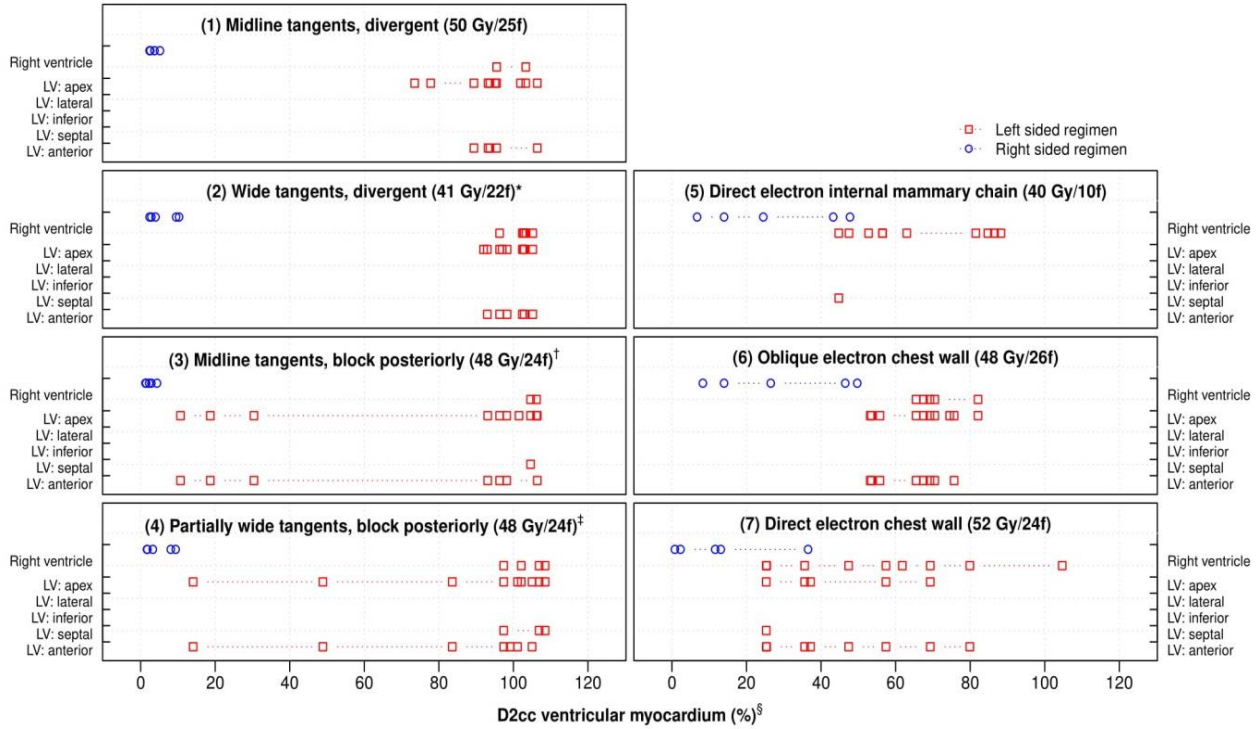


Figure 3-5. D2cc (%) hotspot doses to the ventricular myocardium (right and left ventricles combined) in women receiving tangential or anterior electron regimens for breast cancer in Sweden (1958-2001) or Denmark (1978-2000).

For further details on regimens 1-7 see Table 1.
*medial border: 3cm contralateral
† block tapered inferiorly around breast
‡ block tapered inferiorly below 5th rib, medial border: 3cm contralateral
§ Doses are shown in percent rather than Gy to enable comparison based on patient anatomy, rather than on differing target dose.
The spatial location of the D2cc ventricular myocardial hotspot was identified for each regimen/CT combination using the dose range selection tool on the treatment planning system to highlight the voxels within the volume receiving this dose. Some hotspot volumes spanned more than one structure and were not always contiguous.

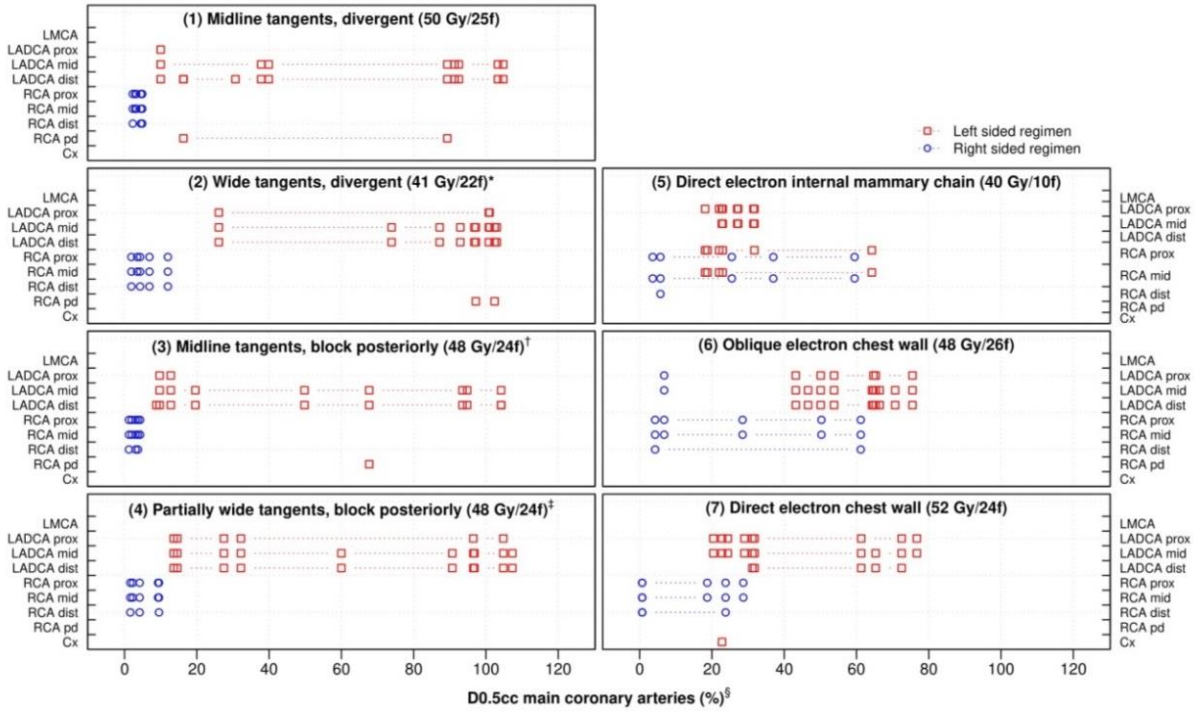


Figure 3-6. D0.5cc (%) hotspot doses to the main coronary arteries (LMCA, LADCA, RCA and Cx combined) in women receiving tangential or anterior electron regimens for breast cancer in Sweden (1958-2001) or Denmark (1978-2000).

For further details on regimens 1-7 see Table 1.
*medial border: 3cm contralateral
† block tapered inferiorly around breast
‡ block tapered inferiorly below 5th rib, medial border: 3cm contralateral
§ Doses are shown in percent rather than Gy to enable comparison based on patient anatomy, rather than on differing target dose.
The spatial location of the D0.5cc main coronary arteries hotspot was identified for each regimen/CT combination using the dose range selection tool on the treatment planning system to highlight the voxels within the volume receiving this dose. Some hotspot volumes spanned more than one structure and were not always contiguous.

Table 3-7. Cardiac segments ordered according to dose received from left breast cancer radiotherapy regimens, comparison of order in typical CT scan with order in nine other scans.

Left breast cancer regimens	Cardiac segments ordered according to dose received Number with order the same as typical CT-scan/ total number of scans assessed									
Midline divergent tangents										
Left ventricle segments	*apical* 9/9	*anterior* 9/9	*septal* 9/9	*lateral* 9/9	*inferior* 9/9					
Whole coronary arteries	*ladca* 9/9	*rca* 9/9	*cflx* 9/9							
Coronary artery segments	*ladca dist* 9/9	*ladca mid* 9/9	*ladca prox* 8/9	*cflx prox* 5/9	*lmca* 4/9	*rca pd* 4/9	*rca prox* 5/9	*rca mid* 9/9	*cflx distal* 9/9	*rca dist* 9/9
Wide divergent tangents										
Left ventricle segments	*apical* 9/9	*anterior* 7/9	*septal* 7/9	*lateral* 9/9	*inferior* 9/9					
Whole coronary arteries	*ladca* 9/9	*rca* 9/9	*cflx* 9/9							
Coronary artery segments	*ladca mid* 1/9	*ladca dist* 1/9	*ladca prox* 6/9	*rca pd* 6/9	*rca prox* 9/9	*cflx prox* 9/9	*lmca* 8/9	*rca mid* 8/9	*cflx dist* 8/9	*rca dist* 8/9
Midline tangents, blocked posteriorly										
Left ventricle segments	*apical* 9/9	*anterior* 9/9	*septal* 8/9	*lateral* 8/9	*inferior* 9/9					
Whole coronary arteries	*ladca* 9/9	*rca* 7/9	*cflx* 7/9							
Coronary artery segments	*ladca mid* 2/9	*ladca dist* 2/9	*ladca prox* 8/9	*rca pd* 6/9	*cflx prox* 7/9	*lmca* 7/9	*cflx dist* 6/9	*rca prox* 5/9	*rca mid* 9/9	*rca dist* 9/9
Partially wide tangents, blocked posteriorly										
Left ventricle segments	*apical* 9/9	*anterior* 7/9	*septal* 7/9	*lateral* 9/9	*inferior* 9/9					
Whole coronary arteries	*ladca* 9/9	*rca* 9/9	*cflx* 9/9							
Coronary artery segments	*ladca mid* 4/9	*ladca dist* 4/9	*ladca prox* 9/9	*rca prox* 7/9	*rca mid* 6/9	*cflx prox* 7/9	*lmca* 8/9	*rca pd* 5/9	*cflx dist* 8/9	*rca dist* 8/9
Direct IMC electrons										
Left ventricle segments	*septal* 7/9	*anterior* 7/9	*apical* 7/9	*lateral* 8/9	*inferior* 6/9					
Whole coronary arteries	*rca* 3/9	*ladca* 3/9	*cflx* 7/9							
Coronary artery segments	*rca prox* 4/9	*ladca prox* 6/9	*lmca* 7/9	*rca mid* 7/9	*ladca mid* 7/9	*cflx prox* 8/9	*ladca dist* 7/9	*cflx dist* 8/9	*rca dist* 9/9	*rca pd* 9/9
Oblique chest wall electrons										
Left ventricle segments	*apical* 7/9	*anterior* 7/9	*septal* 4/9	*lateral* 4/9	*inferior* 9/9					
Whole coronary arteries	*ladca* 9/9	rca 7/9	*cflx* 7/9							
Coronary artery segments	*ladca dist* 5/9	*ladca mid* 5/9	*ladca prox* 8/9	rca mid 2/9	*cflx prox* 3/9	*rca prox* 4/9	*lmca* 8/9	*cflx dist* 6/9	rca pd 6/9	rca dist 8/9
Direct chest wall electrons										
Left ventricle segments	*anterior* 7/9	*apical* 7/9	*septal* 9/9	*lateral* 9/9	*inferior* 9/9					
Whole coronary arteries	*ladca* 9/9	rca 8/9	*cflx* 8/9							
Coronary artery segments	*ladca mid* 9/9	*ladca prox* 7/9	*ladca dist* 5/9	*rca prox* 8/9	rca mid 9/9	*lmca* 9/9	*cflx prox* 7/9	*cflx dist* 8/9	rca pd 8/9	rca dist 8/9

Table 3-8. Cardiac segments ordered according to dose received from right breast cancer radiotherapy regimens, comparison of order in typical CT scan with order in four other scans.

Right breast cancer radiotherapy regimens	Cardiac segments ordered according to dose received Number with order the same as typical CT-scan/ total number of scans assessed									
Midline divergent tangents										
Left ventricle segments	*septal* 4/4	*inferior* 4/4	*anterior* 4/4	*apical* 4/4	*lateral* 4/4					
Whole coronary arteries	rca 4/4	*ladca* 4/4	*cflx* 4/4							
Coronary artery segments	rca mid 4/4	*rca prox* 4/4	rca dist 4/4	*lmca* 4/4	*ladca prox* 4/4	*ladca mid* 4/4	*cflx prox* 4/4	rca pd 4/4	*ladca dist* 4/4	*cflx dist* 4/4
Wide divergent tangents										
Left ventricle segments	*septal* 4/4	*inferior* 4/4	*anterior* 4/4	*apical* 4/4	*lateral* 4/4					
Whole coronary arteries	rca 4/4	*ladca* 4/4	*cflx* 4/4							
Coronary artery segments	*rca mid* 4/4	*rca prox* 4/4	*rca dist* 4/4	*lmca* 4/4	*ladca prox* 4/4	*ladca mid* 4/4	*cflx prox* 4/4	*rca pd* 4/4	*ladca dist* 4/4	*cflx dist* 4/4
Midline tangents, blocked posteriorly										
Left ventricle segments	*septal* 4/4	*inferior* 4/4	*anterior* 4/4	*apical* 4/4	*lateral* 4/4					
Whole coronary arteries	rca 4/4	*cflx* 4/4	*ladca* 4/4							
Coronary artery segments	*rca mid* 4/4	*rca prox* 4/4	*rca dist* 4/4	*lmca* 4/4	*ladca prox* 4/4	*ladca mid* 4/4	*cflx prox* 4/4	*rca pd* 4/4	*ladca dist* 4/4	*cflx dist* 4/4
Partially wide tangents, blocked posteriorly										
Left ventricle segments	*septal* 4/4	*inferior* 4/4	*anterior* 4/4	*apical* 4/4	*lateral* 4/4					
Whole coronary arteries	rca 4/4	*cflx* 3/4	*ladca* 3/4							
Coronary artery segments	*rca mid* 4/4	*rca prox* 4/4	*rca dist* 4/4	*lmca* 4/4	*ladca prox* 4/4	*ladca mid* 4/4	*cflx prox* 4/4	*rca pd* 4/4	*ladca dist* 4/4	*cflx dist* 4/4
Direct IMC electrons										
Left ventricle segments	*septal* 3/4	*inferior* 4/4	*anterior* 3/4	*apical* 4/4	*lateral* 4/4					
Whole coronary arteries	rca 4/4	*cflx* 4/4	*ladca* 4/4							
Coronary artery segments	*rca mid* 4/4	*rca prox* 4/4	*rca dist* 4/4	*lmca* 4/4	*cflx prox* 4/4	*ladca prox* 3/4	*ladca mid* 4/4	*rca pd* 4/4	*ladca dist* 4/4	*cflx dist* 3/4
Oblique chest wall electrons										
Left ventricle segments	*septal* 4/4	*anterior* 2/4	*inferior* 2/4	*apiclal* 4/4	*lateral* 4/4					
Whole coronary arteries	rca 4/4	*ladca* 4/4	*cflx* 4/4							
Coronary artery segments	*rca mid* 4/4	*rca prox* 4/4	*rca dist* 3/4	*ladca mid* 3/4	*ladca prox* 3/4	*lmca* 4/4	*cflx prox* 4/4	*rca pd* 4/4	*cflx dist* 4/4	*ladca dist* 4/4
Direct chest wall electrons										
Left ventricle segments	*septal* 4/4	*inferior* 4/4	*anterior* 4/4	*apical* 4/4	*lateral* 4/4					
Whole coronary arteries	rca 4/4	*cflx* 4/4	*ladca* 4/4							
Coronary artery segments	rca mid 3/4	*rca prox* 3/4	rca dist 4/4	*lmca* 4/4	*ladca prox* 4/4	*cflx prox* 4/4	*ladca mid* 4/4	rca pd 4/4	*ladca dist* 4/4	*cflx dist* 4/4

3.4.6 Correlations between cardiac segments

Doses to all LV segments and all LADCA segments were highly correlated with doses to the whole heart (range of correlation coefficients: 0.7-0.9) (Fig 7). Correlations between the RCA segments and the whole heart were much lower (range of correlation coefficients: 0.1-0.3). LADCA segment doses were highly correlated with doses to the LV segments usually supplied by the LADCA; LV apex, anterior and septal segments (range of correlation coefficients: 0.3-0.9) while RCA segment doses showed little correlation with doses to the LV segments usually supplied by the RCA: LV inferior and septal segments (range of correlation coefficients: -0.1-0.2).

3.5 Discussion

Cardiac segment radiation doses from 41 breast cancer regimens, estimated retrospectively using information from radiotherapy charts, varied substantially. For most regimens, certain segments received >20 Gy whereas others received <1 Gy. Different segments received high doses from different regimens. Such variability provides potential opportunities for the assessment of the effects of different doses to individual segments.

Our study has several strengths. First, detailed information was collated on regimens from several sources, including individual radiotherapy charts for 470 women. Second, doses to coronary artery segments were estimated rather than whole coronary arteries. Arteries are long, thin structures that track in different directions around the heart. Segment doses may be more meaningful as

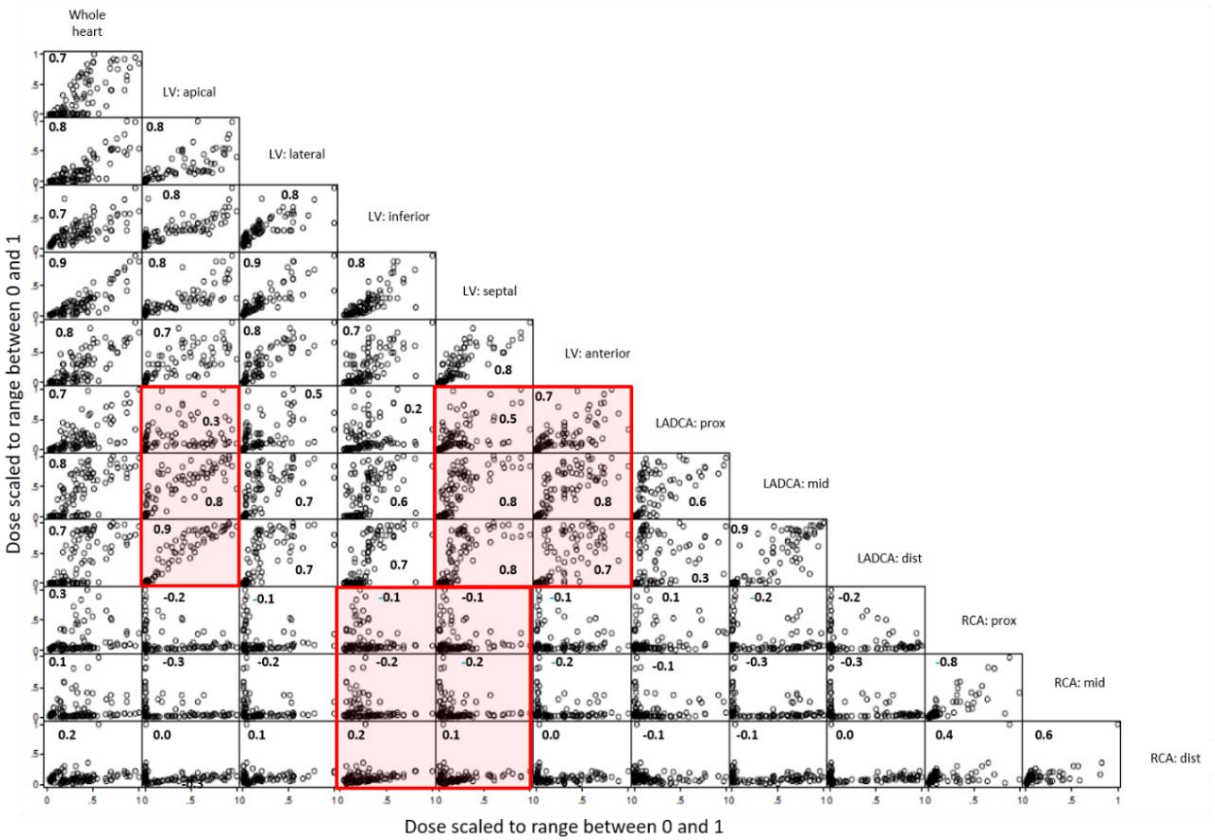


Figure 3-7. Correlations between mean radiation doses to the whole heart and different cardiac segments for women receiving tangential or anterior electron regimens for breast cancer in Sweden (1958-2001) or Denmark (1978-2000).

To display correlations all doses are scaled to range between 0 and 1.
Each panel includes 105 points showing all the estimated mean doses from 7 left-sided regimens reconstructed on 10 CT-scans and 7 right-sided regimens reconstructed on 5 CT-scans.
The panels showing the correlations between LADCA and RCA segment doses and doses to the LV segments usually supplied by the LADCA and RCA are highlighted.

generally only one or two segments of an artery receive substantial dose with other segments receiving only scattered dose. Third we verified that the segments described were those referred to by cardiologists when reporting location of cardiac injury so that segment doses could be directly related to location of damage.

Many years hence, cardiac doses based on patient-specific CT-planning scans may be available for studying long-term adverse effects. At present, however, most patients who have developed clinical heart disease after radiotherapy, were irradiated in the 1970s, 80s and 90s and they did not receive CT-based dosimetry planning. Therefore it is necessary to estimate their cardiac doses using a “typical CT-scan". This method has previously enabled the derivation of a linear dose-response relationship for radiation-related IHD (expressed as a percentage increase in IHD rate per Gy mean whole heart dose) which has been validated in two independent studies[17,18]. When using the "typical CT scan" method, cardiac doses actually received by the individual patients will vary about the estimated dose due principally to inter-patient differences in anatomy. This type of error is known as 'Berkson error[19]. For studies in which the outcome measure of interest is a continuous variable Berkson errors do not bias the slope of the estimated dose-response. In the present case, where the outcome measure is binary, Berkson errors in estimated doses may result in small biases to estimated dose-response relationships[19]. This is in contrast to “classical measurement error” which can lead to considerable attenuation of derived dose-response relationships.

Our mean whole heart doses are consistent with other published estimates for similar regimens (Table 9). Dosimetric uncertainties are larger for cardiac segment doses than for mean whole heart doses because segment doses are more sensitive to interpatient anatomical variability than whole heart doses. Different arm positioning may also have influenced cardiac exposure. Our estimated cardiac doses are subject to several other unavoidable sources of uncertainty that are common to all radiotherapy CT-planning studies, including errors in contouring [11,20], dose calculation algorithm[21], set-up[,22,23], and error caused by cardiac and respiratory motion during treatment[24-26].

The effect of interpatient differences in anatomy varied according to regimen and segment. It was greatest for segments that were near the field edges and therefore close to the high dose gradient at the anterior aspect of the heart. Different segments will be effected in other situations e.g. in patients who received mediastinal irradiation for Hodgkin lymphoma different cardiac segments would be located close to field borders.

Doses to different segments were highly correlated making it difficult to investigate whether myocardial injury resulted from (a) exposure of the myocardium causing disruption of the microvasculature or (b) from exposure of the LADCA causing arterial occlusion and downstream myocardial ischaemia. Interestingly, the RCA segment doses were not correlated with doses to the LV segments usually supplied by the RCA and this may provide an opportunity to

differentiate between myocardial injury caused by microvascular injury versus that caused by macrovascular injury. Differences between doses which were actually delivered to individual segments and surrogate doses assigned based on the typical CT scan (due to positional and anatomical uncertainties) will also be correlated. They may be positively correlated, for example, two adjacent segments may move into or out of the high dose region together such as the LV apex and distal LAD coronary artery in left-tangential radiotherapy (Fig. 3a). Or, they may be negatively correlated, for example, if patient position changed slightly during left direct electron IMC radiotherapy, the proximal LAD might move out of the field, and the proximal RCA move into the field (Fig. 3c).

In cardiac radiation dosimetry high correlations between the estimated segment doses limit the ability to derive meaningful quantitative associations between doses and injury to specific cardiac segments. This difficulty is compounded by the fact that differences between the actual and estimated doses are also strongly correlated. Therefore it would be inappropriate to use them to derive quantitative dose-response relationships. However, "typical CT-scan" doses did consistently indicate whether a particular regimen typically gave a high, medium or low dose to a segment (Tables 7-8) and our segment dose rankings were consistent with those in other publications[9,27-29]. There was also consistency in the locations of hotspots within the ventricular myocardium and the main coronary arteries for each regimen (Figs. 5-6). Segment-specific doses may, therefore, be used to rank segments according to higher-versus-lower dose. These rankings may then be related to the risks of cardiac segment injury in patients who

Table 3-9. Comparison of doses in this study with previously published estimates for comparable regimens used in Sweden (1958-2001) or Denmark (1978-2000).

Radiotherapy regimen*						Mean heart dose (Gy)†								
						Left-sided regimens				Right-sided regimens				
Country	Median year	Medial border	Field arrangement ‡	Usual beam energy	Dose (100%) Gy §	Duane	Taylor	Lorenzen	Thorsen	Duane	Taylor	Lorenzen	Thorsen	Likely reason for dose differences
Tangential														
Sweden	1959	Midline	Tangents (a)	170 kV	10.5	2	2	-	-	1§	1	-	-	
	1975	6cm contra	Wide tangents (b)	Co^{60}	45.0	11.3	16.3	-	-	3.9	6.2	-	-	patient anatomy
	1982	Midline	Tangents (a)	Co^{60}	50.0	5.3	4.7	-	-	1.2	1.2	-	-	
	1990	Midline	Tangents (a)	6 MV	50.0	4.8	2.8	-	-	0.7	2.0	-	-	
Denmark	1981	3cm contra	Wide tangents (b)	6 MV	40.7	9.1	8.5	-	-	1.2	2.7	-	-	
	1982	2cm contra	Wide tangents (McWhirter) (a)	250 kV	36.0	11§	14	-	-	5§	9	-	-	patient anatomy
	1994	Midline	Tangents (a)	8 MV	48.0	4.0	-	2.8	3.4	0.4	-	< 1.0	-	
	1998	3cm contra	Partially wide tangents (i)	8 MV	48.0	4.9	-	3.8	-	0.8	-	< 1.0	0.8	
Anterior electron or orthovoltage														
Sweden	1960	1cm contra	Direct IMC (1-field) (c)	170 kV	28.0	9§	5	-	-	7§	3	-	-	patient anatomy, manual planning uncertainties
	1963	Midline	Direct IMC (2-fields) (c) (j)	12 MeV	40.0	3.7	1.5	-	-	3.1	1.2	-	-	
	1963	1cm contra	Direct chest wall (4 fields) (k)	170 kV	20.0	7§	4	-	-	5§	3	-	-	patient anatomy, manual planning uncertainties
	1974	1cm contra	Oblique chest wall (d)	12 MeV	47.8	9.4	4.1	-	-	4.8	2.0	-	-	patient anatomy, different electron energies
Denmark	1981	Midline	Direct chest wall (1-field)/lat thorax, SCF, axilla (n)	100 kV/8 MV	36.0/50.0	10§	4	-	-	6§	2	-	-	patient anatomy, manual planning uncertainties
	1982	1cm contra	Direct chest wall (1-field)/lat thorax,SCF, axilla (e) (m)	9 MeV/8 MV	51.8/51.7	6.7	3.0	-	-	3.1	1.9	-	-	patient anatomy, different electron energies
	1987	1cm contra	Direct chest wall (2-fields)/lat thorax, SCF, axilla (l)	9 MeV/6 MeV/8 MV	54.0/50.0/54.0	5.4	4.5	-	-	2.4	3.0	-	3.5	
	1991	Midline	Oblique chest wall (d)	12 MeV	51.8	9.9	4.4	-	-	5.2	2.0	-	-	patient anatomy, different electron energies
Anterior megavoltage														
Sweden	1969	4.5cm contra	Oblique IMC/oblique chest wall (f)	Co^{60}/Co^{60}	36.0/32.0	21.9	18.5	-	-	11.6	9.0	-	-	
	1974	4.5cm contra	Direct bilateral IMC (g)	Co^{60}	40.0	21.7	19.5	-	-	21.7	19.5	-	-	
	1983	Midline	Direct IMC/oblique chest wall (h)	Co^{60}/9 MeV	50.6/48.3	20.8	-	-	-	10.4	-	-	-	
Cobalt chain ¶														
Sweden	1963	Midline	Cobalt chain long (overlapping fields) (o)	Co^{60}	7.0	3.9	4.0	-	-	2.6	3.0	-	-	
	1966	Midline	Cobalt chain short (overlapping fields) (p)	Co^{60}	7.0	0.1	0.1	-	-	<0.1	<0.1	-	-	

Where there are differences of > 3 Gy between doses estimated by Duane and Taylor[1,2] or Lorenzen[3] or Thorsen[4], these are highlighted.
"-" Regimen not reconstructed

*For further details on the radiotherapy regimens see Table 1.
†Mean cardiac doses estimated using manual planning i.e. orthovoltage and cobalt chain are given to nearest Gy.
‡Regimens a-p are illustrated in Fig. 1-2.
§Usual total dose (100%) to the target tissues (see Table 1 for dose range). For direct regimens this was the Dmax. For tangential regimens the total dose (100%) was delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.
¶For description of cobalt chain see Taylor 2009[1].
Abbreviations: kV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, Co^{60}: cobalt 60

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received radiotherapy in the past to ascertain if segments that receive higher doses have a higher risk of injury.

Acknowledgements

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I, F Duane extracted information from radiotherapy charts, performed the dosimetry, undertook collection and assembly of the data, the data analysis, the development of the tables and figures and drafted the first version of the manuscript. K Rahimi provided cardiology advice. S Hackett, E Lorenzen and S Warren provided medical physics advice. P McGale, S Darby and C Taylor contributed to the data analysis and interpretation. All authors contributed to the development of the manuscript.

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4 Exposure of the heart, left ventricle and cardiac valves from breast cancer regimens used in the Netherlands 1970-2009.

4.1 Abstract

Background and Purpose

Breast cancer regimens used to irradiate the internal mammary chain (IMC) in the Netherlands during 1970-2009 were associated with significant excesses of valvular heart disease (VHD) and heart failure (HF) relative to non-IMC regimens. Cardiac dose estimates are presented which may enable derivation of new dose-response relationships.

Material and Methods

Radiotherapy charts were abstracted for women irradiated in the Netherlands during 1970-2009. For 44 typical regimens and 771 individual patients, doses were estimated for: whole heart, left ventricle (LV), pulmonary valve (PV), aortic valve (AV), tricuspid valve (TV) and mitral valve (MV) by reconstructing regimens on a typical CT-dataset.

Results

Whole heart doses ranged from <1-33 Gy. They were higher than in other populations due to the frequent use of IMC fields. Different regimens irradiated different cardiac structures. The LV received higher doses than the whole heart from left-tangents but not from other regimens. The TV and AV received >20 Gy from left or right megavoltage IMC irradiation. The MV and PV also received >20 Gy from left megavoltage IMC irradiation.

Conclusions

Different regimens expose different cardiac structures to high doses of radiation. These doses will be used to investigate dose-response relationships for VHD and HF. Information on the sensitivity of the LV and cardiac valves would inform modern 3D CT-planning.

4.2 Introduction

Radiotherapy for breast cancer improves survival in many women[1,2] but may expose the heart to incidental irradiation, which leads to increased risks of heart disease. Most of the radiation-related risk is due to ischaemic heart disease[3,4] but increased risks of valvular heart disease (VHD) and heart failure (HF) have also been reported in some populations of women irradiated for breast cancer[3,5,6] [Appendix E2,5]. In other populations, these risks are not increased[7-10]. Whole heart doses and cardiac dose distributions in breast cancer radiotherapy vary substantially in different regimens, and in different populations,[6,11-14] and differences in risk may be caused by differences in left ventricle (LV) and valve radiation doses. A dose-response relationship for valve disease after Hodgkin lymphoma radiotherapy suggests that radiation does not cause valve disease at doses of ~20 or 30 Gy[15]. The relationship between valve dose and VHD may not be the same in breast cancer patients because they are older on average when they receive their radiotherapy, and they receive different regimens, with differing cardiac dose distributions. At present, there are no known dose-response relationships for the risks of VHD disease or HF after breast cancer radiotherapy. If produced, these could be used to estimate risks of VHD and HF for women being considered for breast cancer radiotherapy today. Such information would be particularly relevant to women who receive IMC radiotherapy which has been shown to improve breast cancer survival in women at high risk of breast cancer recurrence. The IMC is near to the heart so irradiating it may expose the cardiac valves and the LV.

HF and VHD usually take many years to develop. To assess the 20 year risks of radiation it is necessary to study women who received their radiotherapy >20 years ago i.e. during the 1970s, 80s and 90s. Women who received IMC radiotherapy in the Netherlands (NL) during the 1970s and 80s had significant excesses of VHD and HF compared with other similar women who did not receive IMC radiotherapy [Appendix D5]. In this study we describe radiation doses to the whole heart, LV and cardiac valves from breast cancer regimens used in the Netherlands during 1970 to 2009. These doses will be used to investigate associations between cardiac doses and the risks of subsequent VHD and HF.

4.3 Methods and materials

4.3.1 Regimens

Regimens were identified from 771 radiotherapy charts of women who were irradiated during 1970 to 2009 at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute. They had been selected for case-control studies of ischaemic heart disease, HF and VHD after breast cancer radiotherapy [Chapter 5, Appendix E5]. Information on the regimens was extracted from each chart. This included: field borders, surgery type, target, intended target dose, applied total dose, dose per fraction, beam energy and the use of shielding, wedges and bolus.

4.3.2 Selection of a 'typical CT-dataset'

The method for selecting the "typical CT-scan" has been previously described in Chapter 3. First the most commonly used left-sided regimen was identified from

the charts. This was a midline tangential regimen consisting of two opposing beams with alignment of the posterior field borders, used from the 1980s up to the early 2000s. Second, this regimen was reconstructed on each of ten CT scans and whole heart doses were reviewed. Third, anatomical features which may influence cardiac doses were measured, including: sternal length, heart volume, chest wall separation distance and the Haller index (ratio of height between the anterior spine and posterior sternum to the transverse width of the heart). From these 10 scans, one CT-dataset was selected as the "typical CT-scan". It was not atypical for anatomy and it was average in terms of mean heart dose for the most commonly used regimen in the study (MWHD “typical CT-scan”: 4.8 Gy, average MWHD ten CT scans: 4.8 Gy (range 1.9 – 9.1 Gy)).

4.3.3 Contouring

The treatment position was supine, with both arms above the head. Slice thickness was 3mm and no intravenous contrast was used. The following cardiac structures were contoured using validated atlases[16,17]: whole heart, left ventricle (LV), pulmonary valve (PV), aortic valve (AV), mitral valve (MV), and tricuspid valve (TV). To simulate mastectomy the CT scan was copied and the breast was removed from the dose calculations by contouring it and assigning it the CT-value for air. 1 cm of tissue was retained above pectoralis major muscle to account for residual subcutaneous tissue post-mastectomy.

4.3.4 Reconstruction and dose calculation

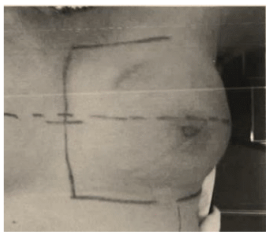
All other regimens identified were reconstructed using the 'typical CT-dataset'. Electron or megavoltage photon regimens were reconstructed using 3-dimensional treatment planning (Varian Eclipse^{TM} Treatment Planning System version 10.0.39 (Varian Medical Systems, Palo Alto, USA)). Clinical landmarks used to plan radiotherapy in previous decades were drawn onto the body surface of the CT scan. Field borders, gantry angles, and custom blocks were guided by these lines and by photographs of the fields and digitally-reconstructed radiographs. The analytical anisotropic algorithm was used to calculate cardiac doses for photon plans, Monte Carlo was used for electron plans, and pencil beam was used for cobalt plans. Mixed energy beams were used if the relevant photon beam energies were not available. The 0.1 cc calculation volume grid was used to calculate doses for all except the cobalt regimens, where the minimum calculation volume grid was 0.25 cc. Tabular differential dose-volume histograms (DVHs) were exported for cardiac structures.

Manual planning was used to estimate doses from orthovoltage fields. Field borders were defined using CT-based 3-dimensional virtual simulation (Varian EclipseTM Treatment Planning System). Ten axial CT images (CT slice spacing=1.2 cm) spanning the heart were printed and scaled-up to life-size. Isodose charts were superimposed onto each CT slice and dose was mapped onto cardiac structures. The isodose shift method was used to correct for lung in the field and to compensate for stand-off at the body surface (isodose shift factor 0.8). The proportions of each cardiac structure included within isodose lines were estimated and used to produce dose volume histograms (DVHs).

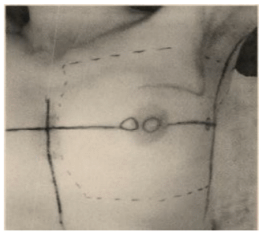
4.3.5 Estimation of cardiac doses

DVHs were used to calculate different measures of cardiac dose. Mean organ doses were calculated for the whole heart, LV and cardiac valves. Dose-volume measures were calculated for the whole heart including: V_{5Gy} (percent volume receiving 5 Gy or more), $V_{10Gy,}$ V_{15Gy} V_{20Gy} V_{25Gy} V_{30Gy} V_{35Gy} and $V_{40Gy.}$ Mean doses in equivalent 2 Gy fractions (EQD2) were calculated for each individual dose-bin in each DVH using $nd[(d+ \alpha/\beta)/(2+ \alpha/\beta)]$, where n was the number of fractions, d was the mean dose to the cardiac structure per fraction (Gy), and α/β was 2 Gy[18,19]. The individual dose-bin EQD2s were summed to estimate the total EQD2 for each structure.

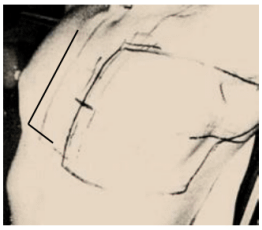
"Typical regimens" were defined as those received by ≥5 women (with either left or right-sided cancer). Cardiac doses for each typical regimen were estimated using the most frequently prescribed total dose (100%) in radiotherapy charts for that regimen. Individual patient doses were estimated using each individual's prescribed target dose in her radiotherapy chart. Individual patient doses were used to estimate changes in cardiac doses over time and relationships between LV and whole heart doses.



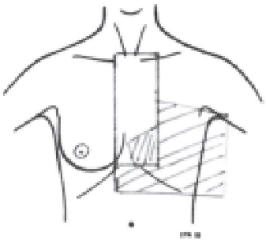
(a) Tangents
Medial border: midline



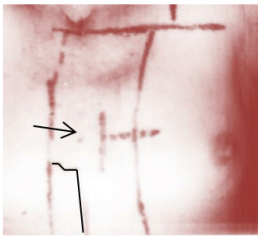
(b) Tangents
Medial border: 1 cm ipsilateral



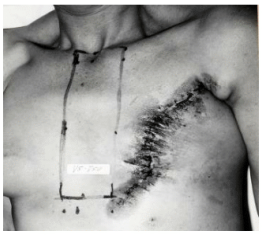
(c) Direct IMC cobalt field, matching tangents



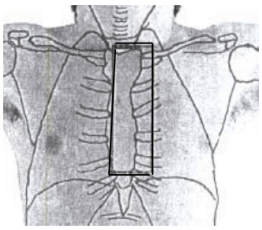
(d) Direct IMC mixed photon and electron fields, matching electron chest wall field



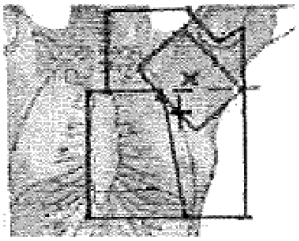
(e) Oblique IMC mixed photon and electron fields, matching tangential pair



(f) Direct IMC orthovoltage field



(g) Direct IMC electron field



(h) Direct electron chest wall field,
Matching lateral thorax, SCF, axillary photon field*

Figure 4-1. Radiotherapy fields used to treat women with breast cancer at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009.

Abbreviations: IMC: internal mammary chain, SCF: supraclavicular fossa
*A posterior axillary boost field was used for some women to achieve a therapeutic dose to the axilla.

Table 4-1. Radiotherapy regimens and dose-fractionation schedules for 754 women with breast cancer at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009.

Years of radiotherapy	Field arrangement*†	*No. of women*	*Beam energy*	Target(s)‡§	*Dose (100%) (Gy)¶*	*Dose/ fraction*	Field borders	*Comments*
Tangential fields (n=290)								
1970-1973	Tangents	5	250 keV	Chest wall	15.0	3.0	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - midline Lateral - mid-axillary line	Posterior border typically divergent Opposing symmetrical fields
1975-1989	Tangents	9	Co^{60}	Breast	50.0	2.0	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - midline Lateral - mid-axillary line	Posterior border typically divergent Opposing symmetrical fields Collimator not angled Fixed SSD 80cm
1981-2001	Tangents (a)	175	4-8 MV	Breast	44.0-52.0	2.0	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - midline Lateral - mid-axillary line	Posterior border typically divergent Opposing symmetrical fields Collimator not angled Isocentric technique
2000-2009	Tangents (b)	101	6-18 MV	Breast/chest wall	46.2-51.5	1.7-2.5	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - 1 cm from midline ipsi Lateral - mid-axillary line	Posterior field edges half-beam blocked Collimator angled to avoid heart Many women received field in field radiotherapy
Megavoltage IMC fields (n=200)								
Megavoltage								
1971-1984	Direct IMC	8	Co^{60}	IMC	40.0-53.0	2.1-3.3	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0° Fixed SSD 80cm
1973-1985	Direct IMC, matching chest wall	15	Co^{60}	IMC§	39.6-40.0	2.5-3.3	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0° Fixed SSD 80cm
			9 MeV	Chest wall	36.8-37.6	2.3-2.4	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	Gantry angle 0°
1977-1989	Direct IMC, matching tangents (c)	45	Co^{60}	IMC§	43.0-53.8	1.9-2.9	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0° Fixed SSD 80cm
			6 MV	Breast	40.0-50.0	1.8-2.0	Superior - clavicular head Inferior - 1cm below inframammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	Medial beam overlapped the IMC field by 5mm on skin

Table 4-1 continued

Year of treament	Field arrangement*†	*No. of women*	*Beam energy*	Target(s)‡§	*Dose (100%) (Gy)¶*	*Dose/ fraction*	Field borders||	*Comments*
1975-1993	Direct IMC, direct SCF/axilla/lateral thorax	21	4-6 MV	IMC	40.1-56.3	2.2-3.0	Superior - suprasternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Six charts had a direct IMC field only
			8 MV	SCF/axilla/lateral thorax	44.5-56.3	2.2-2.5	Superior - inferior border of C6 vertebra Infero-lateral - where rib 7 touches the lung contour Infero-medial - rib 2 Medial - 1cm from midline contra Lateral - 3cm lateral to humeral head	Medial beam overlapped the IMC field by 5mm on skin
1979-2006	Direct IMC, matching tangents	12	4-8 MV	IMC§	16.0-52.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
			4-25 MV	Breast	50.0-52.0	2.0	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframmary fold Medial - matched to IMC field Lateral - mid-axillary line	Medial beam overlapped the IMC field by 5mm on skin
Mixed megavoltage/electron								
1979-1987	Direct IMC, matching tangents	7	Co^{60}	IMC§	15.4-36.0	1.5-2.0	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0° Fixed SSD 80cm
			12 MeV	IMC§	9.7-30.0	1.9-2.7	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
			6 MV	Breast	45.0-50.0	1.8-2.0	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	Medial beam overlapped the IMC field by 5mm on skin
1981-1999	Direct IMC, matching tangents	15	6-8 MV	IMC§	22.5-40.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
			10-12 MeV	IMC§	10.0-26.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
			6-8 MV	Breast	47.5-50.0	2.0-2.5	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - matched to IMC field Lateral - mid-axillary line	Lateral tangent entered through the mid-axillary line to form the pair Medial beam overlapped the IMC field by 5mm on skin

Table 4-1 continued

Year of treament	Field arrangement*†	*No. of women*	*Beam energy*	Target(s)‡§	*Dose (100%) (Gy)¶*	*Dose/ fraction*	Field borders||	*Comments*
1991-2000	Direct IMC, matching chest wall (d)	22	4-8 MV	IMC§	22.5-26.7	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Diagonal block below 4th rib Gantry angle 0°
			10-12 MeV	IMC§	22.5-26.0	2.0-2.5	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Diagonal block below 4th rib Gantry angle 0°
			6-10 MeV	Chest wall	40.0-50.0	2.0-2.5	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial -superior - matched to lateral border of IMC field Medial -inferior - midline sternum Lateral - mid-axillary line	Gantry angle 0°
1993-2006	Direct IMC	15	6-8 MV	IMC	18.0-19.3	2.0-2.8	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
			10-12 MeV	IMC	21.4-32.0	2.0-2.7	Superior - suprasternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
2000-2005	Direct IMC, matching tangents	19	6-10 MV	IMC§	15.8-18.0	2.0-2.3	Superior - cricoid cartilage Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	CT planned to deliver 85% of total dose to lymph nodes Inferior border extended caudally to include the medial aspect of the breast
			8-17 MeV	IMC§	32.0-33.8	2.1-2.3	Superior - cricoid cartilage Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	CT planned to deliver 85% of total dose to lymph nodes Inferior border extended caudally to include the medial aspect of the breast
			6-10 MV	Breast/chest wall	49.6-50.0	2.0-2.2	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - 4.5 cm from midline ipsi matched to IMC field Lateral - mid-axillary line	Opposing symmetrical fields Posterior beam edges aligned Medial beam overlapped the IMC field by 5mm on skin

Table 4-1 continued

Year of treament	Field arrangement*†	*No. of women*	*Beam energy*	Target(s)‡§	*Dose (100%) (Gy)¶*	*Dose/ fraction*	Field borders||	*Comments*
2003-2010	Oblique IMC, matching tangents (e)	21	6-10 MV	IMC§	16.6-18.1	1.7-2.0	Superior - clavicular head Inferior - xiphoid tip Medial - 2cm from midline contra Lateral - 4cm from midline ipsi	CT planned to deliver 85% of total dose to lymph nodes Inferior border extended caudally to include the medial aspect of the breast
			10-20 MeV	IMC§	32.0-34.9	1.7-2.1	Superior - clavicular head Inferior - xiphoid tip Medial - 2cm from midline contra Lateral - 4cm from midline ipsi	CT planned to deliver 85% of total dose to lymph nodes Inferior border extended caudally to include the medial aspect of the breast
			6-10 MV	Breast/chest wall	50.0-51.5	1.7-2.0	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - 3.5 cm from midline ipsi matched to IMC field Lateral - mid-axillary line	Opposing symmetrical fields Posterior beam edges aligned Medial beam overlapped the IMC field by 5mm on skin Many women had field-in-field
Orthovoltage or mixed orthovoltage/megavoltage IMC fields (n=172)||								
1971-1985	Direct IMC (f)	116	250 keV	IMC	36.2-48.8	2.2-2.7	Superior -sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
1981-1989	Direct IMC	33	250 keV	IMC	17.2-21.5	1.8-2.5	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
			Co^{60}	IMC	19.1-31.9	2.1-2.9	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0° Fixed SSD 80cm
1989-1992	Direct IMC	23	250 keV	IMC	16.8-23.5	1.8-2.5	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
			4-8 MV	IMC	21.9-24.0	2.0-2.7	Superior -sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0°
Electron chest wall or IMC fields (n=92)								
1975-1985	Direct IMC (g)	36	10-16 MeV	IMC	45.0	3.0	Superior - sternal notch Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0° The direct MeV IMC field covered intercostal spaces 1-4

Table 4-1 continued

Year of treament	Field arrangement*†	*No. of women*	*Beam energy*	Target(s)‡§	*Dose (100%) (Gy)¶*	*Dose/ fraction*	Field borders||	*Comments*
1978-1985	Direct IMC, matching tangents	22	10-13 MeV	IMC	30.0-45.0	2.0-3.0	Superior - sternal notch Inferior - xiphoid tip Medial - 1cm from midline contra Lateral - 5cm from midline ipsi	Gantry angle 0° The direct MeV IMC field covered intercostal spaces 1-4
			6 MV	Breast	33.4-50.0	1.8-2.2	Superior - middle of 2nd costal cartilage Inferior - 1cm below inframammary fold Medial - matched to lateral border of IMC field Lateral - mid-axillary line	Medial beam overlapped the IMC field by 5mm on skin
1970-1998	Direct chest wall	14	10-13 MeV	Chest wall††	40.1-60.0	2.0-3.0	Superior- matched SCF/axillary field Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 1cm medial to lateral lung contour	Gantry angle 0°
1972-2003	Direct chest wall, direct SCF/axilla/lateral thorax	20	8-13 MeV	Chest wall**	40.0-50.0	2.0-3.0	Superior - matched to SCF/axillary field Inferior - xiphoid process Medial - 1cm from midline contra Lateral - 1cm medial to lateral lung contour	Gantry angle 0°
			8 MV	SCF/axilla/lateral thorax	43.0-53.0	2.0-2.7	Superior - inferior border of C6 vertebra Infero-lateral - where rib 7 touches the lung contour Infero-medial - rib 2 Medial - 1cm from midline contra Lateral - 3cm lateral to humeral head	Gantry angle 0° Large anterior chest wall block (lateral border 1cm medial to lateral lung contour)

*Radiotherapy regimens are ordered as in Table 2
†Regimens a-h are illustrated in Fig. 1.
‡Separate fields to the SCF and/or axilla were not reconstructed as they delivered <0.5 Gy mean heart dose. Separate boost fields were not reconstructed as information was lacking on the location of the surgical bed.
§For IMC fields matched to breast or chest wall fields the inferior border reached the 5th intercostal space including the xiphoid process in many cases. This was to allow coverage of the breast or chest wall tissue medially. The typical field size was 18-25 cm.
¶Usual total dose (100%) to the target tissues. For tangents the total dose was delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast. For direct regimens this was the Dmax.
||Some orthovoltage IMC fields were matched to an electron chest wall field or a tangential pair to the breast. Cardiac doses for these field combinations were not calculated as it was not possible to create a radiotherapy plan using both manual planning and CT-planning.
**For many women who were treated with direct electron chest wall fields the internal mammary chain also received a therapeutic dose.
Abbreviations: IMC: internal mammary chain, keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, SCF: supraclavicular fossa, contra: contralateral, SSD: source-surface distance, AP: antero-postero, ipsi: ipsilateral

4.4 Results

Forty four “typical regimens” were each represented by ≥5 of the 771 radiotherapy charts, including 98% (754/771) charts. Twenty two of these regimens were used to treat left-sided cancer and 22, right-sided cancer. The other 2% of the charts (17/771) described atypical regimens, received by <5 women (left and right combined). Regimen categories were: tangential fields (290 charts), megavoltage or mixed megavoltage/electron IMC fields (200 charts), orthovoltage or mixed orthovoltage/megavoltage IMC fields (172 charts) and electron chest wall or IMC fields (92 charts) (Table 1,2).

4.4.1 Tangential fields

Eight tangential regimens were used: 4 for left-sided and 4 for right-sided cancers (Table 1,2). The position of the medial border was a major determinant of cardiac doses. For left *midline* megavoltage tangents (used 1970s-2000s) (Fig. 1a) mean doses were: whole heart 4.8-5.3 Gy and LV 7.2-7.6 Gy. Of the cardiac valves, the PV was the one nearest the fields and received 2.2-2.8 Gy mean dose and the other valves received <1.6 Gy. For left megavoltage tangents with the medial border *1 cm ipsilateral* to midline (used 2000s) (Fig. 1b) mean doses were lower: whole heart 1.5 Gy, LV 2.1 Gy, and valve doses ≤1.4 Gy. Left orthovoltage tangents were used during 1970-1973 with only 15.0 Gy prescribed skin dose, and all cardiac structures received ≤4 Gy. For all left-tangents, the LV received higher doses than the whole heart due to its position near the fields. For right-tangential regimens, mean doses were whole heart: 0.3-1.2 Gy, LV: 0.1-1 Gy, and all cardiac valves: ≤1.5 Gy.

Table 4-2**.** Mean radiation doses to cardiac structures from breast cancer regimens used at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009.

Radiotherapy regimen*†					Mean doses (Gy)‡											
					Whole heart		*Left ventricle*		*Pulmonary valve*		*Aortic valve*		*Mitral valve*		*Tricuspid valve*	
Years of radiotherapy	*Medial border*	*Field arrangement*	*Beam energies*	*Dose (100%) G §*	*Left||*	*Right||*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
Tangential fields (290 charts)																
1970s	Midline	Tangents	250 keV	15.0	4	1	4	1	3	2	2	2	2	1	2	2
1970s-1980s	Midline	Tangents	Co^{60}	50.0	5.3	1.2	7.6	0.8	2.8	1.3	1.6	1.5	1.4	0.9	1.4	1.5
1980s-2000s	Midline	Tangents (a)	6 MV	50.0	4.8	0.7	7.2	0.2	2.2	0.6	1.2	1.1	1.1	0.4	1.1	1.1
2000s	1cm ipsi	Tangents (b)	6 MV	50.0	1.5	0.3	2.1	0.1	1.4	0.2	0.7	0.5	0.7	0.2	0.5	0.6
Megavoltage IMC fields (200 charts)																
Megavoltage																
1970s-1980s	1cm contra	Direct IMC	Co^{60}	43.0	20.4	13.0	15.6	1.7	32.8	3.8	29.9	25.9	25.1	3.5	27.7	30.7
1970s-1980s	1cm contra	Direct IMC, matching chest wall	Co^{60}/9 MeV	40.0/37.6	22.3	12.3	17.4	1.6	36.4	3.6	30.8	24.2	25.8	3.3	28.4	28.6
1970s-1980s	1cm contra	Direct IMC, matching tangents (c)	Co^{60}/6 MV	53.8/50.0	28.8	16.6	22.6	2.2	46.1	4.9	41.7	32.6	35.1	4.6	38.4	38.7
1970s-1990s	1cm contra	Direct IMC, direct SCF/axilla/lateral thorax	6 MV/8 MV	40.5/44.5	25.8	14.3	20.0	1.6	39.7	3.2	37.2	28.9	32.2	3.0	35.6	35.2
1980s-2000s	1cm contra	Direct IMC, matching tangents	6 MV/6 MV	50.0/50.0	33.1	18.5	25.6	1.9	51.8	3.1	48.3	36.4	41.7	3.3	46.4	46.8
Mixed megavoltage/electron																
1980s	1cm contra	Direct IMC, matching tangents	Co^{60}/12 MeV/6 MV	24.0/22.0/46.0	17.0	10.0	11.8	1.3	33.1	4.2	23.3	19.5	16.4	2.4	18.8	19.9
1980s-1990s	1cm contra	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	24.0/26.0/50.0	20.7	12.0	14.3	1.2	39.6	3.9	28.7	23.3	20.9	1.9	24.3	25.5
1990s	1cm contra	Direct IMC, matching chest wall (d)	6 MV/12 MeV/9 MeV	22.5/22.5/40.0	16.4	9.1	10.0	0.8	39.9	3.3	27.7	22.0	20.2	1.6	23.5	23.9
1990s-2000s	1cm contra	Direct IMC	6 MV/12 MeV	18.7/21.4	14.7	8.5	9.7	0.9	29.2	2.9	20.7	16.6	14.4	1.3	17.2	17.8
2000s	1cm contra	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	18.0/32.0/50.0	16.1	9.4	11.4	1.1	32.9	4.2	20.3	18.5	12.8	1.8	15.3	17.0
2000s	2cm contra	Oblique IMC, matching tangents (e)	6 MV/12 MeV/6 MV	18.0/32.0/50.0	9.0	1.7	11.0	0.5	14.6	1.0	2.9	1.6	1.7	0.6	1.6	1.5
Orthovoltage or mixed orthovoltage/megavoltage IMC fields (172 charts)																
1970s-1980s	1cm contra	Direct IMC (f)	250 keV	37.2	12	9	9	2	25	6	19	17	13	4	19	17
1980s	1cm contra	Direct IMC	250 keV/Co^{60}	17.2/22.7	17	11	12	2	29	6	24	30	19	5	23	35
1990s	1cm contra	Direct IMC	250 keV/6 MV	23.5/24.0	22	13	16	2	38	4	32	19	26	3	32	22
Electron chest wall or IMC fields (92 charts)																
1970s-1980s	1cm contra	Direct IMC (g)	12 MeV	45.0	7.9	5.1	2.8	0.6	25.1	4.0	9.2	9.7	0.9	0.5	3.2	4.9
1970s-1980s	1cm contra	Direct IMC, matching tangents	12 MeV/6 MV	45.0/45.0	8.3	5.3	3.4	0.6	25.5	4.1	9.5	10.0	1.4	0.6	3.4	5.3
1970s-1990s	1cm contra	Direct chest wall	9 MeV	45.0	4.2	1.7	2.3	0.1	14.2	0.8	1.1	1.3	0.4	0.2	0.5	0.6
1970s-2000s	1cm contra	Direct chest wall, direct SCF/axilla/lateral thorax (h)	9 MeV/8 MV	46.0/50.0	6.3	2.8	4.3	0.4	17.8	1.2	3.7	3.9	2.7	0.6	2.8	2.9

Highlighted regimens are those used to irradiate the breast/chest wall and/or the SCF/axilla but not the IMC. All of the other regimens included the IMC.

*For further details on the radiotherapy regimens see Table 1.

†Regimens a-h are illustrated in Fig. 1.

‡Mean cardiac doses estimated using manual planning are given to nearest Gy.

§Usual total dose (100%) to the target tissues (see webtable 1 for dose ranges). For direct regimens this was the Dmax. For tangents regimens this was the dose delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

|| Cardiac doses from regimens used to irradiate left-breast cancer and right-breast cancer.

Abbreviations: IMC: internal mammary chain keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, SCF: supraclavicular fossa, contra: contralateral, ipsi: ipsilateral, Co^{60}: cobalt 60

4.4.2 Megavoltage and mixed megavoltage/electron IMC fields

Twenty-two anterior megavoltage regimens were used: 11 for left-sided and 11 for right-sided cancers (Table 1,2, Figs. 1c-e,2,3). Mean cardiac doses were higher for regimens in which the total dose to the IMC was given using a single megavoltage beam compared to regimens using mixed direct megavoltage and electron fields. Cardiac doses for regimens using a single left anterior megavoltage beam were: mean whole heart dose 20.4-33.1 Gy, mean LV dose 15.6-25.6 Gy, mean cardiac valve doses 25.1-51.8 Gy (Fig. 2 top panel). For those using a single right anterior megavoltage beam mean whole heart dose was 12.3-18.5 Gy and AV and TV doses were 24.2-46.8 Gy. The PV and MV and the LV were usually outside the fields, so doses were lower (< 4.9 Gy).

For left-sided regimens in which mixed direct megavoltage and electron fields (Fig 2 middle panel) were used cardiac doses were: mean whole heart dose 14.7-20.7 Gy, mean LV dose 9.7-14.3 Gy, mean cardiac valve doses 12.8-39.9 Gy. For right-sided regimens (Fig. 3) mean whole heart dose was 8.5-12.0 Gy and TV and AV doses were 16.6-25.5 Gy. The PV and MV and the LV were usually outside the fields and received < 4.2 Gy.

Oblique IMC fields were used after the year 2003 and resulted in lower cardiac doses because the beam was angled away from the heart (Fig. 2 bottom panel) (left-sided: mean whole heart dose 9.0 Gy, mean LV dose 11.0 Gy; right-sided: mean whole heart dose 1.7 Gy, mean LV dose 0.5 Gy). Mean PV dose was 14.6

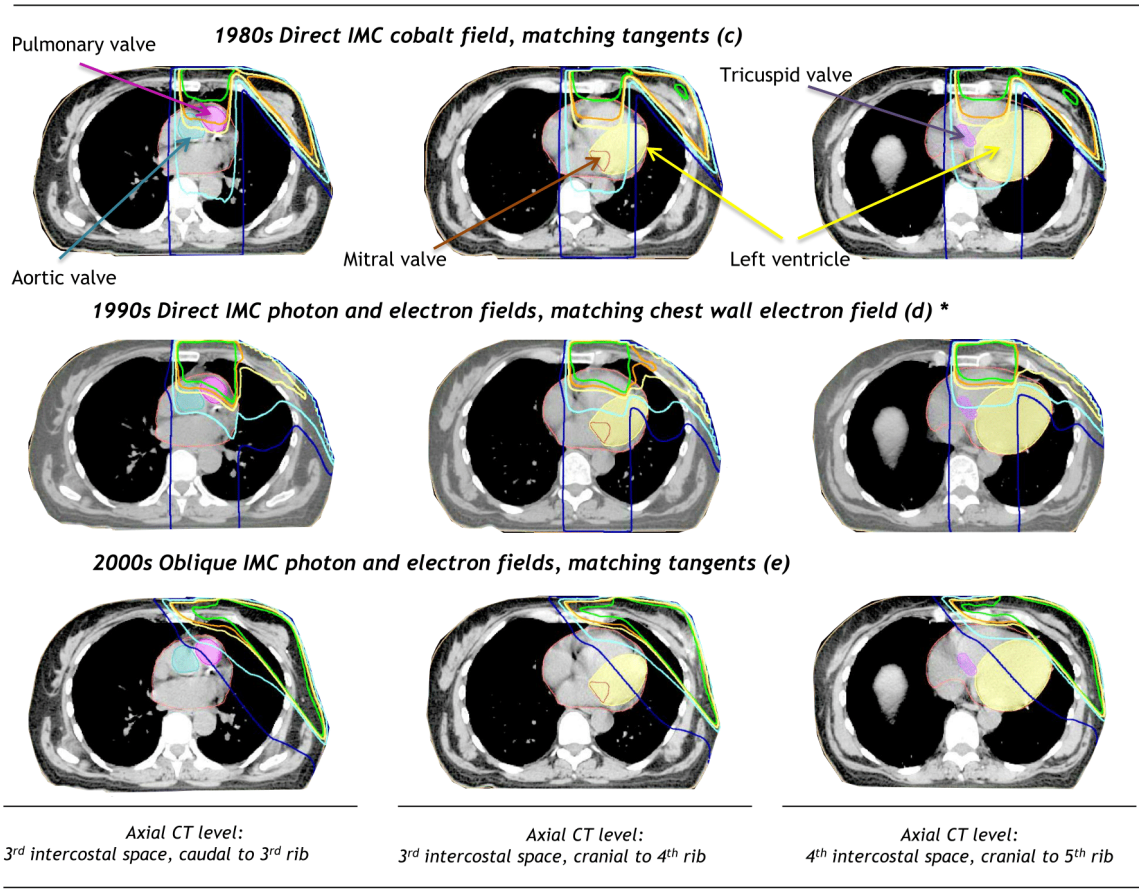


Figure 4-2**.** Spatial distribution of radiation dose to the heart from typical left-breast cancer regimens used to target the breast or chest wall and IMC at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009.

Isodoses (%): **95**, **85**, **30**, **50**, **20**
*Right-sided regimen is illustrated in Fig. 3
See Fig. 1. for illustrations of radiotherapy fields for regimens c-e. Abbreviation: IMC: internal mammary chain

Gy from left-radiotherapy but otherwise mean cardiac valve doses were < 2.9 Gy for both left- and right-radiotherapy.

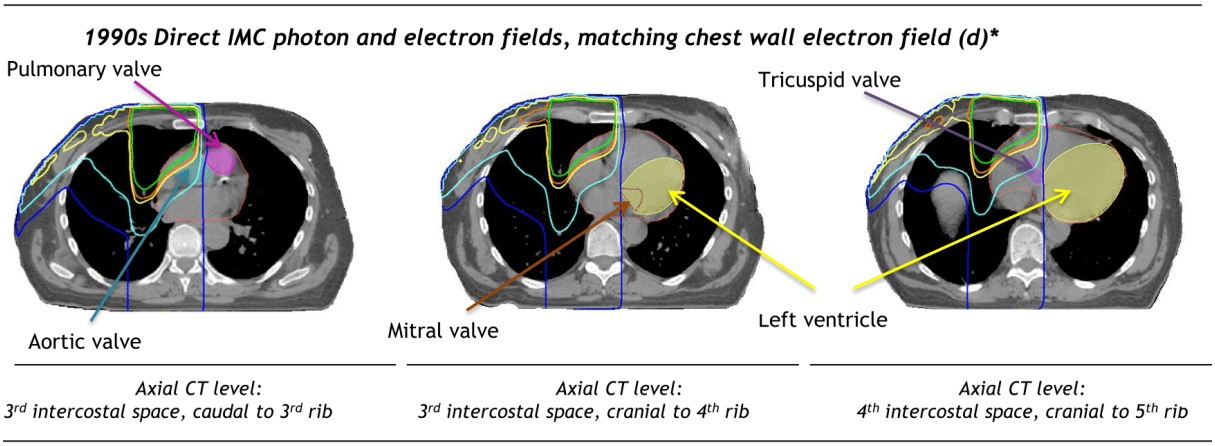


Figure 4-3. Spatial distribution of radiation dose to the heart from a right-breast cancer regimen used to target the chest wall and IMC at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during the 1990s.

Isodoses (%): 95, 85, 80, 50, 20
*The treatment fields included mixed IMC photon and electron fields each giving 50% of the total dose matched to an electron chest wall field. See Fig. 1. for illustration of radiotherapy fields for regimen d. Abbreviations: IMC: internal mammary chain

4.4.3 Orthovoltage or mixed orthovoltage/megavoltage IMC fields

Six anterior orthovoltage regimens were commonly used in the 1970s to 1990s to irradiate the internal mammary chain and supraclavicular fossa: 3 for left-sided and 3 for right-sided cancers (Table 1,2, Fig. 1f). These fields were usually delivered alone, without breast or chest wall irradiation. Cardiac doses depended on the total dose and on whether the regimen included only an orthovoltage field or mixed orthovoltage and megavoltage fields. For orthovoltage-only IMC fields, mean doses from left-radiotherapy were: whole heart 12 Gy, LV dose 9 Gy, cardiac valves 13-25 Gy. For right-sided fields, mean doses were lower: whole heart 9 Gy, LV 2 Gy, cardiac valves 6-17 Gy. Mixed orthovoltage and megavoltage beams were more penetrating than orthovoltage-only fields, hence

cardiac doses were higher. For left-sided fields, mean doses were: whole heart 17-22 Gy, LV 12-16 Gy and cardiac valves 19-38 Gy. For right-sided fields mean doses were: whole heart 11-13 Gy, LV 2 Gy and cardiac valves 3-35 Gy. Of the cardiac valves, the PV received the highest doses (25-38 Gy) from left-sided orthovoltage or mixed orthovoltage/megavoltage regimens, followed by the AV (19-32 Gy), TV (19-32 Gy) and then the MV (13-26 Gy). For right-sided regimens the TV received the highest doses (17-35 Gy), followed by the AV (17-30 Gy), PV (4-6 Gy), and then the MV (3-5 Gy).

4.4.4 Electron chest wall or IMC fields

Eight anterior electron regimens were used to irradiate the chest wall and/or the regional lymph nodes: 4 for left-sided and 4 for right-sided cancers (Table 1,2, Fig. 1g,h). In these regimens most of the whole heart dose was from the anterior electron field, with a small contribution from matching fields. The cardiac dose distributions from these beams depended partly on beam energy. Cardiac doses were higher for the 12 MeV IMC fields (Fig. 1g) (left-sided: whole heart 7.9 Gy, LV 2.8 Gy) than for the 9 MeV chest wall fields (Fig. 1h) (left-sided: whole heart 4.2 Gy, LV 2.3 Gy). Of the cardiac valves the superficial PV received the highest doses (14.2-25.5 Gy) from left-sided regimens, followed by the AV (1.1-9.5 Gy), TV (0.5-3.4 Gy) and then the MV (0.4-2.7 Gy). For right-sided regimens the superficial AV received the highest doses (1.3-10.0 Gy), followed by the TV (0.6-5.3 Gy), PV (0.8-4.1 Gy), and then the MV (0.2-0.6 Gy).

4.4.5 Trends over time

In 771 radiotherapy charts of individual women, cardiac doses varied according to decade and whether an IMC field was included. 122/132 (92%) of the charts included an IMC field in the 1970s, 207/293 (71%) in the 1980s, 74/193 (38%) in the 1990s and 47/153 (31%) in the 2000s (Table 3). Average whole heart dose in the 1970s and the 1980s was 8.9 Gy (1970s IQR: 1.9-8.9; 1980s IQR: 4.8-16.5). It reduced to 4.8 Gy (IQR 4.6-16.5) in the 1990s due to a decrease in IMC radiotherapy.

For radiotherapy that did not include the IMC, there were few such charts in the 1970s (fig. 4, left panel). In left-sided, no IMC radiotherapy during the 1980s and 1990s whole heart doses of around 4-5 Gy were received, which reduced to 1.5 Gy (IQR1.5-1.6) in the 2000s. In right-sided, no IMC radiotherapy, average whole heart or LV doses were <1 Gy in all decades.

For radiotherapy that included the IMC, whole heart and LV doses were higher. Average whole heart doses rose steadily from the 1970s to the 1980s and 1990s. (Fig. 4 right panel, Table 3) This was because in the 1970s it was common to treat the IMC only with a single parasternal field (which was often an electron field) to a total dose of 40-45 Gy (Table 2, Fig. 4 right panel). In the 1980s and 1990s direct parasternal fields were still used but matched to breast/chest wall fields which contributed to increased exposure in these decades and the total dose was higher, 45-50 Gy. During the 2000s, direct megavoltage fields continued to be used in 47/69 women and whole heart doses were similar to 1970s radiotherapy (left-IMC 1970s: 12.2 Gy; 2000s: 11.9 Gy and right-IMC

Table 4-3**.** Whole heart and left ventricle radiation doses according to decade for 771 women selected as cases and controls for case-control studies of heart disease after treatment for breast cancer who underwent radiotherapy at the Netherlands Cancer Institute or the Erasmus MC Centre in the Netherlands during 1970-2009.*

	Treatment period											
	1970s			1980s			1990s			2000s		
Regions irradiated	No. women	Median mean dose (IQR) Whole heart	Median mean dose (IQR) Left ventricle	No. women	Median mean dose (IQR) Whole heart	Median mean dose (IQR) Left ventricle	No. women	Median mean dose (IQR) Whole heart	Median mean dose (IQR) Left ventricle	No. women	Median mean dose (IQR) Whole heart	Median mean dose (IQR) Left ventricle
Left No IMC	**7**	**3.5 (3.0-3.5)**	**4.2 (2.2-4.2)**	**48**	**4.7 (4.3-4.8)**	**6.6 (6.5-7.2)**	**70**	**4.8 (4.8-4.8)**	**7.2 (6.7-7.2)**	**59**	**1.5 (1.5-1.6)**	**2.1 (2.1-2.2)**
Breast	1	4.2 (4.2-4.2)	6.1 (6.1-6.1)	43	4.8 (4.3-4.8)	7.2 (6.5-7.2)	60	4.8 (4.8-4.8)	7.2 (7.2-7.2)	55	1.5 (1.5-1.6)	2.1 (2.1-2.2)
Chest wall	6	3.5 (2.8-3.5)	3.3 (2.1-4.2)	5	4.8 (4.3-4.8)	6.7 (6.5-7.2)	10	6.3 (6.3-6.3)	4.3 (4.3-4.4)	4	1.5 (1.5-2.7)	2.1 (2.1-2.7)
Left IMC	**63**	**12.2 (12.0-12.2)**	**8.9 (8.7-8.9)**	**107**	**16.5 (8.3-25.8)**	**12.4 (4.5-20.0)**	**36**	**18.1 (16.0-20.3)**	**11.1 (9.9-14.4)**	**26**	**11.9 (9.0-16.1)**	**11.0 (11.0-11.4)**
IMC (No chest wall/breast)	44	12.2 (12.0-12.2)	8.9 (8.7-8.9)	56	15.9 (12.2-16.5)	12.0 (8.9-12.4)	13	14.7 (14.7-18.3)	9.7 (9.7-13.7)	1	16.1 (16.1-16.1)	10.0 (10.0-10.0)
IMC, breast	5	13.7 (12.2-15.7)	8.9 (8.7-10.3)	44	26.6 (8.3-28.8)	20.8 (3.4-22.6)	12	21.8 (19.8-21.9)	15.5 (14.1-16.3)	10	9.1 (9.0-13.9)	11.0 (10.7-11.1)
IMC, chest wall	14	12.2 (7.7-12.2)	8.9 (5.5-8.9)	7	22.3 (18.5-22.3)	17.4 (14.1-17.4)	11	16.4 (16.4-18.3)	10.0 (10.0-10.9)	15	16.1 (9.0-16.1)	11.1 (11.0-11.4)
Right No IMC	**3**	**1.4 (1.4-2.1)**	**0.8 (0.6-0.8)**	**38**	**0.6 (0.6-0.7)**	**0.2 (0.2-0.2)**	**49**	**0.7 (0.7-0.7)**	**0.2 (0.2-0.2)**	**47**	**0.3 (0.3-0.3)**	**0.1 (0.1-0.1)**
Breast	0	-	-	34	0.6 (0.6-0.7)	0.2 (0.2-0.2)	43	0.7 (0.7-0.7)	0.2 (0.2-0.2)	44	0.3 (0.3-0.3)	0.1 (0.1-0.1)
Chest wall	3	1.4 (1.4-2.1)	0.8 (0.6-0.8)	4	2.2 (1.6-2.8)	0.4 (0.3-0.4)	6	2.8 (2.8-2.8)	0.4 (0.4-0.4)	3	0.3 (0.3-0.3)	0.1 (0.1-0.1)
Right IMC	**59**	**8.7 (8.7-8.9)**	**1.8 (1.8-1.9)**	**100**	**11.0 (8.9-14.7)**	**1.8 (1.4-1.9)**	**38**	**12.0 (10.1-13.4)**	**1.3 (0.9-1.7)**	**21**	**8.9 (1.7-9.4)**	**1.0 (0.5-1.1)**
IMC (No chest wall/breast)	45	8.7 (8.7-8.9	1.8 (1.8-1.9)	55	8.9 (6.9-11.0)	1.8 (1.0-1.9)	9	8.7 (8.7-11.1)	0.9 (0.9-1.5)	2	8.9 (8.9-9.1)	1.0 (1.0-1.0)
IMC, breast	5	7.3 (4.7-13.2)	0.9 (0.5-1.7)	37	16.2 (11.0-16.6)	2.1 (1.4-2.2)	16	13.4 (12.4-14.2)	1.8 (1.3-2.0)	9	8.9 (1.7-9.4)	1.1 (0.5-1.1)
IMC, chest wall	9	8.9 (8.9-8.9)	1.9 (1.8-1.9)	8	12.3 (11.6-13.0)	1.6 (1.5-1.7)	13	10.5 (10.1-12.3)	0.9 (0.9-1.7)	10	1.7 (1.7-9.4)	0.5 (0.5-1.1)
All women	**132**	**8.9 (8.7-12.2)**	**2.1(1.8-8.9)**	**293**	**8.9 (4.8-16.5)**	**2.8 (1.6-8.9)**	**193**	**4.8 (2.8-12.4)**	**4.5 (0.4-7.2)**	**153**	**1.5 (0.3-6.3)**	**2.1 (0.1-2.2)**

*Radiotherapy charts from all 771 women included in two case-control studies of heart disease after breast cancer treatment - cases and controls. Doses per decade were similar when just the 475 controls were analysed (Appendix C: Table C1).

Abbreviations: IMC: internal mammary chain, IQR: inter-quartile range

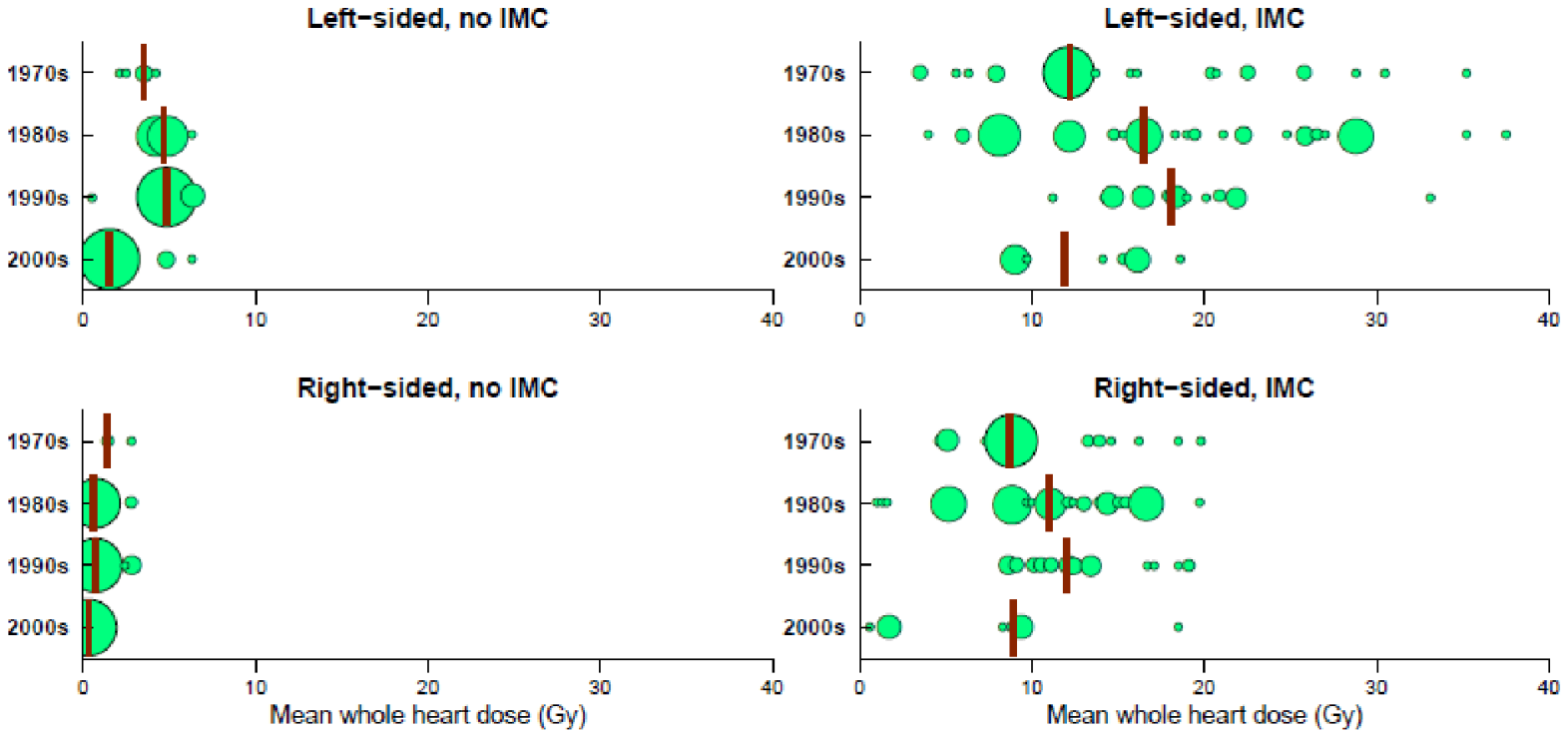


Figure 4-4. Whole heart radiation doses according to decade for women who underwent radiotherapy for breast cancer at the Netherlands cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009.

The median mean heart dose is shown for each decade by a vertical line. Each circle represents a group of women who received a similar heart dose, the area of the circle being proportional to the number of the women in the group.
Abbreviation: IMC: internal mammary chain

1970s: 8.7 Gy; 2000s: 8.9 Gy). Oblique IMC fields were introduced in 2003. These were angled away from the heart and were used in 22/69 (32%) of the women with IMC radiotherapy.

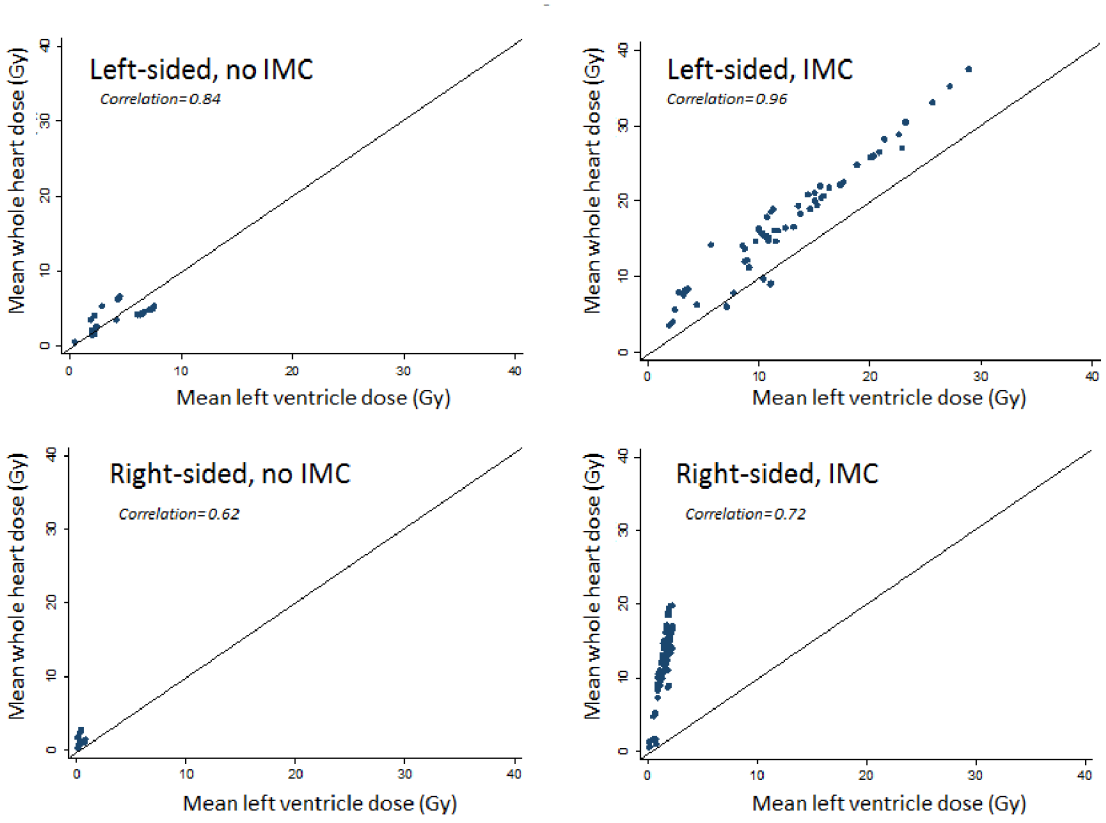


Figure 4-5. Correlations between whole heart and left ventricle mean radiation doses for women who underwent radiotherapy for breast cancer at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970- 2009, by laterality and IMC irradiation.

4.4.6 Correlations between LV and whole heart doses

Mean LV doses were correlated with mean whole heart doses for both left (r= 0.84-0.96) and right-sided radiotherapy (r=0.62-0.72) (Fig.5). For left-regimens without the IMC, mean whole heart doses were similar to, or lower, than mean LV doses (whole heart 3.8 Gy (IQR 1.6-4.8), LV 5.2 Gy (IQR 2.2-7.2)) indicating that much of the cardiac dose was received by the LV. For left-IMC regimens mean whole heart doses were higher than mean LV doses (whole heart 15.9 Gy (IQR 12.0-19.6), LV 11.6 (IQR 8.9-14.4 Gy) indicating that most of the cardiac dose was outside the LV (fig. 2). For right-radiotherapy LV doses were lower than whole heart doses because the LV was usually several cm from the fields (fig. 3).

4.5 Discussion

Doses to the heart from 44 breast cancer radiotherapy regimens in 771 women irradiated in the Netherlands during 1970-2009 varied substantially. For each regimen, some cardiac structures were included in the beams, and others were several centimetres from the beams (Fig. 2-3) resulting in substantial differences in the doses delivered. For example, dose to the PV from IMC radiotherapy was only ~1 Gy from some regimens but it was ~50 Gy from other regimens. This may enable comparison of VHD rates in women who received a wide spread of valve doses to develop dose-response relationships for radiation-induced valve disease. Similarly, LV dose varied from ~0.5 to 26 Gy. HF rates may therefore be compared in women who received a wide spread of LV doses to develop a dose-response relationship for radiation-induced HF.

In this study IMC irradiation was received by 450/771 (58%) of the women. It was included as a target in ~90% of radiotherapy charts from the 1970s, ~70% from the 1980s, ~40% from the 1990s and ~30% from the 2000s. The IMC was usually irradiated using direct megavoltage fields (table 1, fig. 2) which included part of the heart in the fields for both women with left-sided and right-sided breast cancer. Wide tangents were not used. Due to the frequency of use of direct megavoltage IMC fields cardiac doses were higher than in some other parts of the world during the 1970s, 80s and 90s[13].Heart doses were also higher than in some other countries during the 2000s: average whole heart dose from left-IMC radiotherapy was 14.1 Gy (IQR 9.0-16.1) and right-sided was 8.9 Gy (IQR1.7-9.4). In a recent systematic review of heart doses the corresponding values for regimens published worldwide during 2003-2013 were left-IMC radiotherapy 8.4 Gy (SE 0.5) and right-IMC radiotherapy 4.2 Gy (SE 1.2)[20]. The population in this study provides an important opportunity to study the effects of irradiating the valves and the LV given the variation in doses received by the cardiac structures by different regimens and the fact that the risks of several types of heart disease are raised in these women[Appendix E5].

Cardiac doses estimated in this study for 2000s IMC radiotherapy are similar to published doses for similar regimens in the Netherlands (Appendix C: Table C4)[21,22]. Hooning et al. reported whole heart doses from regimens used during 1970 to 1986[9]. 14 commonly used regimens were reconstructed on a typical patient. These cardiac doses were weighted according to frequency of use of each regimen to estimate typical heart doses in the 1970s and 80s. In our study,

we had individual patient information from 771 radiotherapy charts, so our dose estimates are likely to more closely represent doses actually received by women during this time period. Nevertheless, doses reported according to decade were similar between these two studies (Table 4).

Our study has several strengths. First, we obtained the radiotherapy charts of 771 women including, on average, 17 charts per regimen. These included information on field borders, beam energies, field angles and doses delivered. Our reconstructions had input from a radiation oncologist who had delivered them in the past (BA), providing reassurance that we had reconstructed them accurately. Second, we observed a wide range of doses to the valves and the LV which will increase the power for estimating future dose-response relationships. Third, to our knowledge this is the first study to report cardiac valve doses from breast cancer radiotherapy used during the 1970s to the 2000s.

The main limitation of our study is that individual anatomical information (CT-planning scans) were unavailable for the women included. Therefore we used a 'typical CT' to estimate their cardiac doses, which is subject to several sources of uncertainty. The main one is interpatient variability in anatomy. In a study of 10 women, whole heart dose varied between women by 7-9 Gy for left tangents and 3-5 Gy for left electron fields. Whole heart dose variability was lower for right tangents (~1 Gy) and right electron fields (<1-5 Gy). For cardiac structures distant from the fields, dose variability was 3 to 47 Gy for left and 3 to 27 Gy for right-sided regimens (Chapter 3). Contouring variation may also lead to uncertainties in whole heart and LV doses of ~1 Gy [16,17]. Other sources of uncertainty include set-up error, inter- and intra-fraction motion, and dose calculation algorithm error[23-28].

Table 4-4. Comparison of doses per decade in this study with previously published doses per decade in the Netherlands during 1970-1986.

	Mean heart dose (Gy) (range)	
Treatment period	*Hooning**	*Duane†*
1970-1979		
RT fields		
Chest/breast: right-sided	~3 (1.2-3.8)	~2 (1.4-2.8)
Chest/breast: left-sided	~7 (2.5-9.0)	~3 (2.1-4.2)
IMC only: right-sided	7 (0.5-11.6)	~9 (5.1-19.8)
IMC only: left-sided	~9 (0.7-15.6)	~14 (7.9-35.2)
IMC + chest wall/breast: right-sided	~11 (2.7-15.4)	~10 (4.7-18.5)
IMC + chest wall/breast: left-sided	~15 (4.7-18.3)	~13 (3.5-28.8)
1980-1986		
RT fields		
Chest/breast: right-sided	~1.5 (1.2-1.6)	~1 (0.6-2.8)
Chest/breast: left-sided	~5 (2.5-5.3)	~5 (4.0-6.3)
IMC only: right-sided	~6 (0.5-11.6)	~9 (1.0-14.6)
IMC only: left-sided	~7 (0.7-15.6)	~15 (7.9-35.2)
IMC + chest wall/breast: right-sided	~9 (2.5-14.0)	~13 (1.3-16.6)
IMC + chest wall/breast: left-sided	~13 (4.0-19.9)	~19 (4.0-37.5)

*Doses were estimated by reconstructing typical field borders, beam energies and total dose for 14 commonly used regimens on a typical patient. These doses were weighted according to frequency of use in the 1970-1979 and 1980-1986[6].
†Heart doses were estimated by reconstructing 44 regimens based on information from the radiotherapy charts of 771 women. Dose volume histograms were produced for each individual woman taking into account the total dose each woman received.
Abbreviations: IMC: internal mammary chain

In conclusion, radiotherapy regimens delivered for breast cancer in the Netherlands between 1970 and 2009 led to substantial variation in doses to the heart, LV and cardiac valves. These doses will be used to develop quantitative dose response relationships for radiation-induced valvular heart disease and heart failure. Today in 3-dimensional CT planning, it may not be possible to completely avoid the heart for some individuals undergoing IMC radiotherapy but

it may be possible to choose which parts of the heart receive some dose. Knowledge of the sensitivity of the various cardiac structures can inform such decisions and may also be used to assess risks for cancer survivors who received IMC radiotherapy some years ago.

Acknowledgements

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I, F Duane extracted information from radiotherapy charts, performed the dosimetry, undertook collection and assembly of the data, the data analysis, the development of the tables and figures and drafted the first version of the manuscript. S Warren provided medical physics advice. All authors contributed to the interpretation of the data and the development of the manuscript.

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5 Radiation dose-response for risk of myocardial infarction in breast cancer survivors

5.1 Abstract

Background

Previous reports suggest that radiotherapy for breast cancer (BC) can cause ischemic heart disease, with the radiation-related risk increasing linearly with mean whole heart dose (MWHD). This study aimed to validate these findings in BC patients aged ≤70 years and investigate additional risk factors for radiation-related myocardial infarction (MI).

Methods

A nested case-control study was conducted within a Dutch cohort of BC survivors treated between 1970-2009. Cases were 183 patients with MI as first heart disease after BC. One control per case was selected, matched on age and BC diagnosis date. Information on treatment and cardiovascular risk factors was abstracted from medical files and radiation charts. Cardiac doses were estimated for each woman by reconstructing her regimen using modern 3D computed tomography (CT) planning on a typical patient CT-scan.

Results

Median age at BC of cases and controls was 50.2 years (inter-quartile range (IQR): 45.7-54.7). Median MWHD was 9.5 Gray (Gy) (range: 0.3-35.2 Gy). Median time to MI was 13.6 years (IQR: 9.9-18.1). MI rate increased linearly with increasing MWHD (excess rate ratio (ERR) per Gy: 6.5%, 95% confidence interval (95%CI): 1.3%-16.3%). Patients receiving ≥20 Gy MWHD had 3.4-fold (95%CI: 1.3-6.1) higher MI rate than unirradiated patients. ERRs were higher for

younger women, with borderline significance ($ERR_{<45years}$: 24.2%/Gy, $ERR_{\geq 50years}$: 2.5%/Gy, $p_{interaction}$=0.054). Whole heart dose-volume parameters did not modify the dose-response relationship significantly.

Conclusion

MI rate after radiation for BC increases linearly with MWHD. Efforts to further reduce MWHD are expected to contribute to better cardiovascular health of BC survivors.

5.2 Introduction

Survival in women with breast cancer (BC) has improved substantially in recent decades, due to more effective treatments and earlier diagnosis[1–5]. However, radiotherapy, anthracycline-based chemotherapy, and targeted therapies can cause heart disease[6–8]. In the case of radiotherapy, cardiac exposure is associated with an increased risk of ischemic heart disease (IHD)[9–11]. This may occur through injury to the small vessels in the heart muscle (microvascular damage) or through atherosclerosis of the larger blood vessels (macrovascular damage)[12, 13].

The risk of IHD appears to increase linearly with increasing mean whole heart radiation dose (MWHD)[14, 15]. In a large case-control study of women irradiated for BC, the rate of major coronary events increased by 7.4% per Gray (Gy) MWHD[14]. The increase started within five years of exposure, sooner than previously anticipated[16,17]. It was also shown that the percentage increase in IHD per Gy was similar in women with and without cardiovascular risk factors, suggesting that the absolute radiation-related increase is higher in those with pre-existing cardiovascular risk factors. These associations require further study in younger women (i.e. <50 years) diagnosed with BC.

Substantial progress has been made in reducing cardiac radiation doses in BC radiotherapy[18–20]. Nevertheless, some recent regimens used to irradiate the left internal mammary nodes still may expose the heart to ≈8 Gy[21]. Quantification of the effect of radiation on the heart may help to predict IHD risk for women being

considered for BC radiotherapy today. It may also help to identify BC survivors who may benefit from cardiac surveillance.

This study aimed to examine the radiation dose-response relationship in a population of predominantly young BC patients (median age 50 years). It also investigates the effects of different whole heart dose-volume radiation measures and cardiovascular risk factors on the dose-response relationship.

5.3 Methods

5.3.1 Cohort population

A nested case-control study of MI after BC was conducted within a cohort of long-term BC survivors treated in the Netherlands between 1970 and 2009. The cohort was identified through hospital-based registries at the Netherlands Cancer Institute, Amsterdam and Erasmus MC-Cancer Institute, Rotterdam, the Netherlands. Female patients were included in the cohort if: they had histologically confirmed invasive BC stage I-III or ductal carcinoma in situ and were diagnosed before the age of 71 years. For details of the data collection procedures see Appendix E5.

5.3.2 Case–control study

MI diagnoses in the cohort were ascertained from medical files and through questionnaires sent to the general practitioner[1]. When the treating cardiologist was known, a questionnaire was sent to confirm the MI diagnosis. Patients with

[1] In the Netherlands, all residents are expected to have a general practitioner. Medical correspondence from attending physicians is sent to the general practitioner. Such records are preserved by the general practitioner throughout a patient's life and for at least 15 years after a patient's death.

MI after BC were eligible as cases if: (1) BC was the first invasive malignancy (ignoring non-melanoma skin cancer); (2) they were free from BC recurrence, distant metastases, second cancer, heart failure and valvular heart disease until the date of MI. A rhythm disorder or angina pectoris before MI was not an exclusion criterion. In total 183 patients diagnosed with MI after invasive BC were selected as cases. For each MI case, one control was selected from the cohort, matched on age at BC diagnosis (≤5 years) and date of BC diagnosis (≤5 years). Controls had to be alive, free from BC recurrence, distant metastases, second cancer and cardiovascular diseases (MI, heart failure and valvular heart disease), until the cut-off date, which was defined as the date of BC diagnosis plus a time interval equal to the time between BC diagnosis and MI diagnosis for the paired case. Cases were permitted to be controls up to the date when they developed MI, and controls were selected with replacement. In total, 183 controls (178 unique individuals) were matched to the cases.

5.3.3 Data collection

Data at BC diagnosis regarding medical history (including prior cardiovascular disease, diabetes and hypertension), smoking history, and body mass index (BMI) were abstracted from medical files. Hypertension was coded as present if a patient was on medication for hypertension, or if a diagnosis of hypertension was given in the medical record. Information on cardiovascular risk factors diagnosed after BC diagnosis was also collected. Treatment information, including surgery, chemotherapy regimen and endocrine therapy, was abstracted. Copies of radiation charts for individual patients were obtained for patients who received

radiotherapy. Information on target definition, field borders, total dose, dose per fraction, beam energy and the use of shielding, wedges and bolus was obtained from the charts.

5.3.4 Radiotherapy dosimetry

A “typical CT-scan”, was used to estimate cardiac doses retrospectively for each woman in the study (Chapter 4, Appendix D). Radiotherapy charts were available for 314 individual women in the study. Fifty-two regimens were identified and reconstructed on the typical CT-scan. Dose distributions were generated for cobalt, electron and megavoltage beams using modern 3-dimensional CT treatment planning (Varian EclipseTM Treatment Planning System [TPS] version 10.0.39 [Varian Medical Systems, Palo Alto, USA]). Dose distributions from orthovoltage fields were generated using manual planning. Typical MWHD, mean left ventricle dose (MLVD), and the percent volume of heart receiving ≥5, 10, 15, 20, 25, 30, 35, and 40 Gy (V_5-V_{40}) were estimated using dose-volume histograms. Doses were estimated for each individual woman using the total dose (100%) received as recorded in individual radiotherapy charts and the dose volume histogram of the regimen received.

5.3.5 Statistical analyses

Rate ratios (RRs) for MI for different levels of each factor were calculated using logistic regression conditioning on strata, after individual matching. Strata were defined by the matching variables age at BC diagnosis (10-year categories), year of BC diagnosis (10-year categories) and follow-up duration (5-year categories). One individual, who appeared as a control twice within the same stratum, was

included only once in the analysis. Confidence intervals (CIs) were estimated using the Wald method for factors with two levels. For factors with more than two levels Wald method CIs were used to derive CIs for each category, including the reference category, from the amount of information in that category[22]. Multivariable regression was used to assess and control for potential confounders. A factor was considered a potential confounder if the RR after adjustment for the factor changed by 10% or more. The radiation dose-response relationship was estimated using a linear odds model conditional on strata defined by the matching variables. The MI rate was modelled as $K_m(1+\beta d)$ where d is MWHD for each woman, K_m is the MI rate at zero MWHD in the m^{th} stratum, and β is the proportional increase in MI rate per unit increase in dose. Non-linearity was tested by adding an exponential term: $K_m(1+\exp(\beta)d*\exp(\delta d))$. The significance of the dose-response relationship was evaluated using the likelihood ratio test. Interactions were evaluated by including interaction terms as categorical or continuous variables.

Approximate cumulative MI risks were estimated from the treatment specific RRs together with the cumulative MI risk for the entire cohort and death from any cause other than MI or sudden cardiac death was treated as a competing risk. Overall survival rates following a diagnosis of MI were estimated using the Kaplan Meier method with cases censored at either last known follow-up date or date of death. Analyses were performed using STATA statistical software version 13.0 (StataCorp 2013) and Epicure version 1.8 (Hirosoft International).

Table 5-1. Characteristics of myocardial infarction cases and matched controls.

	Cases		Controls		
Total	183 (N)	100 (%)*	182¶ (N)	100 (%)	P-value†
Age at breast cancer diagnosis‡					
Median age (IQR) in years	50.2	45.8-54.7	50.2	45.5-54.6	
<40 (22-39) years	9	4.9	10	5.5	
40-49 years	78	42.6	78	42.9	
50-59 years	77	42.1	75	41.2	
≥60 (60-70) years	19	10.4	19	10.4	
Year of breast cancer diagnosis‡,§					
1970-1979	41	22.4	41	22.5	
1980-1989	95	51.9	92	55.6	
1990-1999	29	15.9	34	18.7	
2000-2009	18	9.8	15	8.2	
Time to MI/cut-off date‡,¶					
Median time (IQR) in years	13.6	10.3-18.2	13.7	10.3-18.2	
<5 (1-4) years	13	7.1	13	7.1	
5-9 years	31	16.9	31	17.0	
10-14 years	60	32.8	59	32.4	
15-19 years	48	26.2	48	26.4	
≥20 (20-29) years	31	16.9	31	17.0	
Age at MI diagnosis/cut-off date¥					
Median age (IQR) in years	64.2	58.5-70.2	63.9	58.5-70.2	
<50 (40-49) years	7	3.8	8	4.4	
50-59 years	51	27.9	50	27.5	
60-69 years	74	40.4	74	40.7	
70-79 years	45	24.6	44	24.2	
≥80 (83-89) years	6	3.3	6	3.3	
Laterality of breast cancer					
Right	85	46.4	81	44.5	
Left	98	53.6	101	55.5	0.72
Nodal status					
Negative	106	57.9	107	58.8	
Positive	75	41.0	74	40.7	
Unknown	2	1.1	1	0.5	0.91
Tumor size*					
<2cm	58	31.7	76	41.8	
2-5cm	88	48.1	72	39.6	
≥5cm	6	3.3	10	5.5	
Unknown	31	16.9	24	13.2	0.09

Abbreviations: IQR, interquartile range; MI, myocardial infarction.
* Percentages may not total 100 because of rounding.
¶ Cases and controls were selected with replacement. When an individual appeared as a control twice within the same stratum, it was included only once in the analysis (n=1).
† P-value for difference between tumor characteristics of cases and controls, calculated within strata (defined by matching variables) and excluding the unknown category.
‡ Matching variables.
¥ Derived from matching factors. Cut-off date for controls was defined as the date of BC diagnosis plus a time interval equal to the time between BC diagnosis and MI diagnosis for the paired case.

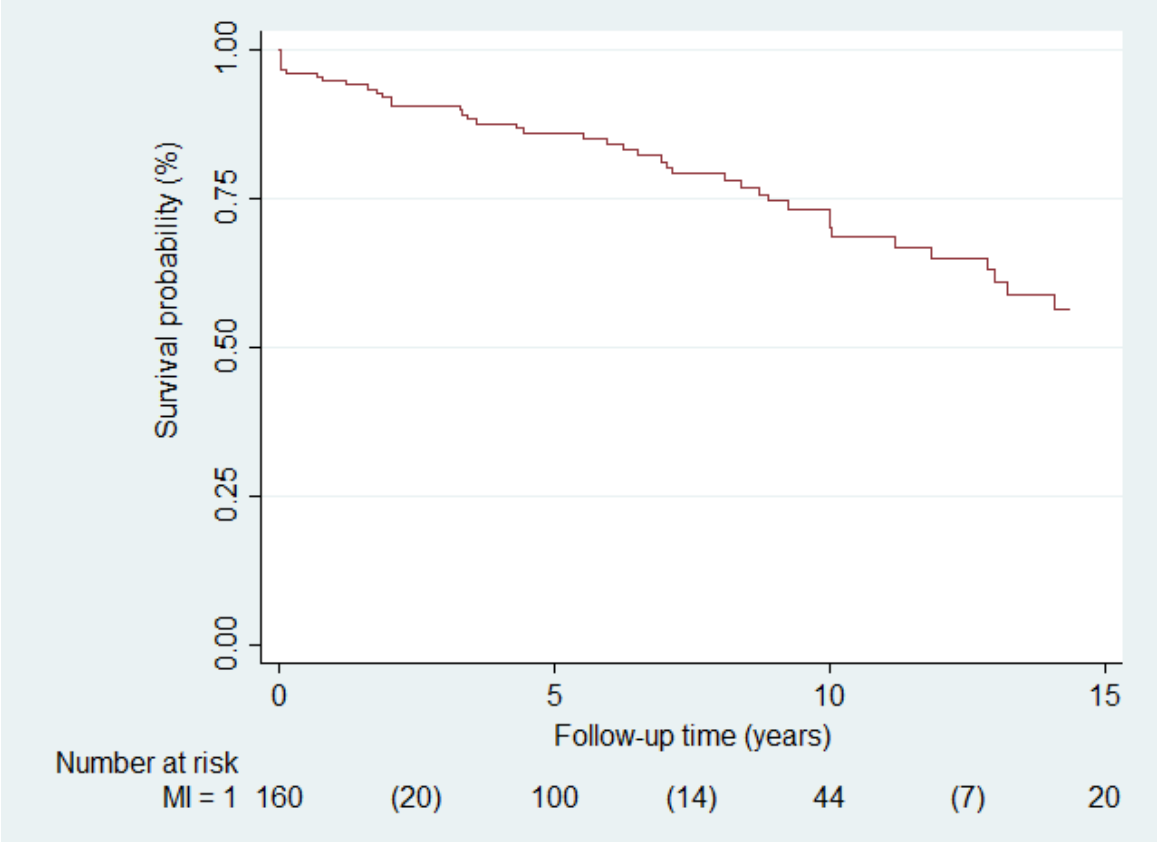


Figure 5-1. Survival after myocardial infarction diagnosis. Calculated using the Kaplan-Meier method.

5.4 Results

5.4.1 Patient characteristics

The median age of cases at BC diagnosis was 50.2 years (IQR: 45.8-54.7) (Table 1). Median time between BC diagnosis and MI diagnosis was 13.6 years (IQR: 10.3-18.2). Left-sided BC was more common than right-sided BC in cases and controls (53.6% and 55.5% left-sided versus 46.4 and 45.5% right-sided, respectively); 57.9% of cases and 58.8% of controls had node-negative disease at diagnosis. Eighty-five percent of cases were alive 5 years after MI diagnosis

and 56% 15 years after MI diagnosis (Fig. 1). Twenty-three cases (13%) died on the day of their MI diagnosis.

5.4.2 Treatment-related risk factors

Surgery, endocrine therapy and chemotherapy (with or without anthracyclines) were not associated with a significantly increased MI rate (RR mastectomy versus breast-conserving surgery 1.04, RR endocrine therapy versus not: 0.71; RR non-anthracycline chemotherapy versus not: 0.59, and RR anthracyclines versus no chemotherapy: 1.04) (Table 2, treatment model I). IMC irradiation was, however, associated with a 2.45-fold increased MI rate (95% CI: 1.97-3.05). Median MWHD was 8.9 Gy (IQR: 4.8-15.0) for cases and 8.5 Gy (IQR: 4.3-12.2) for controls (Table 2). Heart dose estimates were highest for patients who received IMC irradiation plus breast or chest wall irradiation (mean MWHD right-sided IMC+breast/chest wall: 14.5/10.7, left-sided: 18.6/16.3 Gy) (Table 3). MI rate increased with increasing MWHD (p-trend: 0.011), and there was a 3.4-fold (95% CI: 1.54-7.62) increased rate for patients who received a MWHD ≥20 Gy compared to patients who received no radiotherapy (Table 2).

Neither the use of chemotherapy nor the presence of cardiovascular risk factors significantly confounded the association between MWHD and MI rate (Table 4). When we restricted the analysis just to cases and controls who received radiotherapy, similar rate increases for the different radiation dose categories were found (Table 5). Approximate 20-year cumulative incidences were 0.9% 1.3%, 1.6%, 1.9% and 3.1% for no radiotherapy and MWHD categories <2 Gy, 2-9 Gy, 10-19 Gy and ≥20 Gy, respectively (Fig. 2).

Table 5-2. Associations between treatment characteristics and rate of myocardial infarction

	Cases		Controls		Rate ratio¶	95% CI	P-value†
Total	183 (N)	100 (%)*	182 (N)	100 (%)			
Treatment model I							
Surgery							
Breast conserving surgery (BCS)	82	44.8	87	47.8	1.00‡	-	
Mastectomy	101	55.2	95	52.2	1.04	0.58-1.86	0.90
Endocrine therapy (HT)							
No	167	91.3	166	91.2	1.00‡	-	
Yes	16	8.7	16	8.8	0.71	0.29-1.75	0.46
Chemotherapy (CT)							
No	140	76.5	132	72.5	1.00‡	0.89-1.12	
CT, no anthracyclines	29	15.9	36	19.8	0.59	0.33-1.07	
Anthracycline-based CT	14	7.7	14	7.7	1.04	0.41-2.63	0.23
Radiotherapy (RT)							
No	16	8.7	27	14.8	1.00‡	0.50-1.99	
RT, no IMC	51	27.9	65	35.7	1.20	0.67-2.18	
RT, IMC	116	63.4	90	49.5	2.45	1.97-3.05	0.006
Treatment model II§							
Surgery (BCS or mastectomy) only	13	7.1	23	12.6	1.00‡	0.49-2.05	
BCS + RT	53	29.0	57	31.3	1.34	0.89-2.03	
Mastectomy + RT	66	36.1	45	24.7	2.70	1.65-4.43	
Surgery + RT + HT	7	3.8	7	3.9	1.39	0.48-4.07	
Surgery + RT + CT	33	18.0	39	21.4	1.28	0.80-2.06	
Surgery + RT + HT + CT	8	4.4	7	3.9	1.58	0.55-4.60	
Other	3	1.6	4	2.2	1.14	0.26-5.05	0.15
Mean whole heart dose (MWHD)¥							
Median MWHD (IQR) in Gy	8.9	4.8-15.0	8.5	4.3-12.2			
No RT	16	8.8	27	15.0	1.00‡	0.52-1.91	
<2 Gy (mean 1 Gy)	29	15.9	34	18.9	1.44	0.84-2.48	
2-9 Gy (mean 7 Gy)	62	34.1	62	34.4	1.72	1.23-2.42	
10-19 Gy (mean 14 Gy)	57	31.3	48	26.7	2.06	1.40-3.02	
≥20 Gy (mean 26 Gy)	18	9.9	9	5.0	3.42	1.54-7.62	0.011††

Abbreviations: CI, confidence interval, IMC, internal mammary chain.
* Percentages may not total 100 because of rounding.
¶ Rate ratios for MI for different levels of each factor were calculated using logistic regression conditioning on strata defined by the matching variables.
† P-value for difference between treatment characteristics of cases and controls, calculated within strata (defined by matching variables).
‡ Reference category.
§ This model includes only mutually exclusive treatment groups.
¥ This model includes 362 patients. Three patients were dropped; for one irradiated case and one irradiated control dosimetry was not performed. One control was dropped, because it was the only patient left in the stratum.
†† P for trend across categories.

Table 5-3. Mean and median mean whole heart dose, V5 and V25 by prescribed radiation field for all irradiated women (cases and controls).

	N	Mean MWHD ± SD	Median MWHD (IQR)	N	Median V5 (IQR)	Median V25 (IQR)
Total	314*	9.5 ± 7.4	8.9 (4.3-13.3)	292†	24.8 (0-85.3)	7.4 (0-18.9)
	Right-sided BC					
Breast	51	0.6 ± 0.2	0.6 (0.6-0.7)	51	0 (-)	0 (-)
Breast + IMC	30	14.5 ± 3.8	16.1 (13.2-16.6)	29	47.5 (42.0-48.5)	35.3 (31.8-35.8)
Chest wall	3	2.4 ± 0.6	2.8 (1.7-2.8)	3	11.2 (9.2-11.3)	1.9 (1.1-2.0)
Chest wall + IMC	17	10.7 ± 3.5	10.5 (8.9-13.0)	16	46.4 (44.9-90.1)	15.1 (10.7-31.2)
IMC only	49	9.1 ± 2.3	8.9 (8.7-9.4)	43	90.0 (40.3-90.1)	10.6 (9.9-11.0)
	Left-sided BC					
Breast	56	4.0 ± 1.3	4.8 (4.3-4.8)	56	11.8 (11.1-11.8)	7.1 (6.9-7.1)
Breast + IMC	30	18.6 ± 9.6	17.8 (8.3-28.8)	29	81.4 (36.7-87.6)	25.4 (11.8-66.7)
Chest wall	3	4.6 ± 1.5	4.0 (3.5-6.3)	3	19.3 (18.4-24.8)	5.5 (4.3-6.8)
Chest wall + IMC	15	16.3 ± 6.9	16.1 (12.2-22.5)	15	85.2 (65.9-86.7)	20.1 (18.4-51.4)
IMC only	60	14.2 ± 5.1	12.2 (12.1-16.5)	47	98.2 (80.8-99.0)	18.4 (16.2-19.1)

Abbreviations: MWHD, mean whole heart dose, SD, standard deviation, IQR, interquartile range, IMC, internal mammary chain.
* In total, for 314/316 irradiated, *unique* individuals mean whole heart dose was estimated.
† In total, for 292/316 irradiated, *unique* individuals dose-volume parameters were estimated.

Table 5-4. Associations between mean whole heart dose and rate of myocardial infarction, including adjusted rate ratios.

	Cases		Controls									
Total	182† (N)	100 (%)	180§ (N)	100 (%)	Rate ratio*	95% CI	Adjusted rate ratio¥	95% CI	Adjusted rate ratioII	95% CI	Adjusted rate ratio**	95% CI
Median MWHD (IQR) in Gy	8.9	4.8-15.0	8.5	4.3-12.2								
No RT	16	8.8	27	15.0	1.00‡	0.52-1.91	1.00‡	0.52-1.92	1.00‡	0.52-1.92	1.00‡	0.52-1.92
<2 Gy (mean 1 Gy)	29	15.9	34	18.9	1.44	0.84-2.48	1.39	0.80-2.42	1.46	0.84-2.53	1.41	0.81-2.48
2-9 Gy (mean 7 Gy)	62	34.1	62	34.4	1.72	1.23-2.42	1.77	1.26-2.48	1.65	1.17-2.32	1.69	1.20-2.38
10-19 Gy (mean 14 Gy)	57	31.3	48	26.7	2.06	1.40-3.02	2.15	1.46-3.18	2.00	1.35-2.93	2.07	1.40-3.07
≥20 Gy (mean 26 Gy)	18	9.9	9	5.0	3.42	1.54-7.62	3.63	1.63-8.12	3.41	1.52-7.62	3.58	1.60-8.03
P-value††					0.011		0.006		0.015		0.009	
ERR/Gy					6.4	1.3-16.0	7.5	1.8-18.4	6.1	1.1-15.4	7.0	1.5-17.5

Abbreviations: CI, confidence interval, MWHD, mean whole heart dose, IQR, inter quartile range, RT, radiotherapy.
† For one irradiated case dosimetry was not performed.
§ For one irradiated control dosimetry was not performed. One control was additionally dropped, because it was the only patient left in the stratum.
* Rate ratios for MI for different levels of each factor were calculated using logistic regression conditioning on strata defined by the matching variables.
‡ Reference category.
¥ Adjusted for chemotherapy yes/no, in addition to stratification.
II Adjusted for cardiovascular risk factors (combined variable) at BC diagnosis, in addition to stratification.
** Adjusted for cardiovascular risk factors (combined variable) at BC diagnosis and for chemotherapy yes/no, in addition to stratification.
†† P-value for trend across categories.

Table 5-5. Associations between mean whole heart dose and rate of myocardial infarction risk in irradiated cases and irradiated controls

	Cases		Controls				
Total	165 (N)	100 (%)	163 (N)	100 (%)	Rate ratio*	95% CI	P-value
Median MWHD dose (IQR) in Gy	8.9	(4.8-15.0)	8.3	(4.0-12.2)			
<2 Gy (mean 1 Gy)	29	17.6	37	22.7	1.00‡	0.59-1.70	
2-9 Gy (mean 7 Gy)	62	37.6	68	41.7	1.23	0.89-1.70	
10-19 Gy (mean 14 Gy)	56	33.9	50	30.7	1.52	1.03-2.25	
≥20 Gy (mean 26 Gy)	18	10.9	8	4.9	3.03	1.32-6.98	0.029†
ERR/Gy					6.7	1.0-19.6	

Abbreviations: CI, confidence interval, MWHD, mean whole heart dose, IQR, inter quartile range.
* Rate ratios for MI for different levels of each factor were calculated using logistic regression conditioning on strata defined by the matching variables.
† P for trend across categories.
‡ Reference category.

Table 5-6. Associations between mean left ventricle dose and rate of myocardial infarction

	Cases		Controls			
Total	182† (N)	100 (%)	180§ (N)	100 (%)	Rate ratio*	95% CI
Median MLVD (IQR) in Gy	2.2	(1.7-8.9)	2.2	(1.3-8.7)		
No RT	16	8.8	27	15.0	1.00‡	0.52-1.92
<2 Gy (mean 1 Gy)	73	40.1	65	36.1	2.02	1.46-2.77
2-4 Gy (mean 3 Gy)	28	15.4	19	10.6	2.92	1.56-5.47
5-9 Gy (mean 8 Gy)	36	19.8	48	26.7	1.34	0.87-2.07
≥10 Gy (mean 17 Gy)	29	15.9	21	11.7	2.53	1.45-4.43

Abbreviations: CI, confidence interval, MLVD, mean left ventricle dose, IQR, inter quartile range, RT, radiotherapy.
† For 1 case dosimetry was not performed.
§ Two controls were dropped; for one irradiated control dosimetry was not performed and one control was dropped, because it was the only patient left in the stratum.
* Rate ratios for MI for different levels of each factor were calculated using logistic regression conditioning on strata defined by the matching variables.
‡ Reference category.

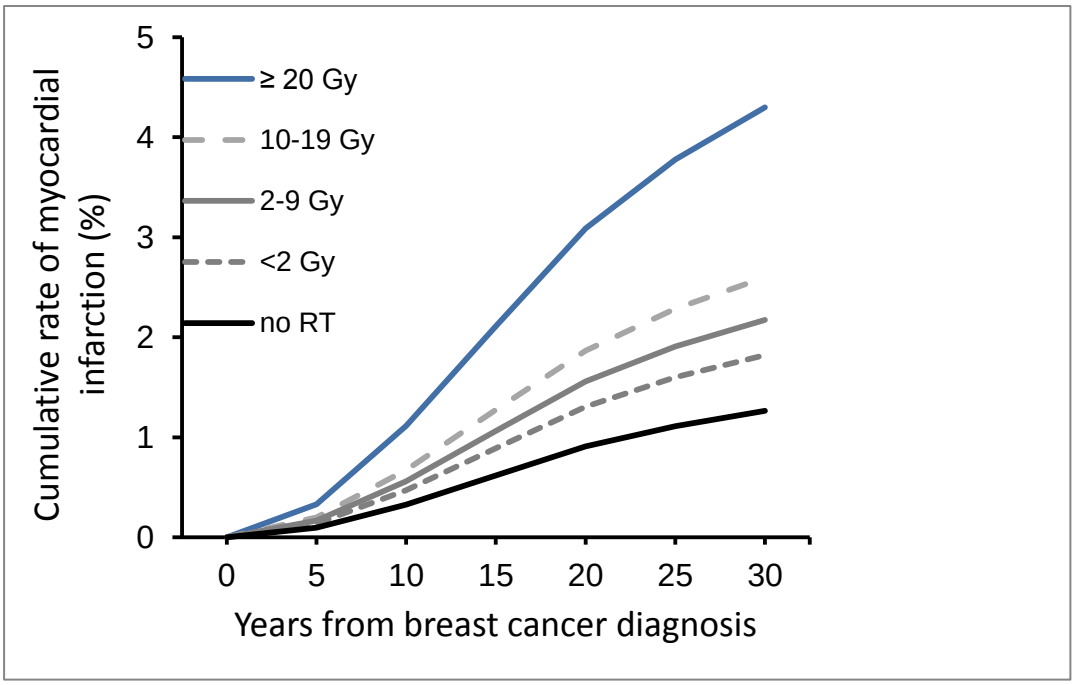


Figure 5-2. Modelled cumulative myocardial infarction rate for cases by categories of mean whole heart dose

Cumulative risks of MI as first cardiac event among women diagnosed with BC when aged ≤70 years (median age at BC diagnosis: 50.2 years (IQR: 45.8-54.7) and median age at MI diagnosis: 64.1 years (IQR: 58.5-70.2)) by time since initial BC treatment for categories of MWHD. Cumulative risks were calculated from the MI RRs for different dose categories (table 2) and the cumulative MI risk for the entire BC cohort in which this study is embedded, with death as a competing event.

5.4.3 Cardiovascular risk factors

Hypertension and a BMI ≥30, recorded at BC diagnosis, were the only individual patient-related cardiovascular risk factors significantly associated with an increased MI rate (Table 7). However, the presence of at least one cardiovascular risk factor (angina pectoris, chronic obstructive pulmonary disease, diabetes, hypertension, smoking, BMI≥30) at BC diagnosis was associated with a rate ratio for MI of 1.70 (95% CI: 1.13-2.55) compared with no cardiovascular risk factors. When cardiovascular risk factors ever diagnosed (i.e.

during follow-up as well as at BC diagnosis) were taken into account, MI rate was higher (RR: 1.86, 95% CI: 1.19-2.90) (Table 7).

Table 5-7 Associations between patient-related risk factors and rate of myocardial infarction

	Cases		Controls				
Total	**183 (N)**	**100 (%)**	**182 (N)**	**100 (%)**	**Rate ratio***	**95% CI**	**P-value**
History of hypertension[II]							
No[**]	159	86.9	175	96.2	1.00‡	-	
Yes	24	13.1	7	3.8	3.85	1.60-9.25	0.003
History of angina pectoris[II]							
No[§]	179	97.8	180	98.9	1.00‡	-	
Yes	4	2.2	2	1.1	1.98	0.35-11.09	0.44
History of diabetes[II]							
No[§]	177	96.7	181	99.5	1.00‡	-	
Yes	6	3.3	1	0.5	6.25	0.74-52.72	0.09
History of COPD[II]							
No[§]	182	99.5	180	98.9	1.00‡	-	
Yes	1	0.5	2	1.1	0.50	0.05-5.51	0.57
Body mass index (BMI)[II,¶]							
BMI<25	77	42.1	94	51.6	1.00‡	0.74-1.36	
BMI 25-29	43	23.5	36	19.8	1.45	0.93-2.24	
BMI ≥30	14	7.7	6	3.3	2.90	1.11-7.56	
Unknown	49	26.8	46	25.3	1.33	0.87-2.03	0.053
Current smoking[II]							
No	93	50.8	92	50.5	1.00‡	0.75-1.33	
Yes	75	41.0	68	37.4	1.11	0.79-1.55	
Unknown	15	8.2	22	12.1	0.68	0.35-1.31	0.67
At least one cardiovascular risk factor[II,¥]							
No	77	42.1	101	55.5	1.00‡	-	
Yes	106	57.9	81	44.5	1.70	1.13-2.55	0.011
Ever smoking[¶]							
No	81	44.3	84	46.2	1.00‡	0.74-1.34	
Yes	87	47.5	76	41.8	1.20	0.87-1.65	
Unknown	15	8.2	22	12.1	0.71	0.37-1.37	0.43
Cardiovascular risk factors ever diagnosed[¥]							
No	51	27.9	75	41.2	1.00‡	-	
Yes	132	72.1	107	58.8	1.86	1.19-2.90	0.007

Abbreviations: CI, confidence interval, COPD, chronic obstructive pulmonary disease.
* Rate ratios for MI for different levels of each factor were calculated using logistic regression conditioning on strata defined by the matching variables.
† P-value for difference between patient-related risk factors of cases and controls, calculated within strata (defined by matching variables) and excluding the unknown category.
‡ Reference category.
II Cardiovascular risk factors recorded at BC diagnosis.
** This category includes women with an unknown history of hypertension at BC diagnosis.
§This category includes women with an unknown history of angina pectoris, COPD, hypertension or diabetes at BC diagnosis.
¶ Percentages may not total 100 because of rounding.
¥ Combined variable including: angina pectoris, COPD, diabetes, hypertension, smoking, BMI≥30.

5.4.4 Radiation dose-response relationship

A linear dose-response relationship between MWHD and MI rate was found. The excess rate ratio (ERR) for MI increased with 6.4% per Gy (95% CI: 1.3%-16.0%) (Fig. 3). A model that allowed for curvature gave no significant improvement in fit and there was no dose threshold below which there was no increase. When

considering potential modifiers of the effect of MWHD on MI rate (Table 8), we found that ERRs were highest in women aged <45 years at BC diagnosis (24.2%/Gy, 95% CI: 4.4%-82.3%) and tended to decrease with older age ($ERR_{\geq 50\text{-}70years}$: 2.5%/Gy, 95% CI: -1.4%-11.9%) ($p_{interaction}$ based on trend test:0.07, $p_{interaction}$ based on test for homogeneity between $ERR_{<45years}$ and $ERR_{\geq 50\text{-}70years}$: 0.054). ERRs increased with longer follow-up ($p_{interaction}$ based on trend test: 0.25, $p_{interaction}$ based on test for homogeneity between $ERR_{<10years}$ and $ERR_{\geq 15years}$: 0.053). The dose-response relationship for women with and without cardiovascular risk factors at BC diagnosis was similar ($p_{interaction}>0.50$). Also, when considering cardiovascular risk factors ever diagnosed, results did not change.

5.4.5 Whole heart dose-volume parameters

MWHD, MLVD and whole heart dose-volume measures were highly correlated (Pearson correlation coefficients ranged from 0.69 to 0.96). In univariable models MI rates were significantly increased when ≥30% of the heart received 5 Gy-30 Gy (RRs: 1.97-2.86) (Table 9).

The addition of MWHD as a continuous parameter to the separate dose-volume models did not significantly improve the fit of the models. Similarly, the addition of V5-V40 to the model for MWHD did not significantly improve the fit of the ERR model (data not shown). No evidence for effect modification was found for any of the dose-volume parameters V5-V40 (data not shown).

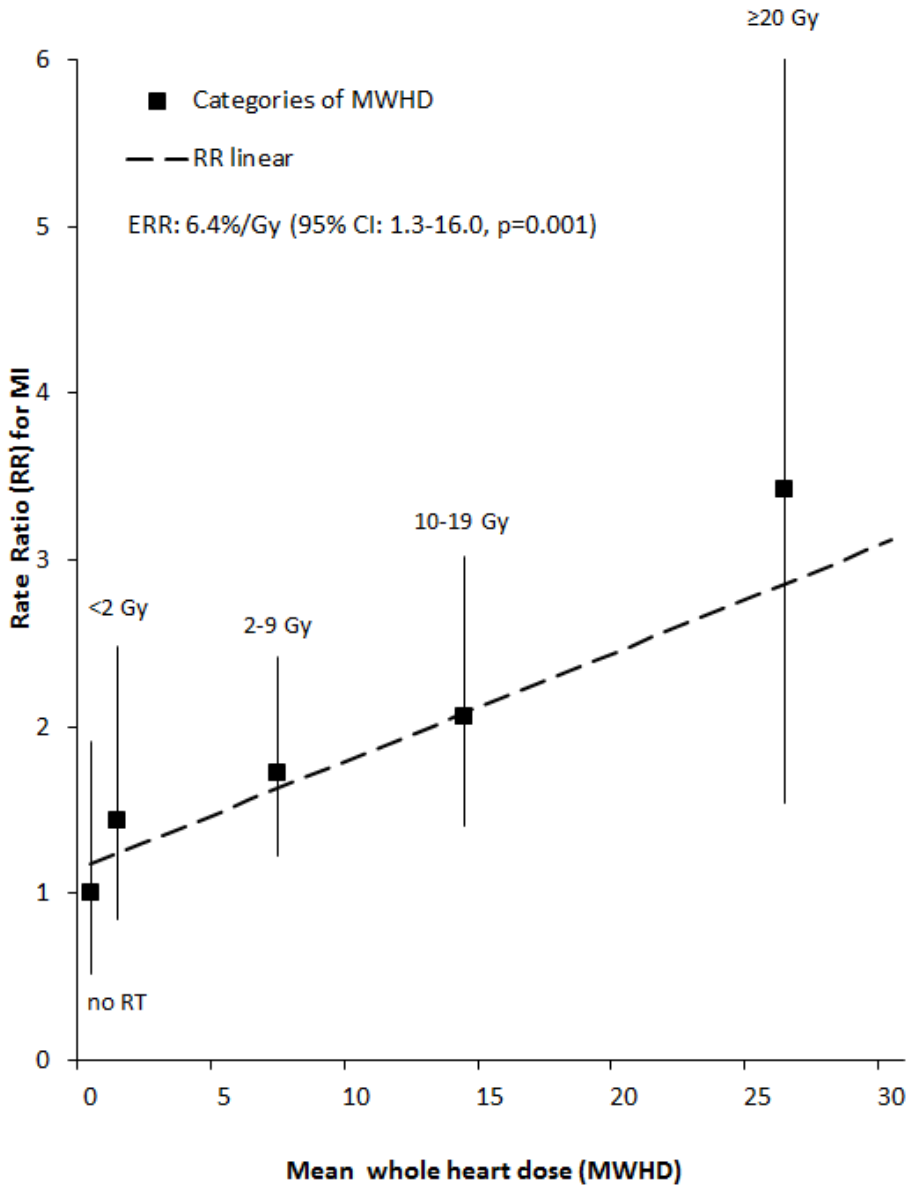


Figure 5-3. Dose-response relationship between rate of myocardial infarction and mean whole heart dose (MWHD).

The regression line is the best fitting linear dose response relationship (RR=κ(1.18+0.06389*MWHD)) ; p=0.006). This results in an excess rate ratio (ERR) of 6.4% per Gy (95% CI: 1.3-16.0) Squares indicate point estimates for dose categories (no RT, <2Gy, 2-9Gy, 10-19Gy, ≥20Gy, see table 2) and are plotted at the mean MWHD of each dose category.
There was no significant departure from linearity observed. The sum of the squared distances between the point estimates for dose categories was used to find the best fit of the linear dose-response to the categorical estimates, resulting in a linear RR of 1.18 at 0 Gy.

Table 5-8. Excess rate ratios of myocardial infarction per Gray mean whole heart dose for subgroups.

	Cases (N)	Controls (N)	ERR (%)	95% CI	P.value
All patients	183	182	6.4	1.3-16.0	0.006*
Age at BC diagnosis					
<45 years	40	41	24.2	4.4-82.3	
45-49 years	47	47	11.1	1.2-40.1	
50-70 years	96	94	2.5	-1.4-11.9	0.07†
Year of BC diagnosis					
1970-1979	41	41	4.0	-3.0-30.2	
1980-1989	95	92	8.0	0.8-26.2	
1990-1999	29	34	10.5	0.0-40.8	
≥2000	18	15	-1.6	-5.1-21.9	>0.50†
Time to MI/cut-off date					
<10 years	44	44	-0.1	-2.9-9.5	
10-14 years	60	59	7.2	-0.8-32.3	
≥15 years	79	79	15.1	2.9-49.3	0.25†
Chemotherapy (CT)					
No	140	132	9.9	2.4-25.5	
CT, no anthracyclines	29	36	1.5	-2.4-24.6	
Anthracycline-based CT	14	14	9.0	-4.2-113	>0.50§
Cardiovascular risk factors at BC diagnosis					
No	77	101	5.1	-0.3-17.3	
Yes	106	81	7.6	0.1-27.6	>0.50§
Cardiovascular risk factors ever diagnosed					
No	54	80	3.9	-1.6-18.7	
Yes	129	102	7.3	0.9-22.0	>0.50§
Smoking					
Never smoked	108	114	6.8	0.4-21.0	
Ever smoked	75	68	5.4	-0.7-21.5	>0.50§

Abbreviations: ERR, excess rate ratio, CI, confidence interval, BC, breast cancer, MI, myocardial infarction.
* P for test of ERR=0%
† P for interaction based on trend test with time/age as a continuous variable.
§ P for interaction based on test for homogeneity across categories.

Table 5-9. Associations between percentage of heart volume receiving ≥ 5-40 Gy and rate of myocardial infarction.

Percentage of heart volume receiving ≥5–40 Gy (V_5 to V_{40})	Median value (IQR)	Cases		Controls		Rate ratio¶	95% CI**	P-value†
Total§		170 (N)	100 (%)*	169 (N)	100 (%)*			
V_5	40.2 (11.1-87.6)							
<10%		44	25.9	62	36.7	1.00‡	0.68-1.47	-
10-29%		29	17.1	35	20.7	1.20	0.73-1.99	0.57
≥30%		97	57.1	72	42.6	2.02	1.43-2.85	0.008
V_{10}	37.1 (8.8-60.7)							
<10%		63	37.1	88	52.1	1.00‡	0.70-1.43	-
10-29%		21	12.4	15	8.9	1.96	0.99-3.87	0.09
≥30%		86	50.6	66	39.1	1.97	1.40-2.78	0.007
V_{15}	29.3 (8.0-40.5)							
<10%		64	37.7	91	53.8	1.00‡	0.72-1.39	-
10-29%		22	12.9	15	8.9	2.01	1.03-3.93	0.07
≥30%		84	49.4	63	37.3	2.05	1.41-2.98	0.005
V_{20}	17.1 (7.4-36.5)							
<10%		73	42.9	97	57.4	1.00‡	0.71-1.41	-
10-29%		34	20.0	33	19.5	1.42	0.87-2.30	0.25
≥30%		63	37.1	39	23.1	2.28	1.53-3.41	0.002
V_{25}	10.7 (6.8-19.1)							
<10%		77	45.3	104	61.5	1.00‡	0.73-1.37	-
10-29%		53	31.2	46	27.2	1.60	1.04-2.45	0.08
≥30%		40	23.5	19	11.2	2.86	1.67-4.90	0.001
V_{30}	6.6 (4.4-11.4)							
<10%		119	70.0	140	82.8	1.00‡	0.78-1.29	-
10-29%		25	14.7	14	8.3	2.15	1.11-4.13	0.033
≥30%		26	15.3	15	8.9	2.12	1.12-4.01	0.033
V_{35}	3.0 (1.2-6.2)							
<10%		132	77.7	149	88.2	1.00‡	0.76-1.31	-
10-29%		24	14.1	12	7.1	2.32	1.17-4.58	0.025
≥30%		14	8.2	8	4.7	2.11	0.89-5.03	0.11
V_{40}	0.3 (0-5.4)							
<10%		143	84.1	154	91.1	1.00‡	0.88-1.13	-
10-29%		23	13.5	14	8.3	1.77	0.88-3.57	0.12
≥30%		4	2.4	1	0.6	5.29	0.57-49.4	0.15

Abbreviations: IQR, inter quartile range, CI, confidence interval.
§ This model includes 339 patients. Twenty-six patients were dropped: for one irradiated case and one irradiated control dosimetry was not performed. For 22 patients (11 cases and 11 controls) it was not possible to estimate dose-volume parameters study as they had a combination of orthovoltage and electron/megavoltage treatment (manual planning). One case and one control were additionally dropped because they were the only patient left in the stratum.
* Percentages may not total 100 because of rounding.
¶ Univariable rate ratios for MI for different levels of each factor were calculated using logistic regression conditioning on strata defined by the matching variables.
** Wald method CIs were used to derive CIs for each category, including the reference category.
† P-value for difference of dose-volume categories of cases and controls, calculated within strata (defined by matching variables), with <10% as a fixed reference group.
‡ Reference category.

The addition of MWHD as a continuous parameter to the separate dose-volume models did not significantly improve the fit of the models. Similarly, the addition of V5-V40 to the model for MWHD did not significantly improve the fit of the ERR model (data not shown). No evidence for effect modification was found for any of the dose-volume parameters V5-V40 (data not shown).

5.5 Discussion

In this study we found that MI rate increased linearly by 6.4% per Gy increase in MWHD rate in BC survivors with a median age of 50 years at BC diagnosis and that there was a 3.4 fold increased MI rate at a MWHD of ≥20 Gy. In addition, we did not find any evidence that the percentage increase in MWHD rate per Gy differed between women with and without cardiovascular risk factors at BC diagnosis. These findings are consistent with the previously published radiation dose-response relationship between MWHD and MI rate in BC survivors, which showed a MI rate of 7.4% per Gy increase in MWHD for women both with and without cardiovascular risk factors at time of radiotherapy[14]. Moreover, similar results were observed in a study assessing the dose-response relationship for MWHD and the risk of IHD in Hodgkin lymphoma (HL) survivors[15].

Our results suggest that ERR per Gy were higher for the youngest women (age <45 years at BC diagnosis) and this effect had borderline significance ($p_{interaction}$=0.054-0.07). It is notable that Van Nimwegen et al also found ERRs to be highest in patients treated for HL at the youngest ages. However, ERRs for HL patients treated at an age comparable to our youngest age group were lower (i.e. 4.2%/Gy versus 24.6%/Gy)[15]. In the case-control study of Darby et al no significant effect of age on the slope of the dose response relationship between MWHD and major coronary event rate was found[14]. Some cohort studies in HL survivors and BC survivors have, however, reported that younger age is associated with higher relative risks of radiation-induced heart disease[23]. Whether radiotherapy is associated with larger percentage increases in the MI

rate per Gy MWHD in very young women (i.e. treated before 40 years of age), remains an important gap in knowledge and requires further investigation.

In some earlier studies, it was found that radiotherapy did not cause IHD during the first 10 years after exposure,[16,17] but evidence is now emerging that radiotherapy can cause IHD within the first 5 years[14,23]. We, however, did not observe increased MI rates within the first follow-up period after BC diagnosis ($ERR_{<10years}$: -0.1%, 95% CI: -2.9%-9.8%). This could be due to the inclusion of relatively young women in our study; almost 90% of patients were aged <60 years at BC diagnosis. In the study of Darby et al almost half of included women were ≥60 years at BC diagnosis[14]. In another study, presenting increased rates of major acute coronary events in relation to MHD within 9 years after radiotherapy, median age of included women was also higher (59 years, range: 26-84 years) compared to median age of our study population[24]. Strong conclusions about the absence or presence of latency in the development of radiation-induced IHD can, however, not be drawn from our data, since follow-up time was not a significant effect modifier and the number of included cases is too small to assess the effects in different follow-up groups.

We found no evidence for either model improvement or effect modification of the dose-response relationship by any of the whole heart dose-volume parameters. In a recent study, among women treated during 2005-2008 for BC or ductal carcinoma in situ, the left ventricle V5 (LV-V5) seemed to be a better predictor of acute coronary events than MWHD[24]. An important limitation of that study is, however, that there were only 30 patients who developed an event; whereas we

included 183 cases of MI after BC radiotherapy. The women included in the two studies were also irradiated in different eras, 1970s-2000s in our study and 2005-2008 in the Van den Bogaard study, so radiation techniques are likely to be different. Hence we cannot compare our findings directly.

More information is needed on whether, for a given MWHD, the dose-response relationship differs in situations where the heart is partly irradiated ("a lot to a little") versus situations where the heart is homogeneously irradiated ("a little to a lot")[25]. There is limited scope for studying this issue in our data because our measures of cardiac exposure (typical MWHD and dose-volume parameters) were all highly correlated and most women received a high dose to a small part of the heart ("a lot to a little"). Schneider et al investigated this topic by modeling the dose-response relationship using relative seriality models to extrapolate to situations where no data are currently available. They suggested the heart radiation dose-response relationship may be sigmoidal rather than linear when the heart is homogeneously irradiated ("a little to a lot").[25] The study of women irradiated since 1990 with CT-based radiotherapy planning will enable more accurate dosimetry, and inclusion of women who received intensity modulated RT. This may help assess relationships between different dose-volume parameters and IHD risk.

A limitation of our study was that we were unable to use dosimetry data derived from CT-planning scans of the cases and controls themselves, as most patients were treated before the CT-planning area. Instead, individual radiotherapy regimens for 314/316 irradiated patients were reconstructed on the CT-scan of a

typical patient and thus the cardiac doses may differ from presented estimates, due principally to variation in anatomy. The magnitude of the differences is unlikely to differ between cases and controls, but it will differ between different regimens. The nature of the error is known as 'Berkson error' and has been shown to cause relatively little attenuation of the resulting dose-response relationship[26]. Furthermore, it should be noted that cumulative MI risks were estimated from cumulative MI risk for our BC cohort.

An important strength of our study is that, in order to investigate the relationship between radiotherapy and MI rate directly, we excluded patients with heart failure and/or valvular heart disease before MI diagnosis. Furthermore, MI diagnosis was ascertained through the patients' GP, who in the Netherlands routinely receives medical correspondence from attending physicians, and/or the treating cardiologist. We found no evidence for selection of irradiated patients according to health status, as our sensitivity analyses restricted to irradiated patients showed similar risk estimates for categories of MWHD.

5.6 Conclusion

To conclude, we found a linear dose-response relationship between MWHD and MI rate in a population of relatively young BC patients with no apparent threshold dose below which MI rate is not increased. Our findings stress the importance of maximally reducing MWHD using modern radiation techniques to optimize cardiovascular health of BC survivors.

Acknowledgements

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*Joint first authors

I, F Duane provided the dosimetry for this case-control study. J Jacobse led the analyses relating dosimetry to cardiac outcome data. All authors contributed to the interpretation of the results and to the development of a manuscript.

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6 Exposure of the lungs in breast cancer radiotherapy: a systematic review of lung doses published 2010-2015

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6.1 Abstract

Background and Purpose

We report a systematic review of lung radiation doses from breast cancer radiotherapy.

Methods and Materials

Studies describing breast cancer radiotherapy regimens published during 2010-2015 and reporting lung dose were included. Doses were compared between different countries, anatomical regions irradiated, techniques and use of breathing adaptation.

Results

471 regimens from 32 countries were identified. The average mean ipsilateral lung dose (MLD_{ipsi}) was 9.0 Gy. MLD_{ipsi} for supine radiotherapy with no breathing adaption was 8.4 Gy for whole breast/chest wall (WB/CW) radiotherapy, 11.2 Gy when the axilla/supraclavicular fossa was irradiated, and 14.0 Gy with the addition of internal mammary chain irradiation; breathing adaptation reduced MLD_{ipsi} by 1 Gy, 2 Gy and 3 Gy respectively ($p<0.005$). For WB/CW radiotherapy, MLD_{ipsi} was lowest for tangents in prone (1.2 Gy) or lateral decubitus (0.8 Gy) positions. The highest MLD_{ipsi} was for IMRT in supine position (9.4 Gy).

The average mean contralateral lung dose (MLD_{cont}) for WB/CW radiotherapy was higher for IMRT (3.0 Gy) than for tangents (0.8 Gy).

Conclusions

Lung doses from breast cancer radiotherapy varied substantially worldwide, even between studies describing similar regimens. Lymph node inclusion and IMRT use increased exposure, whilst breathing adaptation and prone/lateral decubitus positioning reduced it.

6.2 Introduction

Radiotherapy improves survival in several categories of women with early breast cancer[1,2]. When irradiating the breast or chest wall with or without the regional lymph nodes exposing the lungs is unavoidable and this incidental exposure may increase the risk of subsequent primary lung cancer[3-6], pneumonitis[7] and lung fibrosis[8]. The risk of these side-effects increases with lung radiation exposure, so knowledge of the doses received by the lungs with modern breast cancer radiotherapy is important. This topic is particularly relevant today, as three large studies recently demonstrated that in women with high risk breast cancer, radiotherapy to the regional lymph nodes including the internal mammary chain (IMC) significantly reduces breast cancer recurrence[9-11]. These nodes are close to the lungs, so irradiating them can increase lung radiation exposure.

For lung cancer, radiation approximately multiplies a woman's pre-existing risk, so the absolute risk of primary lung cancer from radiotherapy will be much higher for a smoker than for a non-smoker. In an individual patient data meta-analysis of 75 randomized trials of breast cancer radiotherapy, the risk of radiation-related lung cancer increased by ~11 per cent (95% confidence interval 6-19) per Gy mean lung dose[6]. The estimated absolute risk of radiation-related lung cancer from 5 Gy mean whole lung dose was ~4% for a smoker but <1% for a non-smoker. Hence particular attention needs to be paid to minimizing lung doses in smokers[6,12].

Pneumonitis is another possible complication of breast cancer radiotherapy, occurring within three months of radiotherapy[7] and leading to lung fibrosis several

months later[8]. As with radiation-related lung cancer, the risk of pneumonitis increases with increasing lung radiation dose[7,13]. It is also more common in women who receive chemotherapy in addition to radiotherapy[7,14-16].

To assist with weighing the benefit against the risks of different breast cancer radiotherapy regimens, we present a systematic review of lung doses from breast cancer radiotherapy dosimetry studies published during 2010-2015. We describe how lung exposure varies according to country, anatomical regions irradiated, technique, treatment position and the use of breathing adaptation. In addition, we discuss the likely future absolute risks of radiation-related lung cancer for women irradiated recently.

6.3 Methods

6.3.1 Study identification

Studies were identified following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17]. Embase and Scopus were queried using search terms ("dos* AND breast* AND cancer*/carcinom*/tumor*/tumour* AND radiation/radiotherapy*") to retrieve breast cancer radiotherapy dosimetry studies published between 1 January 2010 and 18 September 2015. All studies reporting any measure of lung dose were eligible, regardless of whether the plans were actually delivered. Reference sections of eligible papers were scanned to identify additional eligible studies. Studies reporting only dose from a tumour bed boost were excluded because this is nearly always given alongside whole breast radiotherapy, which delivers higher lung doses. Studies of bilateral breast cancer were also excluded.

Table 6-1.Definitions of radiotherapy planning and delivery used in review

Category	Sub-category	Definition
Patient position	Supine	Patient lying on back
	Prone	Patient lying on front
	Lateral decubitus	Patient lying on side
Treatment planning	2D Conformal	Single slice patient contour information with shaped fields (usually simple block)
	3D Conformal	Multi-CT patient contour slices used, with shaped fields
	3D Conformal with FIF	Multi-CT patient contour slices used, with shaped fields and multiple segments (field in field)
	3D IMRT	Multi-CT patient contour slices used, with inverse-planned IMRT
	Other	Other type of treatment planning
Field type	Tangents	Fixed gantry angles, tangential fields with medial border on midline or to the ipsilateral side
	Tangents plus electron field	Fixed gantry angles, tangential fields with medial border on midline or to the ipsilateral side, plus a single electron field
	Tangents plus boost/direct fields	Fixed gantry angles, tangential fields with medial border on midline or to the ipsilateral side, plus one or more direct photon field(s)
	Wide tangents	Fixed gantry angles, tangential fields with medial border to the contralateral side
	Wide tangents plus boost/direct fields	Fixed gantry angles, tangential fields, with medial border to the contralateral side plus one or more direct photon fields
	Wide tangents plus electron field	Fixed gantry angles, tangential fields with medial border to the contralateral side plus a single electron field
	Partially wide tangents	Fixed gantry angles, tangential fields, with part of medial border to the contralateral side
	Rotational fields	Gantry rotating during treatment, either using tomotherapy or a linear accelerator (e.g. volumetric modulated arc therapy). Topotherapy was defined as static fields, even though the patient moves through the machine aperture during treatment
	Direct fields	Single or multiple direct fields (photon, electron or proton) “en face”
	Oblique fields	Single or multiple fields (photon, electron or proton), at an oblique angle to the skin
	Other	Other field type
Beam energy & Modality	Low energy MV photons	Single energy MV photons, with an energy between 4-8MV
	Mixed energy MV photons	Multiple energy MV photons e.g. 6 and 15MV in the same treatment plan
	High energy MV photons	Single energy MV photons, with an energy between 10-18MV
	MV photons	MV photon beams, with energy not specified
	Mixed photons & electrons	MV photon and MeV electron beams
	Electrons	MeV electron beams
	Protons	Proton beams
	Protons plus photons	Proton plus photon beams
	Brachytherapy	Kilovoltage energies from a brachytherapy source
	Carbon ions	Carbon ion beams
Breathing adaptation	No breathing adaptation	No breathing adaptation used at either planning or treatment stages
	Breathing adaptation	Breathing adaptation used at either planning or treatment stages (multiple methods were used e.g. deep inspiratory breath hold, gating, active breathing control)
RT plan delivered	Yes	The radiotherapy plans were delivered to the women
	No	The radiotherapy plans were not delivered
	Some	Some of the radiotherapy plans were delivered

Table 6-1 continued

Category	Sub-category	Definition
Calculation algorithm	Type A	No modelling of lateral electron transport, MV photons
	Type B	Lateral electron transport modelled, MV photons
	Brachytherapy	Brachytherapy treatment planning
	Protons	Proton treatment planning
	MC	Monte Carlo (MV photons)
	NS	Not specified

Abbreviations:
3D: 3-dimensional
2D: 2-dimensional
FIF: field-in-field
IMRT: intensity modulated radiation therapy
MeV: mega electron volt
MV: megavoltage

Table 6-2. Grouping of sub-categories used to create the types of "radiotherapy technique" shown in figures 3, 4 and 5.

Radiotherapy technique	Sub-categories included
Protons	Beam energy & modality: Protons, Protons plus photons
Brachytherapy	Beam energy & modality: Brachytherapy
Tangents	Treatment planning: 3D Conformal, 3D Conformal with FIF, 2D Conformal plan, NS Field type: Tangents, Tangents plus electron fields, Tangents plus boost/direct field
Wide tangents	Treatment planning: 3D Conformal, 3D Conformal with FIF, 2D Conformal plan, NS Field type: Wide tangents, Wide tangents plus boost/direct fields, Partially wide tangents
IMRT	Treatment planning: 3D IMRT (includes static IMRT and rotational fields (e.g. volumetric modulated arc therapy))
Oblique fields	Treatment planning: 3D Conformal, 3D Conformal with FIF, 2D Conformal plan, NS Beam energy & modality: photons, electrons, protons and combinations Non tangential fields arrangements without inverse planning
Others	Anything not in the above categories

Abbreviations:
3D: 3-dimensional
2D: 2-dimensional
FIF: field-in-field
IMRT: intensity modulated radiation therapy

6.3.2 Data abstraction

Eligible studies were categorised according to radiotherapy technique (Tables 1,2). The information abstracted from each study included: author, year, country of first author, patient position, radiotherapy planning technique (e.g. conformal vs IMRT), field type (e.g. static vs rotational), beam energy, breathing adaptation, whether or not the radiotherapy plans were delivered, region(s) irradiated, prescription dose to the target and number of fractions, number of CT planning scans per regimen included in the study, the type of dose calculation algorithm, the presence of unfavourable anatomy and cancer laterality. Lung dose measures abstracted were: mean ipsilateral lung dose (MLD_{ipsi}), mean contralateral lung dose (MLD_{cont}), mean whole lung dose (i.e. where both lungs were considered a single organ) (MLD_{whole}), $V5_{ipsi}$ (i.e. percent ipsilateral lung volume irradiated to 5 Gy or more), $V10_{ipsi}$, $V20_{ipsi}$, $V30_{ipsi}$ and $V40_{ipsi}$. Dose calculation algorithms[18] were categorised as "type A" (no/poor modelling of lateral electron transport), "type B" (some modelling of lateral electron transport), Monte Carlo and "other**".** Each regimen was classified as to whether or not it was reported for a high income country[19].

6.3.3 Data analyses

Analyses considered the average of the lung dose measures from the CT plans included for each regimen described in each study. We term these "average lung doses". Average lung doses were compared between countries, region(s) irradiated, techniques used, patient treatment positions and whether breathing adaption was used. Variation in the average doses within each of these

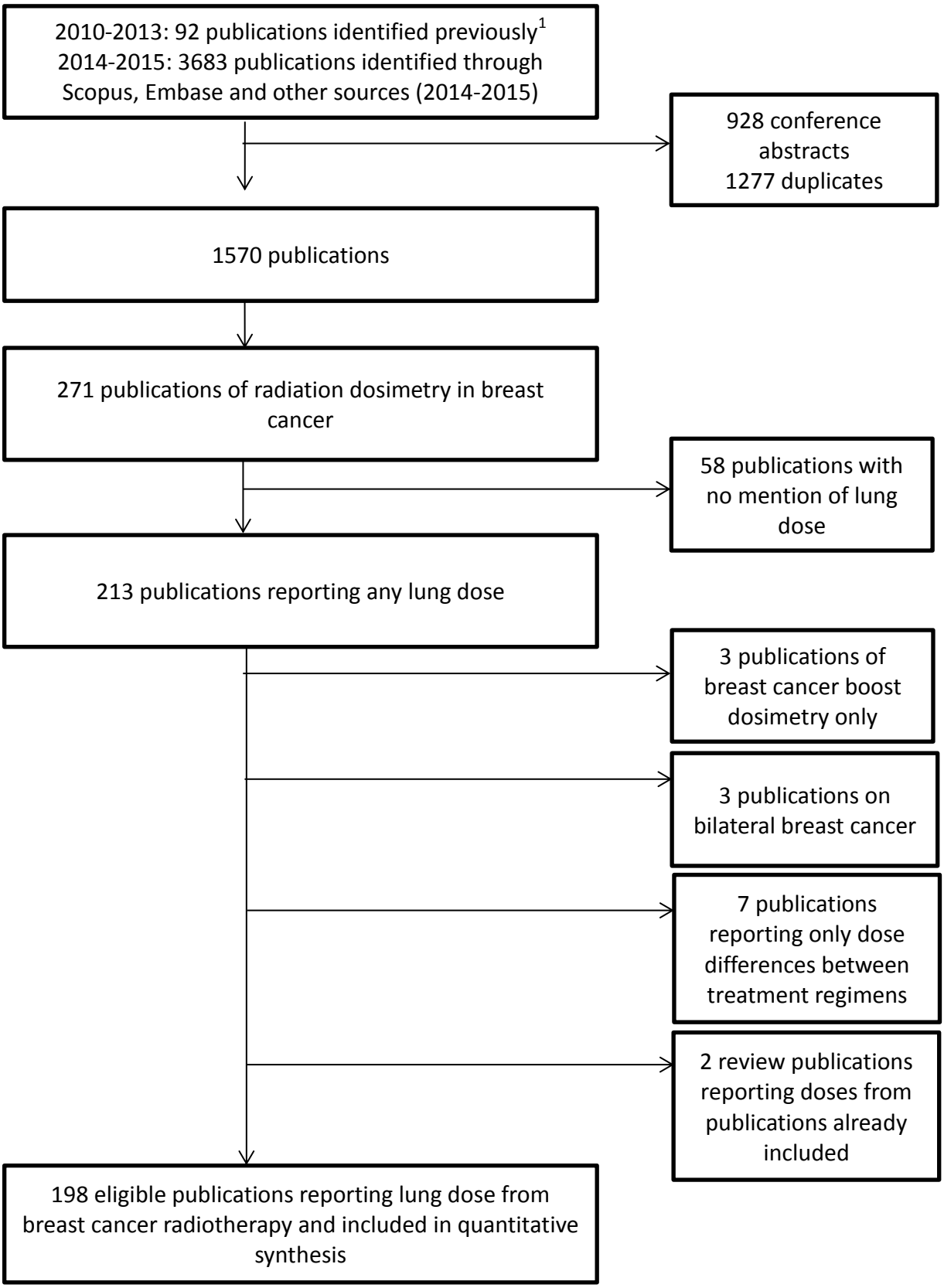


Figure 6-1. The process of study identification for the review

[1] Systematic search of radiation dosimetry publications in breast cancer conducted described in Taylor et al[22]. Only publications from 2010 onwards were included in the present analysis.

categories was assessed using chi-squared tests for heterogeneity, difference or trend, as appropriate.

6.4 Results

Radiation doses to the lungs from breast cancer radiotherapy were reported in 198 studies from 32 countries including 579 regimens* (Fig. 1, Table 3). The year in which the CT plans were generated was reported in 64/198 studies: it was before 2005 in four studies, 2005-09 in 29 studies and 2010-15 in 31 studies. 3D-treatment planning was used in all 198 studies; one study simulated a 2D regimen on 3D CT scans with field borders based on bony structures and midline wire marking[2]. MLD_{ipsi} was available for 471 regimens in 153 studies and was the commonest dose measure reported (Table 1). Among those 153 studies, 94 reported MLD_{ipsi} separately for left-sided and right-sided breast cancer radiotherapy regimens. The difference in average MLD_{ipsi} according to laterality was small and not significant (left-sided 9.5 Gy in 287 regimens, right-sided 8.7 Gy in 38 regimens, p for difference=0.94). Therefore, left-sided and right-sided regimens were considered together in our analyses.

*Table of regimens and lungs doses from each breast cancer radiotherapy publication published in 2010-2015 and a full list of references (198) available at: http://www.thegreenjournal.com/article/S0167-8140(17)32742-1/addons (page 4-56)

Table 6-3. Studies reporting lung doses from breast cancer radiation therapy regimens and published during 2010 to 2015.

Breast cancer laterality	Dose measure	Number of Studies*	Number of regimens†	CT plans per regimen‡		Lung dose	
				Average	Range	Average	Range
Left	MLD_{ipsi}	90	287	16	1-148	9.5 Gy	0.3-27.5§
	MLD_{cont}	39	147	11	1-31	2.5 Gy	0-15.0§
	$V20_{ipsi}$	81	258	17	1-148	16.8 %	0-44.5
	$V5_{ipsi}$	52	162	18	1-148	41.8 %	0.8-94
Right	MLD_{ipsi}	16	38	7	1-45	8.7 Gy	1.2-16.1
	MLD_{cont}	6	13	3	1-14	2.7 Gy	0.2-6.5
	$V20_{ipsi}$	12	25	11	1-45	16.1 %	4.7-35.6
	$V5_{ipsi}$	6	14	6	1-47	42.4 %	1.5-88.7
Unspecified	MLD_{ipsi}	60	146	33	6-494	7.9 Gy	0.3-22.9
	MLD_{cont}	21	58	24	6-246	1.6 Gy	0-6.4
	$V20_{ipsi}$	58	135	40	6-494	13.9 %	0.1-44.5
	$V5_{ipsi}$	27	57	34	8-431	32.2 %	0.7-99.3
All studies reporting	MLD_{ipsi}	153	471	21	1-494	9.0 Gy	0.3-27.5‡
All studies reporting	MLD_{cont}	62	218	14	1-246	2.3 Gy	0-15.0‡
All studies reporting	$V20_{ipsi}$	139	417	19	6-494	15.8 %	0-44.5
All studies reporting	$V5_{ipsi}$	78	233	21	1-431	39.5 %	0.7-99.3
All studies		198|	579	-	-	-	-

Definitions: MLD_{ipsi}: mean dose to the ipsilateral lung, MLD_{cont}: mean dose to the contralateral lung, $V20_{ipsi}$: percent volume of the ipsilateral lung receiving 20 Gy or more, $V5_{ipsi}$: percent volume of the ipsilateral lung receiving 5 Gy or more.
*Some studies reported doses for both left-sided and right-sided regimens and so contribute more than once.
† Some regimens reported several dose measures (e.g. both MLD_{ipsi} and $V20_{ipsi}$)
‡ For four regimens in one study the number of CT planning scans was not reported.
§Four regimens (three from Al-Rabhi 2013, one from Ares 2010) were excluded because doses reported were inconsistent with values presented elsewhere in the publication.
|This total represents the number of unique studies, without the multiple contributions from studies which reported doses for both left-sided and right-sided regimens.

6.4.1 Tangential regimens

Whole breast/chest wall tangential radiotherapy in supine position with no breathing adaption was the most commonly reported combination of technique and regions irradiated (113 regimens in 70 studies) (Fig. 2). The average MLD_{ipsi} for all 113 regimens was 7.9 Gy (SE 0.2) and it varied significantly according to continent (p for heterogeneity <0.001). There was also substantial variation according to country within Europe and Asia (p for heterogeneity <0.001 for both continent (p for heterogeneity <0.001). There was also substantial variation according to country within Europe and Asia (p for heterogeneity <0.001 for both). The average MLD_{ipsi} was lowest for Poland and Korea (5.2 and 7.5 Gy respectively) and highest for Spain and Saudi Arabia (13.5 and 12.9 Gy respectively). The average MLD_{ipsi} in “high income” countries was lower than in other countries (7.7 versus 8.7 Gy, p for difference=0.05), but it did not vary significantly according to calendar year of publication (p for trend=0.16) or whether the treatment plans were actually delivered (p for difference=0.68).

6.4.2 Regions irradiated

After excluding studies of women with unfavourable anatomy and regimens in the prone or lateral decubitus positions, 376 of the 471 regimens remained, with an average MLD_{ipsi} of 9.1 Gy (SE 0.2). The average MLD_{ipsi} was highly correlated with the extent of the regions irradiated (2p for trend <0.001, Fig. 3). For partial breast irradiation (20 regimens) average MLD_{ipsi} was 2.1 Gy (SE 0.3) and for whole breast/chest wall irradiation (262 regimens) it was 8.4 Gy (SE 0.2). The addition of axilla/supraclavicular fossa irradiation (50 regimens) increased it to

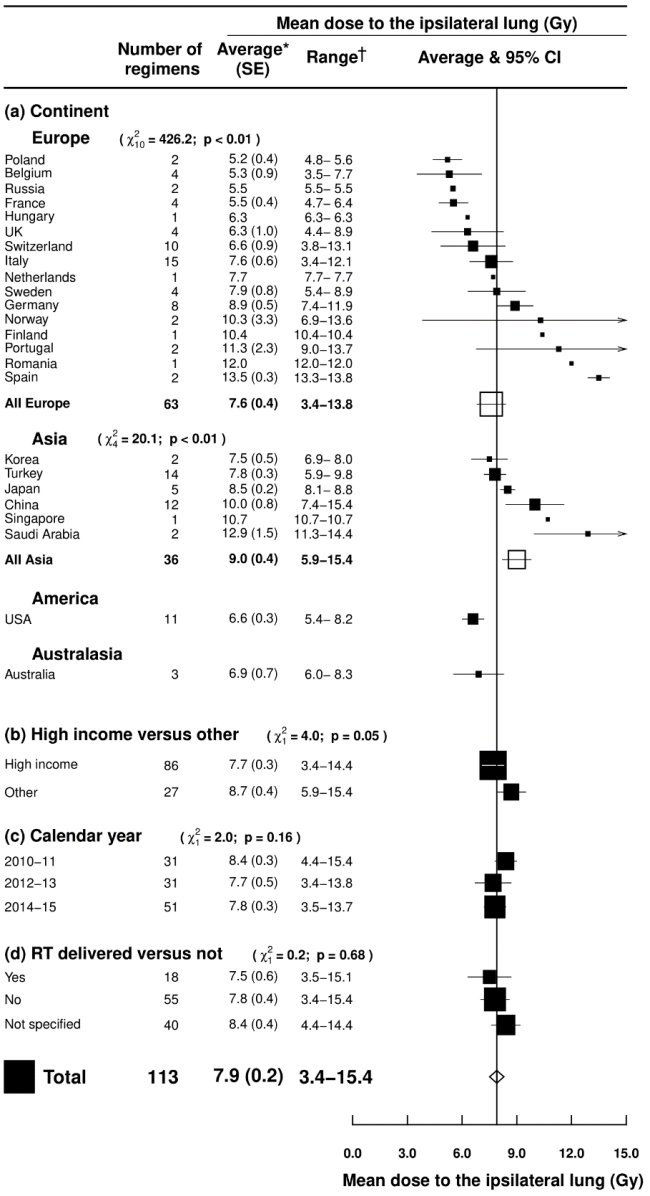


Figure 6-2. Mean ipsilateral lung dose (MLD_{ipsi}) from left or right tangential breast cancer radiotherapy according to country, gross national income per person in the country concerned, calendar year, and whether the radiotherapy plans were actually delivered or just planned.

*Average of mean ipsilateral lung doses for reported regimens.
† Range of mean ipsilateral lung doses for reported regimens.
χ^2 and p values are for: heterogeneity (a), difference (b, d) or trend (c). For (d), the category "Not specified" was omitted from the χ^2.
Abbreviations: SE: standard error; CI: confidence interval.
Regimens that irradiated the internal mammary chain, partial breast, axilla, or supraclavicular fossa were excluded, as were regimens with breathing adaptation, prone or lateral decubitus positioning and studies of women with unfavourable anatomy.

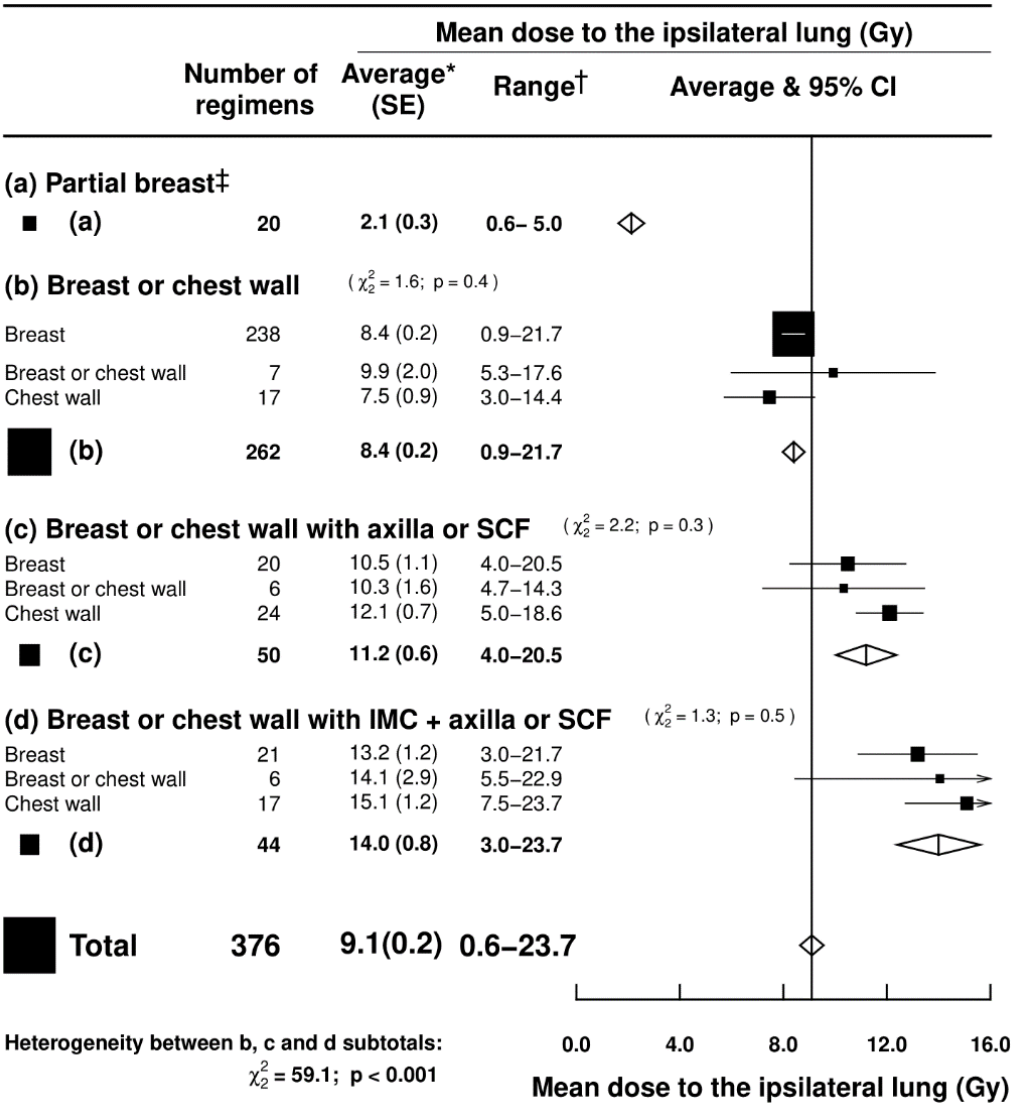


Figure 6-3. Mean ipsilateral lung dose (MLD_{ipsi}) from left or right breast cancer radiotherapy according to regions irradiated.

*Average of mean ipsilateral lung doses for reported regimens.
† Range of mean ipsilateral lung doses for reported regimens.
χ^2 and p values are for heterogeneity.
Abbreviations: SE: standard error; CI: confidence interval.
Studies of women with unfavourable anatomy were excluded as were regimens using prone or lateral decubitus positioning, and regimens irradiating the internal mammary chain (IMC) but not the axilla or the supraclavicular fossa (SCF).

11.2 Gy (SE 0.6) and inclusion of the internal mammary chain (IMC) (44 regimens) further increased it to 14.0 Gy (SE 0.8).

6.4.3 Technique and treatment position

For each combination of region(s) irradiated, the average MLD_{ipsi} varied according to both technique and treatment position (Fig. 4). The commonest treatment position was supine (338 regimens). The commonest techniques were tangents (159 regimens) and intensity modulated radiotherapy (IMRT) (156 regimens). Average MLD_{ipsi} was similar for static field and rotational IMRT so these two types of IMRT were considered together.

For 20 partial breast regimens (Fig. 4, panels a_1 and a_2), the average MLD_{ipsi} for the different techniques and treatment positions varied from 0.3 to 2.6 Gy. For 234 whole breast/chest wall regimens in supine position (Fig. 4, panel b_1) the MLD_{ipsi} was 7.9 (SE 0.2) from tangents and 9.4 (SE 0.3) from IMRT (p for difference<0.001). Doses for these techniques from 17 whole breast/chest wall regimens in prone position were lower: MLD_{ipsi} 1.6 (SE 0.5). The lowest doses were from two whole breast/chest wall regimens in lateral decubitus position: MLD_{ipsi} =0.8 (SE 0.1).

When the axilla/SCF was also irradiated (Fig. 4, panel c), the commonest regimens were tangents (26 regimens) which delivered MLD_{ipsi} =10.9 (SE 0.8) and IMRT (16 regimens), which delivered MLD_{ipsi} =11.7 (SE 1.1). When the IMC

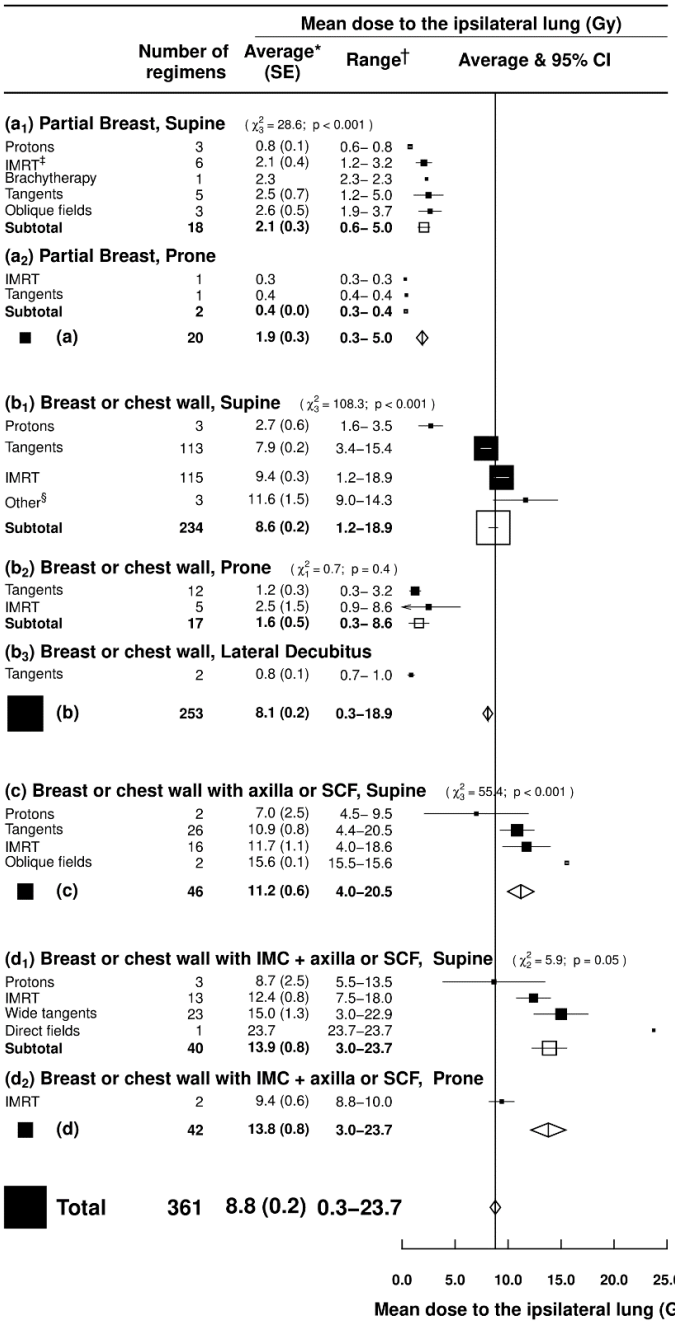


Figure 6-4.Mean ipsilateral lung dose (MLD_{ipsi}) from left or right breast cancer radiotherapy according to regions irradiated and technique used.

*Average of mean ipsilateral lung doses for reported regimens.
† Range of mean ipsilateral lung doses for reported regimens.
‡ Static field IMRT and rotational IMRT are included jointly as “IMRT”.
§ “Other” techniques included two dynamic conformal arc therapy regimens and one unspecified 3D conformal regimen.
χ^2 and p values are for heterogeneity.
Abbreviations: SE: standard error; CI: confidence interval; IMRT: intensity modulated radiotherapy. IMC: internal mammary chain. SCF: supraclavicular fossa.
Regimens using breathing adaptation (e.g. deep inspiration breath hold) were excluded, as were studies of women with unfavourable anatomy and regimens irradiating the internal mammary chain (IMC) but not the axilla or the supraclavicular fossa (SCF).

was also included (Fig. 4, panels d_1 and d_2), there were 23 wide tangential regimens which delivered MLD_{ipsi} =15.0 (SE 1.3) and 13 IMRT regimens, which delivered MLD_{ipsi} =12.4 (SE 0.8). The highest reported MLD_{ipsi} values were for rare techniques that included oblique or direct fields and were not actually delivered to patients.

Doses from proton therapy were reported for 11 regimens. Within each category of regions irradiated, proton therapy resulted in the lowest average MLD_{ipsi}: partial breast 0.8 Gy (SE 0.07), whole breast/chest wall 2.7 Gy (SE 0.6), whole breast/chest wall and axilla/supraclavicular fossa 4.8 Gy (SE 0.3), whole breast/chest wall and axilla/supraclavicular fossa with IMC 8.7 Gy (SE 2.5) (Fig. 4, panels a_1, b_1, c_1 and d_1).

6.4.4 Breathing adaptation

For 29 regimens (21 studies) the average MLD_{ipsi} was reported for a given regimen both with and without breathing adaption in the same women (Fig. 5). Breathing adaptation reduced the average MLD_{ipsi} significantly in all regimens, with the magnitude of the reduction depending on the extent of the regions irradiated. For partial breast irradiation the average reduction was 0.2 Gy; for whole breast/chest wall radiotherapy it was 0.8 Gy; for regimens that included the axilla/supraclavicular fossa it was 2.5 Gy; and for regimens that also included the IMC it was 2.9 Gy. These reductions were seen regardless of radiotherapy technique or patient positioning.

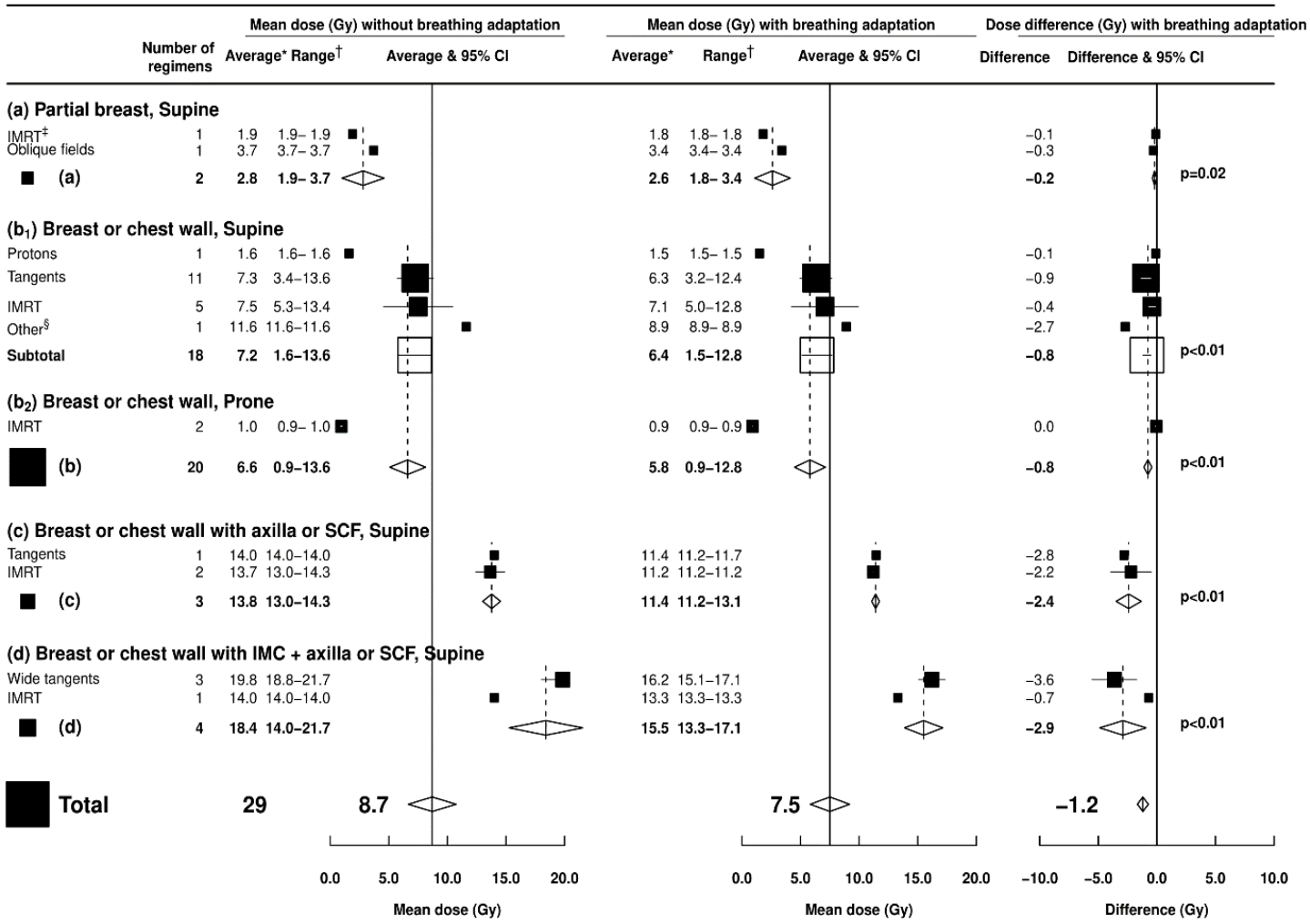


Figure 6-5 Mean ipsilateral lung doses (MLD_{ipsi}) from left or right breast cancer radiotherapy with or without breathing adaptation according to regions irradiated and regimens used.

Only studies providing doses with and without breathing adaptation in the same woman were included.
Studies of women with unfavourable anatomy were excluded.
*Average of mean ipsilateral lung doses for reported regimens.
† Range of mean ipsilateral lung doses for reported regimens.
‡ Static field IMRT and rotational IMRT are included jointly as "IMRT".
§ "Other" includes one unspecified 3D conformal regimen.
p values are calculated using a paired t-test.
Abbreviations:
CI: confidence interval; IMRT: intensity modulated radiotherapy; IMC: internal mammary chain; SCF: supraclavicular fossa.

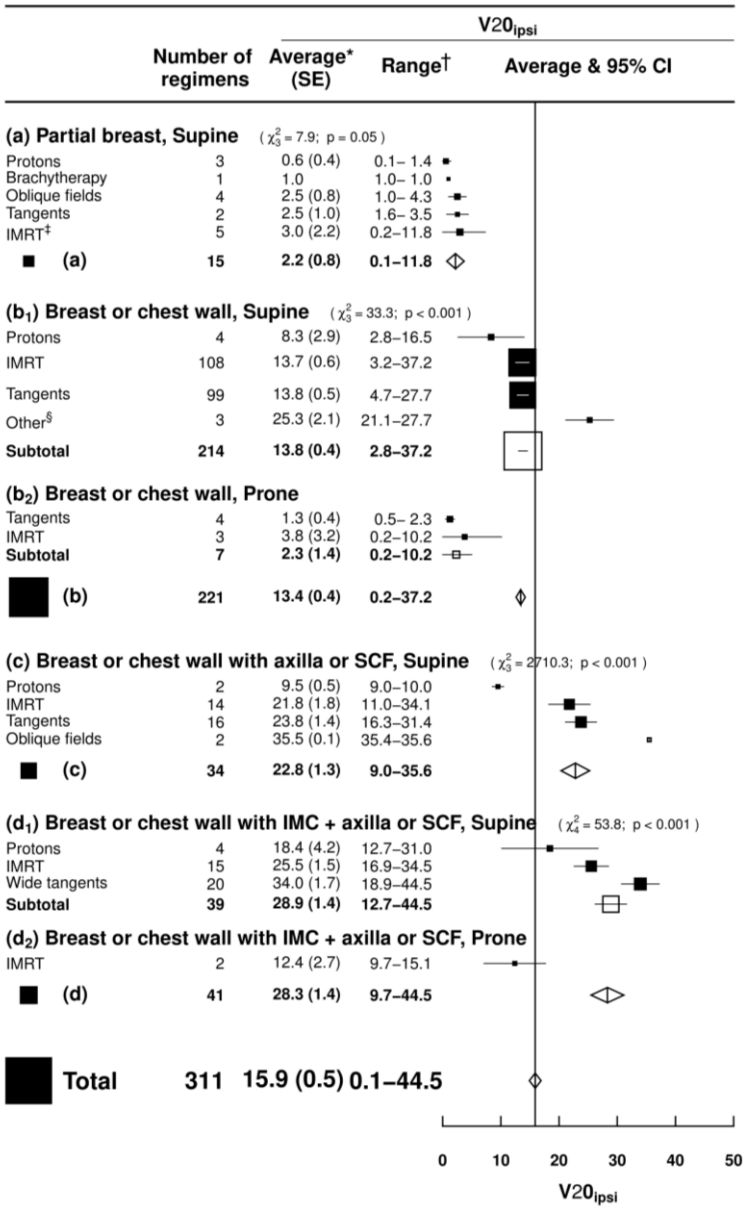


Figure 6-6. Percent volume of ipsilateral lung receiving 20 Gy or more (V20ipsi) from breast cancer radiation therapy according to region irradiated and technique used.

* Average of ipsilateral V20ipsi for reported regimens.
† Range of ipsilateral V20ipsi for reported regimens.
‡ Static field IMRT and rotational IMRT are included jointly as IMRT.
§ Other techniques included two dynamic conformal arc therapy regimens and on unspecified 3D conformal regimen.
χ^2 and p values are for heterogeneity.
Abbreviations: SE: standard error. CI: confidence interval. IMRT: intensity modulated radiotherapy. IMC: internal mammary chain. SCF: supraclavicular fossa.
Regimens using breathing adaptation (e.g. deep inspiration breath hold) and studies of women with unfavourable anatomy were excluded.

6.4.5 Other measures of lung dose

The average $V20_{ipsi}$ (311 regimens, 139 studies) was 15.9% and the average $V5_{ipsi}$ (174 regimens, 77 studies) was 40.9% (Fig 6-7). For treatment in the supine position not including the IMC, there were no material differences in $V20_{ipsi}$ between IMRT and tangents (Fig. 6 panels a, b_1, c). When the IMC was included, IMRT led to a substantially lower $V20_{ipsi}$ than wide tangents ($p < 0.001$) (Fig. 6 panel d_1). Prone positioning was effective at reducing $V20_{ipsi}$, and for each region category for which it was reported average $V20_{ipsi}$ for protons was lower than for other techniques. $V5_{ipsi}$ was higher for IMRT than for tangential regimens regardless of the regions irradiated (Fig. 7). Other volumetric dose measures such as $V30_{ipsi}$ and $V40_{ipsi}$ were each reported in fewer than 50 studies.

The average MLD_{cont} (168 regimens, 62 studies) was 2.2 Gy (Fig. 8). MLD_{cont} was higher for IMRT than for tangential regimens, regardless of the regions irradiated. For partial breast radiotherapy, the average MLD_{cont} was 0.2 Gy. For the other region categories, average MLD_{cont} varied from 1.9 to 2.6 Gy, and did not increase according to the extent of the ipsilateral regions irradiated. The lowest contralateral lung doses within each region category were from proton therapy.

The average MLD_{whole} (218 regimens, 88 studies) was 6.0 Gy (Fig. 9). Variation according to regions irradiated, technique, and patient position was similar to MLD_{ipsi} (Fig. 4).

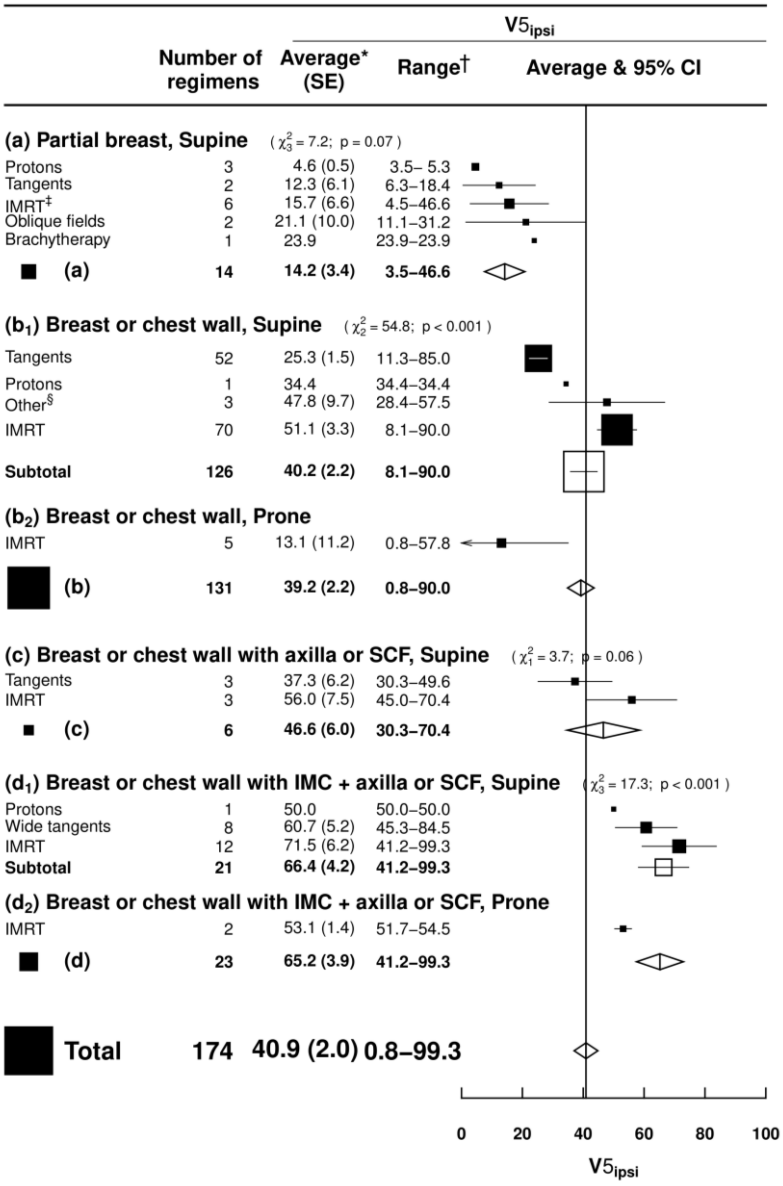


Figure 6-7. Percent volume of ipsilateral lung receiving 5 Gy or more (V5ipsi) from breast cancer radiation therapy according to regions irradiated and technique used.

* Average of ipsilateral V5ipsi for reported regimens.
† Range of ipsilateral V5ipsi for reported regimens.
‡ Static field IMRT and rotational IMRT are included jointly as IMRT.
§ Other techniques included two dynamic conformal arc therapy regimens and on unspecified 3D conformal regimen.
χ^2 and p values are for heterogeneity.
Abbreviations: SE: standard error. CI: confidence interval. IMRT: intensity modulated radiotherapy. IMC: internal mammary chain. SCF: supraclavicular fossa.
Regimens using breathing adaptation (e.g. deep inspiration breath hold) and studies of women with unfavourable anatomy were excluded.

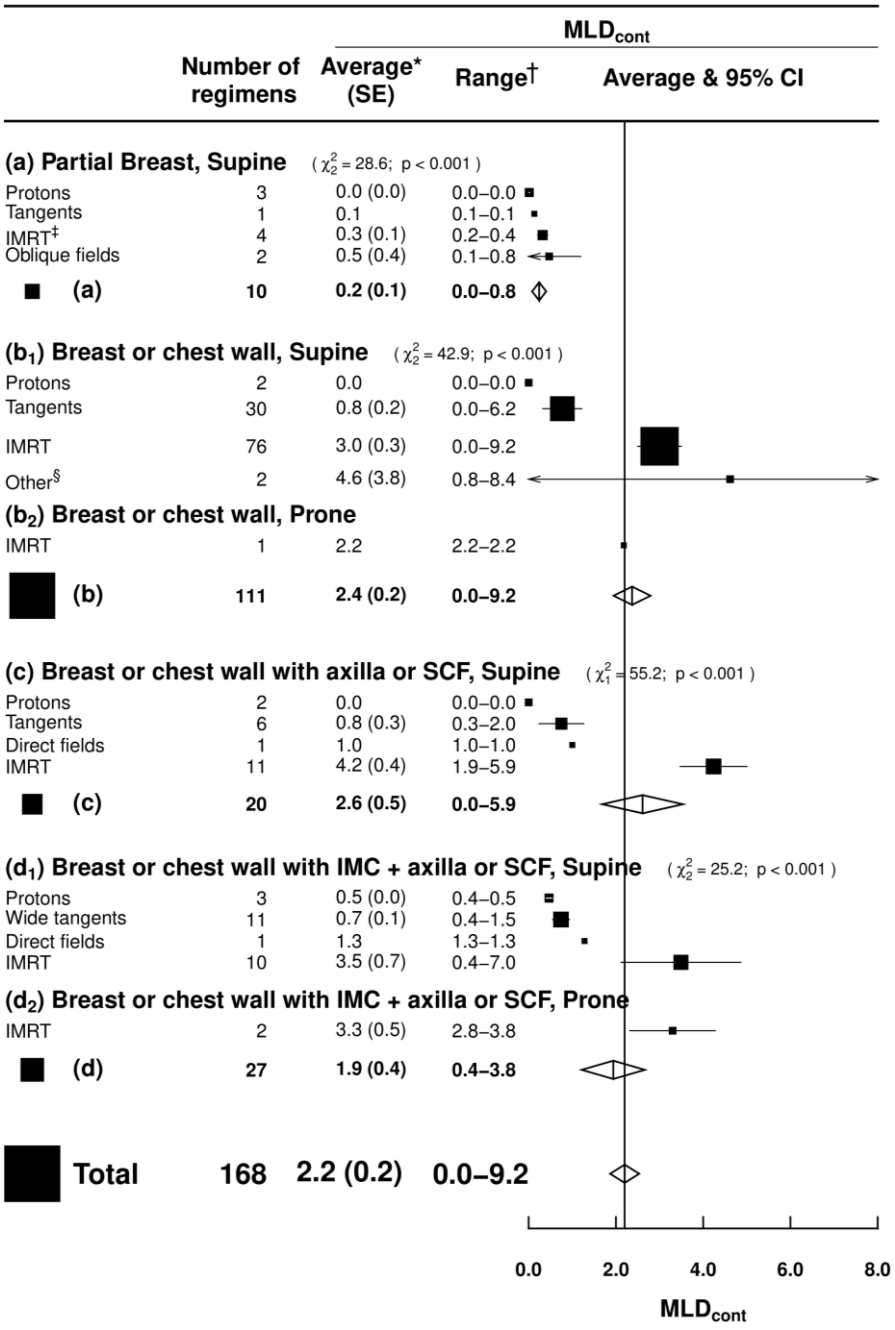


Figure 6-8. Mean contralateral lung doses (MLD_{cont}) from breast cancer radiotherapy according to region irradiated and technique used.

* Average of MLD_{cont} for reported regimens.
† Range of MLD_{cont} for reported regimens.
‡ Static field IMRT and rotational IMRT are included jointly as IMRT.
§ Other techniques included two dynamic conformal arc therapy regimens and on unspecified 3D conformal regimen.
χ^2 and p values are for heterogeneity.
Abbreviations: SE: standard error. CI: confidence interval. IMRT: intensity modulated radiotherapy. IMC: internal mammary chain. SCF: supraclavicular fossa.
Regimens using breathing adaptation (e.g. deep inspiration breath hold) and studies of women with unfavourable anatomy were excluded.

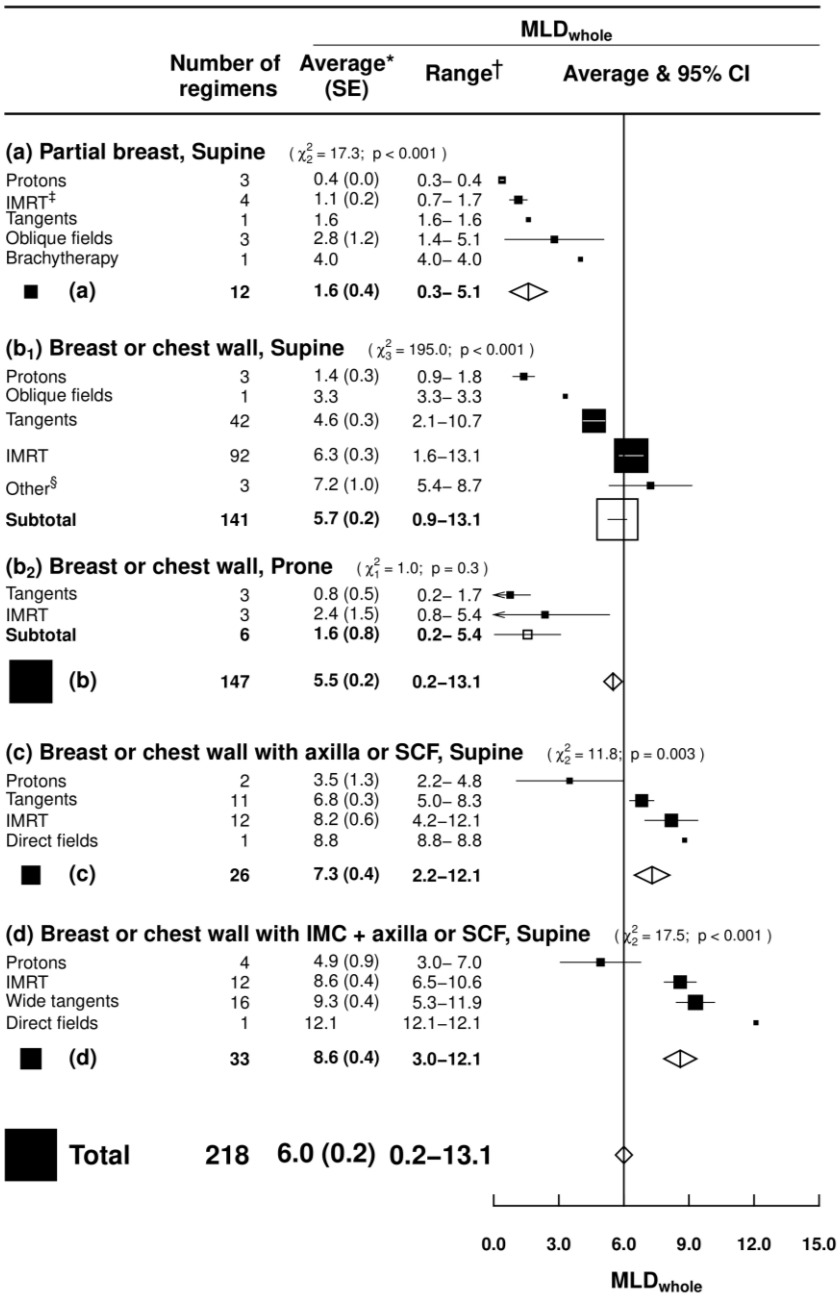


Figure 6-9. Mean whole lung doses (MLD_{whole}) from breast cancer radiotherapy according to region irradiated and technique used.

*Average of MLDwhole for reported regimens.
† Range of MLDwhole for reported regimens.
‡ Static field IMRT and rotational IMRT are included jointly as IMRT.
§ Other techniques included two dynamic conformal arc therapy regimens and on unspecified 3D conformal regimen.
χ^2 and p values are for heterogeneity.
Abbreviations: SE: standard error. CI: confidence interval. IMRT: intensity modulated radiotherapy. IMC: internal mammary chain. SCF: supraclavicular fossa.

6.4.6 Dose calculation algorithm

The dose calculation algorithm used for external beam photon radiotherapy was reported in 147/198 (74%) of the studies. Of these, 108 studies used a type B algorithm, 30 studies used type A and 9 studies used Monte Carlo. No significant differences in MLD_{ipsi}, $V20_{ipsi}$, $V5_{ipsi}$, MLD_{cont} or MLD_{whole} were observed according to algorithm (p for heterogeneity > 0.8 for all dose measures) (data not shown).

6.5 Discussion

This systematic review of lung doses from breast cancer radiotherapy regimens published during 2010-2015 shows that lung exposure varied substantially worldwide but that several factors influenced it systematically. Lung doses increased with more extensive regions irradiated and reduced with the use of breathing adaptation or prone or lateral decubitus positioning. Lung doses also depended on the technique used, with the highest doses from IMRT and lowest doses from proton therapy.

6.5.1 Methods to reduce lung exposure

There are several ways of reducing lung dose in breast cancer radiotherapy today. First, in our study, limiting the extent of irradiated regions reduced MLD_{ipsi} (Fig. 3). This is often done in current practice, for example regional nodal irradiation is only usually recommended in women at high risk of cancer recurrence, while in some women at very low risk of recurrence, radiotherapy may be omitted altogether[21]. Second, lung-sparing techniques may be used. The lowest ipsilateral lung doses for breast/chest wall irradiation were from proton

therapy (<2.7 Gy) or from prone or lateral decubitus positioning (<2.5 Gy) (Fig. 4). These techniques also reduce mean heart doses [22] but are not yet widely used. Only 8 centres (8 studies) reported lung doses from proton therapy which is expensive and available in few centres[23]. One centre (2 studies) reported lung doses for lateral decubitus positioning and 15 centres (20 studies) reported doses for prone positioning. The limited implementation of new positioning techniques is due to the need for specialized equipment and concerns about the reproducibility of daily patient set-up[24]. For regimens that did not include the IMC, tangents resulted in lower MLD_{ipsi} than IMRT (Fig. 4). When the IMC was irradiated, IMRT resulted in lower MLD_{ipsi} and $V20_{ipsi}$ than tangents (Fig. 4, Fig.6) at the cost of higher $V5_{ipsi}$ and MLD_{cont} (Fig. 7-8). In clinical practice, MLD_{cont} may also be reduced by limiting the number of beams (or using a partial arc in the case of rotational treatments) to avoid beam entry through the contralateral lung. In addition, strict optimization constraints and strategic beam placement may minimize $V5_{ipsi}$. Third, lung dose can be reduced by using breathing adaptation. Historically this has been used to reduce cardiac exposure but our study suggests that it also reduces lung exposure, with the magnitude of the gain increasing with more extensive regions irradiated (Fig. 5).

6.5.2 Strengths and limitations

Our study has several strengths. First, this comprehensive systematic review included 471 regimens and 153 studies, with the main analyses based on the most commonly reported measure of lung exposure, MLD_{ipsi}, Second, our doses are likely to represent normal radiotherapy practice, since most included studies

focussed on target volume coverage or heart dose and lung doses were reported only for completeness rather than as a primary endpoint. As such, it is unlikely that the groups who published these doses paid more attention to minimising lung exposure than other groups who did not publish their lung doses. Third, this systematic review was carried out by both a radiation oncologist and a physicist to ensure that all regimens were reliably categorised.

Our study also has some limitations. For a given regimen, there was variation in the lung doses received by individual patients. Kim et al reported lung doses for a tangential field-in-field regimen delivered to 157 women and found that the MLD_{ipsi} for individual women ranged from 2.8-18.7 Gy[25]. Therefore, although our study provides a summary of the average doses from various regimens, lung doses also vary substantially from patient to patient. In addition, lung doses were presented separately for women with left-sided and right-sided breast cancer in only 38 regimens (16 studies), which limited our investigation of the potential differences between left- and right-sided regimens.

6.5.3 Absolute benefits and risks

Our results may be helpful in weighing the benefit against the risks of different breast cancer regimens. Large meta-analyses have shown that in most women irradiated for breast cancer according to current guidelines, the absolute benefits of radiotherapy outweigh the risks[1,2,26]. The risk of lung cancer increases with lung dose (i.e. MLD_{whole}). In our study, the typical MLD_{whole} from modern radiotherapy was around 5 Gy from whole breast or chest wall regimens (Fig. 9). Estimates of absolute risk based on data from 40,000 women in 75 randomised

trials suggest the absolute 30-year risk of radiation-related lung cancer from MLD_{whole} 5 Gy for a typical non-smoker aged 50 years at irradiation would be only ~0.3%. For a long-term continuing smoker it is considerably higher, at ~4%[6], although this would be reduced if the woman stopped smoking[12,27]. In our study, regimens that irradiated the axilla/supraclavicular fossa and IMC increased the MLD_{whole} to around 9 Gy, which would increase the typical absolute 30-year risk of radiation-related lung cancer to ~0.6% for a non-smoker and ~10% for a long-term continuing smoker. Hence, for some long-term smokers, the risks of irradiating the SCF, axilla and IMC may outweigh the benefits, especially if they continue to smoke[6]. In applying these estimated risks, it should be remembered that they are for typical modern radiotherapy in typical populations of women. But, as we have shown, lung doses in breast cancer regimens vary from patient to patient, as do population disease rates, so the absolute risks, and the effect of smoking cessation for individual women will vary around these typical values.

6.6 Conclusions

Lung exposure in breast cancer radiotherapy varied substantially between different countries and regimens, so the radiation-related risks of lung cancer, pneumonitis and lung fibrosis will also vary. Exposure may be reduced by minimising the extent of the irradiated region, by using breathing adaptation and by using prone or lateral decubitus patient positioning or proton therapy. These lung doses may help oncologists tailor treatment for women who have high estimated risks of radiation-related lung cancer and fibrosis.

Acknowledgements

Exposure of the lungs in breast cancer radiotherapy: A systematic review of lung doses published 2010-2015. Aznar MC*, Duane FK*, Darby SC, Wang Z, Taylor CW. Radiother Oncol 2018; 126:148-154.

*Joint first authors

I, F Duane had the original idea to produce the manuscript. I carried out the search for publications from 2010-2013. M Aznar, carried out the search for publications from 2014-2015 and led the quantitative synthesis. All authors interpreted the results and contributed to the development of a manuscript.

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7 International variation in criteria for internal mammary chain radiotherapy

7.1 Abstract

Purpose

Evidence has emerged that internal mammary chain (IMC) radiotherapy reduces breast cancer mortality, leading to changes in treatment guidelines. This study investigates current IMC radiotherapy criteria and the percentage of patients irradiated for breast cancer that fulfil them.

Methods

A systematic search was undertaken for national guidelines published in English during 2013-2018 presenting criteria for "consideration of" or "recommendation for" IMC radiotherapy. Eligibility criteria for clinical studies of IMC radiotherapy published during 2013-2018 and referenced by these guidelines were identified. Patient and tumour variables were collected for patients who received breast cancer radiotherapy in a single institution during July-December 2014. The percentage of patients fulfilling criteria stipulated in the guidelines or the clinical studies was calculated. Information on cardiovascular risk factors was collected for a subset of patients.

Results

Numbers of patients fulfilling IMC radiotherapy criteria in various national guidelines were UK: 53/305 (17%), Germany: 110/305 (36%), Ireland: 171/305 (55%) and USA: 218/305 (71%). Differences between countries occurred because in Ireland and the USA treatment would be considered in some node-

negative patients whereas in the UK, it would only be considered if at least 4 axillary nodes were involved or for high risk patients with 1-3 positive nodes. In Germany, it would be considered for all node-positive patients and in node-negative patients if the primary tumour was locally advanced. For clinical studies, the number of eligible patients varied from 90/305 (30%) for the MA 20 trial to 206/305 (67%) for the EORTC 22922 trial. In a subset of 155 patients, 87 (56%) had at least one cardiovascular risk factor.

Conclusions

There is substantial variability between countries in criteria for consideration of IMC radiotherapy, despite guidelines being based on the same evidence. This is likely to lead to large variations in practice and resource needs worldwide.

7.2 Introduction

Breast cancer radiotherapy reduces the risks of cancer recurrence and death in patients irradiated after breast conserving surgery (BCS) and after mastectomy for node-positive disease[1,2]. In breast cancer, there are a number of different target regions that may be irradiated. Meta-analyses of randomised trials have shown that if radiotherapy is given after BCS, it should include the conserved breast and if given after mastectomy, it should include the chest wall. For patients undergoing nodal radiotherapy there has been debate concerning the role of internal mammary chain (IMC) radiotherapy. This has been reflected in discrepancies in country-specific guidelines and practice[3-12]. Even within some countries, breast cancer radiotherapy practice has varied substantially[13].

In 2015, two large randomised trials, including a total of ~6000 patients showed that irradiating the IMC significantly reduced breast cancer mortality[14,15]. A large cohort study including ~3000 patients, in which IMC radiotherapy was allocated according to tumour laterality also provided support for IMC irradiation[16]. In countries where IMC radiotherapy has been used routinely in node-positive breast cancer, these findings will have little impact on practice[17]. In other countries, these publications have changed radiotherapy guidelines and will affect practice appreciably[8,9,12]. In the UK, IMC radiotherapy has been recommended only in patients with IMC macrometastases visible on CT-scan (N3 disease)[3]. This changed in 2016 when a consensus statement was published by the Royal College of Radiologists. It recommended that IMC radiotherapy should also be considered in patients with T4 and/or N2 disease and in patients with medial or

central breast cancers and 1-3 axillary macrometastases who have been recommended locoregional irradiation[18]. Such changes in recommendations will affect the number of patients receiving IMC radiotherapy, which impacts on radiotherapy planning and contouring and treatment delivery time because IMC radiotherapy can be technically challenging.

When deciding whether to irradiate the IMC for an individual woman the benefits need to be balanced against the risks. Radiotherapy that includes the IMC tends to increase doses to the heart and lungs compared with non-IMC radiotherapy[19,20], which increases the relative risks of radiation-related heart disease and lung cancer[21,22]. Absolute risks for individual patients are higher for patients who smoke or have cardiovascular risk factors prior to their radiotherapy. Therefore cardiac risk factors need to be taken into account when deciding who should receive IMC radiotherapy. In most patients the predicted benefits will outweigh the risks but for a few the risks will outweigh the benefits.

This study aims to inform resource allocation in radiotherapy departments. It first investigates the percentage of patients irradiated for breast cancer in a single UK centre in whom IMC radiotherapy would be considered based on the UK Royal College of Radiologists' consensus (2016)[18]. Second, it investigates the percentages of patients who would fulfil criteria for IMC radiotherapy if they received radiotherapy in other countries and who would have been eligible for large clinical IMC studies referenced by guidelines. Third, it investigates the number of patients with risk factors for heart disease prior to radiotherapy whose risks from IMC radiotherapy may be higher than in other patients.

7.3 Methods

7.3.1 Internal mammary chain radiotherapy guidelines

A systematic search was conducted for country-specific breast cancer radiotherapy guidelines presenting criteria for "consideration of" or "recommendation for" IMC radiotherapy. Studies were identified using the Preferred Reporting Items for Systematic Reviews and Meta-analyses[23]. By the year 2013 the results of two landmark trials investigating the benefit of nodal radiotherapy had been presented at international meetings. The MA. 20 trial was presented at the American Society for Clinical Oncology Annual Meeting[24] and the EORTC 22922/10925 trial was presented at the European Cancer Congress[25]. Therefore the search was limited to studies published between January 2013 and January 2018 as these would be likely to consider this new evidence. The Medline database was searched for studies published in English using the following terms: "breast cancer" AND "radiotherapy" AND "guideline OR statement OR opinion". Four online guideline databases and ten websites were also searched using the search term “breast cancer” (Supplementary Table 1). Local or regional guidelines were excluded. For each guideline, criteria for “consideration of” or “recommendation for” IMC radiotherapy were abstracted.

Table 7-1. List of electronic databases and websites searched for eligible guidelines*

Source	Weblink
National Guideline Clearinghouse	www.guideline.gov
National Institute for Health and Care Excellence	www.nice.org.uk
Scottish Intercollegiate Guidelines Network	www.sign.ac.uk
G.I.N. International Guideline Library	www.g-i-n.net/home
European Society for Radiotherapy & Oncology	www.estro.org
National Comprehensive Cancer Network Ireland	www.nccn.org
Canadian Medical Association	www.cma.ca
Royal College of Physicians and Surgeons in Canada	www.royalcollege.ca
Canadian Association of Radiation Oncology	www.caro-acro.ca
Australian Clinical Practice Guidelines	www.clinicalguidelines.gov.au
The Royal Australian and New Zealand College of Radiologists	www.razcr.com
European Society of Medical Oncology	www.esmo.org
Royal College of Radiologists, U.K.	www.rcr.ac.uk
Ministry of Health, New Zealand	www.health.govt.nz

*Accessed 01 March 2018

7.3.2 Internal mammary chain clinical studies

A second search was conducted for clinical studies that were referenced by these national guidelines and that were published between January 2013 and January 2018. We included studies with a randomised or left-versus-right comparison of IMC irradiation versus not and which included >1,500 patients. Studies published before 2013 would be based on older radiotherapy techniques and therefore are less likely to influence current IMC radiotherapy guidelines so they were not included. Tumour eligibility criteria for patient inclusion in each study were abstracted.

7.3.3 Patients included, variables and information sources

Identifiers of patients who received radiotherapy to the breast or chest wall +/- lymph nodes during 1st July 2014 to 31st December 2014 were obtained from the

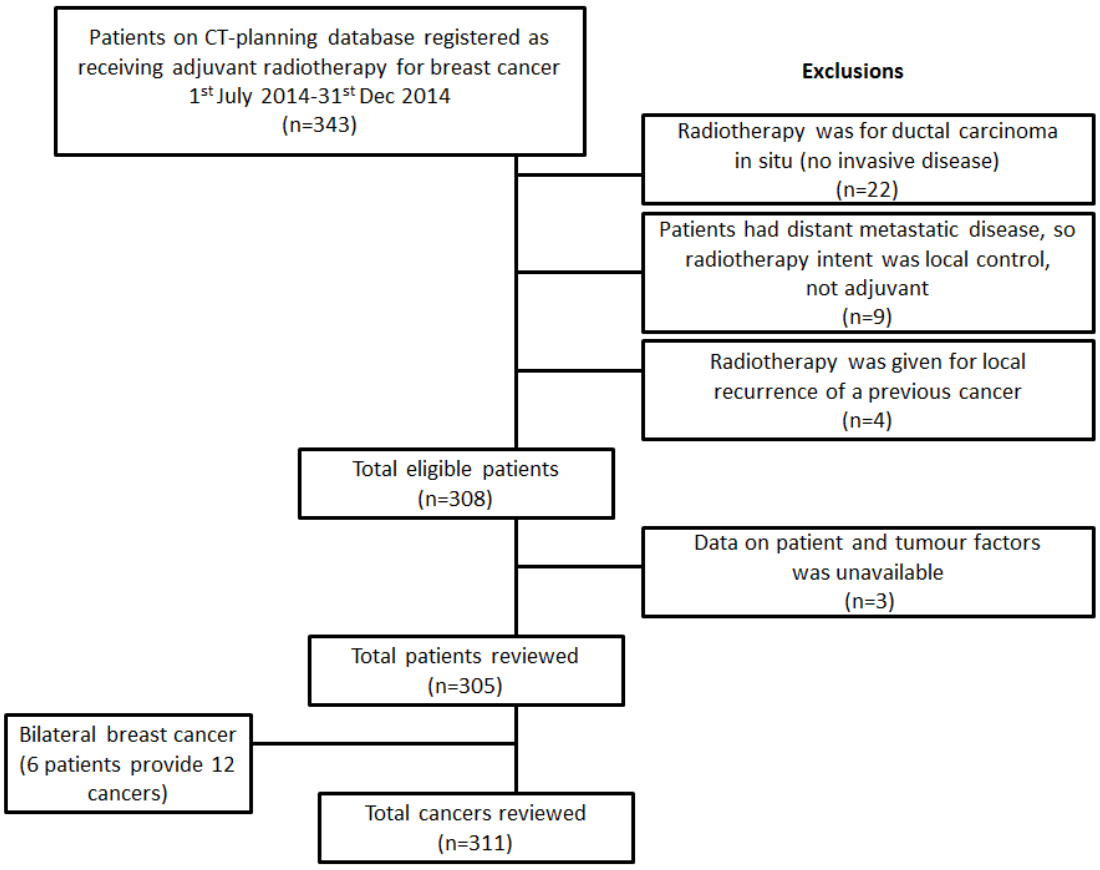


Figure 7-1. Composition of study population with exclusion criteria

radiotherapy CT-planning database at the Oxford Cancer and Haematology Centre, Oxford University Hospitals NHS Foundation Trust (Fig 1). Patients were excluded if they received radiotherapy for ductal carcinoma in situ alone (i.e. they did not have invasive cancer), if they had metastatic disease, or if radiotherapy was given for local recurrence of a previous cancer. The study was reviewed by the Research Governance Team at the Oxford University Hospitals NHS Trust.

Patient variables: age, sex and cardiovascular risk factors were abstracted from clinical notes (Supplementary Table 2). Tumour variables: laterality, location, and

Table 7-2. Information sources used to abstract variables

Variables	Source
Patient	
Age	Clinical notes or letters
Sex	Clinical notes or letters
Smoking status	Clinical notes or letters
Cardiovascular risk factors	Clinical notes or letters
Tumour	
Laterality	Histology reports
Location	Histology reports Mammogram reports Ultrasound reports MRI reports Radiotherapy CT-planning scans
Stage (T and N)	Histology reports Mammogram reports Ultrasound reports MRI reports
Pathological characteristics	
Oestrogen receptor status	Histology reports
Progesterone receptor status	Histology reports
Her2 receptor status	Histology reports
Tumour Grade	Histology reports
Lymphovascular invasion	Histology reports
Systemic Treatment	
Chemotherapy	Chemotherapy database
Endocrine therapy	Clinical notes or letters

stage were extracted both from histology reports and from radiology reports in the following order. Histology records were searched first. If laterality and location were missing then they were sought from radiology reports (mammogram, ultrasound and MRI). If these were still missing, radiotherapy CT-planning scans were used to identify the location of the surgical bed. For patients who received neo-adjuvant chemotherapy histology reports can only describe tumour stage after chemotherapy. For these patients information on tumour stage was sought from pre-chemotherapy investigations including mammogram, ultrasound and

MRI reports. Pathological tumour characteristics were abstracted from histology reports.

7.3.4 Patient categorisation

Each patient was categorised according to whether she/he met criteria for consideration of IMC radiotherapy in each set of national guidelines. Categories were mutually exclusive so each patient was allocated to a single category.

The number of patients in whom IMC radiotherapy would be considered or recommended in each set of national guidelines was calculated by totalling the patients who fulfilled each individual criterion (individual rows, Table 1). The percentage of patients in whom IMC radiotherapy would be considered or recommended was calculated by dividing this number by the total number of patients (305).

For the IMC clinical studies, patients were categorised according to whether they fulfilled each of the criteria for study inclusion (Table 2). The resulting numbers were summed to calculate the number of patients who would have been eligible for each study. The percentage was calculated by dividing by the total number of patients (305).

Cardiac risk factors were recorded only for patients who attended Oxford clinics for their first oncology appointment. In Oxford clinics, a dedicated new patient

proforma, including a section recording past medical history, smoking status and medications, was completed routinely for each patient so information on cardiovascular risk factors is likely to have been recorded consistently. In clinics outside Oxford proformas were not used so cardiac risk factors may not have been consistently documented, and they were not abstracted.

7.4 Results

7.4.1 Internal mammary chain radiotherapy guidelines

Eight publications were identified that presented criteria for "consideration of" or "recommendation for" IMC radiotherapy (Fig. 2)[3,6,8-12,18]. In two of these IMC radiotherapy was not recommended[3,6] but the committees who wrote them planned to update their guidance soon, so these were not included. Six eligible studies from four countries presented criteria for "consideration of" or "recommendation for" IMC radiotherapy and were included in the qualitative synthesis (Table 1)[8-12,18].

7.4.2 Internal mammary chain clinical studies

Guidelines referenced three clinical studies including >1,500 patients, published 2013-2018 with a randomised or left-versus-right comparison of IMC irradiation versus not (Table 2). Two randomised trials included 4004 and 1832 randomised patients respectively[14,15]. One cohort study of 3,089 patients (DBCG-IMN) included a comparison of IMC radiotherapy versus not: patients with right-sided cancers received IMC irradiation and patients with left-sided cancers did not[16].

Table 7-3. Patients irradiated for breast cancer in a UK centre fulfilling criteria for IMC radiotherapy in different countries

Clinical Guidelines	Criteria for "consideration of" and "recommended for" IMC radiotherapy	Patients meeting criteria Number/305	%
Royal College of Radiologists, UK (RCR)[18]			
Consider	T4 and/or N2-3 disease*	31	10
Consider	1-3 axillary macrometastases and central/medial* disease, who have been recommended locoregional irradiation based on risk factors† (including age and tumour biology)	22	7
		53	**17**
German Society of Radiation Oncology (DEGRO)[9,10] ‖			
Recommend	>3 involved lymph nodes	29	9
Strongly consider	1–3 involved nodes, especially if further risk factors such as negative ER or PR receptor, poorly differentiated tumour, medial* location and premenopausal status	76	25
Consider	Negative axillary nodes and locally advanced disease: tumours >5cm or infiltrating the chest wall or patients not receiving anti-Her2 treatments	5	2
		110	**36**
Department of Health, Ireland (NCCP)[12]			
Consider	Positive axillary nodes	105	34
Consider	Negative axillary nodes, inner quadrant tumours*	65	21
		171	**55**
National Comprehensive Cancer Network, USA (NCCN)[8‡§]			
Recommend	≥4 positive axillary nodes	29	9
Strongly consider	1-3 positive axillary nodes	76	25
Consider	Negative axillary nodes and tumour >5 cm post mastectomy	7	2
Consider	Negative axillary nodes, central/medial tumour* ≤5 cm post mastectomy	9	3
Consider	Negative axillary nodes, central/medial* tumour post breast conserving surgery	84	28
Consider	Negative axillary nodes, lateral tumour* >2 cm with high-risk features (young age or extensive LVI¶)	13	4
		218	**71**

Table includes 6 studies in four countries. DEGRO (Germany) included two studies[9,10]. In the USA, a second eligible guideline was identified[11] which was not included in the table. See footnote‡.
Guidelines are ordered according to the total percentage of women fullfilling criteria.

Abbreviations: IMC: internal mammary chain, LVI: lymphovascular invasion; ER: oestrogen receptor, PR: progesterone receptor

*Definitions:
T4: tumour invading skin or chest wall
N2-3: ≥4 positive axillary macrometastases
Lateral: lateral quadrants (upper or lower)
Medial: medial quadrants (upper or lower)
Central: central breast (underlying the areola)

† We defined the following risk factors: age ≤50 years, ER negative, PR negative, Her2 receptor positive and grade 3.

‖ The DEGRO expert panel concluded that IMC radiotherapy should be strongly considered in all patients receiving radiotherapy to the supraclavicular or axillary lymph nodes. It also concluded that nodal irradiation can be discussed with node negative patients with risk factors on a case by case basis.

‡ A second clinical practice guideline (American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology)[11] from the U.S.A was identified. This guideline only related to radiotherapy for patients who received mastectomy and had T1-2 breast cancer with 1-3 positive nodes so it was not included in the table. "The panel found insufficient evidence to unambiguously define specific patient subgroups to which post-mastectomy radiotherapy should be administered. It recommended post-mastectomy radiotherapy for patients with clinical stage I and II cancers with axillary nodal involvement after neo-adjuvant systemic therapy. It recommended that if electing to administer post-mastectomy radiotherapy, targets should generally include both the internal mammary nodes and the supraclavicular-axillary apical nodes in addition to the chest wall or reconstructed breast."

§ IMC RT should also be considered for patients post-mastectomy with positive margins when re-excision to negative margins is not feasible. Twelve patients with positive margins were included in the listed categories.

¶ We defined ≤ 50 years as young and any LVI as extensive LVI because information on the extent of LVI was unavailable.

Table 7-4. Patients irradiated for breast cancer in a UK centre fulfilling eligibility criteria for clinical studies of internal mammary chain radiotherapy.

Clinical Studies*	Eligibility criteria for studies assessing IMC radiotherapy	Patients meeting criteria Number/305	%
National Cancer Institute of Canada MA 20[15]			
	Positive axillary nodes post breast conserving surgery	56	18
	Negative axillary nodes and tumour >5cm post breast conserving surgery	1	<1
	Negative axillary nodes, tumour >2cm and <10 nodes removed and one of: ER receptor negative, tumour grade 3 or LVI post breast conserving surgery	33	11
		90	**30**
Danish Breast Cancer Group IMN*[16]			
	Node positive	105	34
		105	**34**
European Organisation for Research and Treatment of Cancer 22922/10925[14]			
	Lateral* tumour with axillary node invasion	58	19
	Central/medial* tumour, any axillary lymph node status	146	48
		204	**67**

Tumour-related criteria were taken into account but not patient age when irradiated.

Clinical studies are ordered according to the total percentage of women fullfilling criteria.

Abbreviations: IMC: internal mammary chain, LVI: lymphovascular invasion; ER: oestrogen receptor

*Definitions:

Lateral: lateral quadrants (upper or lower)

Medial: medial quadrants (upper or lower)

Central: central breast (underlying the areola)

* The Danish national radiation therapy protocol between years 2003 and 2007 was to irradiate the IMC of women with right-sided breast cancer, but not the IMC of women with left-sided cancer. All Danish radiation oncology centres followed this protocol and all women suitable for breast cancer irradiaton in Denmark were entered into the study (including those who did not get protocol treatment) so the left versus right comparison was considered to be equivalent to randomisation.

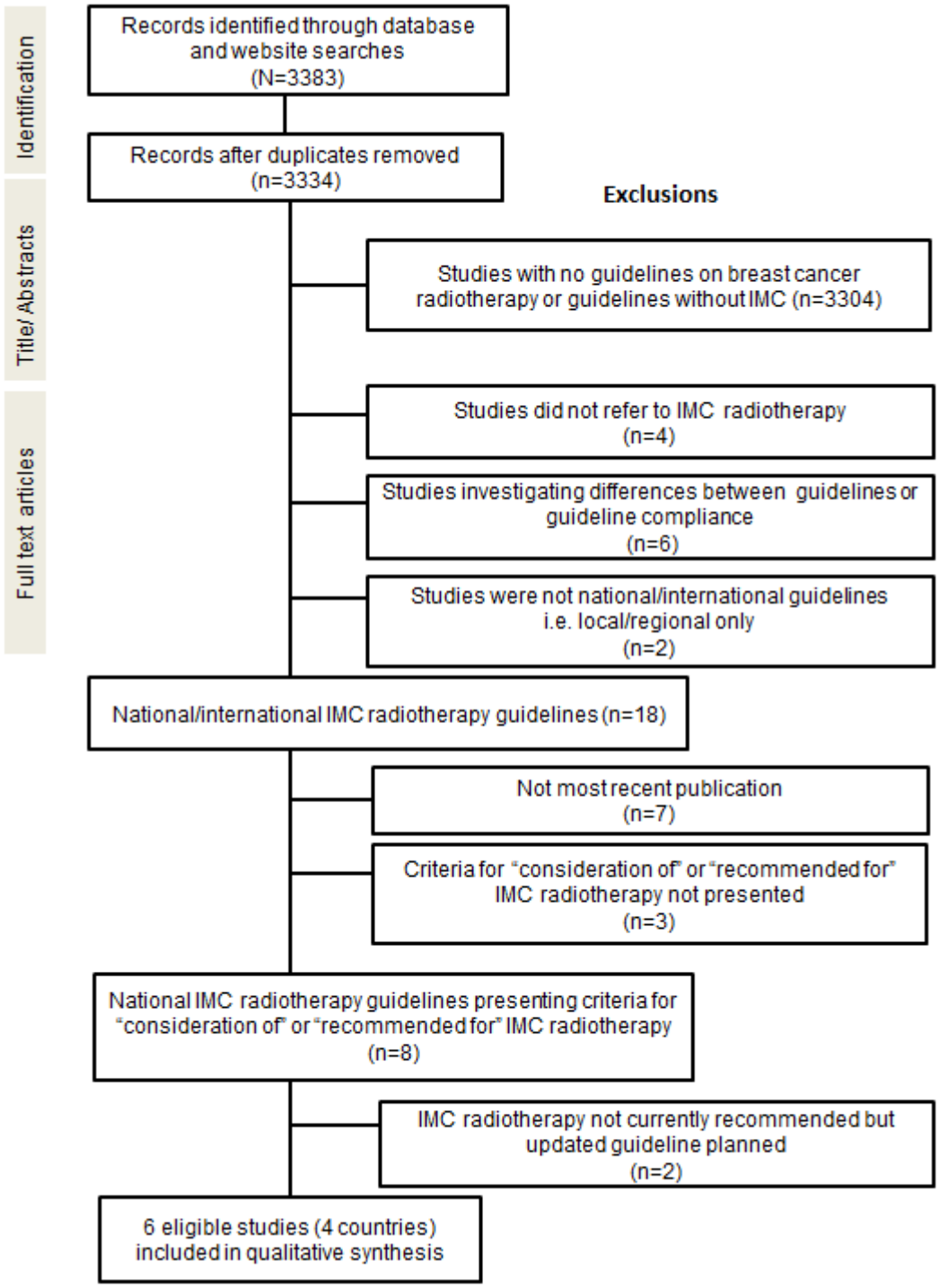


Figure 7-2 Flowchart for the selected clinical practice guidelines

7.4.3 Patients in UK centre

During July-Dec 2014, 343 patients underwent radiotherapy to the breast or chest wall +/- lymph nodes in the Oxford cancer centre (Fig 1). 38 patients were excluded: 22 received radiotherapy for ductal carcinoma in situ only, 9 had metastatic disease, 4 were irradiated for local recurrence of a previous cancer and for 3 patients the clinical notes, histology and radiotherapy reports were unavailable. 305 patients were included. Six patients had bilateral breast cancer yielding 311 cancers for analysis.

The median age at diagnosis was 63 years (range 32-90 years) and 20% of patients were ≤50 years (Table 3). Only one male patient was identified. 51% had left breast cancer and 47% had right breast cancer. The tumour location was lateral for 52%, medial for 31%, central for 16% and unknown for <1%. The percentage of patients with node-positive disease was; N1: 24%, N2: 7% and N3: 3%. The percentage of patients with adverse pathological factors was: oestrogen receptor (ER) negative: 17%, progesterone receptor (PR) negative: 16%, Her2 receptor positive 17%, tumour grade 3: 40% and lymphovascular invasion (LVI): 35%.

7.4.4 Percentage of patients meeting different IMC radiotherapy criteria

The percentage of patients fulfilling IMC radiotherapy criteria varied substantially between countries from (53/305) 17% to (218/305) 71% (Table 1). The highest percentage of patients meeting criteria for IMC radiotherapy recommendation or consideration was for the NCCN USA guidelines (71%) followed by Ireland (55%)

Table 7-5. Patient and tumour variables among 305patients irradiated for invasive breast cancer in a UK centre during July-December 2014.

(a) Patient Variables	No./305	%
Age, years		
32-50	61	20
51-65	125	41
66-80	103	34
81-90	16	5
Sex		
Female	304	>99
Male	1	<1
(b) Tumour Variables	**No./311**	**%**
Breast cancer laterality		
Left	156	51
Right	143	47
Bilateral	6	2
Tumour location*		
Lateral	162	52
Medial	96	31
Central	50	16
Unknown	2	<1
Undetectable primary lesion	1	<1
Tumour stage		
T1: ≤2 cm	149	48
T2: >2-5 cm	128	41
T3: >5 cm	30	10
T4: Spread to skin/chest wall	4	1
Nodal stage*		
N0/N0(i+)	188	60
N1(mi)	18	6
N1	76	24
N2	21	7
N3	8	3
Oestrogen receptor status		
ER positive	259	83
ER negative	52	17
Progesterone receptor status		
PR positive	128	41
PR negative	48	16
Not done	135	43
Her2 receptor status		
Her2 positive	53	17
Her2 negative	253	81
Unknown	5	1
Tumour Grade		
I (well differentiated)	46	15
II (moderately differentiated)	140	45
III (poorly differentiated)	125	40
Lymphovascular invasion		
Positive	109	35
Negative	191	61
Unknown	11	4

Definitions
Lateral: lateral quadrants (upper or lower)
Medial: medial quadrants (upper or lower)
Central: central breast (underlying the areola)
N0/N0(i+): No axillary metastases or isolated tumour cells only
N1(mi): Microscopic axillary disease only
N1: 1-3 positive axillary macrometastases
N2: 4-9 positive axillary macrometastases
N3: ≥ 10 axillary macrometastases

then Germany (36%) and the UK (17%).

For the UK Royal College of Radiologists (RCR) guidelines, 17% (53/305) of the Oxford patients fulfilled criteria for considering IMC irradiation (Table 1). Ten percent (31/305) had T4 and/or N2-3 disease and 7% (22/305) had 1-3 axillary macrometastases and a medial or central lesion and also another risk factor (age ≤50 years, ER negative, PR negative, Her2 receptor positive or tumour grade 3). Based on the German DEGRO guidelines, a total of 36% (110/305) would have been recommended for or considered for IMC radiotherapy. Nine percent (29/305) would have had IMC radiotherapy recommended because they had >3 involved axillary nodes. In 25% (76/305), it would have been strongly considered because they had 1-3 involved nodes and in an additional 2% (5/305) it would have been considered because they had locally advanced primary lesions (T3/T4). Based on the Irish guidelines 55% (171/305) would have been considered for IMC radiotherapy including 34% (105/305) with node-positive disease and 21% (65/305) with node-negative disease but with inner quadrant tumours. For the U.S.A two guidelines were identified. Considering the NCCN guidelines 71% (218/305) of the Oxford patients would have been recommended or considered for IMC radiotherapy. IMC radiotherapy would have been recommended for 9% (29/305) because they had ≥ 4 positive axillary nodes and strongly considered for 25% (76/305) because they had 1-3 positive nodes. It would have been considered in patients who were post mastectomy with negative axillary nodes but whose tumours were >5cm (2% (7/305)) or with central or medial location (3% (9/305)) and in a further 28% (84/305) who had breast conserving surgery with negative axillary nodes but who had a central or medial

lesion. It would also have been considered for patients with negative axillary nodes but whose tumours were >2 cm with other high-risk features (4% (13/305)). A second clinical practice guideline (American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology) from the USA recommended IMC radiotherapy for patients post-mastectomy with clinical stage 1 and II cancers and axillary nodal involvement after neo-adjuvant systemic therapy[11]. 1% (3/305) of the Oxford patients fulfilled this criterion (data not shown). This second clinical practice guideline did not give criteria for other categories of women so it was not possible to calculate the total number of Oxford patients who would be considered for IMC RT based on this guideline.

For the clinical studies, 30% (90/305) of the Oxford patients would have been eligible for MA20 because they underwent breast conserving surgery and had positive axillary lymph nodes or negative axillary lymph nodes and tumour >5 cm or negative axillary lymph nodes and tumour >2cm but with other high-risk features (Table 2). For the DBCG-IMN study 34% (105/305) would have been eligible because they were node-positive. For the EORTC 22922/10925 randomised trial 67% (204/305) would have been eligible because they had central or medial tumours (48% (146/305)) or lateral tumours with positive axillary nodes (19% (58/305)).

Table 7-6. Prevalence of cardiovascular risk factors among 155 women irradiated for breast cancer in a UK centre compared to women in the general UK population.

	Patients in UK centre		Estimate from UK population		
Cardiovascular Risk Factor	No./155*	%	Survey	Year	%
Current smoker	21	14	Health Survey for England[26]	2014	17
Ex-smoker	24	15			
Diabetes	12	8	Diabetes U.K. [27]	2014	6.2
Chronic obstructive airways disease	4	3	Respiratory Health of the Nation Survey[28]	2012	2
History of heart disease†	9	5			
Hypertension‖	44‖	28	Health Survey for England[26]	2014	27
High cholesterol‡	17‡	11			
Total with at least one risk factor	*87*	*56*			
Total with > one risk factor	*30*	*19*			

† Ischaemic heart disease: n=4; arrhythmia: n=4; aortic stenosis: n=1
* Some women had multiple risk factors and so numbers in individual rows exceed the total.
‖ Patients on anti-hypertensive medication.
‡ Patients on medication for hypercholesterolaemia.

7.4.5 Cardiovascular risk factors in a single UK center

Cardiovascular risk factor information was available for 155 patients who attended Oxford clinics for their initial oncology appointment. Fifty-six percent (87/155) of these patients had at least one risk factor and 19% (30/155) had more than one risk factor (Table 4).

7.5 Discussion

The percentage of patients undergoing radiotherapy for early breast cancer in a single UK cancer centre who met the UK Royal College of Radiologists' criteria for IMC radiotherapy was 17%. Based on this guideline, IMC radiotherapy would be considered for around 2 cases per week in the Oxford cancer centre (53/305 of cases during a 6 month period). Criteria in different national guidelines varied, leading to substantial variation in the percentages of patients studied who would be considered for IMC radiotherapy in different countries, from 17 to 71%. Fifty-six percent of the patients with information on medical history had cardiovascular risk factors prior to radiotherapy, and would therefore be at higher absolute risk of radiation-related heart disease.

Our systematic search of national radiotherapy guidelines identified only six guidelines from four countries that presented criteria for "consideration of" or "recommendation for" IMC radiotherapy. This suggests that for many countries either there are no agreed national guidelines or that they have not been published formally in the open literature in English but may be available on local country-specific websites. Two guidelines, including one from Spain and one from the UK, recommended against IMC radiotherapy altogether[3,6]. However, the

Spanish guideline (GEORM) published in 2013[6] reported that they were waiting for publication of the EORTC 22922/10925 trial results and the NICE guidelines[3] are currently being updated so it is likely that updated guidelines for both will be published soon. National guidelines from Japan and Belgium and an international guideline from the European Society of Medical Oncology referred to IMC radiotherapy but did not offer specific criteria for which patients should be considered for this treatment[4,5,29].

In the four countries that published IMC radiotherapy criteria, different expert panels assessed the same large studies but came to different conclusions about how to apply the evidence. For example, in the UK, where historically IMC radiotherapy has rarely been used, criteria for IMC radiotherapy included only node-positive disease[13]. In Germany and Ireland, the criteria included all node-positive patients, and some node-negative patients. In the USA, where historically IMC radiotherapy was given to ~10-30% of patients, IMC radiotherapy criteria for consideration of IMC radiotherapy included all node-positive patients as well as node-negative patients who had other risk factors for cancer recurrence[13]. These differences in guidelines are likely to lead to substantial variations in IMC radiotherapy practice in different countries. For example, our results suggest that over half of all patients receiving breast cancer radiotherapy would be considered for IMC radiotherapy if they were treated in the USA but not if treated in the UK (71% in USA minus 17% in UK=54%).

The main limitation of this study is that it is limited to guidelines published in English therefore the variation in criteria for "consideration of" or

"recommendation for" IMC radiotherapy observed across the world may be underestimated. For example, in Denmark a national guideline is available in Danish which recommends IMC radiotherapy for all patients with positive axillary lymph nodes and for other patients who are node-negative but who have tumours >5 cm post-mastectomy (38% of Oxford patients would have been considered for IMC radiotherapy according to these criteria)[30].

Investigating the percentage of patients meeting various IMC radiotherapy criteria can inform resource allocation. For IMC radiotherapy, contouring of the lymph node regions and organs at risk (heart, lungs, and contralateral breast) is recommended[31,32] which increases radiotherapy planning time. In addition, some patients may need volumetric modulated arc radiotherapy to reduce heart and lung exposure[33,34]. Implications for resource allocation will differ according to country. The RCR UK criteria for IMC radiotherapy were the most limited and were met by only 17% of patients in our study. Extending recommendations beyond the RCR UK criteria to meet the DEGRO criteria would mean considering IMC radiotherapy for around a third of irradiated patients (36%). Extending recommendations to include other subsets of patients with node-negative disease would further increase the number of patients considered for IMC radiotherapy to around 50-70%. Appreciably more resources may be needed in countries using broad criteria for IMC radiotherapy e.g. USA. than in countries with narrow criteria e.g. UK.

Fifty-six percent of patients seen in Oxford clinics had at least one cardiovascular risk factor. The absolute risk of radiation-induced ischaemic heart disease is likely

to be higher for these patients than for patients without risk factors[22]. Fourteen percent were smokers for whom the absolute risk of radiation-induced lung cancer is higher than for non-smokers[21]. Particular care to minimise cardiac and lung exposure during radiotherapy is warranted for these patients. Oncologists may consider using breathing adaptation or advanced radiotherapy techniques. These patients may benefit from counselling on the prevention of cardiovascular disease and smokers may benefit from referral to a smoking cessation advisor. The prevalence of risk factors among the patients in this study was similar to that in the general UK population (Table 4). However, risk factor prevalence varies substantially according to region within the UK and according to country. For example, in Glasgow, Scotland, smoking prevalence in women aged >16 years was 24.8% in 2013[35]. In Germany, Ireland and the USA smoking prevalence in 2015 for women aged >15 years was 28.3%, 21.9% and 15% respectively[36]. The number of patients with cardiovascular risk factors in our centre is likely to be underestimated as it was not possible to reliably record the prevalence of certain risk factors including high BMI or family history of heart disease because they were not always documented in the clinical notes.

7.6 Conclusions

There is substantial variability between countries in criteria for consideration of IMC radiotherapy, despite being based on the same evidence. The percentage of patients in a single centre who would be considered for it, varied substantially based on different national criteria. This is likely to lead to large variations in practice and resource needs. This information may aid decisions regarding the feasibility of offering IMC radiotherapy to different categories of patients.

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Duane FK, Teoh S, Mortimer C, Darby S, Dodwell D, Lavery B, Oliveros S, Vallis K, Taylor C. International Variation in criteria for internal mammary chain radiotherapy. Manuscript submitted for publication.

I, F Duane had the original idea to produce the manuscript, undertook collection and assembly of the data, the data analysis, the development of the tables and figures and drafted the first version of the manuscript. S Teoh and C Mortimer contributed to collection of the data. C Taylor contributed to the design of the study, data analysis and interpretation. All authors contributed to the development of the study.

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8 Trial Concept: Protons for internal mammary chain irradiation

Foreword

This chapter outlines the development of a clinical trial proposal over the last 4 years. The principal investigator is Katherine Vallis (KV)[1], co-investigators are David Cutter (DC)[2], Vanessa Ferreira (VF)[3], Carolyn Taylor (CT)[2], Sarah Darby (SD)[2], Frank Van den Heuvel (FV)[1] and I, Frances Duane (FD). I have participated in designing the trial and in drafting the proposal which is still under development. The proposed study is a multi-centre prospective randomised Phase II trial. The aim is to establish the benefit of proton beam therapy compared to photon therapy with breathing adaptation in reducing acute cardiac injury. The primary endpoint is acute myocarditis detected using cardiac magnetic resonance (CMR) T1-mapping. CMR imaging analysis will be based on work previously carried out by co-investigators DC and VF. Feedback has been received on the trial proposal from Clinical and Translational Radiotherapy Research Working Group (CTRad) experts. Based on discussion with national trialists a decision has been made that more preparatory work is needed before a clinical trial can be started. The focus now is on a cohort study which aims to validate (CMR) T1-mapping as a biomarker for radiation-induced injury.

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8.1 Rationale for a clinical trial

8.1.1 Proton beam therapy is coming soon to the UK

Proton beams have a unique dose distribution (Fig. 1). The effect of a proton beam increases with deeper penetration reaching a "Bragg peak" followed by a rapid fall-off. This unique dose distribution can enable delivery of a high dose to a limited region while avoiding normal tissues close-by, particularly distal to the target. Conventional radiotherapy is very effective for treating most cancer types but the favourable dose distribution of protons make them a better choice in some situations. PBT is approved in the UK for many children's cancers within the NHS Protons Overseas Programme. Limiting exposure of the normal tissues in children decreases the risk of growth problems and the development of secondary cancers. PBT is also approved for a number of cancers in adults where tumour is close to critical structures, for example the spinal cord or brain stem. At present (year 2018), the National Health Service pays for these patients to have treatment in the USA, Germany or Switzerland. In 2009 the government set up a National NHS Proton Beam Therapy Service and high energy proton beam therapy (PBT) is soon to become available in the UK. Two new proton centres are currently being built: one at the Christie Hospital in Manchester is due to open in 2018 and one at University College London Hospital in London which is due to open in 2020.

The benefit of PBT has not been well studied in most cancer types as it has not been widely available and many of the theoretical benefits, e.g. reduction in second cancers, may take a long time to be seen. There may be a subset of

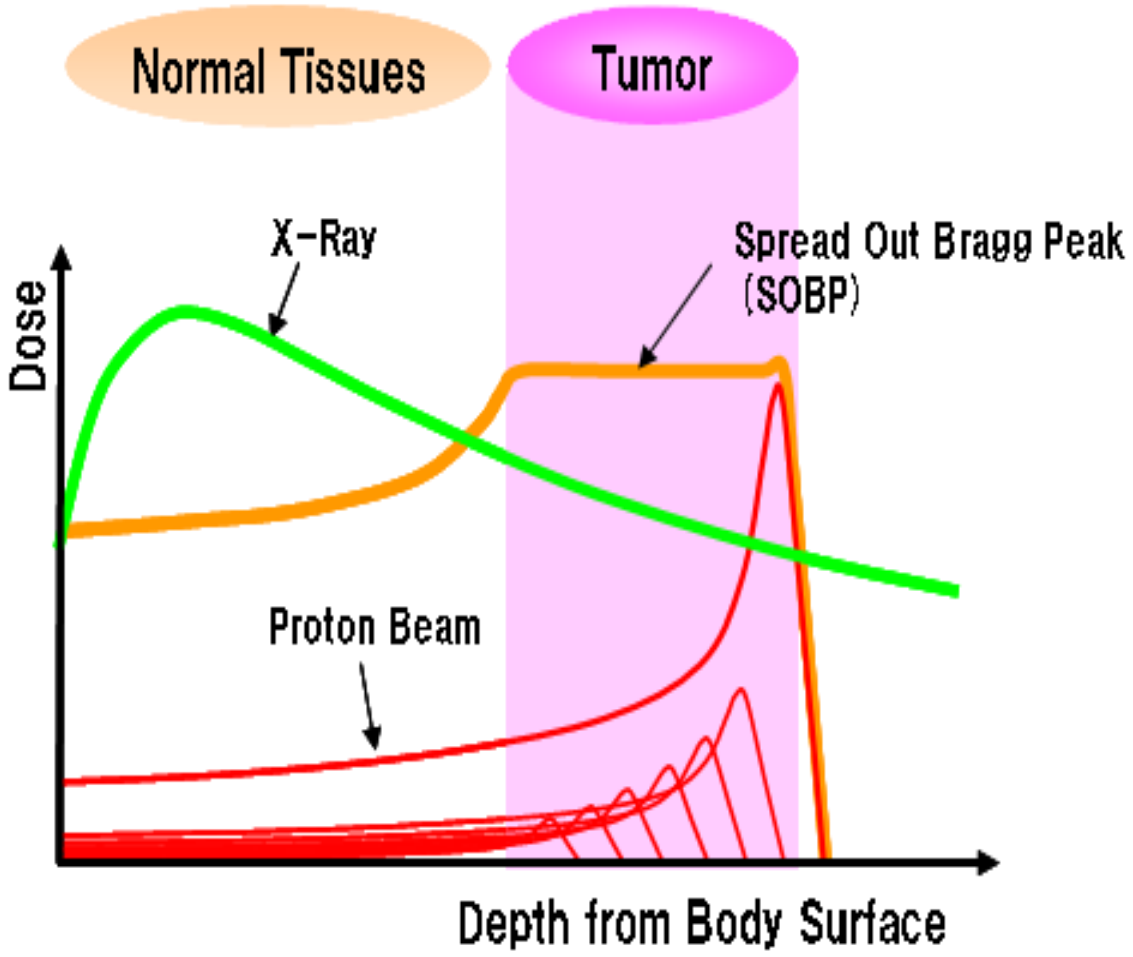


Figure 8-1 Spread out Bragg Peak

The effect of a proton beam increases with deeper penetration reaching a "Bragg peak" followed by a rapid fall-off. The width of the peak may be adjusted depending on the extent of the lesion. Copyright© Sumitomo Heavy Industries, Ltd. All Rights Reserved.

patients across all primary cancer disease sites that can benefit from PBT: patients with complex comorbidity profiles or patients with atypical anatomy. Now that the technology is soon to become available research needs to be done to help choose which patients will most benefit from PBT over conventional therapy. The benefit would need to be enough to justify the extra cost as PBT is much more expensive than X-ray treatment. For the first two years of my DPhil 2014-2016 it was envisaged that a proton centre would be constructed in Oxford which would be a research facility to investigate the benefits of treatment for other

cancers (rather than treating patients on the NHS 'core indications' list). Since 2016, these plans have been on hold but there is still much interest in PBT clinical research and a lot of preparatory work has been carried out supporting the development of clinical trials.

8.1.2 Cardiac radiation exposure may increase with IMC radiotherapy

Meanwhile, in breast cancer, evidence emerged in 2015 that internal mammary chain (IMC) improves survival[1-3]. The EORTC 22922/10925 randomised control trial reported IMC and medial supraclavicular lymph node irradiation improved disease-free survival at 10 years by 3% in patients with node positive disease or central or medial primary tumours[1]. The NCIC MA 20 randomised control trial reported regional nodal irradiation (including IMC, supraclavicular and axillary lymph nodes) increased disease-free survival at 10years by 5% in patients with node positive disease or patients with high-risk node negative breast cancer[2].The DBCG-IMN cohort study using a left-versus-right comparison reported IMC irradiation increased overall survival at 8 years by 3.7% in patients with node-positive disease[3]. The IMC is close to the anterior surface of the heart and when irradiating this region it is difficult to avoid cardiac exposure.

Historically there has been concern that the beneficial effect of IMC radiotherapy may be offset by increased cardiotoxicity. Cardiac exposure increases with IMC irradiation but overall exposure is now lower than it used to be as cardiac-sparing techniques have been implemented. The standard regimen for treating the IMC is with 3D-conformal wide tangents (including breathing adaptation for left breast cancer). Volumetric modulated arc therapy with breathing adaptation is

considered in some centres for women with high normal tissue doses. The UK RCR IMC radiotherapy guidelines proposes a mean heart dose < 6 Gy[4]. Ranger et al reported an average mean heart dose of 2.5 +/- 1.2 for standard therapy using wide tangents with breathing adaptation and an average mean heart dose of 2.6 Gy +/- 1.0 for VMAT with breathing adaptation[5]. This was a study of 14 CT scans, the total dose was 40 Gy and the IMC target objective was 32 Gy. A previous study by Osman et al reported an average mean heart dose of 5.8 Gy for standard therapy using wide tangents with breathing adaptation (for some an oblique anterior field was added to cover the IMC) and an average mean heart dose of 4.1 Gy for VMAT and breathing adaptation[6]. This was a study of 23 CT-scans, the total dose was 42.56 Gy and the target objective was V95% ≥95%. In this new era of cardiac-sparing breast cancer radiotherapy the risk of radiation-induced heart disease is likely to be low for the majority of patients.

Still, for some women the risks of developing a major coronary event from breast cancer radiotherapy including the IMC may be a few percent. This may be due to cardiac irradiation caused by inadequate displacement of the heart during breath hold or unusual anatomy. Or they may have pre-existing cardiovascular risk factors, which also increases the absolute risk of radiation-induced IHD. It is important to identify these individuals who may be at risk of a cardiac event. This is possible using data from a case control study in which the absolute risks of incident and fatal radiation-induced IHD are provided for women, according to age, mean heart dose and cardiovascular risk factors[7]. For women who are predicted to have a high risk of radiation-induced heart disease it is important to then consider advanced techniques to limit cardiac exposure as far as possible.

Proton beam therapy may be one such technique. A number of radiotherapy treatment planning studies of proton beam therapy to the breast or chest wall and regional lymph nodes have reported improved dosimetry[5,8-13]. A systematic review of heart doses during 2003-2013 reported PBT delivered the lowest doses compared to other left-sided IMC radiotherapy techniques (average mean heart dose 2.6 Gy)[14]. Ares et al reported the V5 heart benefited by a factor of 8-10 using PBT versus X-rays[8]. Only one study compared PBT versus VMAT using breathing adaptation. PBT significantly reduced mean heart dose when compared to VMAT with breathing adaptation (mean heart dose 1.0 +/-0.1 versus 2.6 +/- 1.0 respectively)[5].

8.1.3 Clinical studies of proton beam therapy

Implementing PBT may reduce heart doses from breast cancer radiotherapy thereby reducing the risk of radiation-induced heart disease for individual women. Feasibility of administering protons has been demonstrated in prospective studies including studies of patients who underwent breast conserving therapy and other studies of patients after mastectomy[15-19]. The largest study of 91 patients reported PBT displays acceptable toxicities but grade 2 dermatitis was 72%[18]. As yet, no comparative clinical trials of PBT and photons have been reported but there are some international trials underway[20].

Designing a study to investigate if PBT is a cost effective treatment for women at high risk of radiation-induced heart disease is challenging. A phase III randomised trial considering all women for left-sided IMC radiotherapy would need to recruit large numbers to detect a small effect. Thorsen et al calculated

the number needed to treat (1/absolute risk reduction) to avoid one death as 33 patients (based on DBCG-IMN overall survival 3% at seven years)[21]. The number of patients needed to cause one death from ischaemic heart disease 30 years after left-sided IMC radiotherapy (without cardiac risk factors aged 50 years at diagnosis, assuming an estimated increase of 5 Gy (plan 1: 8 Gy plan 2: 3 Gy)) was 143[7,21]. In this scenario the number of patients needed to cause one incident major coronary event 30 years after treatment would be 63 without cardiovascular risk factors and 37 with cardiac risk factors. Another challenge is that there would be a long wait to observe a significant number of events as cardiac toxicity may not become clinically manifest for years after radiotherapy.

Before embarking on a phase III trial with late cardiotoxicity as the primary outcome it would be helpful to answer a number of questions. First, is there is a significant difference in acute cardiac toxicity rates between women undergoing modern cardiac sparing photon techniques versus PBT? Second, does this injury persist? Identifying which patients may benefit from the cardiac-sparing properties of PBT may also inform future studies.

8.1.4 Biomarkers for cardiac injury

Cardiac magnetic resonance (CMR) may be used to detect acute cardiac injury. CMR may include cine (dynamic) imaging for morphology and global function, tagged cine imaging for strain (relative length change of the myocardium) and strain rate (the speed at which the myocardial length changes). T2-weighted imaging for oedema, adenosine stress and rest perfusion imaging for perfusion defects and late gadolinium enhancement for fibrosis may also be done.

Shortened Modified Look-Locker Inversion recovery sequence (ShMOLLI) is a pre-contrast T1-mapping technique which may be used to detect mild myocarditis (Fig. 2)[22,23]. It provides characterisation of the myocardial interstitial space (the fluid filled space around cells). The T1 (proton spin–lattice) relaxation time (the process by which an excited state returns to its baseline state) of tissues is estimated on a pixel-by-pixel basis[22]. T1-maps provides a myocardial T1 value for each participant but also provides visuospatial characterization of changes in the left ventricular myocardium.T1-mapping is more sensitive than T2-weighted imaging and late gadolinium enhancement imaging in diagnosing acute myocarditis. It has a tight normal range (962 +/- 25 ms), and a tight reproducibility (+/- 2%) range[23]. Different blood biomarkers may also be used to detect different types of cardiac injury[24]. Two biomarkers have been validated in studies of breast cancer radiotherapy. A prospective cohort study of 58 patients reported increased high sensitivity troponin T (hscTnT) levels > 30% was associated with cardiac radiation doses (mean heart dose: Group A: 4.0 +/- 1.8 Gy, Group B: 2.8 Gy +/- 1.3) and echocardiographic parameters[25]. In another study of 60 patients N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were significantly higher after radiotherapy than in non-radiotherapy matched controls. Levels correlated with high doses in small volumes of the heart[26]. Inflammatory cytokines may detect inflammation and different miRNAs expressed by different cells of the heart tissue may increase in the circulation depending on the mechanism of injury[24].

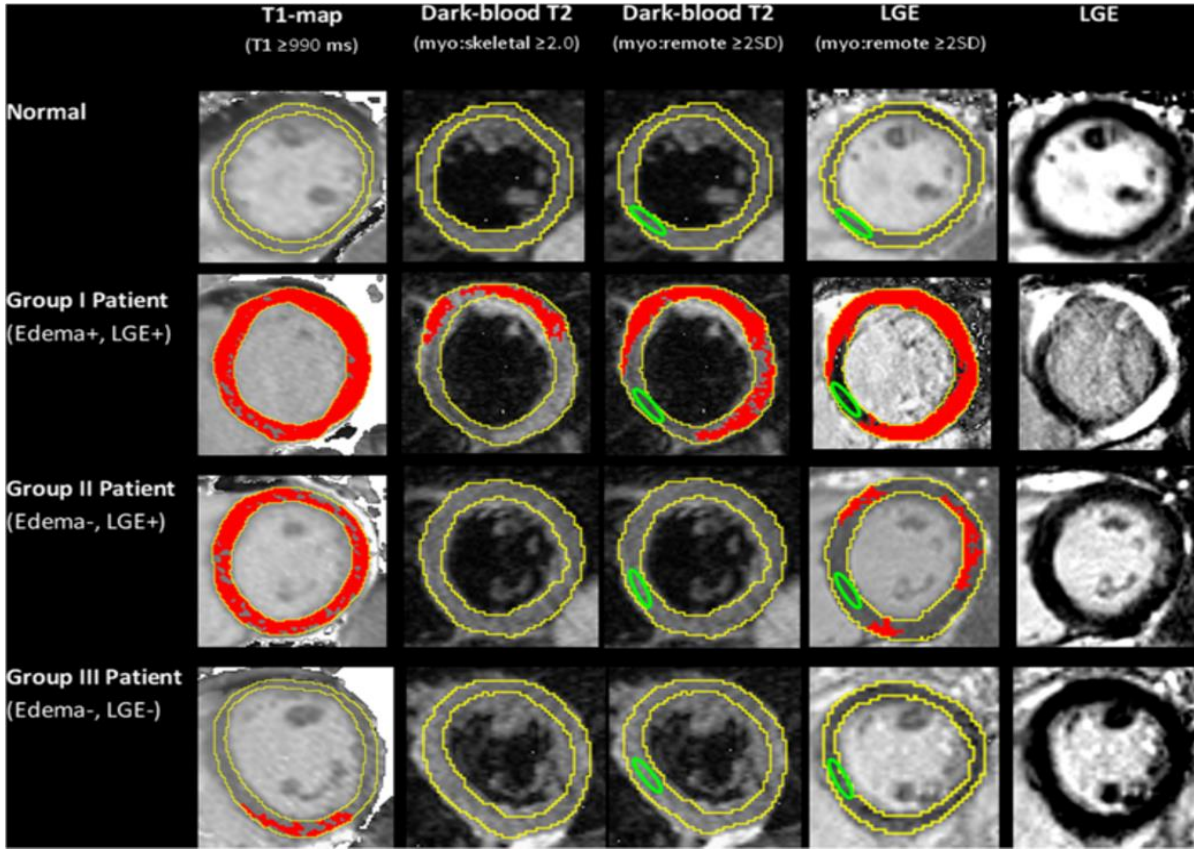


Figure 8-2.T1-maps detected the location and extent of myocardial injury in acute myocarditis.

Areas of myocardial injury (red) as detected by computer-aided analysis of T1-maps, T2-weighted and late gadolinium enhanced (LGE) images in a normal subject (row 1) and patients with acute myocarditis (rows 2–4). Red indicates areas of myocardium with values above the stated threshold for each method. Green contour marks the position of reference region of interest (ROI). Note that a T1 cut-off of ≥ 990 ms detected larger areas of injury than corresponding T2W and LGE imaging analysis. Adapted from Ferreira et al[22].

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A study was proposed to use CMR and blood biomarkers to investigate the benefit of PBT in reducing the risk of acute cardiac injury for women undergoing IMC irradiation compared with modern X-ray radiotherapy using breathing adaptation. This may provide information which may help direct the need for a future phase III clinical trial to investigate if PBT offers a long-term cost-effective benefit over X-rays in reducing cardiac morbidity.

8.2 Methods/Design

The proposed study is a randomised phase II multicentre trial. Patients would be recruited from participating UK centres. If randomised to PBT participants must be willing to travel to either of the two new NHS proton centres. Women who consented to have IMC irradiation and had a radiotherapy CT planning scan in deep inspiration breath-hold would be considered for the trial. A standard plan using wide tangents would be generated for each woman on the radiotherapy treatment planning system. Information on age, the presence of cardiovascular risk factors and mean heart dose from standard treatment would be used to assess the risk of a radiation-induced incident cardiac event using a model by Darby et al (table S13 in the publication)[7]. Women with more than a 2% predicted increased risk of incident ischaemic heart disease at 30 years would be offered randomisation to proton radiotherapy versus photon radiotherapy using volumetric modulated arc therapy (VMAT) and breathing adaptation. For a typical woman aged 50 years when irradiated the usual mean heart doses for a 2% increased risk at 30 years would be > 3Gy in women with cardiovascular risk factors and > 6 Gy in women with no risk factors. Inclusion and exclusion criteria

are summarised in Table 1. Written informed consent would be acquired before entering patients into the trial.

Table 8-1. Inclusion/Exclusion criteria

Inclusion criteria	Exclusion criteria
1. Left breast invasive ductal or lobular carcinoma, confirmed histologically	1. Evidence of distant metastases (including oligometastases)
2. Breast conserving surgery or mastectomy with axillary staging (sentinal lymph node or axillary dissection)	2. Prior cancer or concurrent cancer except non-melanoma skin cancer or in situ carcinoma of the uterine cervix.
3. Regional nodal irradiation including internal mammary chain irradiation recommended	3. Contraindications to radiotherapy
4. Patient has consented to treatment	4. Bilateral breast cancer
5. Female	5. Unable to achieve deep inspiration breath hold during radiotherapy
6. Life expectancy > 10 years	6. Contraindications to CMR
7. WHO performance status ≤ 1	7. Allergy to contrast or adenosine
	8. GFR < 60 mL/min

8.2.1 Interventions

Once registered for the trial the patients would be randomised (Fig. 3). There would be 1:1 assignment to each of the treatment arms. The ESTRO regional nodal contouring atlas would be used for contouring the target volumes[27,28]. A validated atlas would also be used for contouring cardiac substructures (Chapter 2)[29]. This would include contouring of left ventricular segments so that segment doses may be related directly to segment injury. The radiation dose schedule to be used in the study will depend on ongoing discussion with the collaborators. A standard UK dose schedule was proposed for both treatment arms. For the interventional arm of PBT using pencil beam scanning 40 Gy (RBE) in 15 fractions will be delivered over three weeks. The breast or chest wall as well as the nodal regions will be treated with protons. For the comparator arm of VMAT with breathing adaptation 40 Gy in 15 fractions would be delivered over three weeks. Participants would be scheduled to have 3 cardiac assessments which include a clinical examination, electrocardiogram (ECG), blood biomarkers and a

CMR imaging scan (Table 2): the first would be done prior to commencement of radiotherapy, the second within 72 hours of the final fraction of radiotherapy and the third at 4 months after completion of radiotherapy. Patients would be on the study for around 6 months from registration to 4 months from the final day of radiotherapy. Participants would be offered a further assessment at 2 years to ascertain if any cardiac abnormalities on the initial CMR scans resolve (if they are not transient they may contribute to late cardiac morbidity).

Table 8-2. Blood and cardiac magnetic resonance biomarkers for different mechanisms of cardiac injury

Myocardial injury	Biomarker of injury
	Blood*
Cardiomyocyte death	high senstivity Troponin
Cardiomyocyte neuro-hormonal activation	NT-pro-BNP
	Cardiac Magnetic Resonance
Inflammation	T1-mapping technique (ShMOLLI)
Anatomy, function	cine imaging tagged cine imaging peak systolic circumferential myocardial strain strain rate
Oedema	T2-weighted imaging
Perfusion defect	adenosine stress and rest perfusion imaging
Fibrosis	late gadolinium enhancement imaging

*NT-pro-BNP: N-terminal pro-B-type natriuretic peptide
ShMOLLI: Shortened Modified Look-Locker Inversion recovery sequence
Strain: Strain is a measure of the
Strain rate is the speed at which the myocardial length changes.

8.2.2 Outcomes

The primary endpoint would be acute myocarditis detected using a CMR T1-mapping technique. Blood and other CMR biomarkers for different mechanisms of cardiac injury will also be investigated to profile the manifestation of acute cardiac injury for different levels of radiation exposure between the two treatment arms (Table 2). Cardiac substructure dosimetry would be correlated to areas of acute myocardial injury. Other secondary considerations would be loco-regional control of breast cancer, acute skin and lung toxicity, the feasibility of willingness for randomisation and patient travel, and the feasibility of proton beam therapy delivery. Acute skin toxicity and radiation pneumonitis would be graded by the Common Terminology Criteria for Adverse Events (CTCAE). Late skin toxicity would be monitored using a photograph scoring method[30].

8.2.3 Monitoring

The trial would incorporate a prospective Radiation Therapy Quality Assurance (RTQA) programme. A detailed proton beam therapy protocol would be developed including a care pathway detailing how treatment may be adapted for women who develop inflammation leading to a change in the surface contour of the breast or chest wall. External review by international experts would be arranged. On-trial peer review of radiotherapy treatment plans prior to treatment would be undertaken supported by web-conferencing facilities. An online database system would be arranged for data submission. The Oncology Clinical Trial Office in Oxford, in conjunction with the CTUs in Manchester and London, could co-ordinate and manage the trial. The imaging analysis component of the

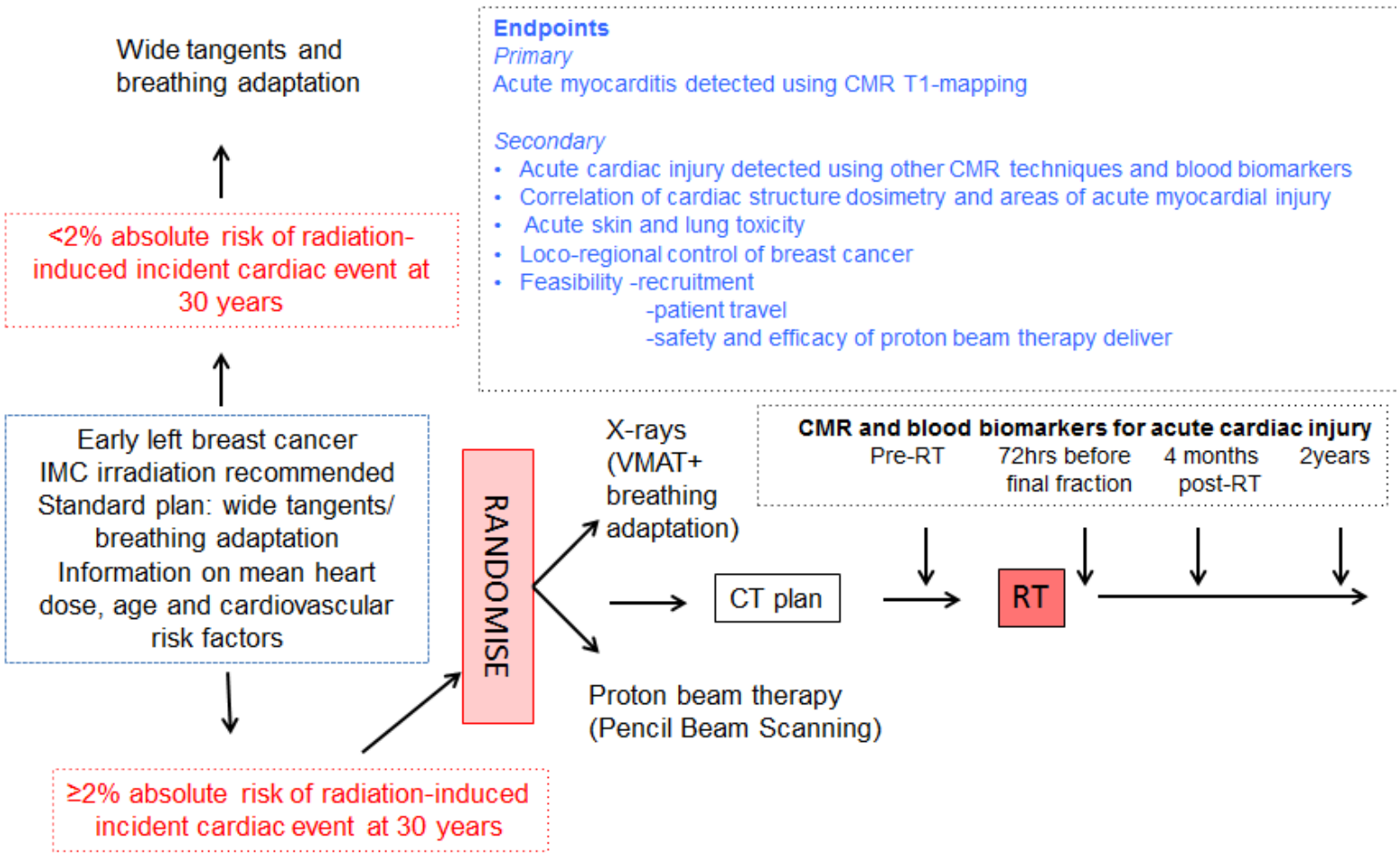


Figure 8-8-3. ProIMC Trial Design

Abbreviations: IMC: internal mammary chain; VMAT: volumetric modulated arc radiotherapy; DIBH: deep inspiration breath hold, VMAT: volumetric modulated arc therapy, CMR: cardiac magnetic resonance

study would be led by VF. In Oxford CMR would be undertaken at the John Radcliffe Hospital University of Oxford Centre for Clinical Magnetic Research. It has been confirmed these scans may also be undertaken in both the Christie Hospital and the University of London hospital.

8.2.4 Sample size considerations

To estimate a sample size for the trial, which aims to validate the CMR T1-mapping technique (ScMOLLI) as a biomarker for myocarditis, the difference in T1 measures to be expected between those receiving PBT versus photons with breathing adaptation was quantified. Information from a study by Ferreira et al (VF) published in 2014 was used for this purpose[22]. This study of patients presenting with suspected acute myocarditis to the cardiology service reported average T1 measures for different degrees of acute myocarditis (mild, moderate and severe with very small troponin rises). The median area of myocardial injury detected by T1 mapping (T1>990ms) was 0.7% (IQR 0-3%) for normal controls, 6% (IQR 2-7%) for the mild myocarditis group, 15% (IQR 12 to 29%) for the moderate myocarditis group and 49% (24 to 70) for the severe myocarditis group. To calculate the conventional effect size it was assumed that patients for PBT are likely to have very little cardiac exposure and will have no signs of myocarditis similar to the normal controls and conservatively assumed that the patients for photon treatment with breathing adaptation are likely to have some cardiac exposure and develop mild myocarditis similar to the mild myocarditis group (Fig 1, Group III). The effect size was calculated by subtracting the mean T1 value given for the normal control group from the mean value given for the acute

myocarditis group and then dividing the result by the standard deviation. We assume area of injury is normally distributed, the median is taken to be the mean and the standard deviation was estimated from IQR as (quartile3-quartile 1/1.35) provided in the Cochrane Handbook[31].

$$\text{Effect size (d)} = \frac{6.0\% - 0.7\%}{0.7X[\sqrt{(5^2+3^2)}]}$$

$$= 1.22$$

Assuming a power of 80% and a level of significance of 5%, two-tailed, a sample size of 12 per group was calculated[32]. This low number reflects how sensitive T1 mapping is for detecting myocarditis. T1-mapping has a very tight normal range (962 +/- 25 ms), and a tight reproducibility (+/- 2%) range[23].This number was then doubled to account for dropouts, patients lost to follow up, patients not tolerating the protocol, and to ensure flexibility around the calculated effect size. The total number to be recruited is 48 women. An evaluable patient for primary endpoint analysis is defined as one who has completed a course of IMC irradiation and has had a cardiac assessment at 2 or more time points.

Seventeen percent of patients in Oxford fulfil the UK RCR IMC radiotherapy criteria (53/305 women over a 6 month period) (Chapter 7). Approximately half of these have left-sided disease. Therefore around 50 patients per year will have left IMC radiotherapy in the next few years. We are considering women with more

than a 2% predicted increased risk of incident ischaemic heart disease at 30 years. Over 50% of these women are likely to have at least one cardiovascular risk factor (see Chapter 7). It is not yet clear what proportion of these patients have mean heart doses of > 3 Gy with standard wide tangents and breathing adaptation. These numbers suggest that a multicentre trial is required if aiming to recruit 48 women to the trial over a 2 year period.

8.3 Peer review

The proposed trial has been presented for peer review both locally and nationally. There has also been engagement with international experts (Table 4). It has been agreed that the proposal addresses an important question, it is timely and it is a priority. Major discussion points included: the need for a randomised study, the need for a clinical study, the need for a feasibility study, the risk of acute skin toxicity, how best to select participants and the need for biomarker validation. Seeking formal peer review is valuable when developing a trial proposal. Input from experts, trialists, and patient representatives add value to a proposal. The main funding bodies seek endorsement of trial proposals from expert groups. These expert groups include the National Cancer Institute Clinical and Translational Radiotherapy Research Working Group (CTRad) and Breast Clinical Studies Group (CSG Breast) which both offer research support and a formal trial concept peer review service.

Table 8-3. Peer review of a clinical trial proposal of proton beam therapy for IMC irradiation in the U.K

Steps towards protocol endorsement	Date		Feedback received
Local engagement			
Oxford Clinical Trials Development Group	15-Apr-15	Trial proposal presented (FD) Written trial proposal reviewed	• Need to identify one primary outcome • Consider randomised design to avoid selection bias • Consider if it is possible to predict long-term risks of radiation-induced heart disease using a virtual planning study, comparing the difference in DVH parameters between the groups and using a predictive model to estimate risks. • Concern that CMR T1 mapping is not validated for detecting radiation-induced acute myocarditis. Consider validated tools such as echocardiography for measuring strain or SPECT for assessing perfusion • Consider cost-effectiveness • Consider cardiotoxicity from anthracyclines and traztuzumab
Engagement with national trialists			
NCRI CTRad Clinical Trials Workshop	14-Oct-14	Attended by two investigators (CT and FD)	• Consider randomised design to avoid selection bias • Consider participating in an international trial • Consider feasibility study when testing new technology • Seek the views of patient representatives • Carefully consider radiotherapy quality assurance
NCRI CTRad Clinical Trials Sandpit Day	24-Mar-15	Trial concept presented (FD)	• Consider a randomised design to avoid selection bias • Consider defining a high risk group receiving cardiotoxic systemic treatment or with pre-existing risk factors who may benefit most from PBT • Consider prospective planning study to compare DVH parameters between the groups • Consider acute skin toxicity as a primary endpoint for the study
NCRI CTRad Trial Proposals meeting	04-Nov-15	Trial proposal presented (KV) to a group of experts and patient representatives Attended by DC and FD Written trial proposal reviewed	Protocol received an "AMBER" rating • Consider equipoise • Consider a non-randomised pilot study • Consider investigating macrovascualr injury • Consider inflammation and contour changes during treatment • Sample size appears conservative • Need to identify specific primary endpoint • Consider practicalities for patients as they will need to travel for PBT • Concern that CMR T1 mapping is not validated for detecting radiation-induced acute myocarditis. • Concern regarding acute skin toxicity in the literature • Consider a feasibility study when testing new technology • Consider incorporating fractionation question into study
NCRI CTRad Strategy for IMC RT research workshop	14-Dec-16	Draft of protocol presented (KV) Attended by CT, DC and FD	• It was agreed that a UK breast IMC proton study should be developed within this group and that the Oxford group would focus on validating CMR T1 mapping as a biomarker for radiation-induced myocarditis.
Engagement with international trialists			
US RADCOMP trial		Teleconference with principal investigator (KV)	• Keen for UK centres to be international sites • Primary endpoint would be underpowered for UK patients. • Concern that mean heart dose of < 15 Gy is permissable in photon arm
CRUK Oxford Centre PBT Workshop	9-Sept-15	Trial concept presented (KV) to a group of international clinicians and academics Attended by SD, DC, CT and FD	• Consider staging PET CT for patients on study • A randomised study may be more feasible in the U.K. and may recruit more women than the US

Abbreviations:
NCRI CTRad: National Cancer Research Institute Clinical and Translational Radiotherapy Research Working Group
RADCOMP: Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness Consortium Trial
CMR: cardiac magnetic resonance
SPECT: single positron emission computed tomography

8.3.1 The need for a randomised study

One issue to consider is whether it is ethical to randomise this trial when in the patients allocated to the conventional arm may be more likely to suffer cardiac damage. At present there are no reported randomised studies comparing PBT with photon therapy or evidence that PBT is better or worse at treating cancer or at limiting cardiac toxicity. Although planning studies have shown that proton therapy gives less dose to the heart it is important that this theoretical benefit is proven to be an actual benefit in a randomised clinical study. Within the Bragg peak clustered ionisation events cause complex DNA damage resulting in enhanced biological effects. However, there are a number of uncertainties regarding the dose delivered by PBT[33] which include sensitivity to organ motion, the radiobiologic equivalent dose may increase beyond the Bragg peak, penumbra uncertainty, target margins, and treatment planning system dose-calculation accuracy. It is particularly important to consider these uncertainties when treating the left breast given that the left ventricle and the left anterior descending coronary artery are located just beyond the spread out Bragg peak. Breast contour changes due to respiratory motion or breast swelling may result in variability of Bragg peak placement which may be disadvantageous for these nearby normal tissues. These uncertainties are currently being studied by one of the trial investigators (FV). Another issue to consider is selection bias (risk of sample obtained not being representative of population intended to be analysed). If the study is not randomised it is likely more patients with cardiovascular risk factors and higher mean heart doses from standard wide tangents with breathing adaptation would be selected for PBT. The effect of cardiac exposure may therefore be underestimated in the VMAT and breathing adaptation group and it

would be more difficult to show a significant difference between the groups. A randomised design would avoid selection bias because neither doctors nor patients would have control over which treatment is allocated.

8.3.2 Planning study and predictive modelling versus clinical study

It is possible to compare DVH parameters between the groups by doing a planning study. Predictive modelling may be used to estimate the long term risks of radiation-induced IHD with information on mean heart dose, age and cardiovascular risk factors (Table S13, Darby 2013)[7]. Planning studies have shown that proton therapy gives less dose to the heart than VMAT with breathing adaptation[5]. Stick et al compared PBT versus 3-D conformal radiotherapy which used the predictive model by Darby et al. This reported the excess absolute risk of cardiac toxicity may be up to 2.9% at 30 years in individual patients[13]. In the proposed trial we would expect the difference in mean heart dose between the two groups to be larger than that seen by Ranger et al. This is because we would be selecting patients with a predicted risk of radiation-induced heart disease > 2% which depends on mean heart dose, age and cardiovascular risk factors. It would be possible to perform a prospective planning study of these particular patients to show this difference but this would not be evidence that PBT limits cardiotoxicity.

8.3.3 The value of a feasibility study

The first ten of 24 patients to be recruited for PBT could be considered part of a feasibility study to establish the treatment delivery pathway and allow for refinement of the radiotherapy planning protocol. It would also provide

information on recruitment, willingness for randomisation and patient travel. If the treatment delivery pathway is deemed feasible recruitment of a further 14 patients to this arm of the study may then be undertaken.

8.3.4 Acute skin toxicity as a primary endpoint

Acute skin toxicity from proton beam therapy has been reported by a number of studies of accelerated partial breast irradiation in the past[34,35]. Clinical studies of PBT to the breast/ chest wall and regional nodes report skin toxicity rates are acceptable[18,19] but the largest PBT study of 91 patients reported higher rates of dermatitis than in the NCIN MA 20 trial[18]. Passive-scattering techniques were used in all of these studies which are limited in terms of field size, field-matching and dose-shaping. Technical advancements are ongoing and skin sparing is now possible as there is a move away from double-scattering proton techniques towards pencil-beam scanning. In passively scattered proton beam irradiation the beam is manipulated through a scattering foil but in proton pencil beam irradiation it is manipulated using magnets to accurately scan through the target volume. With the use of multiple fields, treatment of all fields per treatment session and the use of scanning techniques acute toxicity rates would not be expected to be significantly different compared to rates from photon treatment. This has been demonstrated in a study by Bush et al of partial breast irradiation which included 100 patients[36].

8.3.5 Patient selection: risk factors versus complicated anatomy

Women with cardiovascular risk factors have a higher absolute risk of radiation-induced heart disease than women without. Women receiving cardiotoxic

systemic treatments such as anthracyclines or trastuzumab may also be at an increased risk. Recruiting all patients for IMC irradiation with at least one cardiovascular risk factor or who have anthracyclines, trastuzumab or both was considered. There were a number of arguments against this approach. This may preferentially recruit smokers to trials of advanced techniques over non-smokers. Almost all patients for IMC radiotherapy have anthracyclines and so this would mean almost all women for IMC radiotherapy would be offered randomisation. Women without risk factors receiving high heart doses from standard treatment due to their anatomy would be excluded.

8.3.6 CMR versus validated imaging tools

There was concern CMR T1-mapping is not a validated research tool for detecting radiation-induced acute myocarditis. Before proceeding with a trial it is necessary to show an effect may be detected by CMR specifically for the population of patients to be recruited. CMR offers a number of advantages over echocardiography which has been validated to detect radiation-induced including longitudinal peak systolic strain and strain rate rate[37,38]. CMR may detect multiple abnormalities. It is less operator dependent and not as affected by body habitus as echocardiography. Also, it does not involve exposure to ionising radiation which is an issue with single-photon emission computed tomography (SPECT) which has been used in multiple studies to detect perfusion defects.

8.4 Where are we now?

Having taken all the feedback received into account the focus now is on a cohort study which aims to validate CMR T1-mapping as a biomarker for radiation-

induced injury after IMC radiotherapy. A prospective longitudinal study, to characterise the heart during and after breast cancer radiotherapy using CMR has already been undertaken in Oxford, led by DC and VF, This study recruited 35 patients during January 2010-November 2011 who had left-sided whole breast radiotherapy (mean heart dose 1.5 Gy (range 0.65-4.20)) and did not receive adjuvant chemotherapy[39]. The results are pending. It has been agreed that this study protocol may be amended to include patients for left-sided IMC radiotherapy who have had chemotherapy and patients with other thoracic cancers requiring adjuvant radiation therapy to the chest with high cardiac exposure (e.g. lymphoma or oesophageal cancers).

Twenty-five patients will be recruited from The Churchill Hospital, Department of Clinical Oncology. Patients may be up to 75 years and may have pre-existing cardiovascular risk factors. Similar to the initial cohort, these patients will have a cardiac assessment including an ECG, blood biomarkers and CMR prior to radiotherapy, within 72 hours of completing radiotherapy, and at 3-6 months and 6-12 months following radiotherapy. For those who are having chemotherapy an extra CMR will be undertaken at baseline before chemotherapy. CMR will be undertaken at the John Radcliffe Hospital University of Oxford Centre for Clinical Magnetic Research (OCMR).

The primary objective of this study will be to investigate the extent of radiation induced acute myocarditis using the ShMOLLI T1-mapping technique for different levels of cardiac exposure. Secondary objectives will be to investigate the extent of cardiac damage using other CMR and blood biomarkers. Radiation doses to

the cardiac substructures will be investigated and related directly to location of injury as demonstrated by CMR imaging. Combining this new cohort with the initial cohort may provide opportunity to validate CMR biomarkers for detecting radiation-induced cardiac injury. This purpose driven preparatory study may determine the most appropriate question for future study.

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9 General Summary and Clinical Implications

9.1 General Summary and Clinical Implications

This thesis adopts a variety of approaches in the investigation of the potentially harmful exposure of the heart and lungs to radiation during breast cancer radiotherapy.

The first few chapters of the thesis consider exposure of the heart. A case-control study by Darby et al included ~ 1,000 women irradiated for breast cancer who developed or died from ischaemic heart disease (IHD)[1]. Within this study a dose-response relationship was developed which showed a linear increase in the rate of major coronary events of 7.4% per Gy mean heart dose. IHD may be caused by microvascular myocardial injury or macrovascular coronary arterial injury. The myocardium and coronary arteries have different structures and functions and may respond differently to radiation. In the study by Darby et al the best predictor of IHD was mean heart dose. However it remained unclear if using doses to cardiac substructures would improve prediction of IHD risk from radiotherapy.

The development of dose-response relationships for individual cardiac substructures (segments) requires long-term outcome data in conjunction with dosimetry for women irradiated in the past who received a wide range of segment doses. **Chapter 2 and 3** provide dosimetry for a cross-sectional study of cardiac segment injury after breast cancer radiotherapy [Appendix E4]. The study included 456 cases from the Scandinavian case-control study reported by Darby et al for whom detailed cardiac outcome information was available. Doses were allocated to each woman according to her regimen and total dose and dosimetry was related to cardiac outcome data. It was found that both myocardial and coronary arterial

structures are sensitive to radiation. Therefore it suggests whole heart dose is minimised as far as possible to avoid injury to all of the cardiac structures[Appendix E4].

Chapter 2 presents an atlas which provides a reliable and reproducible method for contouring the cardiac substructures. This was developed for identifying the atrioventricular and interventricular grooves, the heart chamber boundaries, five left ventricular segments and ten coronary arterial segments on non-contrast radiotherapy CT-planning scans. Segments were defined from cardiology models and matched those described by cardiologists regarding the location of injury in echocardiography and angiogram reports. The atlas was validated by quantifying inter-observer variation using spatial analyses. Six oncologists tested it. Spatial overlap averaged over the six radiation oncologists who tested the atlas was more than 60% for left ventricular segments but less than 50% for most coronary artery segments. The separation between the contours averaged over the six observers was larger for coronary artery segments (1.3mm-5.1mm) than for left ventricle segments (1.3mm-2.2mm). The effect of inter-observer contouring variation on radiation doses to cardiac segments from breast cancer radiotherapy regimens was quantified. Spatial variation resulted in <1 Gy dose variation for most regimens and segments, but 1.2-21.8 Gy variation for segments close to a field edge. This atlas aimed to minimise dose variation from one source of uncertainty: differences in contouring. In 2010, the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) Report highlighted that contouring cardiac substructures is a challenge and that there was a need for developing contouring guidelines[2]. This validated atlas may be used as a

research tool which will facilitate consistent reporting of cardiac doses in radiotherapy research studies and in clinical trials so that radiation doses to cardiac segments may be related to clinical outcome data for the development of dose-response relationships. It expands on a previously published guideline by the University of Michigan which describes the heart chambers, coronary arteries and valves but does not describe cardiac segments[3].

In **Chapter 3** detailed cardiac segment dosimetry for breast cancer radiotherapy regimens used in Denmark and Sweden during 1958-2000 is presented. Forty-one regimens were identified from 470 radiotherapy charts of women who received radiotherapy before the era of radiotherapy CT-planning. Given the lack of anatomical information all regimens were reconstructed on a 'typical CT-scan' to estimate left ventricle (LV) and coronary artery segment doses. A 'typical CT-scan' was selected from ten randomly selected CT-scans which had mean heart doses closest to average for the two most commonly used left-sided techniques and which was not anatomically atypical. Dose distributions were generated for cobalt, electron and megavoltage beams using modern 3-dimensional CT treatment planning. Dose distributions from orthovoltage fields were generated using manual planning. A wide range of doses were received by the cardiac segments which provided the opportunity to assess dose-response relationships for cardiac segment injury. The effect of patient to patient variability in anatomy on cardiac segment doses was assessed by reconstructing 14 regimens (with different field arrangements) from the two most common radiotherapy technique categories (tangential and anterior electron). Seven left-sided regimens were reconstructed on ten CT scans and seven right-sided regimens were

reconstructed using five CT-scans. Doses varied substantially between women receiving the same regimen. Whole heart dose varied by 7 to 9 Gy for various left tangential regimens and by 3 to 5 Gy for left anterior electron regimens. Whole heart dose variability was lower for right tangents (<1 to 1 Gy) and right electrons (1 to 4 Gy). For cardiac structures distant from the fields, dose variability was <1 to 2 Gy but for cardiac structures near a field edge variability was higher (3 to 47 Gy for left-sided and 3 to 27 Gy for right-sided regimens). Hence, estimation of segment doses near a field edge using a typical CT-scan is subject to considerable uncertainty due to inter-patient variation in anatomy. Doses to adjacent segments at the anterior border of the heart are highly correlated. The LADCA segment doses were highly correlated with doses to the LV segments usually supplied by the LADCA (range of correlation coefficients: 0.3-0.9). The scope is therefore limited for investigating whether myocardial injury of the LV apical, anterior and septal segments results from direct exposure of the myocardium causing disruption of the microvasculature or from exposure of the LADCA causing occlusion of the artery and downstream myocardial ischaemia. Segment dose estimates may, however, be used to rank segments according to higher-versus-lower dose for qualitative dose response relationships.

In a cohort study of 14,645 women with breast cancer in the Netherlands women who received IMC radiotherapy during the 1970s and 80s had significant excesses of myocardial infarction (MI), valvular heart disease (VHD) and heart failure (HF) compared with other similar women who did not receive IMC radiotherapy[Appendix E4]. From this cohort three nested case-control studies of MI, HF and VHD after breast cancer are in progress. Within these case-control

studies cardiac doses are being related to cardiac outcome data. They aim to validate previously reported dose-response relationships for radiation-induced MI and to investigate new dose-response relationships for radiation-induced HF and VHD[1,4,5]. At present, there are no dose-response relationships for the risks of VHD or HF after breast cancer radiotherapy. Cutter et al. suggested that radiation doses up to 20-30 Gy to the cardiac valves do not cause disease after Hodgkin lymphoma radiotherapy[6]. However, patients with breast cancer are generally older than patients with Hodgkin lymphoma and the relationship between valve dose and VHD may not be the same in this population.

Chapter 4 describes radiation doses to the whole heart, left ventricle and cardiac valves from 44 breast cancer regimens used in the Netherlands during 1970 to 2009. These 44 regimens were identified from 771 radiotherapy charts of the women selected as cases and controls for the MI and HF case-control studies. A 'typical CT-scan' was used to estimate doses retrospectively given that no anatomical information was available for these women. Average whole heart dose in the 1970s and 1980s was 8.9 Gy. It reduced to 4.8 Gy during in the 1990s and then to 1.5 Gy in the 2000s. These reductions were caused by a steady decrease in IMC radiotherapy. These data provide a unique opportunity to develop dose-response relationships for radiation-induced heart disease for a number of reasons.

(1) Cardiac exposure for women in this population who received IMC irradiation was substantial compared to that received by women irradiated today[7-8]. Direct megaovoltage fields were commonly used which led to increased cardiac

exposure. For radiotherapy that included the IMC, average whole heart doses remained high even in the 2000s both for women with left breast cancer (14.1 Gy (IQR 9.0-16.1)) and women with right breast cancer (8.9 Gy (IQR1.7-9.4)). Direct megavoltage fields were still being used. Oblique megavoltage IMC fields were introduced in 2003, which were angled away from the heart and gave lower heart doses than direct megavoltage IMC fields but even after 2003 oblique fields were used for less than half of the women who underwent IMC irradiation.

(2) The cardiac doses estimated are highly heterogeneous given the wide variety of regimens used. For example, dose to the pulmonary valve from IMC radiotherapy was only ~1 Gy from some regimens but it was ~50 Gy from other regimens. This may enable comparison of VHD rates in women who received a wide spread of valve doses to develop dose-response relationships for radiation-induced valve disease. Similarly, LV dose varied from ~0.5 to 26 Gy. HF rates may therefore be compared in women who received a wide spread of LV doses to develop a dose-response relationship for radiation-induced HF.

(3) Radiation-induced heart disease usually takes many years to develop. To assess the 20 year risks of radiation it is necessary to study women who received their radiotherapy >20 years ago during the 1970s, 80s and 90s.

Chapter 5 presents the case-control study of MI after breast cancer. In this study cardiac doses were allocated to each of 314 women, including both cases and controls, according to her regimen and total dose. Doses were related to cardiac outcome data. This study validates previous reports that breast cancer

radiotherapy increases the risk of ischaemic heart disease linearly with mean whole heart dose. The risk of MI increased linearly with mean whole heart dose by 6.5% per Gy. No dose threshold was apparent below which there was no increased risk. The percentage increase in MI rate per Gy did not differ between women with and without cardiovascular risk factors at diagnosis. No increased risk was found during the first ten years after exposure. Interestingly, this study included younger women than previous reports (median age 50 years at breast cancer diagnosis) and suggests that the increased risk of MI is highest for women < 45 years and decreases with older age.

Chapter 6 focuses on exposure of the lungs in breast cancer radiotherapy. A systematic review of lung doses was undertaken in studies describing breast cancer radiotherapy regimens published during 2010-2015. Lung exposure varied according to country, anatomical regions irradiated, technique, treatment position and the use of breathing adaptation. Doses increased with the addition of nodal irradiation. The average mean ipsilateral lung dose (MLD_{ipsi}) for supine radiotherapy with no breathing adaptation was 2.1 Gy for partial breast radiotherapy, 8.4 Gy for whole breast/chest wall radiotherapy, 11.2 Gy when the axilla or supraclavicular fossa was irradiated, and 14.0 Gy with the addition of internal mammary chain irradiation. Breathing adaptation reduced lung exposure. The magnitude of the reduction depended on the extent of the region irradiated. The average reduction in MLD_{ipsi} was 0.2 Gy, 0.8 Gy, 2.5 Gy and 2.9 Gy for partial breast, whole breast/chest wall, whole breast/chest wall and axilla/supraclavicular fossa, and whole breast/chest wall and axilla/supraclavicular fossa with IMC respectively. Doses were lowest for

treatment in the prone/lateral decubitus position. Implementation of new positioning techniques has been limited due to the need for specialized equipment and the reproducibility of daily set up.

Lung doses also depended on the technique used. Doses were highest from IMRT and lowest from proton therapy. For regimens that did not include the IMC, tangents spared the lungs better than IMRT. When the IMC was irradiated, IMRT resulted in lower mean ipsilateral lung dose than tangents but it increased contralateral lung dose. It is likely that strict optimization constraints and strategic beam placement may minimize low doses both to the contralateral and ipsilateral lungs. Proton therapy remains expensive and is not widely available.

Prior to this study a comprehensive review of lung exposure after breast cancer radiotherapy had not been done. The results guide oncologists on how breast cancer radiotherapy may be modified to limit lung exposure if this is a priority for certain individuals. Treatment may be modified by limiting the irradiated volume, using breathing adaptation, using lateral or prone positioning or using a lung sparing technique. Limiting lung exposure is particularly relevant to women with pre-existing lung disease which may be exacerbated by radiation and to continuing smokers who have an increased risk of radiation-induced lung cancer. This review was undertaken as part of a broader project investigating the effect of radiotherapy on the risk of lung cancer. As well as estimating lung doses for modern breast cancer radiotherapy lung doses were estimated for ~40,000 women irradiated for breast cancer in the past in 75 randomised trials[9, Appendix E2]. This information on past lung doses was combined with lung cancer incidence

rate ratios for the women in the trials. Radiotherapy doubled the risk of lung cancer after ten years, corresponding to 11% excess relative risk per Gy whole-lung dose. The excess RRs/Gy were then applied to the modern doses from the systematic review and modern population-wide death rates to predict hazards in both smokers and non-smokers. The estimated absolute risks from modern radiotherapy at 30 years were approximately 4% for long-term continuing smokers and 0.3% for non-smokers. Smoking status determined the net effect of radiotherapy on mortality and smoking cessation is a high value intervention. The results of this study emphasise the importance of incorporating smoking cessation programs for smokers with newly diagnosed breast cancer.

New evidence has emerged that IMC irradiation improves survival but the IMC is close to the anterior surface of the heart and when irradiating this region it is difficult to avoid cardiac exposure. There has been debate around the role of IMC irradiation which is reflected by discrepancies between country-specific guidelines. In **Chapter 7** a systematic search for national breast cancer radiotherapy guidelines published during 2013-2018 identified guidelines from four different countries presenting criteria for "consideration of" or "recommended for" IMC radiotherapy. The percentage of women undergoing radiotherapy for early breast cancer in a single centre who met the criteria presented by each country was determined. This varied markedly between countries from 17% to 71%. These differences occurred because in some countries, all patients with 1-3 axillary nodes and some node negative women are considered for IMC radiotherapy but not in others. 17% fulfilled the U.K. RCR IMC criteria (53/305 over a typical 6 month period) including patients with T4 or N2-3 disease and

patients with 1-3 nodes and a central/medial lesion with risk factors for recurrence[10]. A higher percentage of women fulfilled IMC radiotherapy criteria set out by other countries: Germany 36% (T3/4 disease and/or node positive disease), Ireland 55% (inner quadrant tumours or node positive disease), and USA 71% (included other subsets of node negative disease). In a subset of 155 patients, 87 of them (56%) had at least one cardiovascular risk factor). This information may aid decisions regarding the feasibility of offering IMC radiotherapy to different categories of women. Over half of women for breast cancer radiotherapy in our centre may benefit from counselling on the prevention of cardiovascular disease.

The RCR U.K. IMC radiotherapy guidelines currently recommend a mean heart dose < 6 Gy when considering IMC irradiation[10]. For some women who have poor displacement of the heart with breathing adaptation it may be challenging to meet this constraint with standard wide tangents. For these women it is necessary to consider an advanced photon technique such as tangential volumetric arc therapy, with breathing adaptation. In the case-control study by Darby et al no threshold dose for the development of radiation-induced ischaemic heart disease was reported[1]. Given this finding, it is important to investigate the feasibility of techniques which may minimise heart doses further than modern photon techniques for women undergoing IMC irradiation. A systematic review of heart doses in breast cancer radiotherapy delivered worldwide has shown that proton beam therapy delivered the lowest average mean heart dose (average mean heart dose 2.6 Gy) compared to other techniques[10, Appendix E3]. Proton beam therapy (PBT) achieves a sharp distal dose gradient enabling avoidance of

normal tissues and so may increase the therapeutic index by maintaining the benefits of radiotherapy while minimising the risks.

Chapter 8 details the development of a phase II clinical trial proposal (2014-2017) which aimed to show that for women undergoing IMC irradiation the extent of acute myocarditis is less with proton beam therapy than it is with modern photon therapy with breathing adaptation. Such a trial may direct the need for a future phase III clinical trial investigating whether protons can mitigate the potential for increased late cardiotoxicity when the IMC is irradiated. The primary endpoint is acute myocarditis detected using cardiac magnetic resonance (CMR) T1-mapping. Blood and other CMR biomarkers for different mechanisms of cardiac injury would be used to profile how acute cardiac injury manifests for different levels of radiation exposure. Secondary outcomes included loco-regional control, acute skin and lung toxicity, the feasibility of willingness for randomisation and patient travel, and the feasibility of proton beam therapy delivery. Eligible patients would have more than a 2% predicted risk of radiation induced ischaemic heart disease based on pre-existing cardiovascular risk factors and the estimated mean heart dose that would be received with standard photon treatment. 48 patients would be recruited. This proposal received positive feedback from Clinical and Translational Radiotherapy Research Working Group experts. Based on the feedback received a preliminary cohort study is underway investigating the extent of radiation-induced acute myocarditis in women with left-sided breast cancer undergoing IMC irradiation. This study aims to validate T1-mapping as a biomarker for radiation-induced acute myocarditis in women undergoing radiotherapy for breast cancer.

The findings in this thesis contribute to knowledge of radiation-induced heart disease and radiation-induced lung cancer so that patients may be better informed during the consent process for breast cancer radiotherapy, oncologists may be better informed when making management decisions for individual patients and radiotherapy planning may better informed in an era of rapidly advancing radiotherapy technologies .

9.2 Future research plans relating to studies in the thesis

A number of projects are in progress or planned to further study the effects of breast cancer treatment on the normal tissues and the role of internal mammary chain irradiation.

Epidemiology

In collaboration with colleagues from the Netherlands two further observational studies of heart disease after breast cancer treatment will be completed.

1. Heart failure after breast cancer: a case-control study assessing associations with radiation dose and systemic treatments.
2. Valvular heart disease after breast cancer radiotherapy: a case control study.

Meta-analyses

I will continue to contribute to the Early Breast Cancer Trialists Collaborative Group meta-analysis assessing the benefits and risks of regional nodal irradiation in breast cancer. This study is currently under development.

Literature review

In collaboration with others two further systematic reviews of breast cancer radiation dosimetry will be completed.

1. Exposure of the oesophagus in breast cancer radiotherapy: a systematic review of oesophageal doses published 2013-2018.

2. Breast cancer radiotherapy: a systematic review of internal mammary chain dose coverage published 2013-2018.

Clinical Trials

I will continue to work with the U.K. Breast Proton Group and contribute to the development of a European collaborative prospective clinical trial of proton beam therapy for breast cancer.

Translational Research

I am a co-investigator of a planned longitudinal study "Characterisation of the Heart Using CMR Imaging in Cancer Patients Receiving Thoracic Radiotherapy". This is a study of patients for internal mammary chain radiotherapy or mediastinal irradiation investigating CMR and serological biomarkers of acute radiation-related cardiac injury.

Dosimetry

A dosimetry study " Internal mammary chain irradiation: exposure of the cardiac substructures" is planned which will describe cardiac exposure from modern photon techniques in breath hold and for proton beam therapy. This will inform future prospective studies comparing advanced techniques.

9.3 References

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10 Appendices

Appendix A. Supplementary material to Chapter 2……..……A1

Appendix B. Supplementary material to Chapter 3……..……A7

Appendix C: Supplementary material to Chapter 4……..…….……A13

Appendix D: Supplementary material to Chapter 5……A19

Appendix E: Authored publications cited within thesis……..……A25

Appendix A

Supplementary material to Chapter 2:

A cardiac contouring atlas for radiotherapy

Cardiac structure margins in radiotherapy treatment planning

Using symmetrical margins to estimate doses to organs at risk retrospectively

In breast radiotherapy the threat of a high dose to the cardiac substructures comes broadly from one direction. When the boundary of a cardiac structure lies close to the edge of a high dose region, positional uncertainty may lead to inaccurate representation of the dose to structure[1]. In our study the addition of margins to the cardiac segments located near the high dose gradient reduced the range of doses recorded between the six observers for each structure but this does not improve the accuracy of individual segment dose estimates (Table A1).

The addition of margins to structures near the high dose gradient caused the doses recorded to either become progressively lower or progressively higher depending on the volume of the structure within the high dose region. For structures which were mostly positioned outside the high dose region adding margins increased the dose. This was because the expanded structure was situated further inside the high dose region compared to the structure without a margin e.g. the left ventricular lateral, septal and anterior segments for the left-sided PWT regimen. For structures which were mostly positioned inside the high dose region adding a margin decreased the dose. This was because more of the expanded structure was situated outside the high dose region compared to the structure without a margin e.g. the left ventricular apical segment and the LADCA distal for the left-sided PWT regimen.

Table A1. Variation in doses from left breast cancer regimens for cardiac segments contoured near the field edge by six observers on one CT-planning dataset using margins.

Left-sided radiotherapy regimen	Cardiac segments	Dose range (Gy), dose difference (Gy) between the minimum and maximum doses for six observers (Gy)			
		Margin:0mm	*Margin:10mm*	*Margin:20mm*	*Margin:30mm*
PWT	LV: apical	18.8-26.4, 7.6	15.7-19.2, 3.5	15.0-18.4, 3.4	14.8-18.0, 3.2
	LV: lateral	2.0-4.6, 2.6	3.4-6.4, 3.0	5.1-8.0, 2.9	6.6-9.3, 2.7
	LV: septal	3.1-5.3, 2.2	5.2-7.9, 2.7	7.2-9.8, 2.6	9.0-11.1, 2.1
	LV: anterior	5.1-17.3, 12.2	9.5-16.6, 7.1	12.2-16.9, 4.7	13.9-17.3, 3.4
	LADCA mid	22.1-28.5, 6.4	23.4-28.8, 5.4	23.6-27.6, 4.0	23.4-26.4, 3.0
	LADCA distal	33.5-40, 6.5	29.6-32.4, 5.3	27.4-30.7, 3.1	25.5-27.5, 2.0
OPP	LV: apical	18.6-24.1, 5.5	16.2-19.4, 3.2	15.5-18.8, 3.3	15.0-18.2, 3.2
	LV: lateral	4.3-7.9, 3.6	5.5-8.7, 3.2	6.7-9.9, 3.2	8.0-10.9, 2.9
	LV: septal	3.7-6.9, 3.2	5.7-8.5, 2.8	7.4-9.8, 2.4	9.0-11.0, 2.0
	LV: anterior	9.3-20.7, 11.4	12.6-18.9, 6.3	14.3-18.6, 4.3	15.1-18.7, 3.6
	LADCA mid	23.7-29.1, 5.4	24.9-29.6, 4.7	24.2-27.8, 3.6	23.5-26.3, 2.8
	LADCA distal	28.0-37.8, 9.8	26.8-31.7, 4.9	24.7-28.2, 3.5	23.3-25.5, 2.2
E^-/MV	LV: apical	9.1-10.9, 1.8	11.1-12.7, 1.6	11.8-12.9, 1.1	12.6-13.7, 1.1
	LV: lateral	7.2-9.7, 2.5	9.7-10.8, 1.1	10.1-10.6, 0.5	10.3-10.5, 0.2
	LV: anterior	15.2-18.9, 3.7	15.4-17.4, 2.0	15.8-17.1, 1.3	15.8-17.0, 1.2
	LADCA distal	12.1-33.9, 21.8	16.1-27.1, 11.0	16.6-22.7, 6.1	17.3-20.3, 3.0
	Cx distal	16.9-18.0, 1.1	17.4-17.7, 0.3	16.7-17.2, 0.5	15.1-16.2, 1.1
	RCA post desc	11.8-16.8, 5	9.7-13.9, 4.2	7.8-11.3, 3.5	7.7-9.7, 2.0

Abbreviations:

PWT: partially wide tangential technique; OPP: oblique parasternal photon technique; E^-/MV: mixed electron/photon direct parasternal technique; LADCA: left anterior descending coronary artery, Cx: circumflex coronary artery; RCA: right coronary artery; post desc: posterior descending.

Deriving planning organ at risk volumes for prospective avoidance

To ensure prospective avoidance of the cardiac structures in the radiotherapy treatment planning process it would be useful to produce a planning organ at risk volume (PRV) for each structure to account for systematic treatment preparation and random treatment execution geometric uncertainties. The DVH calculated for the PRV will not be identical to the organ at risk but its use is preferable to using

the bare structure to flag the risk of tissue complications. McKenzie et al. have described a 'margin recipe' such that the maximum dose delivered to the structure is not underestimated by the planned dose to the PRV in at least 90% of cases.[1] Different approaches are used for deriving PRV margins depending on technique used which in turn dictates the dose distribution close to or surrounding the structure. Inter-observer variation in contouring the structures is accounted for in deriving the margin for the systematic uncertainties component of the margin and so the data presented in our study may be of interest to investigators aiming to the develop PRV margins for cardiac structures for breast cancer radiotherapy in the future.

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Appendix B

Supplementary material to Chapter 3:

Cardiac structure doses in women irradiated for breast cancer in the past and their use in epidemiological studies

Table B1. Mean radiation therapy EQD2 doses to myocardial structures from left-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000).

Radiotherapy regimen*							Mean cardiac EQD2† doses (Gy_2)‡							
	Median	Medial			Dose	No. of	Whole	Ventricles:		Left ventricular myocardial segments:				
Country	year	border	Field arrangement §¶	Usual beam energy	(100%) Gy ||	fractions	heart	Left	Right	Apex	Lateral	Inferior	Septal	Anterior
Tangential														
Sweden	1959	Midline	Tangents, divergent (a)	170 keV**	10.5	3	2	.	.	.	.	.	.	.
	1975	6 cm contra	Wide tangents, divergent (b)	Co^{60}	45.0	26	8.6	10.4	14.1	30.3	4.2	1.0	12.3	14.6
	1982	Midline	Tangents, divergent (a)	Co^{60}	50.0	25	3.8	5.7	3.0	28.6	1.7	0.6	3.4	6.5
	1990	Midline	*(1)* Tangents, divergent (a)	6 MV	50.0	25	3.8	5.8	2.4	34.2	1.2	0.5	2.8	5.7
Denmark	1981	3 cm contra	*(2)* Wide tangents, divergent (b)	6 MV	40.7	22	7.8	10.8	11.1	37.0	4.2	0.7	10.9	16.2
	1982	2 cm contra	Wide tangents (McWhirter) (b)	250 keV**	36.0	20	8	.	.	.	.	.	.	.
	1994	Midline	*(3)* Tangents, block posteriorly (a)	8 MV	48.0	24	3.1	4.7	1.9	28.2	1.1	0.3	2.0	5.6
	1998	3 cm contra	*(4)* Partially wide tangents, block posteriorly (i)	8 MV	48.0	24	3.7	4.2	4.3	18.8	1.4	0.4	2.9	8.6
Anterior electron or orthovoltage														
Sweden	1960	1 cm contra	Direct IMC (1-field) (c)	170 keV**	28.0	7	11	.	.	.	.	.	.	.
	1963	Midline	*(5)* Direct IMC (2-fields) (c) (j)	12 MeV	40.0	10	3.6	0.5	8.4	0.3	0.2	0.2	1.3	0.8
	1963	1 cm contra	Direct chest wall (4 fields) (k)	170 keV**	20.0	5	8	.	.	.	.	.	.	.
	1974	1 cm contra	*(6)* Oblique chest wall (d)	12 MeV	47.8	26	6.9	6.2	10.7	22.9	3.2	0.4	6.1	14.1
Denmark	1981	Midline	Direct chest wall (1-field)/lat thorax, SCF, axilla (n)	100 keV**/8 MV††	36.0/50.0	12/ 12	.	.	.	.	.	.	.	.
	1982	1 cm contra	*(7)* Direct chest wall (1-field)/lat thorax,SCF, axilla (e) (m)	9 MeV/8 MV	51.8/51.7	24/ 24	4.9	2.9	7.0	6.6	1.7	1.1	2.5	10.5
	1987	1 cm contra	Direct chest wall (2-fields)/lat thorax, SCF, axilla (l)	9 MeV/6 MeV/8 MV	54.0/50.0/54.0	25/25/25	3.6	1.7	5.6	2.2	1.8	1.3	1.7	2.8
	1991	Midline	Oblique chest wall (d)	12 MeV	51.8	24	8.1	7.3	12.6	27.5	3.6	0.4	7.1	16.7
Anterior megavoltage														
Sweden	1969	4.5 cm contra	Oblique IMC/oblique chest wall (f)	Co^{60}/Co^{60}	36.0/32.0	9/9	23.1	30.3	42.7	41.1	23.1	21.5	36.5	31.9
	1974	4.5 cm contra	Direct bilateral IMC (g) ‡‡	Co^{60}	40.0	10	25.5	13.1	37.9	1.1	3.3	22.0	27.7	4.8
	1983	Midline	Direct IMC/oblique chest wall (h)	Co^{60}/9 MeV	50.6/48.3	23/23	19.7	11.9	22.8	3.6	3.8	12.8	22.7	9.2
Cobalt chain §§														
Sweden	1963	Midline	Cobalt chain long (overlapping fields) (o)	Co^{60}	7.0	1	6	.	.	.	.	.	.	.
	1966	Midline	Cobalt chain short (overlapping fields) (p)	Co^{60}	7.0	1	<1	.	.	.	.	.	.	.

Highlighted tangential regimens are *wide* tangents, others are *midline* tangents. Highlighted anterior electron or orthovoltage regimens are *oblique* electron fields, others include *direct* fields.

*For further details on the radiotherapy regimens see Table 1.

†EQD2 = nd(d + α/β)/(2 + α/β); EQD2: equivalent dose in 2Gy per fraction; n: number of fractions; d: dose per fraction; α/β: fractionation sensitivity for a specified tissue.

‡Mean cardiac doses estimated using manual planning i.e. orthovoltage and cobalt chain are given to nearest Gy.

§Regimens a-p are illustrated in Fig. 1 and Fig. 2.

¶Regimens 1-7 were reconstructed on 10 CT scans to study the effect of patient anatomy on segment doses (Fig. 4-6).

||Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

**EQD2 doses were not estimated for the cardiac substructures because of the uncertainties of manual planning.

††Whole heart EQD2 dose was not calculated as it was not possible to combine the DVH for the orthovoltage field generated using manual planning with the DVH for the megavoltage field using CT-planning.

‡‡Cardiac doses are the same for left-sided and right-sided breast cancer as the same field was used for both.

§§For description of cobalt chain see Taylor 2009[1].

Abbreviations: keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, Co^{60}: cobalt 60.

[1]Taylor CW, Nisbet A, McGale P, et al. Cardiac dose from Swedish breast cancer radiotherapy since the 1950s. *Radiother Oncol* . 2009;90:127-35.

Table B2. Mean radiation therapy EQD2 doses to coronary arterial structures from left-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000).

Radiotherapy regimen*							Mean coronary artery EQD2† doses (Gy_2)‡											
	Median	Medial			Dose	No. of	left	left anterior descending				right					circumflex		
Country	year	border	Field arrangement §¶	Usual beam energy	(100%) Gy ||	fractions	main	whole	prox	mid	dist	whole	prox	mid	dist	pd	whole	prox	dist
Tangential																			
Sweden	1959	Midline	Tangents, divergent (a)	170 keV**	10.5	3	.	.	.	.	.	.	.	.	.	.	.	.	.
	1975	6 cm contra	Wide tangents, divergent (b)	Co^{60}	45.0	26	2.0	30.7	22.8	34.9	33.8	3.4	4.6	4.8	1.0	3.2	0.9	1.6	0.8
	1982	Midline	Tangents, divergent (a)	Co^{60}	50.0	25	1.0	28.2	7.6	38.5	37.6	0.8	0.9	0.8	0.6	0.9	0.7	0.9	0.6
	1990	Midline	*(1)* Tangents, divergent (a)	6 MV	50.0	25	0.8	32.0	6.0	44.5	44.3	0.6	0.7	0.6	0.4	0.7	0.5	0.8	0.4
Denmark	1981	3 cm contra	*(2)* Wide tangents, divergent (b)	6 MV	40.7	22	0.9	34.5	22.9	40.7	38.7	1.4	1.2	1.1	0.6	2.4	0.6	0.9	0.5
	1982	2 cm contra	Wide tangents (McWhirter) (b)	250 keV**	36.0	20	.	.	.	.	.	.	.	.	.	.	.	.	.
	1994	Midline	*(3)* Tangents, block posteriorly (a)	8 MV	48.0	24	0.6	31.2	6.0	45.0	41.4	0.4	0.5	0.4	0.2	0.5	0.3	0.6	0.3
	1998	3 cm contra	*(4)* Partially wide tangents, block posteriorly (i)	8 MV	48.0	24	1.1	31.4	15.7	48.0	29.2	1.0	1.4	1.4	0.3	0.6	0.4	0.9	0.3
Anterior electron or orthovoltage																			
Sweden	1960	1 cm contra	Direct IMC (1-field) (c)	170 keV**	28.0	7	.	.	.	.	.	.	.	.	.	.	.	.	.
	1963	Midline	*(5)* Direct IMC (2-fields) (c) (j)	12 MeV	40.0	10	2.8	2.2	4.8	1.7	0.3	3.8	11.2	2.5	0.2	0.1	0.4	1.0	0.3
	1963	1 cm contra	Direct chest wall (4 fields) (k)	170 keV**	20.0	5	.	.	.	.	.	.	.	.	.	.	.	.	.
	1974	1 cm contra	*(6)* Oblique chest wall (d)	12 MeV	47.8	26	4.9	28.7	24.1	30.8	30.8	3.7	5.8	7.1	0.5	0.8	0.8	2.7	0.5
Denmark	1981	Midline	Direct chest wall (1-field)/lat thorax, SCF, axilla (n)	100 keV**/8 MV††	36.0/50.0	12/ 12	.	.	.	.	.	.	.	.	.	.	.	.	.
	1982	1 cm contra	(7) Direct chest wall (1-field)/lat thorax,SCF, axilla (e) (m)	9 MeV/8 MV	51.8/51.7	24/ 24	2.3	28.1	32.4	45.6	6.2	4.2	7.6	6.9	1.4	0.4	4.2	2.0	1.4
	1987	1 cm contra	Direct chest wall (2-fields)/lat thorax, SCF, axilla (l)	9 MeV/6 MeV/8 MV	54.0/50.0/54.0	25/25/25	1.9	9.1	9.8	12.2	4.8	3.5	7.1	4.4	1.0	0.7	1.5	1.8	1.4
	1991	Midline	Oblique chest wall (d)	12 MeV	51.8	24	5.6	34.7	28.9	37.3	37.3	6.5	10.2	12.5	1.1	1.5	1.6	5.3	1.0
Anterior megavoltage																			
Sweden	1969	4.5 cm contra	Oblique IMC/oblique chest wall (f)	Co^{60}/Co^{60}	36.0/32.0	9/9	35.0	43.9	40.7	44.9	45.5	35.7	46.7	46.9	21.3	25.3	20.9	28.2	19.7
	1974	4.5 cm contra	Direct bilateral IMC (g) ‡‡	Co^{60}	40.0	10	33.7	3.0	6.9	1.0	1.3	34.6	42.5	44.6	30.1	22.7	22.6	26.2	22.2
	1983	Midline	Direct IMC/oblique chest wall (h)	Co^{60}/9 MeV	50.6/48.3	23/23	28.4	23.2	29.2	19.2	18.8	5.6	11.8	0.2	9.0	3.0	16.9	24.3	15.7
Cobalt chain §§																			
Sweden	1963	Midline	Cobalt chain long (overlapping fields) (o)	Co^{60}	7.0	1	.	.	.	.	.	.	.	.	.	.	.	.	.
	1966	Midline	Cobalt chain short (overlapping fields) (p)	Co^{60}	7.0	1	.	.	.	.	.	.	.	.	.	.	.	.	.

Highlighted tangential regimens are *wide* tangents, others are *midline* tangents. Highlighted anterior electron or orthovoltage regimens are *oblique* electron fields, others include *direct* fields.

*For further details on the radiotherapy regimens see Table 1.

†EQD2 = nd(d + α/β)/(2 + α/β); EQD2: equivalent dose in 2Gy per fraction; n: number of fractions; d: dose per fraction; α/β: fractionation sensitivity for a specified tissue.

‡Mean cardiac doses estimated using manual planning i.e. orthovoltage and cobalt chain are given to nearest Gy.

§Regimens a-p are illustrated in Fig. 1 and Fig. 2.

¶Regimens 1-7 were reconstructed on 10 CT scans to study the effect of patient anatomy on segment doses (Fig. 4-6).

||Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

**EQD2 doses were not estimated for the cardiac substructures because of the uncertainties of manual planning.

††Whole heart EQD2 dose was not calculated as it was not possible to combine the DVH for the orthovoltage field generated using manual planning with the DVH for the megavoltage field using CT-planning.

‡‡Cardiac doses are the same for left-sided and right-sided breast cancer as the same field was used for both.

§§For description of cobalt chain see Taylor 2009[1].

Abbreviations: keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, prox: proximal, dist: distal, pd: posterior descending, Co^{60}: cobalt 60.

[1]Taylor CW, Nisbet A, McGale P, et al. Cardiac dose from Swedish breast cancer radiotherapy since the 1950s. *Radiother Oncol* . 2009;90:127-35.

Table B3. Mean radiation therapy EQD2 doses to myocardial structures from right-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000).

Radiotherapy regimen*							Mean cardiac EQD2† doses (Gy_2)‡							
	Median	Medial			Dose	No. of	Whole	Ventricles:		Left ventricular myocardial segments:				
Country	year	border	Field arrangement §¶	Usual beam energy	(100%) Gy ||	fractions	heart	Left	Right	Apex	Lateral	Inferior	Septal	Anterior
Tangential														
Sweden	1959	Midline	Tangents, divergent (a)	170 keV**	10.5	3	1	.	.	.	.	.	.	.
	1975	6 cm contra	Wide tangents, divergent (b)	Co^{60}	45.0	26	2.4	0.7	4.0	0.7	0.5	0.6	1.0	0.7
	1982	Midline	Tangents, divergent (a)	Co^{60}	50.0	25	0.6	0.4	0.7	0.3	0.3	0.4	0.5	0.4
	1990	Midline	*(1)* Tangents, divergent (a)	6 MV	50.0	25	0.4	0.1	0.5	0.1	0.0	0.2	0.2	0.1
Denmark	1981	3 cm contra	*(2)* Wide tangents, divergent (b)	6 MV	40.7	22	0.7	0.3	0.9	0.2	0.1	0.2	0.5	0.2
	1982	2 cm contra	Wide tangents (McWhirter) (b)	250 keV**	36.0	20	3	.	.	.	.	.	.	.
	1994	Midline	*(3)* Tangents, block posteriorly (a)	8 MV	48.0	24	0.2	0.1	0.3	<0.1	<0.1	0.1	0.1	<0.1
	1998	3 cm contra	*(4)* Partially wide tangents, block posteriorly (i)	8 MV	48.0	24	0.4	0.1	0.6	<0.1	<0.1	0.1	0.2	0.1
Anterior electron or orthovoltage														
Sweden	1960	1 cm contra	Direct IMC (1-field) (c)	170 keV**	28.0	7	14	.	.	.	.	.	.	.
	1963	Midline	*(5)* Direct IMC (2-fields) (c) (j)	12 MeV	40.0	10	2.9	0.1	1.9	0.0	0.1	0.2	0.2	0.1
	1963	1 cm contra	Direct chest wall (4 fields) (k)	170 keV**	20.0	5	10	.	.	.	.	.	.	.
	1974	1 cm contra	*(6)* Oblique chest wall (d)	12 MeV	47.8	26	3.3	0.3	3.3	0.2	0.2	0.3	0.5	0.4
Denmark	1981	Midline	Direct chest wall (1-field)/lat thorax, SCF, axilla (n)	100 keV**/8 MV††	36.0/50.0	12/ 12	.	.	.	.	.	.	.	.
	1982	1 cm contra	*(7)* Direct chest wall (1-field)/lat thorax,SCF, axilla (e) (m)	9 MeV/8 MV	51.8/51.7	24/ 24	2.1	0.2	2.0	0.1	0.1	0.3	0.3	0.2
	1987	1 cm contra	Direct chest wall (2-fields)/lat thorax, SCF, axilla (l)	9 MeV/6 MeV/8 MV	54.0/50.0/54.0	25/25/25	1.5	0.2	1.1	0.1	0.2	0.3	0.2	0.2
	1991	Midline	Oblique chest wall (d)	12 MeV	51.8	24	3.7	0.3	3.7	0.3	0.3	0.3	0.5	0.4
Anterior megavoltage														
Sweden	1969	4.5 cm contra	Oblique IMC/oblique chest wall (f)	Co^{60}/Co^{60}	36.0/32.0	9/9	12.1	0.3	27.1	<0.1	0.1	0.3	1.3	0.1
	1974	4.5 cm contra	Direct bilateral IMC (g) ‡‡§§	Co^{60}	40.0	10	25.5	13.1	37.9	1.1	3.3	22.0	27.7	4.8
	1983	Midline	Direct IMC/oblique chest wall (h)	Co^{60}/9 MeV	50.6/48.3	23/23	9.8	<0.1	3.7	<0.1	<0.1	0.1	<0.1	<0.1
Cobalt chain §§														
Sweden	1963	Midline	Cobalt chain long (overlapping fields) (o)	Co^{60}	7.0	1	3	.	.	.	.	.	.	.
	1966	Midline	Cobalt chain short (overlapping fields) (p)	Co^{60}	7.0	1	<1	.	.	.	.	.	.	.

Highlighted tangential regimens are *wide* tangents, others are *midline* tangents. Highlighted anterior electron or orthovoltage regimens are *oblique* electron fields, others include *direct* fields.
*For further details on the radiotherapy regimens see Table 1.
†EQD2 = nd(d + α/β)/(2 + α/β); EQD2: equivalent dose in 2Gy per fraction; n: number of fractions; d: dose per fraction; α/β: fractionation sensitivity for a specified tissue.
‡Mean cardiac doses estimated using manual planning i.e. orthovolatge and cobalt chain are given to nearest Gy.
§Regimens a-p are illustrated in Fig. 1 and Fig. 2.
¶Regimens 1-7 were reconstructed on 10 CT scans to study the effect of patient anatomy on segment doses (Fig. 4-6).
||Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.
**EQD2 doses were not estimated for the cardiac substructures because of the uncertainties of manual planning.
††Whole heart EQD2 dose was not calculated as it was not possible to combine the DVH for the orthovoltage field generated using manual planning with the DVH for the megavoltage field using CT-planning.
‡‡Cardiac doses are the same for left-sided and right-sided breast cancer as the same field was used for both.
§§For description of cobalt chain see Taylor 2009[1].
Abbreviations: keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, Co^{60}: cobalt 60.

[1]Taylor CW, Nisbet A, McGale P, et al. Cardiac dose from Swedish breast cancer radiotherapy since the 1950s. *Radiother Oncol* . 2009;90:127-35.

Table B4. Mean radiation therapy EQD2 doses to coronary arterial structures from right-sided breast cancer radiotherapy regimens used in Sweden (1958-2001) or Denmark (1978-2000).

Radiotherapy regimen*							Mean coronary artery EQD2† doses (Gy_2)‡											
	Median	Medial			Dose	No. of	left	left anterior descending				right					circumflex		
Country	year	border	Field arrangement §¶	Usual beam energy	(100%) Gy ||	fractions	main	whole	prox	mid	dist	whole	prox	mid	dist	pd	whole	prox	dist
Tangential																			
Sweden	1959	Midline	Tangents, divergent (a)	170 keV**	10.5	3	.	.	.	.	.	.	.	.	.	.	.	.	.
	1975	6 cm contra	Wide tangents, divergent (b)	Co^{60}	45.0	26	1.0	1.2	0.9	1.2	1.4	9.1	7.8	25.9	2.5	0.6	0.6	0.7	0.6
	1982	Midline	Tangents, divergent (a)	Co^{60}	50.0	25	0.6	0.5	0.5	0.5	0.4	0.9	1.1	1.7	0.6	0.4	0.4	0.4	0.4
	1990	Midline	*(1)* Tangents, divergent (a)	6 MV	50.0	25	0.3	0.1	0.1	0.1	0.1	0.7	0.8	1.3	0.5	0.2	0.2	0.1	0.2
Denmark	1981	3 cm contra	*(2)* Wide tangents, divergent (b)	6 MV	40.7	22	0.5	0.4	0.3	0.4	0.4	2.1	1.4	5.9	0.8	0.4	0.2	0.3	0.2
	1982	2 cm contra	Wide tangents (McWhirter) (b) ††	250 keV**	36.0	20	.	.	.	.	.	.	.	.	.	.	.	.	.
	1994	Midline	*(3)* Tangents, block posteriorly (a)	8 MV	48.0	24	0.2	<0.1	<0.1	<0.1	<0.1	0.5	0.6	1.1	0.3	0.1	0.1	0.1	0.1
	1998	3 cm contra	*(4)* Partially wide tangents, block posteriorly (i)	8 MV	48.0	24	0.3	0.1	0.1	0.1	0.1	1.1	1.3	2.8	0.5	0.1	0.1	0.2	0.1
Anterior electron or orthovoltage																			
Sweden	1960	1 cm contra	Direct IMC (1-field) (c)	170 keV**	28.0	7	.	.	.	.	.	.	.	.	.	.	.	.	.
	1963	Midline	*(5)* Direct IMC (2-fields) (c) (j)	12 MeV	40.0	10	0.4	0.1	0.2	0.1	<0.1	14.3	23.3	30.8	0.7	0.1	1.2	0.3	0.2
	1963	1 cm contra	Direct chest wall (4 fields) (k)	170 keV**	20.0	5	.	.	.	.	.	.	.	.	.	.	.	.	.
	1974	1 cm contra	*(6)* Oblique chest wall (d)	12 MeV	47.8	26	0.5	0.8	1.2	0.8	0.4	9.0	13.7	19.9	1.5	0.3	0.3	0.4	0.3
Denmark	1981	Midline	Direct chest wall (1-field)/lat thorax, SCF, axilla (n)	100 keV**/8 MV ††	36.0/50.0	12/ 12	.	.	.	.	.	.	.	.	.	.	.	.	.
	1982	1 cm contra	(7) Direct chest wall (1-field)/lat thorax,SCF, axilla (e) (m)	9 MeV/8 MV	51.8/51.7	24/ 24	0.4	0.2	0.3	0.2	0.1	7.0	9.0	16.1	1.3	0.5	0.5	0.3	0.6
	1987	1 cm contra	Direct chest wall (2-fields)/lat thorax, SCF, axilla (l)	9 MeV/6 MeV/8 MV	54.0/50.0/54.0	25/25/25	0.4	0.2	0.3	0.2	0.1	5.8	8.7	12.0	1.1	0.3	0.4	0.3	0.4
	1991	Midline	Oblique chest wall (d)	12 MeV	51.8	24	0.5	0.8	1.3	0.8	0.4	10.3	15.6	22.8	1.7	0.3	0.4	0.4	0.4
Anterior megavoltage																			
Sweden	1969	4.5 cm contra	Oblique IMC/oblique chest wall (f)	Co^{60}/Co^{60}	36.0/32.0	9/9	1.3	0.1	0.1	0.1	0.1	26.8	44.4	48.4	19.7	1.2	0.3	0.2	0.4
	1974	4.5 cm contra	Direct bilateral IMC (g) ‡‡	Co^{60}	40.0	10	33.7	3.0	6.9	1.0	1.3	34.6	42.5	44.6	30.1	22.7	22.6	26.2	22.2
	1983	Midline	Direct IMC/oblique chest wall (h)	Co^{60}/9 MeV	50.6/48.3	23/23	0.1	<0.1	<0.1	<0.1	<0.1	17.4	22.0	39.5	13.0	0.3	0.2	<0.1	0.3
Cobalt chain §§																			
Sweden	1963	Midline	Cobalt chain long (overlapping fields) (o)	Co^{60}	7.0	1	.	.	.	.	.	.	.	.	.	.	.	.	.
	1966	Midline	Cobalt chain short (overlapping fields) (p)	Co^{60}	7.0	1	.	.	.	.	.	.	.	.	.	.	.	.	.

Highlighted tangential regimens are *wide* tangents, others are *midline* tangents. Highlighted anterior electron or orthovoltage regimens are *oblique* electron fields, others include *direct* fields.

*For further details on the radiotherapy regimens see Table 1.

†EQD2 = nd(d + α/β)/(2 + α/β); EQD2: equivalent dose in 2Gy per fraction; n: number of fractions; d: dose per fraction; α/β: fractionation sensitivity for a specified tissue.

‡Mean cardiac doses estimated using manual planning i.e. orthovoltage and cobalt chain are given to nearest Gy.

§Regimens a-p are illustrated in Fig. 1 and Fig 2.

¶Regimens 1-7 were reconstructed on 10 CT scans to study the effect of patient anatomy on segment doses (Fig. 4-6).

||Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

**EQD2 doses were not estimated for the cardiac substructures because of the uncertainties of manual planning.

††Whole heart EQD2 dose was not calculated as it was not possible to combine the DVH for the orthovoltage field generated using manual planning with the DVH for the megavoltage field using CT-planning.

‡‡Cardiac doses are the same for left-sided and right-sided breast cancer as the same field was used for both.

§§For description of cobalt chain see Taylor 2009[1].

Abbreviations: keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, prox: proximal, dist: distal, pd: posterior descending, Co^{60}: cobalt 60.

[1]Taylor CW, Nisbet A, McGale P, et al. Cardiac dose from Swedish breast cancer radiotherapy since the 1950s. *Radiother Oncol* . 2009;90:127-35.

Appendix C

Supplementary material to Chapter 4:

Exposure of the heart, left ventricle and cardiac valves in breast cancer regimens in the Netherlands 1970-2009

Table C1. Whole heart and left ventricle radiation doses according to decade for 475 women selected as controls for case-control studies of heart disease after treatment for breast cancer who underwent radiotherapy at the Netherlands Cancer Institute or the Erasmus MC Centre in the Netherlands during 1970-2009.*

Regions irradiated	Treatment period											
	1970s			1980s			1990s			2000s		
	No. women	Median mean dose (IQR)		No. women	Median mean dose (IQR)		No. women	Median mean dose (IQR)		No. women	Median mean dose (IQR)	
		Whole heart	Left ventricle		Whole heart	Left ventricle		Whole heart	Left ventricle		Whole heart	Left ventricle
Left No IMC	3	3.5 (2.8-3.9)	2.0 (2.0-4.1)	33	4.3 (4.3-4.8)	6.5 (6.5-7.2)	54	4.8 (4.8-4.8)	7.2 (7.2-7.2)	46	1.5 (1.5-1.5)	2.1 (2.1-2.1)
Left IMC	39	12.2 (12.0-12.2)	8.9 (8.7-8.9)	65	16.5 (8.3-25.8)	12.4 (7.1-20.0)	21	16.4 (14.7-18.3)	10.0 (9.7-13.7)	18	9.1 (9.0-15.3)	11.0 (11.0-11.1)
Right No IMC	0	-	-	24	0.6 (0.6-1.1)	0.2 (0.2-0.3)	40	0.7 (0.7-0.7)	0.2 (0.2-0.2)	29	0.3 (0.3-0.3)	0.1 (0.1-0.1)
Right IMC	30	8.7 (8.7-8.9)	1.8 (1.8-1.9)	60	10.9 (7.9-14.3)	1.8 (1.0-1.9)	22	11.6 (9.1-12.9)	1.2 (0.9-1.5)	11	1.7 (1.7-9.4)	0.5 (0.5-1.1)
All women	72	8.9 (8.7-12.2)	2.8(1.8-8.9)	182	8.9 (4.8-16.4)	2.8 (1.6-7.7)	137	4.8 (0.7-10.5)	4.4 (0.3-7.2)	104	1.5 (0.3-4.8)	2.1 (0.1-2.2)

* The radiotherapy charts used for this study were from women included in case-contol studies of heart disease after breast cancer treatment. Similar dose changes per decade were observed when both cases and controls were were included (Chapter 4: Table 3).

Abbreviations: IMC: internal mammary chain, IQR: inter-quartile range

Table C2. Mean radiation EQD2 doses to cardiac structures from breast cancer radiotherapy regimens used at the Netherlands Cancer Institute or the Erasmus MC Cancer Institute in the Netherlands during 1970-2009.

Radiotherapy regimen*†						Mean doses (Gy_2)‡											
						Whole heart		Left ventricle		Pulmonary valve		Aortic valve		Mitral valve		Tricuspid valve	
Years of radiotherapy	*Medial border*	*Field arrangement*	*Beam energies*	*Dose (100%) G §*	*Dose per fraction*	*Left||*	*Right||*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*
Tangential fields (290 charts)																	
1970s	Midline	Tangents	250 keV¶	15.0	3	3	1	3	0	-	-	-		-	-	-	-
1970s-1980s	Midline	Tangents	Co^{60}	50.0	2.0	3.8	0.6	5.7	0.4	1.5	0.7	0.8	0.8	0.7	0.5	0.7	0.8
1980s-2000s	Midline	Tangents (a)	6 MV	50.0	2.0	3.8	0.4	5.8	0.1	1.1	0.3	0.6	0.5	0.5	0.2	0.5	0.6
2000s	1cm ipsi	Tangents (b)	6 MV	50.0	2.0	0.9	0.2	1.3	0.0	0.7	0.1	0.4	0.2	0.4	0.1	0.3	0.3
Megavoltage IMC fields (200 charts)																	
Megavoltage																	
1970s-1980s	1cm contra	Direct IMC	Co^{60}	43.0	2.9	19.3	12.5	13.9	1.0	34.4	2.4	30.0	25.5	23.1	2.0	26.7	31.2
1970s-1980s	1cm contra	Direct IMC, matching chest wall	Co^{60}/9 MeV	40.0/37.6	3.3/2.9	22.9	11.9	17.3	0.9	45.9	2.3	35.2	25.7	26.8	2.0	31.1	31.6
1970s-1980s	1cm contra	Direct IMC, matching tangents (c)	Co^{60}/6 MV	53.8/50.0	2.2/2.0	25.0	14.2	18.5	1.2	44.3	2.9	38.2	28.2	29.9	2.6	34.0	34.5
1970s-1990s	1cm contra	Direct IMC, direct SCF/axilla/lateral thorax	6 MV/ 8 MV	40.5/44.5	2.3/2.5	23.7	12.9	17.5	0.9	41.7	1.8	37.8	27.9	30.6	1.7	35.5	34.9
1980s-2000s	1cm contra	Direct IMC, matching tangents	6 MV/6 MV	50.0/50.0	2.0/2.0	31.1	17.3	22.9	1.0	53	1.7	48	34.4	38	1.8	44.8	45.4
Mixed megavoltage/electron																	
1980s	1cm contra	Direct IMC, matching tangents	Co^{60}/12 MeV/6 MV	24.0/22.0/46.0	2.0/2.0/2.0	11.8	8.1	6.8	0.1	28.7	2.4	17.7	14.6	11.1	1.3	13.3	14.5
1980s-1990s	1cm contra	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	24.0/26.0/50.0	2.0/2.0/2.0	18.8	10.6	12.3	0.7	36	2.1	22.8	18.4	14.8	1.0	18.1	19.5
1990s	1cm contra	Direct IMC, matching chest wall (d)	6 MV/12 MeV/9 MeV	22.5/22.5/40.0	2.5/2.5/2.5	16.3	9.0	8.7	0.5	43	1.9	24.8	19.3	15.7	0.8	19.5	2.2
1990s-2000s	1cm contra	Direct IMC	6 MV/12 MeV	18.7/21.4	2.7/2.7	14.6	8.1	9.2	0.4	29	1.6	18	14.1	11	0.7	13.6	14.4
2000s	1cm contra	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	18.0/32.0/50.0	2.0/2.0/2.0	12.0	6.9	7.5	0.6	27.7	2.4	14.6	13.5	8.0	1.0	10.1	11.7
2000s	2cm contra	Oblique IMC, matching tangents (e)	6 MV/12 MeV/6 MV	18.0/32.0/50.0	2.0/2.0/2.0	6.4	0.9	7.5	0.3	10	0.5	1.5	0.9	0.9	0.3	0.8	0.8
Anterior orthovoltage or mixed orthovoltage/megavoltage (172 charts)																	
1970s-1980s	1cm contra	Direct IMC (f)	250 keV¶	37.2	2.5	12	9	6	1	-	-	-	-	-	-	-	-
1980s	1cm contra	Direct IMC	250 keV/Co^{60}**	17.2/22.7	2.5/2.8	-	-	-	-	-	-	-	-	-	-	-	-
1990s	1cm contra	Direct IMC	250 keV/6 MV**	23.5/24.0	1.8/2.0	-	-	-	-	-	-	-	-	-	-	-	-
Anterior electron (92 charts)																	
1970s-1980s	1cm contra	Direct IMC (g)	12 MeV	45.0	3.0	7.1	4.3	1.9	0.3	24.0	2.4	6.9	7.5	0.5	0.3	2.0	3.6
1970s-1980s	1cm contra	Direct IMC, matching tangents	12 MeV/6 MV	45.0/45.0	3.0/1.8	7.3	4.5	2.1	0.3	24.6	2.5	7.1	7.8	0.7	0.3	2.1	3.8
1970s-1990s	1cm contra	Direct chest wall	9 MeV	45.0	3.0	3.4	1.3	1.5	0.1	12.0	0.4	0.6	0.8	0.2	0.1	0.3	0.3
1970s-2000s	1cm contra	Direct chest wall, direct SCF/axilla/lateral thorax (h)	9 MeV/8 MV	46.0/50.0	2.0/2.2	4.5	1.8	2.7	0.2	13.6	0.6	2.1	2.2	1.4	0.3	1.5	1.5

Highlighted regimens are those used to irradiate the breast/chest wall and/or the SCF/axilla but not the IMC. All of the other regimens included the IMC.

*For further details on the radiotherapy regimens see Chapter 1: Table 1.

†Regimens a-h are illustrated in Chapter 1: Fig. 1.

‡Mean cardiac doses estimated using manual planning are given to nearest Gy.

§Usual total dose (100%) to the target tissues (see webtable 1 for dose ranges). For direct regimens this was the Dmax. For tangents this was the dose delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

||Cardiac doses from regimens used to irradiate left-breast and right-breast cancer.

¶ EQD2 doses were not estimated for the cardiac valves because these structures were too small to generate dose volume histograms from manual planning

** No values are given for these mixed field techniques as the dose distribution from the orthovoltage field was generated using manual planning and the dose distribution from the megavoltage field was generated using CT-planning. It was not possible to generate combined dose-volume histograms from the two different planning methods.

Abbreviations: IMC: internal mammary chain, keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, SCF: supraclavicular fossa, contra: contralateral, ipsi: ipsilateral, Co^{60}: cobalt 60

Table C3. Whole heart cardiac radiation doses from breast cancer radiotherapy regimens used at the Netherlands Cancer Institute of the Erasmus MC Cancer Institute in the Netherlands during 1970-2009.

Radiotherapy regimen*†					Whole heart dose-volume measures (%) ‡															
Years of radiotherapy	*Medial border*	*Field arrangement*	*Beam energy*	*Dose (100%) Gy §*	V_{5Gy} *Left||*	V_{5Gy} *Right||*	V_{10Gy} *Left*	V_{10Gy} *Right*	V_{15Gy} *Left*	V_{15Gy} *Right*	V_{20Gy} *Left*	V_{20Gy} *Right*	V_{25Gy} *Left*	V_{25Gy} *Right*	V_{30Gy} *Left*	V_{30Gy} *Right*	V_{35Gy} *Left*	V_{35Gy} *Right*	V_{40Gy} *Left*	V_{40Gy} *Right*
Tangential fields (290 charts)																				
1970s	Midline	Tangents	250 keV	15.0	33	5	11	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
1970s-1980s	Midline	Tangents	Co^{60}	50.0	16.8	<0.1	12.2	<0.1	10.1	<0.1	8.6	<0.1	7.4	<0.1	6.1	<0.1	4.6	<0.1	2.6	<0.1
1980s-2000s	Midline	Tangents (a)	6 MV	50.0	11.8	<0.1	9.1	<0.1	8.2	<0.1	7.6	<0.1	7.1	<0.1	6.6	<0.1	6.2	<0.1	5.4	<0.1
2000s	1cm ipsi	Tangents (b)	6 MV	50.0	3.0	<0.1	1.7	<0.1	1.3	<0.1	1.1	<0.1	1.0	<0.1	0.8	<0.1	0.6	<0.1	0.3	0.0
Megavoltage IMC fields (200 charts)																				
Megavoltage																				
1970s-1980s	1cm contra	Direct IMC	Co^{60}	43.0	80.8	46.4	74.1	41.5	69.5	38.5	64.0	35.6	45.5	31.3	22.0	20.8	3.6	6.9	<0.1	<0.1
1970s-1980s	1cm contra	Direct IMC,matching chest wall	Co^{60}/9 MeV	40.0/37.6	85.5	45.5	77.8	40.7	72.7	37.4	67.1	33.8	50.9	25.4	28.1	11.5	11.1	1.5	2.3	<0.1
1970s-1990s	1cm contra	Direct IMC, direct SCF, axilla, lateral thorax	6 MV/8 MV	40.5/44.5	85.3	42.9	73.3	40.0	69.6	38.5	67.8	36.9	66.0	35.8	58.3	34.2	34.1	29.4	11.5	17.6
1970s-1980s	1cm contra	Direct IMC, matching tangents (c)	Co^{60}/6 MV	53.8/ 50.0	87.6	48.5	78.3	43.4	73.8	40.5	70.4	38.0	66.7	35.8	60.8	32.9	44.8	27.1	27.9	17.2
1980s-2000s	1cm contra	Direct IMC ,matching tangents	6 MV/6 MV	50.0/50.0	82.8	42.0	72.8	38.2	70.8	37.5	69.2	36.6	67.7	35.8	66.2	35.1	64.5	34.0	54.4	31.0
Mixed megavoltage/electron																				
1980s	1cm contra	Direct IMC, matching tangents	Co^{60}/12 MeV/6 MV	24.0/22.0/46.0	79.7	45.0	60.1	39.1	29.0	32.7	21.1	19.4	15.6	12.9	10.9	8.4	6.5	4.5	2.3	1.4
1980s-1990s	1cm contra	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	24.0/26.0/50.0	80.0	41.8	71.8	38.0	68.2	36.1	57.0	31.7	30.2	19.6	21.8	13.8	16.2	9.9	11.5	6.5
1990s	1cm contra	Direct IMC, matching chest wall (d)	6 MV/12 MeV/9 MeV	22.5/22.5/40.0	65.9	34.7	58.3	30.3	53.4	28.0	39.4	57.0	23.0	13.6	16.3	9.7	11.2	6.8	7.3	4.1
1990s-2000s	1cm contra	Direct IMC	6 MV/12 MeV	18.7/21.4	73.9	35.4	68.9	30.8	59.0	28.3	27.6	24.8	19.1	15.5	12.9	11.3	7.0	8.4	1.6	5.9
2000s	1cm contra	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	18.0/32.0/50.0	81.4	43.7	73.0	39.1	36.7	23.3	26.0	16.2	20.1	12.0	15.1	8.5	10.5	5.5	6.1	2.7
2000s	2cm contra	Oblique IMC, matching tangents (e)	6 MV/12 MeV/6 MV	18.0/32.0/50.0	44.8	7.5	38.5	2.6	22.9	1.0	13.8	0.4	8.9	0.1	5.2	0.0	2.4	0.0.	1.2	0.0
Orthovoltage or mixed orthovoltage/megavoltage IMC fields (172 charts)																				
1970s-1980s	1cm contra	Direct IMC (f)	250 keV	37.2	99	89	78	59	61	38	38	23	18	10	8	6	2	2	0	0
1980s	1cm contra	Direct IMC ¶	250 keV/Co^{60}	17.2/22.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1990s	1cm contra	Direct IMC ¶	250 keV/6 MV	23.5/24.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Electron chest wall or IMC fields (92 charts)																				
1970s-1980s	1cm contra	Direct IMC (g)	12 MeV	45.0	35.0	23.2	26.1	16.7	20.3	12.6	15.9	9.4	12.0	6.8	8.4	4.4	5.0	2.3	1.7	0.4
1970s-1980s	1cm contra	Direct IMC, matching tangents	12 MeV/6 MV	45.0/45.0	36.7	23.6	26.3	16.9	20.2	12.8	15.6	9.6	11.8	6.9	8.4	4.6	5.1	2.4	2.1	0.5
1970s-1990s	1cm contra	Direct chest wall	9 MeV	45.0	19.3	9.2	13.9	5.8	10.4	3.6	7.7	2.2	5.5	1.1	3.7	0.3	2.2	0.0	1.0	0.0
1970s-2000s	1cm contra	Direct chest wall, direct SCF, axilla, lateral thorax (h)	9 MeV/8 MV	46.0/50.0	24.8	11.2	16.5	7.0	12.3	4.7	9.2	3.2	6.8	2.0	4.8	1.1	3.2	0.5	1.8	0.1

Highlighted regimens are those used to irradiate the breast/chest wall and/or the SCF/axilla but not the IMC. All of the other regimens included irradiation to the IMC.
*For further details on the radiotherapy regimens see Chapter 4: Table 1.
†Regimens a-h are illustrated in Chapter 4: Fig. 1.
‡ V_{XGy} (%): the percent volume of the whole heart receiving X Gy.
§Usual total dose (100%) to the target tissues (see webtable 1 for dose ranges). For direct regimens this was the Dmax. For tangential regimens this was the dose delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.
||Cardiac doses from regimens used to irradiate left-sided and right-sided breast cancer.
¶ No values are given for these mixed field techniques as the dose distribution from the orthovoltage field was generated using manual planning and the dose distribution from the megavoltage field was generated using CT-planning. It was not possible to generate combined dose-volume histograms from the two different planning methods.
Abbreviations: keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, lat: lateral, SCF: supraclavicular fossa, IMC: internal mammary chain, contra: contralateral, ipsi: ipsilateral, Co^{ov}: cobalt 60

Table C4. Comparison of doses in this study with previously published estimates for comparable regimens used in the Netherlands during 1970-2009.

Radiotherapy regimen*†					Whole heart doses							
					Left-sided regimens						Right-sided regimens	
Years of	Medial			Dose	Mean (Gy)		V_{10Gy} (%)		V_{40Gy} (%)		Mean (Gy)	
radiotherapy	border	Field arrangement		(100%) Gy ‡	Duane	van der Laan	Duane	Hurkmans	Duane	Hurkmans	Duane	van der Laan
Tangential fields (290 charts)												
1970s	Midline	Tangents	250 keV	15.0	-	-	-	-	-	-	-	-
1970s-1980s	Midline	Tangents	Co^{60}	50.0	-	-	-	-	-	-	-	-
1980s-2000s	Midline	Tangents (a)	6 MV	50.0	-	-	-	-	-	-	-	-
2000s	1cm ipsi	Tangents (b)	6 MV	50.0	-	-	-	-	-	-	-	-
Megavoltage IMC fields (200 charts)												
Megavoltage												
1970s-1980s	1cm contra	Direct IMC	Co^{60}	43.0	-	-	-	-	-	-	-	-
1970s-1980s	1cm contra	Direct IMC, matching chest wall	Co^{60}/9 MeV	40.0/37.6	-	-	-	-	-	-	-	-
1970s-1980s	1cm contra	Direct IMC, matching tangents (c)	Co^{60}/6 MV	53.8/50.0	-	-	-	-	-	-	-	-
1970s-1990s	1cm contra	Direct IMC, direct SCF/axilla/lateral thorax	6 MV/8 MV	40.5/44.5	-	-	-	-	-	-	-	-
1980s-2000s	1cm contra	Direct IMC, matching tangents	6 MV/6 MV	50.0/50.0	-	-						
Mixed megavoltage/electron												
1980s	1cm contra	Direct IMC, matching tangents	Co^{60}/12 MeV/6 MV	24.0/22.0/46.0	-	-	-	-	-	-	-	-
1980s-1990s	1cm contra	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	24.0/26.0/50.0	-	-	-	-	-	-	-	-
1990s	1cm contra	Direct IMC, matching chest wall§ (d)	6 MV/12 MeV/9 MeV	22.5/22.5/40.0	-	-	-	-	-	-	-	-
1990s-2000s	1cm contra	Direct IMC	6 MV/12 MeV	18.7/21.4	-	-	-	-	-	-	-	-
2000s	1cm contra	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	18.0/32.0/50.0	16.1	12.9	73	60(43-80)	6	4(0-8)	9.4	7.2
2000s	2cm contra	Oblique IMC, matching tangents (e)	6 MV/12 MeV/6 MV	18.0/32.0/50.0	-	-	39	30(23-40)	1	2(0-7)	-	-
Orthovoltage or mixed orthovoltage/megavoltage IMC fields (172 charts)												
1970s-1980s	1cm contra	Direct IMC (f)	250 keV	37.2	-	-	-	-	-	-	-	-
1980s	1cm contra	Direct IMC	250 keV/Co^{60}	17.2/22.7	-	-	-	-	-	-	-	-
1990s	1cm contra	Direct IMC	250 keV/6 MV	23.5/24.0	-	-	-	-	-	-	-	-
Electron chest wall or IMC fields (92 charts)												
1970s-1980s	1cm contra	Direct IMC (g)	12 MeV	45.0	-	-	-	-	-	-	-	-
1970s-1980s	1cm contra	Direct IMC, matching tangents	12 MeV/6 MV	45.0/45.0	8.3	7.5	-	-	-	-	5.3	4.3
1970s-1990s	1cm contra	Direct chest wall	9 MeV	45.0	-	-	-	-	-	-	-	-
1970s-2000s	1cm contra	Direct chest wall, direct SCF/axilla/lateral thorax (h)	9 MeV/8 MV	46.0/50.0	-	-	-	-	-	-	-	-

V10Gy (%): the percent volume of the whole heart receiving 10 Gy.

V40Gy (%): the percent volume of the whole heart receiving 40 Gy.

*For further details on the radiotherapy regimens see Chapter 4: Table 1.

†Regimens a-h are illustrated in Chapter 4: Fig. 1.

‡Usual total dose (100%) to the target tissues (see Webtable 1 for dose range). For direct regimens this was the Dmax. For tangential regimens the total dose (100%) was delivered to the centre of the breast or chest wall apart from orthovoltage tangents where the total dose was the skin dose at the surface of the breast.

Abbreviations: IMC: internal mammary chain keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, SCF: supraclavicular fossa, contra: contralateral, ipsi: ipsilateral, Co60: cobalt 60

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Appendix D

Supplementary material to Chapter 5:

Radiation dose-response for risk of myocardial infarction in breast cancer survivors**.**

Supplementary methods D1

For the women in this study CT-planning was only available from 2005. Individual anatomical information was not available. Cardiac doses were estimated retrospectively by two of the authors (FD and CT).

Chart categorisation

Information was abstracted from 314 radiotherapy charts including: surgery type, target definition, field borders, total dose and dose per fraction, beam energy and the use of shielding, wedges and bolus. In total, 52 regimens were received, 28 regimens for left-sided and 24 for right-sided BC (supplementary table 1). The main regimen categories were: tangential (35%, n=109), megavoltage IMC (25%, n=80), orthovoltage or mixed orthovoltage/megavoltage IMC (28%, n=89), and electron chest wall or IMC (12%, n=36).

Selection of a 'typical CT-scan'

Ten CT-planning scans were randomly selected from women referred for BC radiotherapy in 2010. The treatment position for all women was supine, with both arms above the head. Slice thickness for each scan was 3mm, and intravenous contrast was not used. The whole heart and left ventricle were contoured on each of the 10 scans [1]. To simulate mastectomy duplicate copies of the CT were created and the relevant breast was virtually removed from the dose calculations. To select a "typical CT-scan", first the most commonly used left-sided regimen was identified from the charts. This was a midline tangential regimen consisting of two opposing beams with alignment of the posterior field borders, used from the 1980s up to the early 2000s. Second, the regimen was reconstructed on each

of the ten CT scans and whole heart doses were reviewed. Third, anatomical features which may influence cardiac doses from BC radiotherapy were measured, including: sternal length, heart volume, chest wall separation distance and the Haller index (ratio of height between the anterior spine and posterior sternum to the transverse width of the heart). The 'typical CT-scan', which was not atypical for any of the anatomical factors reviewed, was then selected as the scan with a MWHD closest to average which was not atypical for any of the anatomical factors reviewed (MWHD “typical CT-scan”: 4.8 Gy, average MWHD ten CT scans: 4.8 Gy (range 1.9 – 9.1 Gy)).

Regimen reconstruction

All other regimens identified from the radiotherapy charts were then reconstructed on the “typical CT-scan”. Dose distributions were generated for cobalt, electron and megavoltage beams using modern 3-dimensional CT treatment planning (Varian EclipseTM Treatment Planning System [TPS] version 10.0.39 [Varian Medical Systems, Palo Alto, USA]). The analytical anisotropic algorithm was used to calculate cardiac doses for photon plans, Monte Carlo was used for electron plans, and pencil beam for cobalt plans. Dose distributions from orthovoltage fields were generated using manual planning. MWHD, MLVD, V_5 to V_{40} were estimated using dose volume histograms.

Allocation of doses to individual women

Doses were estimated for each individual woman using the total dose (100%) received as recorded in individual radiotherapy charts and the dose volume histogram of the regimen received.

Limitations

The cardiac doses estimated are subject to several sources of uncertainty. Many of these uncertainties are common to all radiotherapy CT-planning studies and include delineation error, dose calculation algorithm error, set-up error, and cardiac and respiratory motion during treatment. In this study of women for whom no anatomical information is available another important source of uncertainty is inter-patient differences in anatomy. For left tangential radiotherapy inter-patient dose variability was assessed by reconstructing midline divergent tangential fields on ten CT scans. The difference between the highest and lowest mean doses estimated for the whole heart and LV was 7.2 Gy and 10.7 Gy respectively. For right tangential radiotherapy inter-patient dose variability was assessed by reconstructing fields on five of the ten CT-scans. The inter-patient dose variability for the whole heart and LV was 0.5 Gy and 0.2 Gy respectively.

[1] Duane, Aznar M, Bartlett F, et al. A cardiac contouring atlas for radiotherapy. *Radiother Oncol* 2017;122:416-22

Table D1. Radiotherapy techniques identified from 314 radiotherapy charts of women treated for breast cancer in the Netherlands during 1970-2009.

Radiotherapy regimen					
Years of radiotherapy	*Field arrangement*	*Beam energies*	*Prescribed dose (100%) Gy**	*Number of women Left†*	*Right†*
Tangential (109 charts)					
1980s	Tangents	Co^{60}	50.0	3	3
1980s	Tangents, parasternal boost	6 MV, 10 MeV	45.0/9.0	2	0
1980s-2000s	Tangents	6 MV	50.0	42	36
2000s	Tangents	6 MV	50.0	11	12
Megavoltage IMC (80 charts)					
Megavoltage					
1970s-1980s	Direct IMC	Co^{60}	43.0	3	2
1970s-1980s	Direct IMC, matching direct chest wall	Co^{60}/9 MeV	40.0/37.6	6	5
1970s-1980s	Direct IMC, matching tangents	Co^{60}/6 MV	53.8/50.0	11	17
1970s-1990s	Direct IMC, direct SCF/axilla/lateral thorax	6 MV/8 MV	40.5/44.5	4	3
1980s	Direct IMC, matching direct chest wall	Co^{60}/6 MV/9 MeV	35.4/14.1/40.0	0	1
1990s	Direct IMC, matching direct chest wall	6 MV/9MeV	46.1/40.0	0	1
1980s-2000s	Direct IMC, matching tangents	6 MV/6 MV	50.0/50.0	1	4
Mixed megavoltage/electron					
1980s	Direct IMC, matching tangents	Co^{60}/12 MeV/6 MV	28.0/24.0/50.0	2	0
1980s	Direct IMC	Co^{60}/12 MeV	25.5/26.0	1	1
1980s	Direct IMC, matching direct chest wall	Co^{60}/12 MeV/9 MeV	20.0/18.8/37.6	1	0
1980s-1990s	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	27.2/24.0/50.0	1	4
1990s	Direct IMC, matching direct chest wall	6 MV/12 MeV/9 MeV	22.5/22.5/40.0	3	1
1990s-2000s	Direct IMC	6 MV/12 MeV	18.7/21.4	1	3
2000s	Direct IMC, matching tangents	6 MV/12 MeV/6 MV	18.0/32.0/50.0	2	1
2000s	Oblique IMC, matching tangents	6 MV/12 MeV/6 MV	18.0/32.0/50.0	1	0
Orthovoltage or mixed orthovoltage/megavoltage IMC (89 charts)					
1970s-1980s	Direct IMC	250 keV	37.2	29	27
1970s-1990s	Direct IMC, matching tangents	250 keV/Co^{60}	37.2/30.0	1	0
1970s	Direct IMC, matching direct chest wall	250 keV/9 MeV	37.2/40.0	3	7
1980s	Direct IMC	250 keV/Co^{60}	17.2/22.7	10	6
1990s	Direct IMC	250 keV/6 MV	16.8/21.9	3	0
1990s	Direct IMC, matching tangents	250 keV/6 MV/6 MV	23.5/24.0/50.0	1	2
Electron chest wall or IMC (36 charts)					
1970s-1980s	Direct IMC	12 MeV	45.0	9	7
1970s-1980s	Direct IMC, matching tangents	12 MeV/6 MV	45.0/45.0	8	3
1970s-1980s	Direct IMC, matching direct chest wall	12 MeV/9 MeV	45.0/45.0	2	1
1970s-1990s	Direct chest wall	9 MeV	45.0	2	1
1970s-2000s	Direct chest wall, direct SCF/axilla/lateral thorax	9 MeV/8 MV	45.0/53.0	1	2

Highlighted regimens did not include the IMC but all other regimens did.

*Usual total dose (100%) to the target tissues. For direct regimens this was the Dmax. For tangents this was the dose delivered to the centre of the breast or chest wall.

†Number of women irradiated for left breast cancer and right breast cancer.

Abbreviations: IMC: internal mammary chain keV: kilovoltage, MV: megavoltage; MeV: mega electron-volts, SCF: supraclavicular fossa, contra: contralateral, ipsi: ipsilateral, Co60: cobalt 60

Appendix E

Authored publications cited within thesis

E1. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014;383:2127-35.

Supplementary material available at:
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60488-8/supplemental

E2. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, Dodwell D, Ewertz M, Gray R, Jagsi R, Pierce L. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. J Clin Oncol.2017;35:1641-9

Supplementary material available at:
http://ascopubs.org/doi/suppl/10.1200/JCO.2016.72.0722

E3. Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the heart in breast cancer radiation therapy: a systematic review of heart doses published during 2003 to 2013. Int J Radiat Oncol Biol Phys 2015;93:845-53.

Supplementary material available at:
http://www.redjournal.org/article/S0360-3016(15)03103-X/addons

E4. Taylor C, McGale P, Brønnum D, Correa C, Cutter D, Duane F, Gigante B, Jensen M, Lorenzen E, Rahimi K, Wang Z, Darby S, Hall P, Ewertz M. Cardiac structure injury after breast cancer radiotherapy: cross-sectional study with individual patient data. Accepted for publication by J Clin Oncol.

E5. Boekel N, Jacobse J, Schaapveld M, Hooning M, Gietma J, Duane F, Taylor C, Darby S, Hauptmann M, Seynaeve C, Baaijens M, Sonke G, Rutgers E, Russell N, Aleman B, van Leeuwen F. Cardiovascular disease incidence after internal mammary chain irradiation and anthracycline-based chemotherapy for breast cancer. Under review by Br J Cancer.

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

*EBCTCG (Early Breast Cancer Trialists' Collaborative Group)**

Summary

Background Postmastectomy radiotherapy was shown in previous meta-analyses to reduce the risks of both recurrence and breast cancer mortality in all women with node-positive disease considered together. However, the benefit in women with only one to three positive lymph nodes is uncertain. We aimed to assess the effect of radiotherapy in these women after mastectomy and axillary dissection.

Methods We did a meta-analysis of individual data for 8135 women randomly assigned to treatment groups during 1964–86 in 22 trials of radiotherapy to the chest wall and regional lymph nodes after mastectomy and axillary surgery versus the same surgery but no radiotherapy. Follow-up lasted 10 years for recurrence and to Jan 1, 2009, for mortality. Analyses were stratified by trial, individual follow-up year, age at entry, and pathological nodal status.

Findings 3786 women had axillary dissection to at least level II and had zero, one to three, or four or more positive nodes. All were in trials in which radiotherapy included the chest wall, supraclavicular or axillary fossa (or both), and internal mammary chain. For 700 women with axillary dissection and no positive nodes, radiotherapy had no significant effect on locoregional recurrence (two-sided significance level [2p]>0·1), overall recurrence (rate ratio [RR], irradiated *vs* not, 1·06, 95% CI 0·76–1·48, 2p>0·1), or breast cancer mortality (RR 1·18, 95% CI 0·89–1·55, 2p>0·1). For 1314 women with axillary dissection and one to three positive nodes, radiotherapy reduced locoregional recurrence (2p<0·00001), overall recurrence (RR 0·68, 95% CI 0·57–0·82, 2p=0·00006), and breast cancer mortality (RR 0·80, 95% CI 0·67–0·95, 2p=0·01). 1133 of these 1314 women were in trials in which systemic therapy (cyclophosphamide, methotrexate, and fluorouracil, or tamoxifen) was given in both trial groups and, for them, radiotherapy again reduced locoregional recurrence (2p<0·00001), overall recurrence (RR 0·67, 95% CI 0·55–0·82, 2p=0·00009), and breast cancer mortality (RR 0·78, 95% CI 0·64–0·94, 2p=0·01). For 1772 women with axillary dissection and four or more positive nodes, radiotherapy reduced locoregional recurrence (2p<0·00001), overall recurrence (RR 0·79, 95% CI 0·69–0·90, 2p=0·0003), and breast cancer mortality (RR 0·87, 95% CI 0·77–0·99, 2p=0·04).

Interpretation After mastectomy and axillary dissection, radiotherapy reduced both recurrence and breast cancer mortality in the women with one to three positive lymph nodes in these trials even when systemic therapy was given. For today's women, who in many countries are at lower risk of recurrence, absolute gains might be smaller but proportional gains might be larger because of more effective radiotherapy.

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See Comment page 2104

*Collaborators listed in appendix

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See Online for appendix

Introduction

For many women with early-stage breast cancer, mastectomy can remove any detectable macroscopic disease, but some tumour foci might remain in locoregional tissue (ie, chest wall or regional lymph nodes) that could, if untreated, lead to recurrence of the disease and death from breast cancer. Radiotherapy has the potential to eliminate such tumour foci, and guidelines[1–6] now recommend that postmastectomy radiotherapy be given for women with four or more positive axillary lymph nodes, but not given for most women with node-negative disease. Most of these guidelines conclude, however, that there is insufficient evidence to make firm recommendations for women with one to three positive lymph nodes. A previous Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis of individual patient data from randomised trials of postmastectomy radiotherapy[7] did not give detailed results for women who had one to three positive lymph nodes after axillary dissection to at least level II, nor did it distinguish between trials in which radiotherapy included the chest wall and the regional lymph nodes and other trials in which radiotherapy was given only to the regional lymph nodes. For the present report, additional data regarding the extent of axillary dissection and regarding the number of positive lymph nodes have

been obtained and reviewed for each woman, and we present detailed results according to these factors for trials that included radiotherapy to the chest wall, as is usual in current practice.

Methods

Study design

Trials beginning before 2000 of adjuvant radiotherapy versus no radiotherapy but the same surgery after mastectomy for invasive cancer were eligible for inclusion in our meta-analysis of individual patient data. Trial identification and data handling were as previously reported.[7] For every woman, information was sought about initial patient and tumour characteristics, allocated treatment, time to first recurrence, whether the first recurrence was locoregional or distant, and date last known alive or date and underlying cause of death. When no recurrence was reported before breast cancer death, distant recurrence was assumed to have just preceded it. If contralateral breast cancer occurred before any other recurrence, follow-up was censored on that date in analyses of recurrence. Information about the extent of axillary surgery was reviewed. Women were classified as having axillary dissection if they were in a trial in which the protocol required removal of axillary lymph nodes in at least levels I and II. For the few trials in which the extent of axillary dissection was not described in terms of levels, women were classified as having axillary dissection if the trial protocol or publications indicated that the median number of resected nodes was at least ten or, if individual information was available,[8–11] at least ten nodes had been resected. Women with less extensive axillary surgery were classified as having axillary sampling.

Statistical analysis

As in the recent overview of radiotherapy after breast-conserving surgery,[12] the main emphasis in analyses of recurrence was on overall recurrence (ie, any first recurrence, irrespective of whether locoregional or distant), although observed risks of locoregional

	Women	Deaths	Woman-years since diagnosis*					Women given systemic therapy† (%)		
			Median per woman	Total (×10³)	Distribution by years (×10³)			Chemo-therapy	Tamox-ifen and ER+‡	Any
					<10	10–19	≥20			
(A) Axillary dissection										
pN0	700	480	20·1	13·5	6·1	4·4	3·0	22%	27%	47%
pN+	3131	2074	7·2	30·1	20·3	7·9	1·9	75%	22%	91%
pN1–3	1314	759	12·3	17·3	10·3	5·3	1·6	65%	24%	86%
pN4+	1772	1286	4·8	12·4	9·7	2·5	0·3	81%	21%	95%
pN?+	45	29	6·7	0·4	0·3	0·1	<0·1	100%	0%	100%
pN unknown	56	39	10·6	0·7	0·4	0·2	0·1	29%	71%	98%
Total	3887	2593	9·0	44·3	26·8	12·5	4·9	64%	24%	83%
(B) Axillary sampling										
pN0	870	595	17·6	15·4	7·5	5·1	2·8	10%	11%	21%
pN+	2541	1689	7·8	24·2	17·0	6·4	0·2	56%	28%	84%
pN unknown	654	460	9·3	7·1	4·6	2·1	0·4	44%	30%	74%
Total	4065	2744	9·8	46·8	29·1	13·7	4·0	44%	25%	69%
(C) Axillary surgery, but extent unknown										
pN0	24	12	8·5	0·2	0·2	<0·1	..	100%	0%	100%
pN+	149	69	11·5	1·3	1·1	0·2	..	100%	0%	100%
pN unknown	10	6	11·0	0·1	0·1	<0·1	..	100%	0%	100%
Total	183	87	10·1	1·6	1·4	0·2	..	100%	0%	100%
Total (A)+(B)+(C)	8135	5424	9·4	92·7	57·3	26·4	9·0	55%	24%	77%

Data were available for 22 trials, start dates 1964–86, and were unavailable for four trials including about 400 women. In all 22 trials for which data were available, radiotherapy was given to the chest wall and the supraclavicular or the axillary fossa (or both). In 20 of these 22 trials it was also given to the internal mammary chain. Details of the treatments given in these 22 trials are in appendix pp 10–12. Details of other trials of radiotherapy in combination with mastectomy are in appendix pp 52–53, 64–65, 70–71, 78–79. pN0=pathologically node-negative. pN+=pathologically node-positive. pN1–3=one to three pathologically positive nodes. pN4+=at least four pathologically positive nodes. pN?+=known to be pN+, but not whether pN1–3 or pN4+. pN unknown=pathological nodal status unknown.
*Numbers of woman-years of follow-up for mortality; many trials followed up women for only 10 years for recurrence.
†Chemotherapy was usually cyclophosphamide, methotrexate, and fluorouracil (CMF); only 3% of women were classified as oestrogen-receptor positive (ER+) and were in trials where both tamoxifen and chemotherapy were given.
‡Oestrogen-receptor positive.

***Table*: Availability of data from randomised trials beginning before the year 2000 and comparing radiotherapy to the chest wall and regional nodes after mastectomy and axillary surgery versus no radiotherapy but the same surgery**

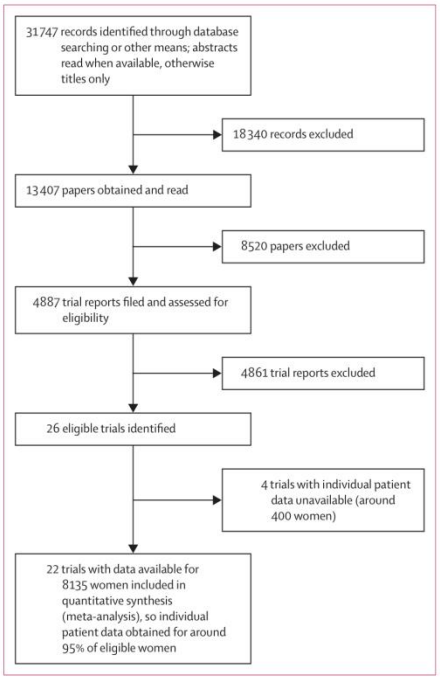


***Figure 1*: Trials included in analysis**

recurrence as a first event are also presented. All recurrence analyses present data only to year 10, because many trials did not follow women beyond this time for recurrence. Analyses of mortality present data to year 20. Deaths of unknown cause before recurrence were assumed to be from causes other than breast cancer, because most occurred many years after trial entry, by which time non-breast-cancer mortality predominated. Most other aspects of the statistical methods were as previously described,[7] but further information is given in the appendix pp 7–9. Person-years up to Jan 1, 2009, were included. Analyses were stratified by trial, individual follow-up year, age at entry (<40, 40–49, 50–59, 60–69, or ≥70 years), and pathological nodal status (node-negative disease, one to three positive nodes, four or more positive nodes, node-positive disease with unknown number of nodes affected, or nodal status unknown). Analyses were programmed in the statistical package Stata (version 12.1) and the programming language R (version 2.13.2).

Role of the funding sources

The Secretariat had full access to all data and analyses. The funding agencies had no role in data collection, analysis, interpretation, or reporting. A preliminary manuscript was presented to collaborators in October, 2013, and then revised on the basis of their comments. SD, CT, and PMcG had responsibility for submission of the report for publication.

Results

Information was available for 8135 women in 22 trials in which radiotherapy included the chest wall and regional lymph nodes (table; figure 1). Median length of follow-up was 9·4 years per woman (IQR 3·7–17·3) and 5424 women (67%) were known to have died. The extent of axillary surgery was known for all but 183 (2%) women. 1594 (20%) women had pathologically node-negative disease, 5821 (72%) had pathologically node-positive disease, and for 720 pathological nodal status was unknown. There were 3831 women for whom pathological

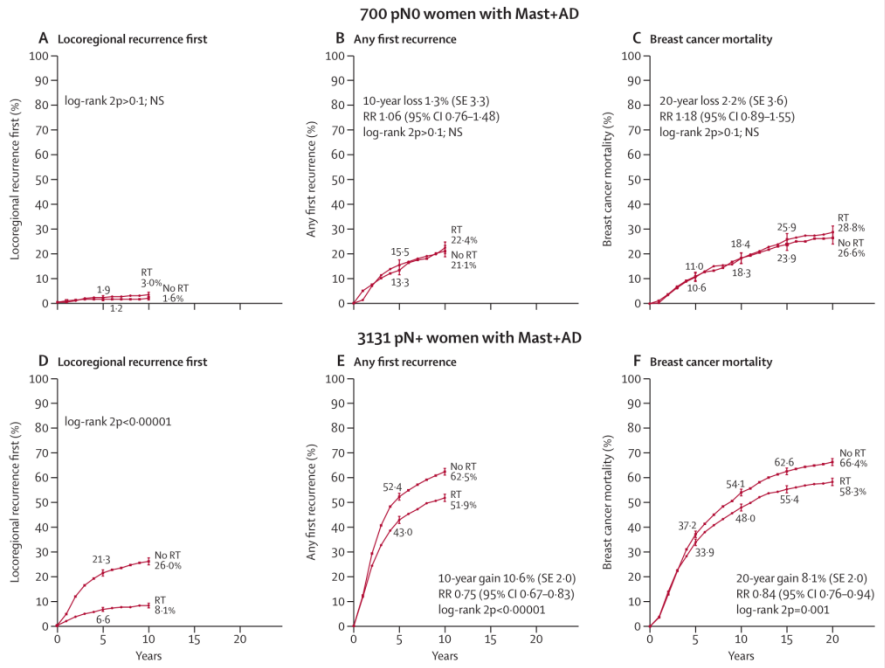


Figure 2: **Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 700 women with pathologically node-negative (pN0) disease and in 3131 women with pathologically node-positive (pN+) disease**

Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8–9 for details. See appendix pp 14, 16, for analyses of both locoregional and distant recurrences, and appendix pp 13, 15, for analyses of overall mortality. RR=rate ratio. NS=not significant. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.

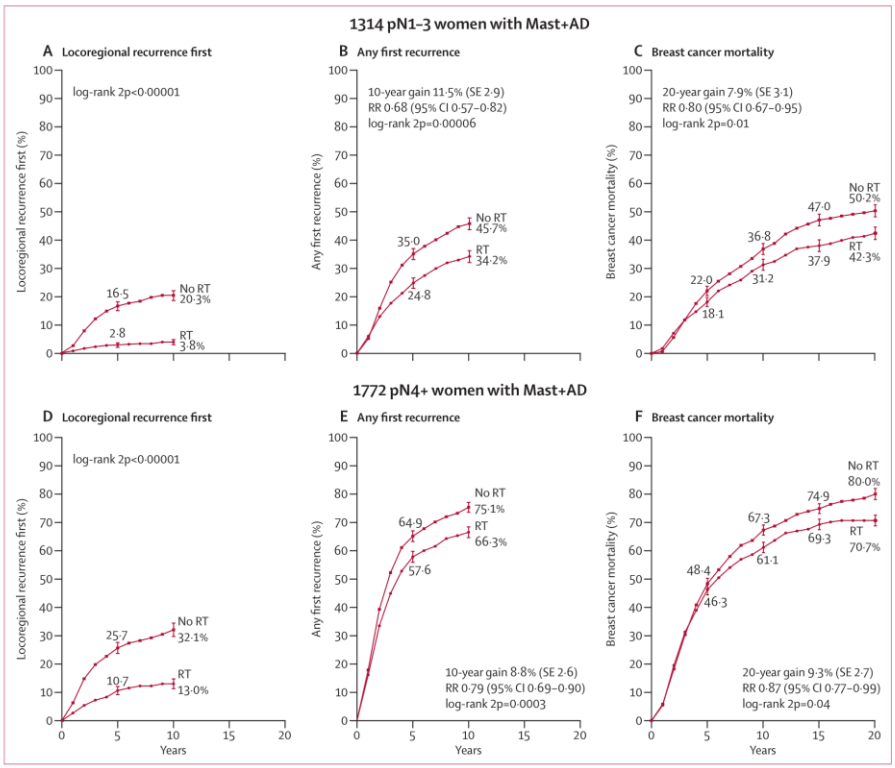


***Figure 3*: Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1314 women with one to three pathologically positive nodes (pN1–3) and in 1772 women with four or more pathologically positive nodes (pN4+)**

Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8–9 for details. See appendix pp 19, 28, for analyses of both locoregional and distant recurrences, and appendix pp 18, 27, for analyses of overall mortality. RR=rate ratio. NS=not significant. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.

nodal status was known and who were classified as having axillary dissection (however, for 45 women with node-positive disease, the number of nodes affected was not known); all of these women were in trials in which radiotherapy included the chest wall, the supraclavicular or axillary fossa (or both), and the internal mammary chain (appendix pp 10–12).

Of the 1594 women with node-negative disease, 700 (44%) had axillary dissection, 870 (55%) had axillary sampling, and for 24 (1%) the extent of axillary surgery was unknown. For the 700 women who had axillary dissection, only 1·4% of unirradiated women had a locoregional recurrence before a distant recurrence (appendix p 14), and radiotherapy had no significant effect on locoregional recurrence (2p>0·1), overall recurrence (rate ratio [RR], irradiated *vs* not, 1·06, 95% CI 0·76–1·48, 2p>0·1), or breast cancer mortality (RR 1·18, 95% CI 0·89–1·55, 2p>0·1; figure 2A–C). Radiotherapy did, however, increase overall mortality (RR 1·23, 95% CI 1·02–1·49, 2p=0·03; appendix p 13). By contrast, for the 870 women with node-negative disease who had only axillary sampling, 16·3% of unirradiated women had a locoregional recurrence before any distant recurrence (appendix p 37), and radiotherapy reduced locoregional recurrence (2p<0·00001) and overall recurrence (RR 0·61, 95% CI 0·47–0·80, 2p=0·0003), but had no significant effect either on breast cancer mortality (RR 0·97, 95% CI 0·77–1·22, 2p>0·1) or on overall mortality (RR 1·00, 95% CI 0·84–1·18, 2p>0·1; appendix p 36).

Of the 5821 women with node-positive disease, 3131 (54%) had axillary dissection, 2541 (44%) had axillary sampling, and for 149 (2%) the extent of axillary surgery was unknown. Radiotherapy reduced locoregional recurrence and overall recurrence both for women who

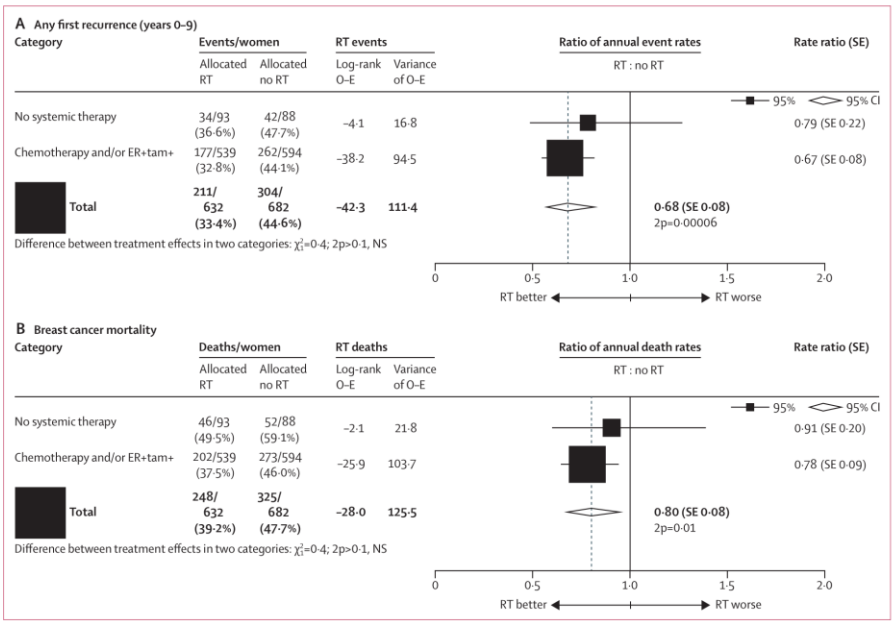


Figure 4: **Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0–9 and on breast cancer mortality for the entire follow-up in 1314 women with one to three pathologically positive nodes, according to whether or not they were in trials in which systemic therapy was given to both randomised treatment groups**

Chemotherapy was usually cyclophosphamide, methotrexate, and fluorouracil. ER-negative women in trials in which tamoxifen was given to both groups are included in the "no systemic" category. ER=oestrogen receptor. tam=tamoxifen. NS=not significant. SE=standard error.

had axillary dissection and for women who had axillary sampling (2p<0·00001 for all four comparisons). However, 29·0% of the unirradiated women with axillary sampling had a locoregional recurrence before any distant recurrence (appendix p 39) compared with only 19·4% of the unirradiated women who had axillary dissection (appendix p 16) and the proportional reduction in the rate of overall recurrence was larger after axillary sampling (RR 0·59, 95% CI 0·53–0·66; appendix p 38) than after axillary dissection (RR 0·75, 95% CI 0·67–0·83, figure 2E; 2p for difference between RRs, 0·003).

For the 3131 women with node-positive disease who had axillary dissection, the proportional reductions in the overall recurrence rates did not differ significantly between years 0–4 and 5–9 (appendix p 17). Overall recurrence rates in the absence of radiotherapy were, however, higher during years 0–4 than during years 5–9 (figure 2E). Consequently, the absolute reduction with radiotherapy in the 10-year overall recurrence risk (10·6%—ie, 62·5% *vs* 51·9%), was only slightly greater than the 5-year absolute reduction (9·4%—ie, 52·4% *vs* 43·0%). The proportional reduction in the overall recurrence rate with radiotherapy did not differ according to whether or not there was a trial policy of giving systemic therapy (ie, either chemotherapy or, for oestrogen-receptor positive women, tamoxifen), or with any other known factor. For these 3131 women, radiotherapy reduced breast cancer mortality (RR 0·84, 95% CI 0·76–0·94, 2p=0·001). There was no significant heterogeneity in the proportional reduction in the breast cancer mortality rate according to any known tumour-related or treatment-related factor. There appeared to be little effect of radiotherapy on breast cancer mortality in the first few years, but after that the breast cancer mortality rate was lower in the radiotherapy group than in the controls until years 10–15 and possibly beyond (appendix p 17). Radiotherapy also reduced overall mortality in these 3131 women with node-positive disease who had axillary dissection (RR 0·89, 95% CI 0·81–0·97, 2p=0·01; appendix p 15).

Among the 1314 women who had axillary dissection and only one to three positive nodes, radiotherapy reduced locoregional recurrence (2p<0·00001), overall recurrence (RR 0·68, 95% CI 0·57–0·82, 2p=0·00006), and breast cancer mortality (RR 0·80, 95% CI 0·67–0·95, 2p=0·01; figure 3A–C). 813 women (62%) were in trials in which the policy regarding systemic therapy for both randomised groups was to give only chemotherapy,

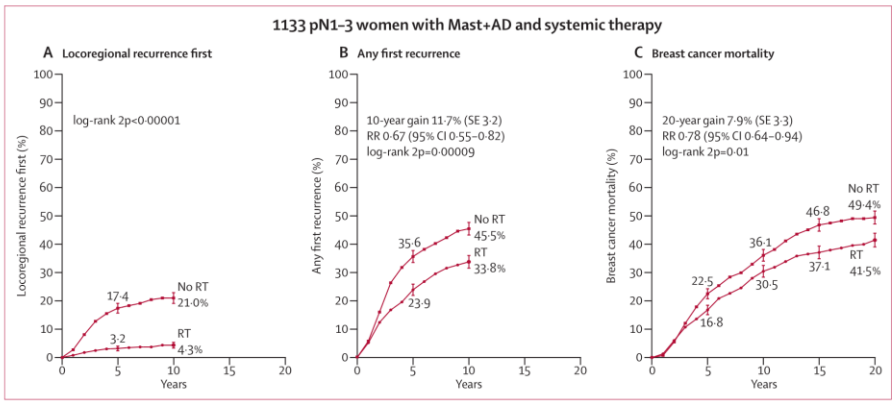


Figure 5: **Effect of radiotherapy (RT) after mastectomy and axillary dissection (Mast+AD) on 10-year risks of locoregional and overall recurrence and on 20-year risk of breast cancer mortality in 1133 women with one to three pathologically positive nodes (pN1–3) in trials in which systemic therapy was given to both randomised treatment groups**

Analyses of locoregional recurrence first ignore distant recurrences, see appendix pp 8–9 for details. See appendix p 22 for analyses of both locoregional and distant recurrences, and appendix p 21 for analyses of overall mortality. RR=rate ratio. Vertical lines indicate 1 SE above or below the 5, 10, 15, and 20 year percentages.

274 (21%) had oestrogen-receptor positive disease and were in trials in which the policy was only to give tamoxifen, 46 (3%) had oestrogen-receptor positive disease and were in trials in which the policy was to give both tamoxifen and chemotherapy, and 181 (14%) were in trials in which the policy was not to give systemic therapy. The proportional reductions in the rates of overall recurrence and of breast cancer mortality did not differ significantly according to whether or not systemic therapy was given (figure 4) or according to any other known tumour-related or treatment-related factor (appendix p 20). When we considered separately the 1133 women with one to three positive nodes after axillary dissection who were in trials in which the policy was to give systemic therapy, radiotherapy reduced the rates of overall recurrence by a third (RR 0·67, 95% CI 0·55–0·82, 2p=0·00009) and breast cancer mortality by slightly more than a fifth (RR 0·78, 95% CI 0·64–0·94, 2p=0·01; figure 5).

For 683 of these 1133 women, additional information about the number of positive nodes was available. 318 women had only one positive node, of whom 145 were randomly assigned to receive radiotherapy and 173 were randomly assigned not to receive it. 17·8% of the 173 unirradiated women with one positive node had a locoregional recurrence before any distant recurrence compared with only 2·3% of the irradiated women (2p<0·00001; appendix p 24), and radiotherapy reduced the rate of overall recurrence (0·60, 95% CI 0·39–0·92, 2p=0·02; figure 6A). This proportional reduction did not differ significantly from the corresponding reduction for the 365 women with two to three positive nodes after axillary dissection and who received systemic therapy (2p for difference >0·10). Likewise the proportional reduction in breast cancer mortality did not differ significantly according to the number of positive nodes (figure 6B).

For the 1772 women who had four or more positive nodes after axillary dissection, radiotherapy reduced locoregional recurrence (2p<0·00001) and overall recurrence (RR 0·79, 95% CI 0·69–0·90, 2p=0·0003) and breast cancer mortality (RR 0·87, 95% CI 0·77–0·99, 2p=0·04; figure 3D–F). 1677 (95%) of these women received systemic therapy and among them the proportional reductions in the overall recurrence and breast cancer mortality rates with radiotherapy did not differ significantly from those for the few who did not (2p for all differences >0·1; appendix p 29). Additional information about the number of positive nodes was available for 973 of the 1772 women with four or more positive nodes after axillary dissection. There were no significant differences in the proportional reductions with radiotherapy in the rates of overall recurrence or breast cancer mortality between the 542 women with four to nine positive nodes and the 431 women with ten or more positive nodes (2p>0·1 for all differences). Further information about women with four or more positive lymph nodes is given in appendix pp 27–35.

Information was also available from several other trials of postmastectomy radiotherapy. In eight trials (see appendix pp 52–53 for references) in which axillary surgery was performed and radiotherapy was given to the regional nodes but not to the chest wall, a total of 2304 women were randomised and the median follow-up was 7·2 years per woman (IQR 3·4–16·5; appendix pp 52–63). Pathological nodal status was available for 1494 women. Among the 1029 women with node-positive disease, 20·9% of unirradiated women had a locoregional recurrence before any distant recurrence compared with

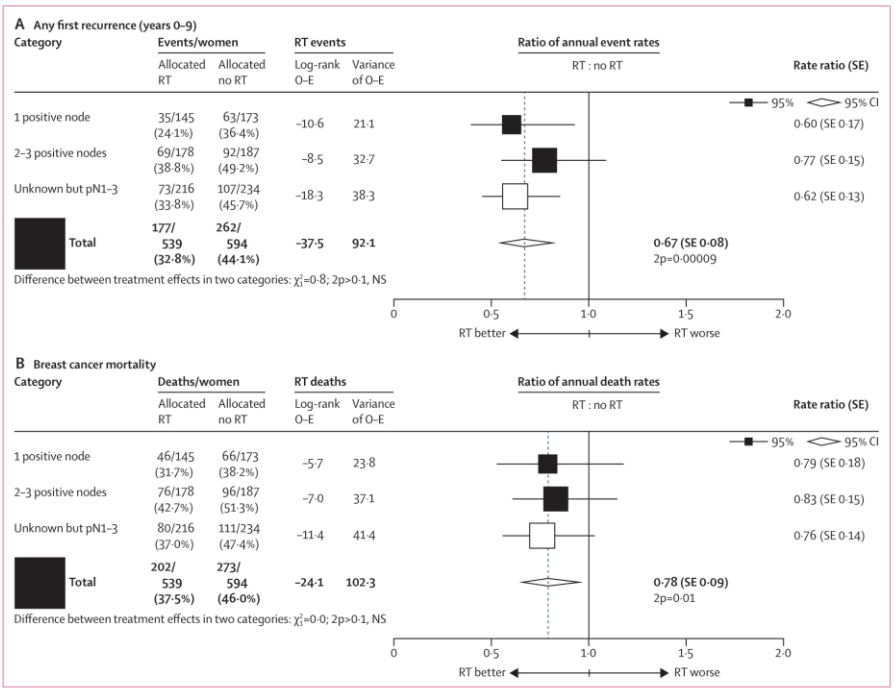


Figure 6: **Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0–9 and on breast cancer mortality for the entire follow-up in 1133 women with one to three pathologically positive nodes (pN1–3) in trials in which systemic therapy was given to both randomised treatment groups, by number of positive nodes**

See also appendix pp 23–26. NS=not significant. SE=standard error.

only 6·8% of irradiated women (2p<0·00001; appendix p 57) but radiotherapy had no significant effect on overall recurrence (RR 0·88, 95% CI 0·73–1·06, 2p>0·1), and no effect at all on the rate of breast cancer mortality (RR 1·00, 95% CI 0·82–1·20, 2p>0·1; appendix p 56). Information about further categories of trials of radiotherapy in combination with mastectomy is presented in appendix pp 64–85.

Discussion

Previous meta-analyses have shown that, for women with node-positive disease, postmastectomy radiotherapy reduced the risks of both recurrence and breast cancer mortality.[7] There has, however, been much debate as to whether this benefit was seen only because some women had limited axillary surgery. To investigate this issue, we reviewed all available evidence regarding the extent of axillary surgery for the women in these trials, including trial protocols, publications, and individual patient information if it was available. Additionally, we included the longer follow-up now available for many trials. The revised analyses of these updated data show that in these women who had mastectomy and axillary dissection of at least levels I and II, radiotherapy that included the chest wall, the supraclavicular or axillary fossa (or both), and the internal mammary chain reduced recurrence, breast cancer mortality, and overall mortality for all node-positive women considered together. When women with one to three and four or more involved axillary nodes were considered separately, the benefits of postmastectomy radiotherapy were clearly seen in each group. In these trials, 90% of women with one to three positive nodes and 95% of women with four or more positive nodes received some form of systemic treatment for their breast cancer. The most common chemotherapy was cyclophosphamide, methotrexate, and fluorouracil and the most common endocrine therapy was tamoxifen. The beneficial effects of radiotherapy on recurrence and breast cancer mortality remained apparent when women with one to three involved lymph nodes who were in trials in which the policy was to give systemic therapy were considered on their own. By contrast, in women with node-negative disease who received mastectomy and axillary dissection, among whom the proportion of

women who had a locoregional recurrence before any distant recurrence was small, there was no evidence that radiotherapy provided any benefit. Non-breast-cancer mortality and the incidence of contralateral and other second cancers in these and other trials of radiotherapy in early breast cancer will be reported elsewhere.

There have been substantial changes in practice since these women were treated. For example, breast screening has improved and local therapies are more targeted. Also, the accuracy of lymph-node analysis has increased, with more frequent use of serial sectioning and more frequent recognition of micrometastases. Hence, some of the women who were classified as having node-negative disease in these trials might have been found to be node-positive if they had been assessed today.[13,14] Furthermore, many women now receive better systemic therapy that is more effective at treating both local and distant disease.[15,16] Therefore the absolute risk of a recurrence is likely to be lower for women being considered for postmastectomy radiotherapy today than for the women in these trials and the absolute risk reductions achieved with radiotherapy are also likely to be smaller.

The proportional risk reductions we observed could be applied to women today with one to three positive nodes if they have appreciable risks of recurrence in the absence of radiotherapy and they might be the best guide that is currently available to help to estimate the likely absolute benefits from radiotherapy for women today. For example, for cancer recurrence, the unirradiated women in these trials with one to three positive nodes had an absolute 10-year risk of overall recurrence of 45·7%, which was reduced to 34·2% by their radiotherapy, so their absolute gain was 11·5%. If the absolute 10-year risk of overall recurrence for women being considered for postmastectomy radiotherapy today were about half of this (ie, 23%), then the absolute gain might also be roughly halved (ie, to around 6%). Similarly, if the 20-year risk of breast cancer mortality in women with one to three positive nodes were roughly halved for women today, the absolute gain from radiotherapy would also be roughly halved from 7·9% to around 4%.

The proportional gains from radiotherapy might, however, be greater for women irradiated today than suggested by this example, because radiotherapy planning has changed substantially and women today receive better coverage of target areas. Furthermore, doses to normal tissues are lower today, so the risks of radiotherapy are also likely to be lower.

The most common site of locoregional cancer recurrence after mastectomy is the chest wall.[8,17] Eight trials have been carried out, including around 2000 women, in which the chest wall was not irradiated. In these eight trials radiotherapy reduced locoregional recurrence in women with pathologically node-positive disease but had no significant effect on overall recurrence and no effect at all on breast cancer mortality. This finding suggests that the chest wall is an important target in postmastectomy radiotherapy. Direct evidence regarding the effect of radiotherapy to the chest wall is being collected,[18] but mature results from this current trial will not be available for some time. In the trials that are the main focus of the present report the chest wall, the supraclavicular or the axillary fossa (or both), and the internal mammary chain were all irradiated. Which regional lymph nodes should be irradiated after mastectomy is currently uncertain. Other randomised trials are investigating the risks and benefits of regional node irradiation in addition to chest wall or whole breast radiotherapy,[19–21] but again long-term results of these trials are not yet available.

In circumstances in which, even without radiotherapy, only a small percentage of women have locoregional recurrence as a first event after mastectomy, radiotherapy is unlikely to reduce either overall recurrence or breast cancer mortality. This scenario is illustrated by the women in these 22 trials who had axillary dissection and node-negative disease. If, however, a substantial percentage of women have locoregional recurrence as a first event in the absence of radiotherapy, then radiotherapy is likely to provide benefit both by preventing locoregional recurrence and by reducing distant recurrence and breast cancer mortality. This situation is illustrated by the 3131 women in these 22 trials who had axillary dissection and node-positive disease, for whom radiotherapy reduced the 10-year risk of a recurrence of any type by 10·6% (62·5% *vs* 51·9%) and the 20-year risk of death from breast cancer by 8·1% (66·4% *vs* 58·3%). We previously reported that in the trials of radiotherapy after breast-conserving surgery, the findings for both node-negative and node-positive disease were consistent with about one breast cancer death being avoided in the first 15 years after radiotherapy for every four recurrences of any type (ie, either locoregional or distant) avoided in the 10 years after radiotherapy.[12] The women with node-positive disease in the 22 trials reported here generally had more advanced cancers and more extensive radiotherapy than the women in the trials of radiotherapy after breast-conserving surgery and, for these women, about one breast cancer death was avoided in the 20 years after radiotherapy for every 1·5 recurrences of any type (ie, either locoregional or distant) avoided during the first 10 years after radiotherapy.

Breast cancer is a disease with a long natural history. Many of the women in these trials have now been followed up for 20 years and therefore they provide information about the long-term benefits of radiotherapy. Radiotherapy techniques have improved in the past few decades and so the proportional benefits of radiotherapy are likely to be larger than in these trials. However, the absolute risks of breast cancer recurrence and mortality have reduced in many countries because of advances in detection and treatment of breast cancer, so the absolute benefits from postmastectomy radiotherapy today are likely to be smaller than those reported here.

Contributors

PMcG, CT, and SD designed and carried out the analyses with computing assistance from YW and ZW. DC, FD, GM, and RP acted as internal advisers and CC, ME, and TW as external advisers. All writing committee members contributed to the report. The EBCTCG secretariat, including SD, PMcG, CT, CD, RG, YW, and RP, identified trials and received, collated, and checked datasets.

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Declaration of interests

All authors declare that they have no competing interests.

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ORIGINAL REPORT

Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials

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ABSTRACT

Purpose
Radiotherapy reduces the absolute risk of breast cancer mortality by a few percentage points in suitable women but can cause a second cancer or heart disease decades later. We estimated the absolute long-term risks of modern breast cancer radiotherapy.

Methods
First, a systematic literature review was performed of lung and heart doses in breast cancer regimens published during 2010 to 2015. Second, individual patient data meta-analyses of 40,781 women randomly assigned to breast cancer radiotherapy versus no radiotherapy in 75 trials yielded rate ratios (RRs) for second primary cancers and cause-specific mortality and excess RRs (ERRs) per Gy for incident lung cancer and cardiac mortality. Smoking status was unavailable. Third, the lung or heart ERRs per Gy in the trials and the 2010 to 2015 doses were combined and applied to current smoker and nonsmoker lung cancer and cardiac mortality rates in population-based data.

Results
Average doses from 647 regimens published during 2010 to 2015 were 5.7 Gy for whole lung and 4.4 Gy for whole heart. The median year of irradiation was 2010 (interquartile range [IQR], 2008 to 2011). Meta-analyses yielded lung cancer incidence ≥ 10 years after radiotherapy RR of 2.10 (95% CI, 1.48 to 2.98; $P < .001$) on the basis of 134 cancers, indicating 0.11 (95% CI, 0.05 to 0.20) ERR per Gy whole-lung dose. For cardiac mortality, RR was 1.30 (95% CI, 1.15 to 1.46; $P < .001$) on the basis of 1,253 cardiac deaths. Detailed analyses indicated 0.04 (95% CI, 0.02 to 0.06) ERR per Gy whole-heart dose. Estimated absolute risks from modern radiotherapy were as follows: lung cancer, approximately 4% for long-term continuing smokers and 0.3% for nonsmokers; and cardiac mortality, approximately 1% for smokers and 0.3% for nonsmokers.

Conclusion
For long-term smokers, the absolute risks of modern radiotherapy may outweigh the benefits, yet for most nonsmokers (and ex-smokers), the benefits of radiotherapy far outweigh the risks. Hence, smoking can determine the net effect of radiotherapy on mortality, but smoking cessation substantially reduces radiotherapy risk.

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INTRODUCTION

Randomized trials show that radiotherapy substantially reduces breast cancer recurrence and moderately reduces absolute breast cancer mortality by a few percentage points, depending on cancer characteristics.[1,2] For suitable patients, these benefits outweigh any long-term risks.[3,4]

Because most women with early breast cancer are cured of their disease, the issue of survivorship is important. Late hazards may be caused by radiotherapy or systemic therapy. Tamoxifen can cause endometrial cancer,[5,6] cytotoxic drugs can cause leukemia,[7] and trastuzumab and anthracyclines can cause cardiac disease.[5,7-9] For breast cancer radiotherapy, the main long-term hazards are second primary lung cancer and heart disease.[8,10]

ASSOCIATED CONTENT

See accompanying Editorial on page 1633

Data Supplement
DOI: 10.1200/JCO.2016.72.0722

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The absolute hazards from modern breast cancer radiotherapy regimens for typical patients depend on the lung and heart doses from modern regimens, the excess rate ratios (ERRs) per Gy for lung cancer and heart disease, and future lung cancer and heart disease mortality rates in the population. Rates of lung cancer and heart disease in the general population depend strongly on smoking. Women who smoke throughout adulthood have approximately 20 times the lung cancer mortality rates and four times the cardiac mortality rates of nonsmokers.[11] Particularly for lung cancer, therefore, the absolute risks from breast cancer radiotherapy could be appreciable for smokers, even if they are small for nonsmokers (because a given proportional increase has less absolute effect on a small risk than on a big risk). Hence, absolute risks of radiotherapy should be estimated separately for smokers and nonsmokers.

The objectives of this study were to estimate the main absolute risks of modern breast cancer radiotherapy. Randomized data on women with long-term follow-up were used to derive rate ratios (RRs) for incident second cancers and causes of death before recurrence of breast cancer and ERRs per Gy for incident primary lung cancer and cardiac mortality. These ERRs per Gy were combined with lung and heart doses from modern regimens and with population-based modern lung cancer and cardiac mortality rates in smokers and in nonsmokers to estimate the absolute risks of modern breast cancer radiotherapy.

METHODS

Systematic Review of Worldwide Modern Lung and Heart Doses

A systematic review of lung and heart doses from recently published (years 2010 to 2015, any language) breast cancer radiotherapy regimens was performed (Data Supplement, Methods S2, Reference S1). Mean organ doses were abstracted (ie, radiation doses averaged across organ volumes). The unweighted average was calculated for all published mean whole-lung doses (averaging ipsilateral and contralateral doses) and mean whole-heart doses. These are termed typical modern doses.

Randomized Trials

Data handling. Data were sought from trials that began before 2000 of radiotherapy versus no radiotherapy or of radiotherapy versus extra surgery (Table 1) in early breast cancer or ductal carcinoma in situ (DCIS). DCIS trials were included because the radiotherapy regimens were similar to those in some breast cancer trials. Trial identification methods are available online.[3,12] For every woman, information was sought about patient and tumor characteristics, allocated treatment, time to first recurrence, time to any contralateral breast cancer or second cancer before recurrence, and date last known to be alive or date and cause of death. Information on molecular subtype, smoking, incident cardiac disease, and lung cancer laterality was unavailable. For lung cancer incidence (after the first decade) and cardiac mortality, the ERRs per Gy were calculated.

Average doses. Radiotherapy details for each trial were extracted from publications and protocols. Regimens were reconstructed on one computed tomography scan with typical anatomy using virtual simulation, three-dimensional computed tomography planning, and sometimes manual planning (Data Supplement, Methods S1).[13] The mean dose to each organ was calculated for the ipsilateral and contralateral lung; the esophagus; the whole heart; and the left-anterior-descending, right, and circumflex coronary arteries. Mean doses were allocated according to trial regimen and breast cancer laterality. The averages of the lung, heart, and esophagus trial doses were weighted by trial size. Contralateral breast and bone marrow doses were not reliably estimable because of exposure uncertainties for structures several centimeters from the beams.

Statistical methods (RRs and ERRs per Gy). RRs of annual events were estimated using standard log rank methods. Analyses were stratified by trial, individual year of follow-up, age at entry, and pathologic nodal status (Data Supplement, Methods S1). Forest plots illustrate proportional risks, and actuarial curves illustrate absolute risks. All confidence intervals are 95%. For lung cancer, the ERR per Gy was calculated by dividing (RR − 1) by the average trial whole-lung dose, because there were too few events to use individual patient doses. Smoking status data were unavailable; therefore, the ERRs were based on all women (smokers and nonsmokers combined). For cardiac mortality, there were sufficient events to investigate the ERR per Gy using trial-specific and laterality-specific doses. These were modeled as a linear function of continuous dose, after assessment for departure from linearity.

Application of Trial ERRs per Gy and Modern Doses to Population Mortality Data

To estimate absolute risks for women today, the ERRs per Gy were multiplied by typical modern lung and heart doses and applied to current smoker and nonsmoker population mortality rates in 5-year age groups (Data Supplement, Methods S1). Background rates of death from lung cancer were taken from nonsmokers in the American Cancer Society Cancer Prevention Study II[14,15] and from smokers in the Million Women Study in the United Kingdom.[11] Background rates of death from ischemic heart disease were taken from those (mostly from 2010) in Western Europe (represented by the original 15 countries of the European Union).[16] These data were also used to estimate the risks for women irradiated at different ages and the effects of smoking cessation.

Table 1. Data Availability From Trials of Radiotherapy Versus No Radiotherapy That Began by the Year 2000

Surgery	No. of Trials	No. of Women	Year Randomly Assigned, (median [IQR])	Woman-Years (thousands) Without Recurrence by Years Since Entry			Deaths	
				< 10	10-19	> 20	Without Recurrence	Any Cause
Mastectomy	36	16,156	1975 (1972-1983)	96	42	13	2,921	11,201
BCS	18	11,655	1992 (1987-1997)	77	18	1	1,270	3,260
Various*	17	9,066	1976 (1972-1983)	59	29	10	1,666	5,512
BCS for DCIS	4	3,904	1992 (1990-1995)	25	5	0	207	372
All trials	75	40,781	1983 (1974-1989)	257	94	24	6,064	20,345

NOTE. Individual trial details are in the Data Supplement Table S3. For balance, unirradiated controls in six 3-arm trials were counted twice, and four of these trials contributed to two categories of surgery. Data sets were not available from 11 trials that included approximately 2,000 women.
Abbreviations: BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; IQR, interquartile range.
*In some of these trials, the control group had more surgery than did the radiotherapy group.

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The risk attributable to radiotherapy was taken as the difference in cumulative risks with the ERR per Gy and dose applied and not applied to the population-based rates.

RESULTS

Systematic Review of Worldwide Modern Lung and Heart Doses

A systematic review of all breast cancer radiotherapy dosimetry reports published during 2010 to 2015 identified 214 reports, including 647 regimens with median year of irradiation 2010 (interquartile range [IQR], 2008 to 2011; Data Supplement, Methods S2, Reference S1). The averages of the lung doses were as follows: ipsilateral, 9.0 Gy (IQR, 5.5 to 12.6 Gy), and contralateral, 2.4 Gy (IQR, 0.4 to 3.8 Gy). Averaging the doses to the two lungs, the typical modern whole-lung dose was 5.7 Gy (IQR, 3.4 to 8.3 Gy).[17-19] Average whole-heart doses were as follows: left-sided, 5.2 Gy (IQR, 1.9 to 7.4 Gy), and right-sided, 3.7 Gy (IQR, 1.2 to 5.0 Gy). Averaging these, the typical modern whole-heart dose was 4.4 Gy. Some centers, however, achieved much lower cardiac exposure and reported a whole-heart dose $\leq$ 2 Gy, even in left-sided radiotherapy.[20]

Randomized Trials

Data handling. Information was available from 75 trials involving 40,781 women (Table 1; Data Supplement Table S3), all evenly randomized (1:1 or 1:1:1) with median year of randomization of 1983 (IQR, 1974 to 1989) and median age at randomization of 56 years (IQR, 48 to 64 years). Median follow-up was 10 years (IQR, 5 to 17 years) with 20,345 deaths, 6,064 without breast cancer recurrence. Few women had systemic therapy: 23% (9,470) received tamoxifen and 19% (7,540) received chemotherapy (mainly cyclophosphamide, methotrexate, and fluorouracil).

Average doses. In comparison with typical modern doses, lung and heart doses were higher in the trials: 10 Gy whole lung and 6 Gy whole heart (Data Supplement Table S1: ipsilateral lung, 17.6 Gy; contralateral lung, 1.6 Gy; whole lung, 9.6 Gy; whole heart, 6.3 Gy; left-anterior-descending coronary artery, 13.5 Gy; right coronary artery, 7.7 Gy; circumflex artery, 4.1 Gy; esophagus in trials with internal mammary irradiation, 9.5 Gy, and esophagus in other trials, 0.8 Gy).

RRs and ERRs per Gy. The main risks in the trial were contralateral breast cancer, lung cancer, leukemia, esophageal cancer, and heart disease (Table 2). There was no significant heterogeneity in trial-specific RRs. The RR for contralateral breast cancer was 1.20 (95% CI, 1.08 to 1.33; 881 *v* 673 cancers; $P < .001$; Table 2, Fig 1,

Table 2. Effect of Allocation to RT on Incidence of Second Cancers and on Mortality From Causes Other Than Breast Cancer

Second Cancers and Mortality	No. First Events or Deaths (total woman-years) RT (n = 194,957)	No RT (n = 180,250)	Adjusted Excess* (95% CI)	Rate Ratio (95% CI)	*P*
Second cancer incidence of specified site without prior breast cancer recurrence					
Contralateral breast	881	673	130 (56 to 204)	1.20 (1.08 to 1.33)	< .001
Leukemia	43	23	17 (2 to 33)	1.71 (1.05 to 2.79)	.03
Lung, years 0-9	71	60	5 (−17 to 27)	1.08 (0.76 to 1.53)	.66
Lung, years ≥ 10	94	40	47 (25 to 69)	2.10 (1.48 to 2.98)	< .001
Pleura	3	0	2 (−1 to 5)	—	.18
Esophagus	23	10	13 (3 to 24)	2.42 (1.19 to 4.92)	.01
Pancreas	42	25	14 (0 to 29)	1.64 (0.98 to 2.76)	.06
Stomach	55	63	−12 (−32 to 8)	0.80 (0.55 to 1.17)	.25
Large intestine	164	136	19 (−14 to 51)	1.15 (0.91 to 1.45)	.26
Ovary	68	68	−1 (−22 to 21)	0.99 (0.70 to 1.41)	.95
Endometrium	109	83	20 (−6 to 47)	1.26 (0.94 to 1.69)	.12
Cervix	31	27	2 (−13 to 16)	1.06 (0.62 to 1.83)	.83
Melanoma	32	25	7 (−8 to 21)	1.28 (0.75 to 2.19)	.36
Soft tissue	23	17	6 (−6 to 17)	1.36 (0.71 to 2.59)	.35
Lymphoma	45	41	4 (−14 to 21)	1.09 (0.71 to 1.70)	.69
Other specified site	171	143	5 (−7 to 58)	1.20 (0.95 to 1.51)	.13
All sites except breast	974	761	168 (90 to 246)	1.23 (1.12 to 1.36)	< .001
Death without breast cancer recurrence					
Ischemic heart disease	424	327	90 (39 to 140)	1.31 (1.13 to 1.53)	< .001
Heart failure	63	33	28 (10 to 46)	1.94 (1.27 to 2.98)	.002
Heart valve disease	31	15	14 (1 to 26)	1.97 (1.07 to 3.67)	.03
Other heart disease	187	173	11 (−14 to 36)	1.08 (0.86 to 1.35)	.52
Subtotal: All cardiac	705	548	143 (78 to 208)	1.30 (1.15 to 1.46)	< .001
Cancer of specified site	475	375	67 (12 to 121)	1.19 (1.03 to 1.37)	.02
Other specified cause	638	629	6 (−78 to 91)	1.01 (0.90 to 1.14)	.83
Subtotal: Specified cause	1,818	1,552	216 (111 to 322)	1.16 (1.08 to 1.25)	< .001
Unspecified cause	1,413	1,281	153 (58 to 247)	1.14 (1.05 to 1.24)	.002
All causes of death except breast cancer	3,231	2,833	369 (228 to 510)	1.15 (1.09 to 1.22)	< .001

NOTE. Cancer incidence excludes nonmelanoma skin cancer. Other specified sites include uterus, part unspecified.
Abbreviation: RT, radiotherapy.
*The adjusted excess number of events (or deaths) in the RT group is calculated as twice the log rank observed minus expected (Data Supplement, Methods S1) and allows for RT delaying recurrence.

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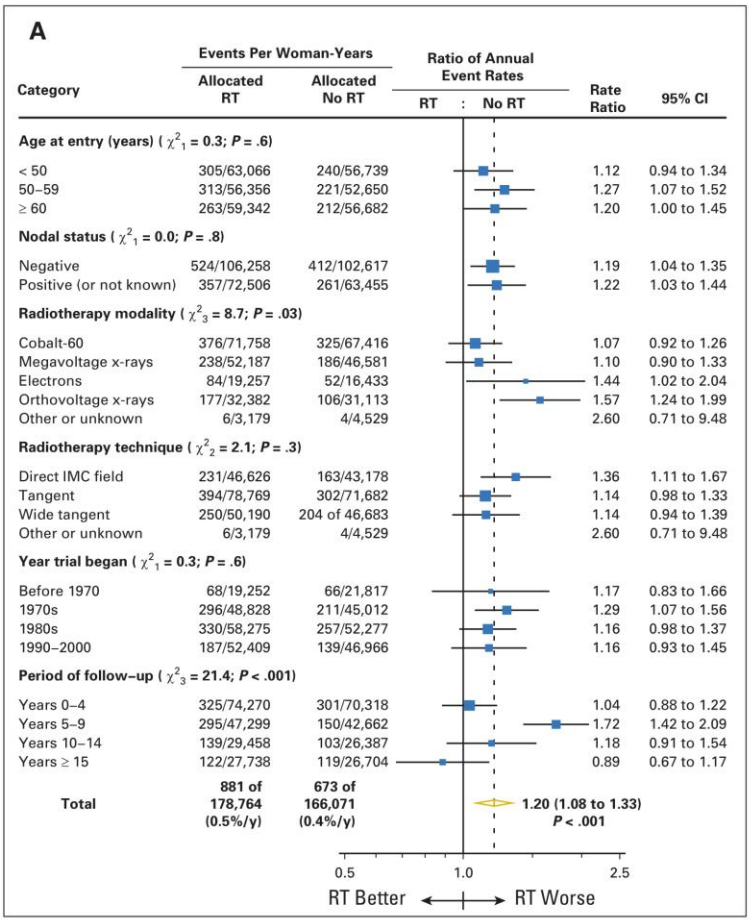


Fig 1. Effect of allocation to radiotherapy (RT) on (A) contralateral breast cancer and on (B) lung cancer incidence (≥ 10 years). IMC, internal mammary chain.

Data Supplement Figure S4). Contralateral cancers were not mainly misclassified recurrences, because incidence was unrelated to nodal status (Data Supplement Table S5). The contralateral breast cancer RR was greater in the old trials of orthovoltage (low-energy) radiotherapy (RR, 1.57; 95% CI, 1.24 to 1.99) than in the other trials (RR, 1.12; 95% CI, 1.00 to 1.26; Data Supplement Figs S4, S5). But in both cases, contralateral breast radiation doses were not reliably known, so the contralateral breast cancer ERR per Gy could not be estimated. In the non-orthovoltage trials, the absolute 15-year increase in contralateral breast cancer risk was 1.0% (95% CI, 0.2 to 1.8; 7% *v* 6%; Data Supplement Fig S5).

Allocation to radiotherapy increased the incidence of primary lung cancer (Table 2, Data Supplement Figs S7, S9). These cancers were not mainly misclassified pulmonary metastases, because their incidence was unrelated to nodal status (Data Supplement Table S7). There was no significant excess in the first decade after radiotherapy. Thereafter, there were 94 versus 40 cases (RR, 2.10; 95% CI, 1.48 to 2.98; $P < .001$; Fig 1), corresponding to 0.11 (95% CI, 0.05 to 0.20) ERR per Gy.

The incidence RR, radiotherapy versus control, for second cancers other than breast or lung was 1.19 (95% CI, 1.07 to 1.32; Data Supplement Fig S10). The main components were leukemia (RR, 1.71; 95% CI, 1.05 to 2.79) and esophageal cancer (RR, 2.42; 95% CI, 1.19 to 4.92, with 30 of the 33 cases occurring in the trials in which radiotherapy involved the internal mammary chain and supraclavicular fossa; Table 2). ERRs per Gy were not calculated for leukemia or esophageal cancer because both CIs were wide and bone marrow doses were not estimable.

All-cause mortality among women without breast cancer recurrence was increased by radiotherapy (RR, 1.15; 95% CI, 1.09 to 1.22; Table 2; Data Supplement Figs S1-S3, Table S4), predominantly because of cardiac disease (RR, 1.30; 95% CI, 1.15 to 1.46). Most of the excess cardiac mortality was from ischemic heart disease (RR, 1.31; 95% CI, 1.13 to 1.53; Table 2). However, the main analyses are of all

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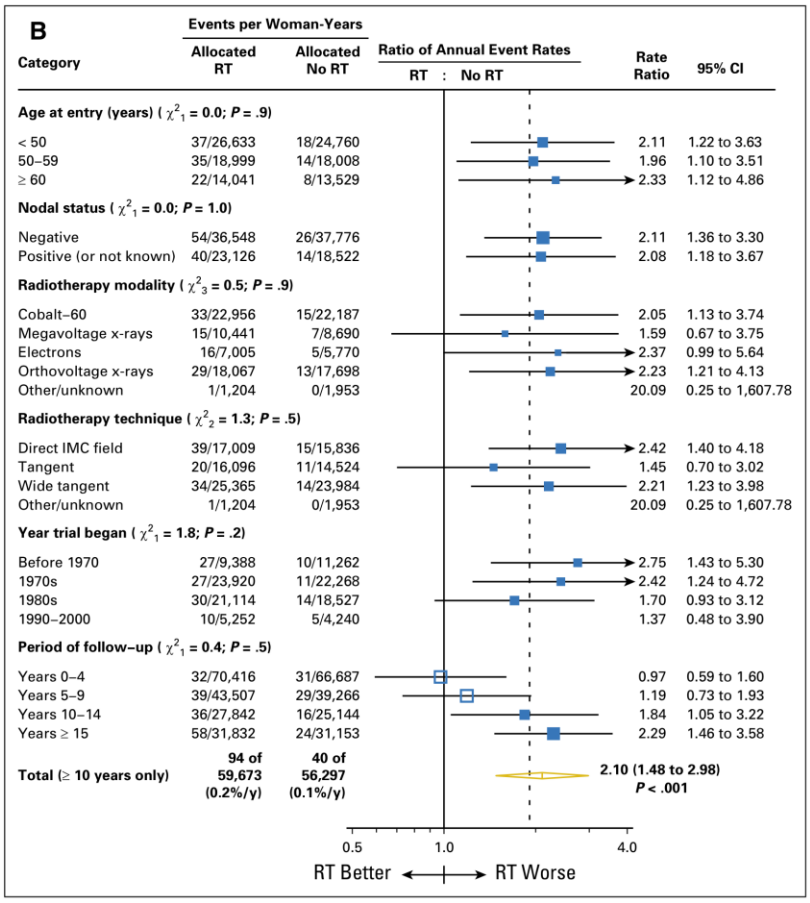


Fig 1. (Continued).

cardiac mortality, defined as mortality from all circulatory disease with the exception of stroke or pulmonary embolism (Data Supplement Fig S14). Some excess cardiac mortality emerged within 5 years, with the RR in years 0 to 4 similar to that in years ≥ 15. However, because cardiac mortality increases steeply with age, the absolute excess risk was much greater in the later time period (Data Supplement Figs S11-S12). The cardiac mortality RR, radiotherapy versus no radiotherapy, was strongly related to the estimated whole-heart radiation dose. Analyses that related risk to the trial radiotherapy regimen and to breast cancer laterality yielded an ERR per Gy of 0.041 (95% CI, 0.024 to 0.062; $P < .001$; Fig 2).

Application of Trial ERRs per Gy and Modern Doses to Population Mortality Data

The typical whole-lung dose from modern regimens was approximately 5 Gy. Combining this with the 0.11 ERR per Gy for lung cancer > 10 years after radiotherapy and with the population-based lung cancer rates[11,14,15] yielded estimates of lung cancer risks by age 80 years from typical modern breast cancer regimens (Fig 3A; Data Supplement Fig S15, Table S9). For a 50-year-old nonsmoker, a 5-Gy whole-lung dose that increases lung cancer rates by approximately 55% would increase lung cancer mortality before age 80 years from approximately 0.5% to 0.8% (ie, an estimated absolute increase of 0.3%). In contrast, for a 50-year-old woman who has smoked since adolescence and does not stop, a 55% increase in the lung cancer mortality rate would change her risk of death from lung cancer before age 80 years from approximately 9.4% to 13.8% (an absolute increase of 4.4%). Smoking cessation at the time of radiotherapy would reduce this estimate of the radiation-related increase in lung cancer mortality from 4.4% to 1.3% (Data Supplement Table S9).

Lung doses published during 2010 and 2015 varied according to regimen (IQR, 3.4 to 8.3 Gy). If a woman's whole-lung dose was

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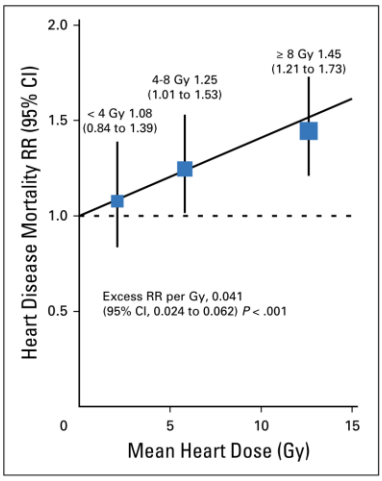


Fig 2. Heart disease mortality rate ratio (RR) by trial-specific mean radiation dose to the heart. The line was estimated using doses for individual women. Squares (with areas proportional to information content) show dose categories < 4, 4 to 8, and > 8 Gy, with mean doses of 2.1, 5.8, and 12.6 Gy.

only one half the typical dose, these absolute excess risks would be halved, but if it exceeded the typical dose of approximately 5 Gy, the estimated risks would be correspondingly higher.

The typical whole-heart dose from modern radiotherapy regimens was approximately 4 Gy. Combining 4 Gy with the 0.041 ERR per Gy for cardiac mortality, cardiac mortality risks from modern breast cancer radiotherapy were estimated. On the basis of 2010 female death rates in the 15 European Union member states in Western Europe,[16] the estimated risk of death before age 80 years as a result of heart disease was 1.8% for a nonsmoker and 8.0% for a smoker.[11] If, as this study suggests, a 4-Gy mean heart dose multiplies these risks by approximately 1.16, then the absolute increase in cardiac mortality would be 0.3% for a nonsmoker and 1.2% for a smoker (Fig 3B). Whole-heart doses in modern regimens varied widely (IQR for left radiotherapy, 1.9 to 7.4 Gy; IQR for right radiotherapy, 1.2 to 5.0 Gy). For doses > 4 Gy, the absolute hazards would be somewhat greater. For cancer centers reporting whole-heart doses of < 2 Gy, the estimated excess cardiac mortality would be less than half as great.

DISCUSSION

Breast cancer radiotherapy has changed since these trials, with a reduction in lung and heart radiation doses. However, the ERRs per Gy in the past trials remain relevant and can be used to estimate risks from modern radiotherapy.

For lung cancer, radiotherapy had its main effect > 10 years later (Fig 1, Data Supplement Figs S6-S7). The lack of any material early hazard and the substantial hazard during the second decade in these randomized trials are confirmed by nonrandomized SEER registry data (Data Supplement Table S8).[10] The ERR per Gy in this study is quantitatively consistent with estimates from published epidemiologic studies, which together included 334 lung cancers in patients with known smoking status (Data Supplement Fig S8). Lung cancer is rare in nonsmokers; only 52 of the 334 cancers in those epidemiologic studies were in nonsmokers. Although smoking information was unavailable for women in the trials, our estimate of the ERR per Gy, as in the epidemiologic studies, will be based primarily on the findings among smokers; hence it is likely to be reliable for them. For nonsmokers, even if the ERR per Gy is not exactly the same as in smokers, their absolute risk would still be small.

Because quitting smoking greatly reduces lung cancer incidence,[11,15] the estimated absolute increase in lung cancer mortality from radiotherapy in ex-smokers is likely to be much closer to that in never-smokers than in current smokers (Data Supplement Table S9). Even smoking cessation at the time of radiotherapy should substantially reduce the risk of radiation-induced lung cancer,[11,15] because cessation greatly reduces the

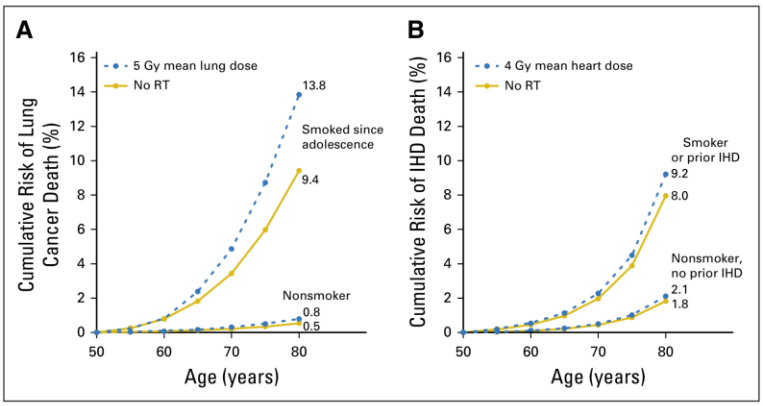


Fig 3. Estimated effects among 50-year-old smokers and nonsmokers of typical modern radiotherapy (RT) regimens on mortality from (A) lung cancer and (B) ischemic heart disease (IHD). Epidemiologic estimates of the risks without radiotherapy are multiplied by the rate ratios attributed to 5 Gy whole-lung dose and 4 Gy whole-heart dose (Data Supplement Methods S1).

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risk > 10 years later, which is when the main effects of radiotherapy on lung cancer occur (Data Supplement Table S9). Therefore, by quitting smoking at the time of radiotherapy, smokers would reduce their absolute risk of radiation-induced lung cancer and would achieve a much greater absolute reduction in other tobacco-attributable risks.[11] For smokers irradiated after age 70 years, radiotherapy would be expected to have no material effect on lung cancer risk before age 80 years.

Radiotherapy increased contralateral breast cancer as in nonrandomized studies (Data Supplement Table S6).[21-23] In the trials, the risk was greatest for women who received orthovoltage radiotherapy (Fig 1), which tends to deliver scattered radiation to nearby organs[24] but is rarely used nowadays. Considering just the women in non-orthovoltage trials, the absolute radiation-induced risk of contralateral breast cancer was only approximately 1%, and many of these cancers could be treated successfully. Since these trials, contralateral breast doses have decreased[24-27]; moreover, contralateral breast cancer incidence is reduced by effective systemic therapy.[5,6,28] Hence, the absolute risk of contralateral breast cancer from modern radiotherapy should be well under 1%, and the risk of death from this late effect should be smaller still.

Radiotherapy increased esophageal cancer incidence as in some nonrandomized studies.[29-31] Most cases arose in trials in which the regional lymph nodes were irradiated with fields that included part of the esophagus. It is now usual to angle fields away from the esophagus, so the absolute esophageal cancer risk from modern breast cancer regimens should be very small.[32,33]

For cardiac death, the estimated absolute cardiac hazards are much smaller now than in these trials, because population cardiac mortality rates are now much lower than they were 30 years ago. Moreover, the absolute cardiac risks from radiotherapy will continue to decrease if population heart disease death rates continue to decrease.

Risks were estimated for typical modern radiotherapy in typical populations of women. But heart and lung doses in breast cancer regimens vary, as do population disease rates; therefore the absolute risks and the effect of smoking cessation will vary for individual women. The absolute benefits of radiotherapy also vary with cancer characteristics. For women with invasive cancer, radiotherapy reduces breast cancer mortality by a few percentage points. For women with DCIS, the benefit is smaller. The absolute risks from radiotherapy for some smokers who continue smoking could exceed the absolute benefit. For example for a 50-year-old long-term smoker with a small, node-negative breast cancer, her estimated absolute benefit from radiotherapy after breast-conserving surgery is an approximately 2% to 5% reduction in breast cancer mortality,[2] whereas her estimated absolute risks from typical modern radiotherapy are approximately 4% for lung cancer and approximately 1% for cardiac mortality if she does not quit smoking. These findings reinforce the need to limit lung and heart doses without unduly compromising the dose to the target tissues, and the need for smokers to stop smoking.

This study has the advantage of being randomized; therefore, any definite excesses reflect causality. However, it has some limitations. Causes of death were not all known, and data on smoking habits were unavailable. Lung and heart doses were estimated retrospectively, and (with the exception of laterality) only trial-level rather than individual-level radiotherapy information was used. Hence, the estimates of ERRs per Gy cardiac mortality and lung cancer depend on trial-level doses (not individual patient doses) being approximately correct. Lung doses from the trial regimens have not been reported elsewhere, but the estimated cardiac doses from trial regimens are similar to other published estimates.[13,34-36] Our analyses rely on the assumption that the risks per Gy lung and heart dose have not changed over time (ie, that if the doses have halved, the risks have halved). However, the biologic effects of radiotherapy are unlikely to have changed over time, and the risks per Gy lung or heart dose in this study are consistent with other published estimates for patients irradiated in different decades[37] (Data Supplement Fig S8). The proportional increase in cardiac mortality of 0.041 per Gy is somewhat lower than a recent population-based estimate of a 0.074 per Gy increase in major coronary events,[37] but the difference is not statistically significant and the end points differ.

Information on incident heart disease was unavailable; therefore, it was not possible to study the relationship between heart dose and incident heart disease. Any history of heart disease prior to radiotherapy was also unknown, and it could have substantially increased the absolute cardiac effects of radiotherapy. Few women in these trials received anthracyclines, and none received trastuzumab, so the combined cardiac effects of these cardiotoxic systemic therapies with radiotherapy could not be assessed. However, although these systemic therapies can affect the absolute risks of heart disease, they may not materially affect the ERR per Gy.

For long-term smokers irradiated today, the estimated combined risks from radiotherapy are a few percentage points if smoking continues, which may outweigh the reduction in breast cancer mortality; however, smoking cessation substantially reduces risk. For healthy nonsmokers, the estimated absolute risks of lung cancer or cardiac mortality from radiotherapy add up to < 1%, which, for most women, is much smaller than the benefit from radiotherapy.[1-5]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors
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Clinical Investigation

Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Review of Heart Doses Published During 2003 to 2013

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Summary

In a systematic review of studies published during 2003 to 2013, typical heart doses from left-sided breast cancer radiation therapy varied widely between studies, even for apparently similar regimens. Nevertheless, in left-tangential radiotherapy, maneuvers to reduce heart dose were successful, proton beam radiation therapy delivered the lowest heart doses, and inclusion of the internal mammary chain, doubled the heart dose. For

Purpose: Breast cancer radiation therapy cures many women, but where the heart is exposed, it can cause heart disease. We report a systematic review of heart doses from breast cancer radiation therapy that were published during 2003 to 2013.

Methods and Materials: Eligible studies were those reporting whole-heart dose (ie, dose averaged over the whole heart). Analyses considered the arithmetic mean of the whole-heart doses for the CT plans for each regimen in each study. We termed this "mean heart dose."

Results: In left-sided breast cancer, mean heart dose averaged over all 398 regimens reported in 149 studies from 28 countries was 5.4 Gy (range, <0.1-28.6 Gy).

In regimens that did not include the internal mammary chain (IMC), average mean heart dose was 4.2 Gy and varied with the target tissues irradiated. The lowest average mean heart doses were from tangential radiation therapy with either breathing control (1.3 Gy; range, 0.4-2.5 Gy) or treatment in the lateral decubitus position (1.2 Gy; range, 0.8-1.7 Gy), or from proton radiation therapy (0.5 Gy; range, 0.1-0.8 Gy). For intensity modulated radiation therapy mean heart dose was 5.6 Gy (range, <0.1-23.0 Gy). Where the IMC was irradiated, average mean heart dose was around 8 Gy and varied little according to which other targets were irradiated. Proton radiation

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most women receiving breast cancer radiation therapy today, the benefits are likely to outweigh the risks.

therapy delivered the lowest average mean heart dose (2.6 Gy, range, 1.0-6.0 Gy), and tangential radiation therapy with a separate IMC field the highest (9.2 Gy, range, 1.9-21.0 Gy). In right-sided breast cancer, the average mean heart dose was 3.3 Gy based on 45 regimens in 23 studies.

Conclusions: Recent estimates of typical heart doses from left breast cancer radiation therapy vary widely between studies, even for apparently similar regimens. Maneuvers to reduce heart dose in left tangential radiation therapy were successful. Proton radiation therapy delivered the lowest doses. Inclusion of the IMC doubled typical heart dose. © 2015 Elsevier Inc. All rights reserved.

Introduction

Breast cancer radiation therapy improves overall survival after breast-conserving surgery, as well as after mastectomy in node-positive disease (1, 2), and radiation therapy is now given to approximately half of all breast cancer patients in the United States (3). It does, however, inevitably involve some unwanted irradiation of normal tissues, including the heart. This may increase the risk of subsequent heart disease, with the magnitude of the risk increasing linearly with whole-heart radiation dose (4-7).

As awareness of radiation therapy cardiotoxicity has grown, and technology has developed, heart doses from breast cancer radiation therapy have evolved. In the 1950s to 1970s, direct fields or wide tangents were often used to irradiate the internal mammary chain (IMC) and typical whole-heart doses for many left-sided regimens were >10 Gy (8). Since then, radiation therapy fields have become less extensive, with many women now receiving standard breast tangents alone. Increasing availability of 3-dimensional (3D) computed tomography (CT) planning has enabled clinicians to reduce normal tissue doses generally (9), but some other changes may have increased whole-heart dose. Inverse-planned intensity modulated radiation therapy (IMRT) can deliver highly conformal target doses and avoid areas of high heart dose, but it can involve radiation beams passing through the heart, exposing it to a "low dose bath" (10). There is also increasing evidence that irradiating the IMC improves survival in node-positive disease, but, given its close proximity to the heart in left-sided breast cancer, irradiating it without exposing the heart is challenging.

Numerous studies reporting heart doses from breast cancer radiation therapy have been published recently, and we present a systematic review of them. Our aims were to document typical whole-heart doses from breast cancer radiation therapy worldwide over the past decade; to identify factors associated with high or low whole-heart doses from different regimens; and to assess the extent to which whole-heart doses vary for a given combination of technique, target and laterality. We also discuss the likely cardiac risks for women irradiated recently.

Methods and Materials

Study eligibility criteria

Studies were identified using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11). Studies published between January 1, 2003, and December 31, 2013, and reporting whole-heart dose (ie, dose averaged over the whole heart), for specific regimens (ie, different ways of irradiating target tissues) were eligible. Eligibility was not affected by whether the radiation therapy plans were subsequently delivered to patients. Studies not reporting whole-heart dose were excluded, as were studies of tumor bed boost radiation therapy alone, because boost radiation therapy is nearly always given alongside whole breast radiation therapy, which delivers substantially higher heart doses (8).

Study identification

Embase and SCOPUS databases were searched to identify publications with the following terms in the title or abstract: dos* AND breast* AND cancer*/carcinom*/tumor*/tumour* AND radiation/radiotherap*. Broad searches were necessary because studies did not always mention the heart in the title or abstract. Other techniques used to identify eligible studies were Google Scholar alerts for key publications, and manual searches of reference lists from eligible studies and contents pages for 25 journals from November 1, 2010, to December 31, 2013 (Table E1; available online at www.redjournal.org). 167 eligible studies were identified (Fig. 1).

Data collation and analysis

Each regimen reported in these 167 studies was categorized by radiation therapy technique using the authors' descriptions of radiation therapy planning and delivery (Tables E2 and E3; available online at www.redjournal.org). The following variables were also noted: number of CT plans for the regimen; mean, standard deviations and ranges of the whole-heart doses for these CT plans; patient treatment position; treatment planning method(s); field type(s); beam energy and modality; use of breathing control measures; whether the radiation therapy plans were

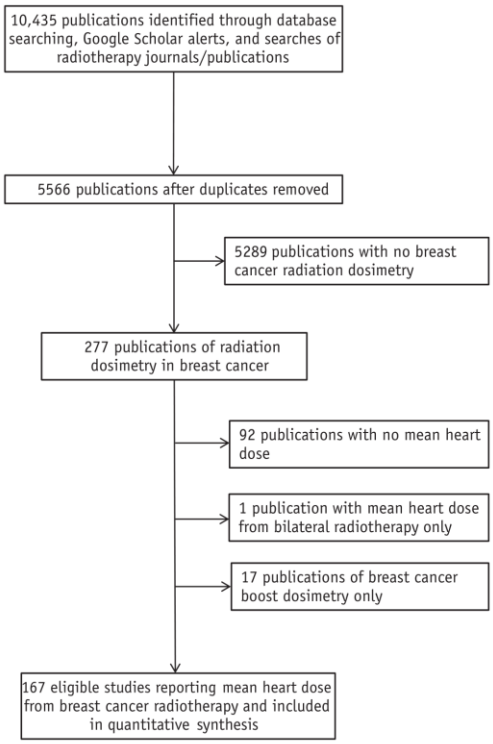


Fig. 1. The process of study identification for the review.

delivered to patients; target(s) irradiated; cancer laterality; country; publication year; target dose; and fractionation (Tables E4-E9; available online at www.redjournal.org). Dose-volume measurements of heart dose, including V5 (percentage of the heart volume irradiated to ≥5 Gy), V10, V20, V30, and V40 were also noted where available. For left-sided radiation therapy, regimens were classified by the gross national income per person of the country (12). In studies of women with unfavorable anatomy, selection criteria were noted.

Our analyses considered the arithmetic mean of the whole-heart doses for the CT plans used for each regimen in each study. In presenting our results, we refer to these quantities using the term "mean heart dose." Analyses related mean heart dose to radiation therapy technique and the variables listed above.

Results

In the 167 eligible studies, mean heart doses were reported for 496 regimens. Prescribed target dose and fraction sizes were reported for 418 of the regimens (84%). For 381 of these regimens (91%), target doses were within the range of 40.0 to 50.7 Gy, and fraction sizes within the range of 1.8 to 2.8 Gy. For left-sided breast cancer, average mean heart dose was 5.4 Gy (based on 398 regimens in 149 studies) (Table 1). For right-sided breast cancer, average mean heart dose was 3.3 Gy (45 regimens in 23 studies). For right-sided regimens that irradiated the IMC, average mean heart dose was 4.2 Gy (16 regimens in 9 studies). For right-sided regimens not irradiating the IMC, mean heart doses of 0.5 to 14.3 Gy were reported for 11 regimens using IMRT or rotational beams but for other regimens, average mean heart dose was 1.8 Gy (18 regimens in 14 studies). The number of regimens published each year increased from 17 in 2003 to 115 in 2013. Dose-volume parameters were inconsistently reported, for example, 33% of studies (55 of 167) reported V20 and 25% (42 of 167) reported V10.

Left tangential radiation therapy

Left tangential whole-breast or chest wall radiation therapy in the supine position with no breathing control was the combination most commonly reported for laterality, technique, and targets (102 regimens in 66 studies) (Fig. 2). Average mean heart dose for these regimens was 4.1 Gy. It did not vary significantly by continent (Europe reported 3.9 Gy, Asia reported 4.7 Gy, and North America reported 3.5 Gy; P value for heterogeneity was .10), but there was highly significant variation among countries within Europe ($P<.001$) and Asia ($P<.001$), with the lowest values reported in Europe for the United Kingdom (1.6 Gy), and in Asia for Japan (3.4 Gy), and the highest values reported in Europe for Germany (6.5 Gy), and in Asia for Saudi Arabia (7.9 Gy). There were no significant differences between the average mean heart dose in high-income countries and that in other countries ($P=.4$) or according to whether the radiation therapy plans had actually been delivered ($P=.9$). Radiation therapy plans published recently had higher mean heart doses than those published earlier (published 2011 to 2013: 4.5 Gy, published 2003 to 2010: 3.6 Gy, P for difference .03) but, when regimens that involved chest wall, supraclavicular fossa (SCF) or axillary radiation therapy were excluded, there was little difference in mean heart dose according to period of publication (Fig. E1; available online at www.redjournal.org). For these regimens, which irradiated only the whole breast, average mean heart dose was 3.5 Gy (71 regimens in 46 studies), with considerable variation between countries.

Radiation therapy technique with and without left IMC irradiation

For left-sided regimens that included the IMC as a target, average mean heart dose was 8.4 Gy in 93 regimens from 35 studies, double the value for regimens that did not include it (4.2 Gy in 264 regimens from 101 studies, 2P for difference: <.001) (Fig. 3).

For left-sided regimens that did not include the IMC (Fig. 3a), tangential radiation therapy was the most frequently reported technique. For supine left-tangential radiation therapy with no breathing control, average mean

Table 1 Studies reporting whole-heart doses from breast cancer radiation therapy regimens and published during 2003 to 2013

Laterality	Number of studies	Number of radiation therapy regimens*	CT plans per regimen†		Mean heart dose (Gy)	
			Average	Range	Average‡	Range§
Left-sided	149	398	16.2	1-217	5.4‖	<0.1-28.6
Right-sided	23	45	26.1	1-219	3.3‖	0.4-21.6¶
Left and right combined#	18	53	17.4	5-154	5.9	0.1-21.1
Totals	167**	496	17.2	1-219	5.2	<0.1-28.6

* Field borders, beam angles, and so forth differ among studies. Regimens in different studies were therefore classified separately, even though descriptions may be similar.

† For 10 regimens in 5 studies, the number of computed tomography (CT) plans was not specified.

‡ Average of the mean heart doses reported for the different radiation therapy regimens. For each radiation therapy regimen, the mean heart dose was the whole-heart dose averaged across the CT plans for that regimen.

§ Range of mean heart doses for radiation therapy regimens.

‖ Difference between left-sided and right-sided categories: $\chi^2_1=9.2$; $P<.01$.

¶ For right-sided regimens that irradiated the internal mammary chain (IMC), average mean heart dose was 4.2 Gy (16 regimens in 9 studies). For right-sided regimens not irradiating the IMC, mean heart doses of 0.5-14.3 Gy were reported for 11 regimens using intensity modulated radiation therapy or rotational beams, but for other regimens, mean heart dose was 1.8 Gy (18 regimens in 14 studies).

Results are given only for left-sided and right-sided regimens combined and not separately.

** Some studies reported doses for both left- and right-sided regimens.

heart dose was 3.8 Gy based on 112 regimens in 71 studies. Twenty studies reported maneuvers for reducing heart dose from left-tangential radiation therapy. Breathing control (ie, deep inspiration breath-hold, respiratory gating, or active breathing control) reduced the average mean heart dose to 1.3 Gy (2*P* for difference: <.001). Alternative treatment positions reduced it to 2.4 Gy for prone position (2*P* for difference: .004) and to 1.2 Gy for lateral decubitus position (2*P* for difference: <.001). The use of field-in-field technique made little difference to heart dose (Fig. E2; available online at www.redjournal.org). For radiation therapy not including the IMC, the lowest average mean heart doses were from proton irradiation (0.5 Gy based on 6 regimens in 3 studies) and brachytherapy (2.2 Gy based on 8 regimens in 7 studies). These techniques were used for either partial or whole breast radiation therapy. The technique that resulted in the highest average mean heart doses was inverse-planned IMRT (standard IMRT: 5.4 Gy based on 76 regimens in 42 studies; rotational fields: 6.3 Gy based 26 regimens in 20 studies).

Common left-sided techniques that included the IMC as a target were tangential fields to the breast or chest wall matched to electron or angled photon IMC fields, wide tangents, and IMRT (85 regimens from 35 studies) (Fig. 3b). For most techniques average mean heart doses were around 9 Gy, but with a wide range of doses for the regimens in each technique. For example, for standard IMRT mean heart dose in 17 studies varied from 0.7 to 23.4 Gy. The lowest average mean heart dose from radiation therapy including the left IMC was 2.6 Gy from proton irradiation (4 regimens in 3 studies).

Other targets in left-sided radiation therapy

Among regimens that did not irradiate the IMC, average mean heart dose varied according to the targets included (2*P* for heterogeneity: <.001) (Fig. 4a). In general, average mean heart dose increased as the targets became more extensive. For example, average mean heart dose from partial breast irradiation was only 1.1 Gy (14 studies), whereas it was 3.7 Gy for whole breast without inclusion of the axilla or SCF (69 studies) and 6.1 Gy for chest wall irradiation (6 studies). Where the IMC was irradiated, average mean heart dose was 8.5 Gy in 72 regimens from 24 studies with little variation according to inclusion of other targets (Fig. 4b). Similar patterns were observed for analyses restricted to just the 212 regimens with target doses of 45.0 to 50.7 Gy and fraction sizes of 1.8 to 2.0 Gy (Fig. E3; available online at www.redjournal.org).

Women with unfavorable anatomy

Sixteen studies reported average mean heart doses for left-sided regimens in women with unfavorable anatomy (Fig. 5). For whole-breast radiation therapy, the highest value was for pectus excavatum (14.8 Gy, 4 regimens), whereas values for large breasts and high predicted heart dose were 3.0 Gy (11 regimens) and 6.3 Gy (14 regimens), respectively. For women with unfavorable anatomy, the value for all other target combinations was 7.1 Gy (7 regimens).

Discussion

This large, systematic review of cardiac exposure from breast cancer radiation therapy has confirmed that typical heart doses in left breast cancer vary widely but with clear evidence of several factors influencing them systematically. For regimens that included the IMC, average mean heart dose was ~8 Gy, whereas for other regimens, it was ~4 Gy. Mean heart dose was also affected by technique, with the lowest average doses resulting from proton radiation therapy and the highest from IMRT.

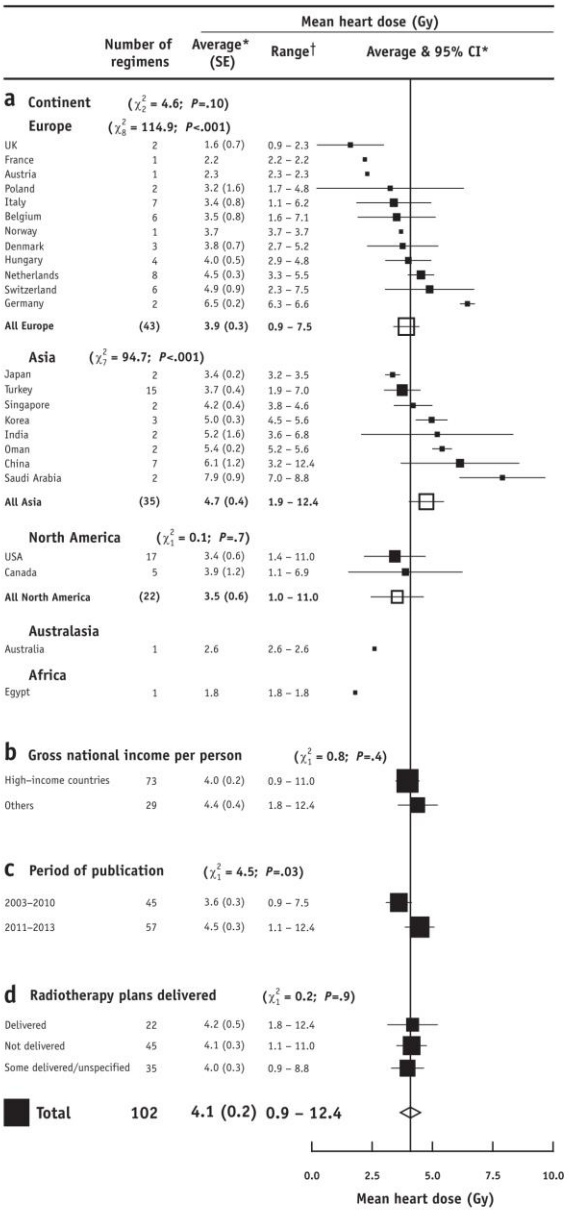


Fig. 2. Mean heart doses from left tangential breast cancer radiation therapy according to country, gross national income per person in the country concerned, period of publication, and whether the radiation therapy plans were actually delivered or just planned. Regimens that involved internal mammary chain, partial breast irradiation, breathing control, orprone or lateral decubitus positioning were excluded, as were studies of women with unfavorable anatomy. Regimens that irradiated the supraclavicular fossa oraxilla as well as the breast or chest wall were included. *Average of mean heart doses for reported regimens. †Range of mean heart doses for reported regimens. SE = standard error; CI = confidence interval.

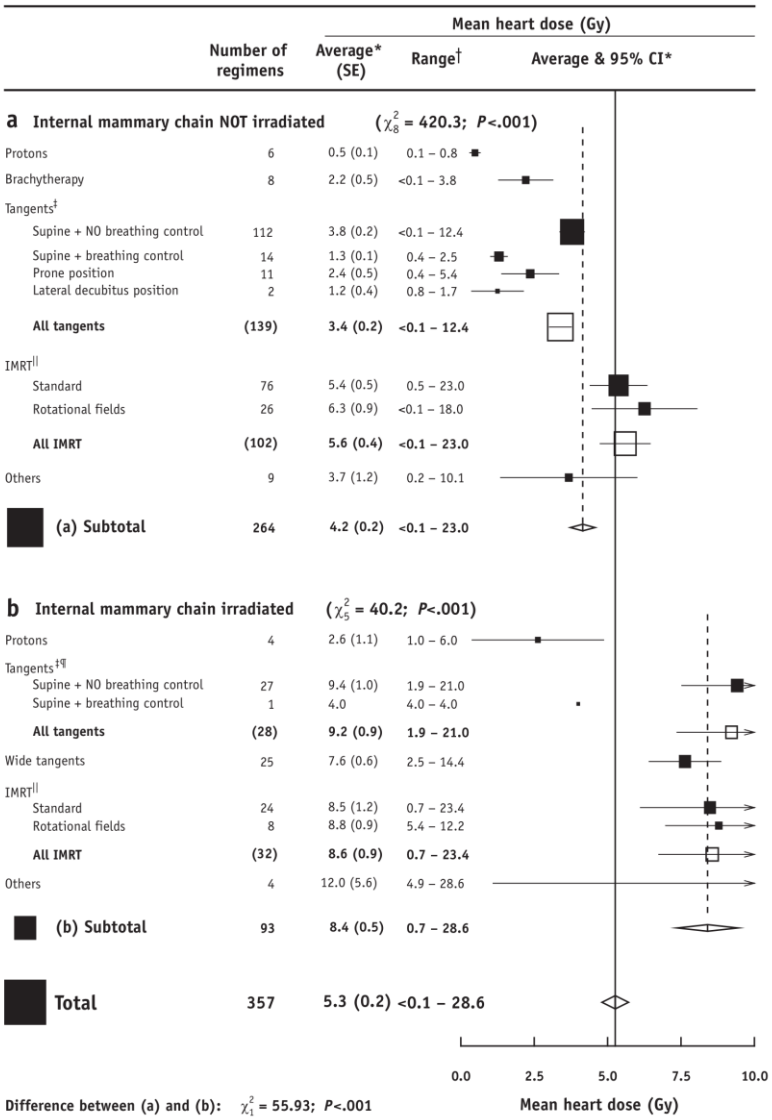


Fig. 3. Mean heart doses from left-sided breast cancer radiation therapy regimens according to technique and whether or not internal mammary chain irradiation was given. Studies of women with unfavorable anatomy were excluded. *Average of mean heart doses for reported regimens. †Range of mean heart doses for reported regimens. ‡Some women had field-in-field radiation therapy. Regimens where treatment position was not specified are categorized as supine; regimens where breathing control was not specified are categorized as NO breathing control. ||IMRT = inverse-planned intensity modulated radiation therapy. ¶The internal mammary chain was irradiated with an electron and/or a photon field. *Abbreviations:* SE = standard error; CI = confidence interval.

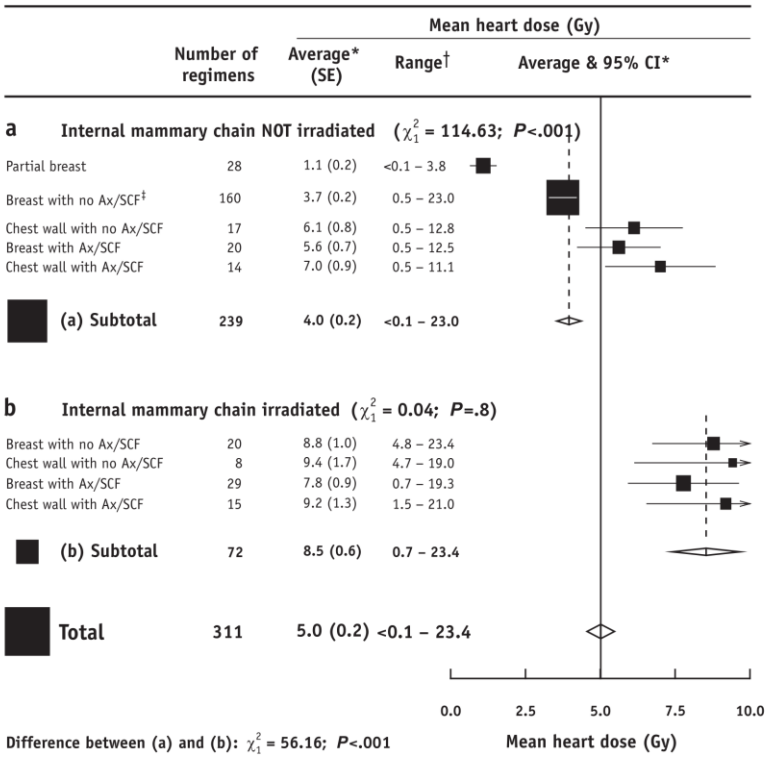


Fig. 4. Mean heart doses from left-sided breast cancer radiation therapy regimens according to targets irradiated and whether or not internal mammary chain irradiation was given. Studies of women with unfavorable anatomy and the few regimens that irradiated other target combinations were excluded. *Average of mean heart doses for reported regimens. †Range of mean heart doses for reported regimens. ‡Ax/SCF = axilla and/or supraclavicular fossa. *Abbreviations:* SE = standard error; CI = confidence interval.

Left-sided radiation therapy not involving the IMC

For standard left-tangential radiation therapy, average mean heart dose was approximately 4 Gy, with wide variation among countries (Fig. 2). This is likely to be caused chiefly by variations in radiation therapy protocols such as differences in beam angles and field borders, which affect beam divergence into the heart. Maneuvers to reduce heart dose from left-tangential radiation therapy included breathing control to expand the lungs and increase the distance between the heart and the radiation therapy fields and prone or lateral decubitus patient positioning, which pulls breast tissue anteriorly and enables shallower tangents to be used. Our results suggest that these maneuvers approximately halve mean heart dose, but they are infrequently used in some countries at present, perhaps due to difficulties positioning patients reproducibly.

IMRT resulted in higher average mean heart doses than left tangents, but the range was very wide, from <0.1 to 23.0 Gy, with heart dose depending heavily on dose constraints. For example, in whole-breast IMRT, one study with generous cardiac dose constraints reported mean heart doses of 12 to 15 Gy (13), whereas a similar study with tight heart dose constraints reported doses ~2 Gy (14).

When the IMC was not irradiated, increasing the target tissues irradiated increased the mean heart dose. Our results suggest that chest wall fields are more extensive than breast fields, and that SCF and axillary fields can involve some radiation dose to the heart (Fig. 4a).

Irradiating the left IMC while avoiding the heart

The left IMC is very close to the heart, so irradiating it inevitably involves some cardiac exposure. In this review, irradiating the IMC approximately doubled mean heart dose in left-breast cancer. As the rate of major coronary events increases approximately linearly with whole-heart dose (7), doubling heart dose should also double any radiation-related

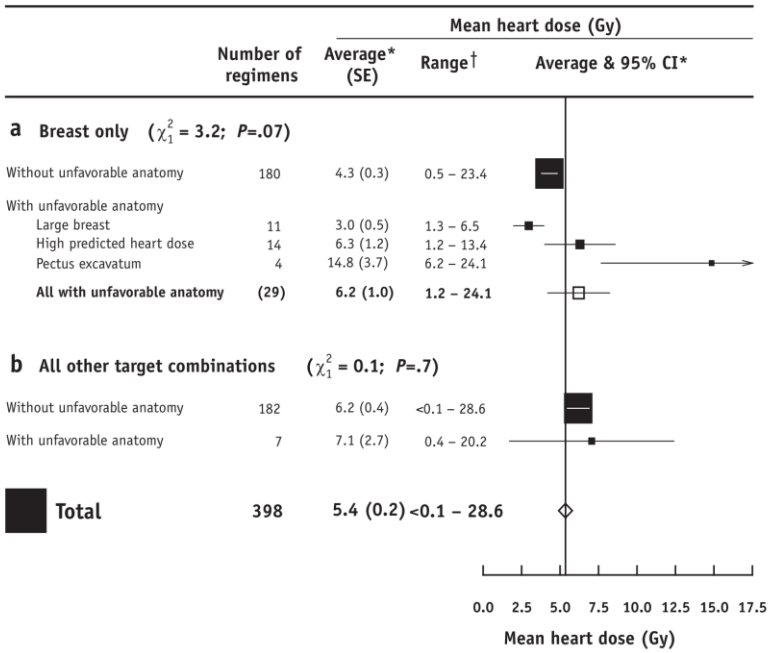


Fig. 5. Mean heart doses from left-sided breast cancer radiation therapy regimens according to whether the regimen included only the breast as a target and whether the study was of women with unfavorable anatomy. *Average of mean heart doses for reported regimens. †Range of mean heart doses for reported regimens. *Abbreviations:* SE = standard error; CI = confidence interval.

cardiac risk. The technique that stands out as enabling IMC irradiation while avoiding the heart is proton beam therapy, which delivered an average mean heart dose of 2.6 Gy, versus approximately 8 Gy for nonproton techniques. This reflects the ability of protons to deliver conformal dose to target tissues with lower exit doses to normal tissues (15). Although the availability of proton therapy is growing, at present few patients have access to it. Certain other techniques may also achieve low heart doses. For example, mean heart doses of ~2 Gy may be achieved using tangential and segmental photon beams with blocking of the heart (16). However, this requires dosimetric and physics expertise that is not available everywhere.

Study limitations

Our review could include only published estimates of heart dose. Oncology groups who publish their heart doses are likely to be aware of the risks of cardiac irradiation, and therefore reduce cardiac exposure. Therefore it is possible that heart doses in other centers may be somewhat higher. Published radiation dosimetry studies may also focus on challenging situations, including left-laterality, IMC irradiation, and unfavorable anatomy. We have, therefore, presented results separately by laterality, technique, targets, and the presence of unfavorable anatomy.

This review presents only whole-heart dose (ie, dose averaged over the whole heart) and does not consider the dose distribution within the heart. We selected whole-heart dose as our metric because it is the most commonly reported measure, can be compared across regimens and studies, and has been shown to be associated with radiation-related cardiac risks of breast cancer radiation therapy.

Our approach treated each regimen equally without accounting for the number of plans per regimen. Some regimens included >100 CT plans and others included only one. Heart doses from regimens with multiple plans revealed considerable variability in whole-heart dose for different CT plans within a single study. Such inter-patient variability arises even when radiation therapy was performed within the same institution using the same protocol. For example, among 144 women irradiated with the same left-tangential protocol at a single hospital, the resulting whole-heart dose for different patients varied from 0.8 to 6.2 Gy (17), probably due mainly to differences in anatomy. The heart is located on the edge of left-tangential fields and is sometimes out of the fields and sometimes partly in the fields, and small differences in anatomy can substantially affect heart dose. There may also be interobserver

variability in cardiac contouring. Hence heart dose for individual women may be difficult to predict.

Weighing risks against benefits

Oncologists need to weigh risks and benefits of radiation therapy for each patient. After breast-conserving surgery, radiation therapy typically reduces the absolute risk of breast cancer death at 15 years by ~4% (2). For those 50 years of age at irradiation, with no cardiac risk factors, and receiving ~4 Gy whole-heart dose, the absolute risks of radiation-related ischemic heart disease would be ~1.3% for incident disease and ~0.6% for mortality (7). In node-positive disease, postmastectomy radiation therapy typically reduces the absolute risk of breast cancer death by at 15 years ~7% (1). For those aged 50 at irradiation, with no cardiac risk factors, whose radiation therapy includes the IMC and delivers ~8 Gy whole-heart dose, the absolute risks of radiation-related ischemic heart disease would be ~2.5% for incident disease and ~1.2% for mortality (7).

Most of the cardiac risk in breast cancer radiation therapy is from ischemic heart disease (18). However, the risks of pericarditis, valve disease, and myocardial fibrosis may also be increased (18, 19). Available data suggest that as dose to each of these structures increases (pericardium, valves, myocardium) so the risk of damage increases (19-21). Individual cardiac structures are not routinely contoured, so doses to them were unavailable in the studies reviewed. However, pericardial, valvular, and myocardial doses are likely to correlate strongly with whole-heart dose, so regimens delivering low whole-heart doses are likely to deliver low doses to other cardiac structures, resulting in low risks of other types of cardiac disease.

Conclusions

This systematic review has shown that mean heart dose varies substantially and is affected by technique and targets irradiated. Even in modern studies, cardiac dose is often substantial. Our calculations suggest that for most women who receive breast cancer radiation therapy, the benefits, in terms of reduction in breast cancer outcomes, far outweigh the risk. However, the risk-benefit analysis may not be favorable for all women. Some women achieve a small absolute gain from radiation therapy, for example, women receiving radiation therapy for carcinoma-in-situ. For such women, even a small cardiac risk from radiation therapy may outweigh the benefits.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cardiac Structure Injury After Radiotherapy for Breast Cancer: Cross-Sectional Study With Individual Patient Data

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A B S T R A C T

Purpose
Incidental cardiac irradiation can cause cardiac injury, but little is known about the effect of radiation on specific cardiac segments.

Methods
For 456 women who received breast cancer radiotherapy between 1958 and 2001 and then later experienced a major coronary event, information was obtained on the radiotherapy regimen they received and on the location of their cardiac injury. For 414 women, all with documented location of left ventricular (LV) injury, doses to five LV segments were estimated. For 133 women, all with documented location of coronary artery disease with ≥ 70% stenosis, doses to six coronary artery segments were estimated. For each segment, numbers of women with left-sided and right-sided breast cancer were compared.

Results
Of women with LV injury, 243 had left-sided breast cancer and 171 had right-sided breast cancer (ratio of left *v* right, 1.42; 95% CI, 1.17 to 1.73), reflecting the higher typical LV radiation doses in left-sided cancer (average dose left-sided, 8.3 Gy; average dose right-sided, 0.6 Gy; left minus right dose difference, 7.7 Gy). For individual LV segments, the ratios of women with left- versus right-sided radiotherapy were as follows: inferior, 0.94 (95% CI, 0.70 to 1.25); lateral, 1.42 (95% CI, 1.04 to 1.95); septal, 2.09 (95% CI, 1.37 to 3.19); anterior, 1.85 (95% CI, 1.39 to 2.46); and apex, 4.64 (95% CI, 2.42 to 8.90); corresponding left-minus-right dose differences for these segments were 2.7, 4.9, 7.2, 10.4, and 21.6 Gy, respectively ($P_{trend} < .001$). For women with coronary artery disease, the ratios of women with left- versus right-radiotherapy for individual coronary artery segments were as follows: right coronary artery proximal, 0.48 (95% CI, 0.26 to 0.91); right coronary artery mid or distal, 1.69 (95% CI, 0.85 to 3.36); circumflex proximal, 1.46 (95% CI, 0.72 to 2.96); circumflex distal, 1.11 (95% CI, 0.45 to 2.73); left anterior descending proximal, 1.89 (95% CI, 1.07 to 3.34); and left anterior descending mid or distal, 2.33 (95% CI, 1.19 to 4.59); corresponding left-minus-right dose differences for these segements were −5.0, −2.5, 1.6, 3.5, 9.5, and 38.8 Gy (P_{trend} = .002).

Conclusion
For individual LV and coronary artery segments, higher radiation doses were strongly associated with more frequent injury, suggesting that all segments are sensitive to radiation and that doses to all segments should be minimized.

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INTRODUCTION

Radiotherapy with curative intent is given to many patients with cancer. In breast cancer, radiotherapy reduces the risks of recurrence and death,[1,2] but incidental cardiac irradiation may increase the risk of heart disease.[3-5] Thoracic radiotherapy can also increase heart disease risk in Hodgkin lymphoma, childhood cancer, esophageal cancer, and lung cancer.[6,7] Ischemic heart disease (IHD) is the most common radiation-related heart disease, and radiation-related risk increases approximately linearly with mean whole-heart radiation dose.[6,8,9]

Radiation-related IHD may be caused by microvascular myocardial disease or macrovascular coronary artery disease.[7] Doses from radiotherapy to individual myocardial or coronary artery segments differ substantially depending on regimen, and

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regimens differ by tumor type, stage, and location and, for breast and lung cancer, laterality.[10,11] Considerable resources are being invested in reducing cardiac exposure from radiotherapy.[12,13] At present, however, little is known about the long-term effects of irradiating specific segments of the left ventricle (LV) or coronary arteries. Such knowledge may help guide the adoption of cardiac-sparing techniques, and help oncologists to identify the optimal radiotherapy plan for each individual patient.

Several studies have provided insight into the risk of radiation-related heart disease after breast cancer radiotherapy by comparing the numbers of women with left- and right-sided breast cancer and calculating the likely difference in cardiac dose between the two groups.[7,8] Here, we extend this technique by considering women irradiated for breast cancer who subsequently developed IHD and for whom the location (segment) of cardiac injury and the radiotherapy regimen, including cancer laterality, were documented. Any differences between women irradiated for left-sided compared with right-sided breast cancer in the distribution of cardiac injuries across the different cardiac segments is likely to reflect differences in the spatial distribution of radiation received by different segments during left-sided and right-sided radiotherapy.

In this study, for each cardiac segment, we calculated the ratio of the number of women with injury to that segment after left-sided radiotherapy to the number of women with injury to that segment after right-sided radiotherapy. We related these ratios to differences in the typical doses delivered to the various segments from left-sided and right-sided radiotherapy.

METHODS

All women who received adjuvant breast cancer radiotherapy in Stockholm from 1958 to 2001 or Denmark from 1977 to 2000 and who subsequently had a major coronary event (defined as myocardial infarction [International Classification of Diseases, 10th Revision, codes I21 to I24], coronary revascularization [Nordic Medico-Statistical Committee Classification of Surgical Procedures, version 1.9, code FN], or death from IHD [hospital or community; International Classification of Diseases, 10th Revision, codes I20 to I25]) were identified from Swedish national patient and cause of death registers and the Danish Breast Cancer Cooperative Group, patient discharge, and cause of death registers.[8] Each woman's radiotherapy regimen and medical history before breast cancer diagnosis were abstracted from her hospital oncology record. Women without histopathologic confirmation of cancer, with bilateral or metastatic disease, with previous cancer (except nonmelanoma skin cancer), with previous thoracic radiotherapy, or whose breast cancer recurred before their major coronary event were excluded. A total of 963 eligible women were identified. This study was approved by the Danish Data Protection Agency and by the Ethics Review Board of the Karolinska Institutet in Stockholm.

Location and Type of Cardiac Injury

Hospital cardiology notes were sought for all 963 women. Information on the location, nature, and extent of any LV myocardial injury and on any disease of the left anterior descending (LAD), right, and circumflex coronary arteries was abstracted by four research nurses. Two cardiologists and an oncologist (K.R., B.G., and C.C.) who were blinded to the cancer laterality used this information to code site of injury. Injury location included five LV segments (anterior, inferior, apex, lateral, and septal; Data Supplement) and two segments (proximal, mid/distal, or distal) of each of the LAD, right, and circumflex coronary arteries.[14] LV injury was defined as evidence of: myocardial infarction on ECG, permanent perfusion defects on multiple-gated acquisition or myocardial perfusion scan, regional wall motion abnormalities on echocardiogram, or LV infarction on autopsy record. Coronary artery disease was defined as $\geq$ 70% coronary artery stenosis at angiogram or autopsy. Coronary artery disease with $<$ 70% stenosis was excluded because it is often subclinical and thus would be under-reported. Information on other locations (eg, right ventricle) was rarely reported in cardiology notes and thus was not included.

Radiation Dosimetry

Radiation doses were estimated for five LV segments and two segments each of the LAD, right, and circumflex coronary arteries (Figs 1 and 2; Data Supplement).[14] First, each woman's radiotherapy chart was used to categorize her according to regimen. Second, a typical computed tomography (CT) scan was selected. Third, all regimens were reconstructed on the typical CT scan to derive regimen-specific doses for each segment. Fourth, each woman was allocated segment doses according to regimen category and total dose. Fifth, dosimetry uncertainties were assessed.

Statistical Methods

Radiation dose estimates for individual cardiac segments were available only for women with recorded cardiac injury and not for otherwise comparable women in the population without a major coronary event. Therefore, it was not possible to assess dose-response relationships in terms of the percentage increase per gray in segment injury rate.

Separate analyses were conducted for LV and coronary arteries. The ratio of the number of women receiving left-sided radiotherapy to the number receiving right-sided radiotherapy was calculated (termed left-versus-right ratio). Tests for heterogeneity in the left-versus-right ratio with various characteristics were conducted using logistic regression.

For each injured LV or coronary artery segment, the typical dose to that segment was calculated based on radiotherapy regimen, including

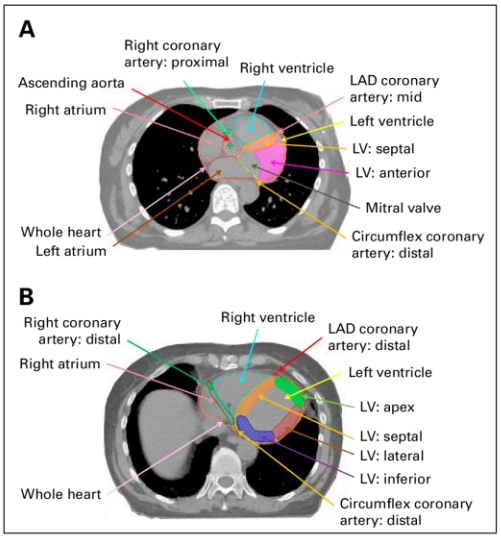


Fig 1. Axial computed tomography images illustrating left ventricle (LV) and coronary artery segments. (A) Level of proximal (superior) LV. (B) Level of mid LV. As is usual in radiotherapy planning, the patient's right is on the reader's left. LAD, left anterior descending coronary artery.

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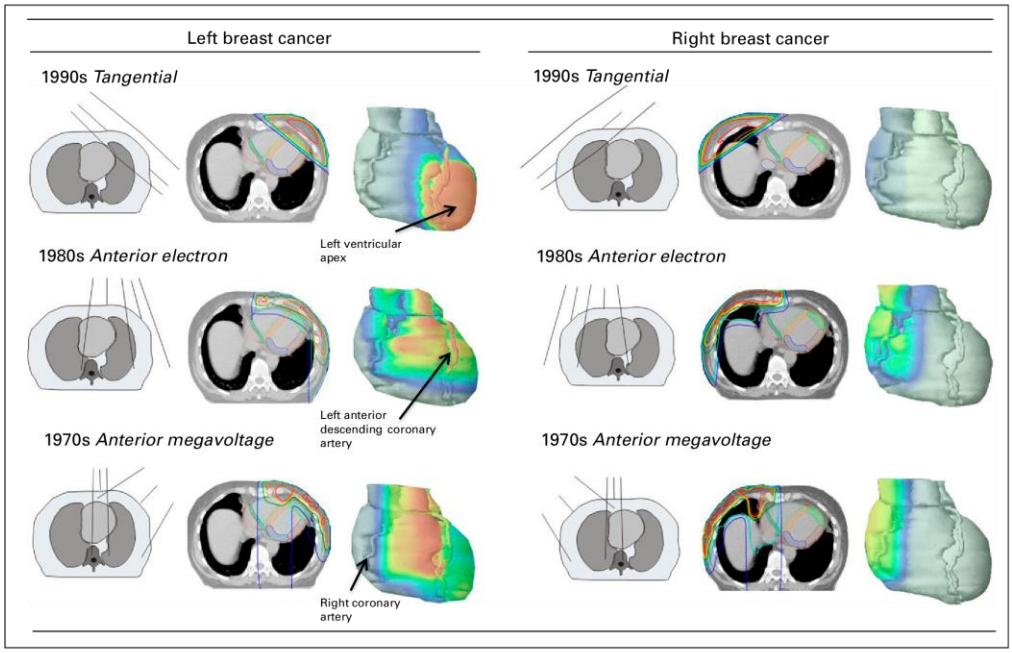


Fig 2. Spatial distribution of radiation dose in the heart from breast cancer regimens commonly used in different decades for women in the study. Isodoses were as follows: red, 50 Gy; orange, 48 Gy; yellow, 44 Gy; green, 40 Gy; blue, 25 Gy; and purple, 10 Gy. Field borders were usually 25 Gy. Left ventricular segments are as follows: orange, septal; green, apex; brown, lateral; and purple, inferior. Anterior electron included an electron field to chest wall and internal mammary lymph nodes, and a photon field to lateral thorax and axillary and supraclavicular nodes. Anterior megavoltage included a cobalt-60 field to internal mammary lymph nodes and an oblique electron field to chest wall projecting to contralateral side.

cancer laterality. The average of the typical doses was then calculated separately for left-sided and right-sided cancer, and the difference between these average typical doses was derived (termed left-minus-right dose difference). The segments were then ranked according to left-minus-right dose differences. A test for trend in the left-versus-right ratios was conducted using logistic regression with rank as the independent variable (Data Supplement). Calculations were performed using Stata statistical software version 13.0 (StataCorp, College Station, TX).

RESULTS

Location of cardiac injury was identified for 456 women, and these women were included in the study. The other 507 eligible women were not included because their cardiology record was unavailable (n = 250), their injury location was not documented (n = 243), or their regimen was identical in left-sided and right-sided breast cancer (n = 14; Data Supplement).

LV Injury

Information on location of LV injury was obtained for 712 LV segments in 414 women. The case-defining event was myocardial infarction in 91% of women (376 of 414 women), coronary artery disease in 7% (29 of 414 women), and death certificate information in 2% (nine of 414 women; Table 1). For 57% of women (234 of 414 women), available information included at least one of the following: echocardiogram, multiple-gated acquisition or myocardial perfusion scan, or autopsy. For the remaining 43% of women (180 of 414 women), information on LV injury location was available only from ECGs.

Radiotherapy was for left-sided cancer in 243 women and right-sided cancer in 171 women, giving a left-versus-right ratio of 1.42 (95% CI, 1.17 to 1.73), resulting from the larger LV radiation doses in left-sided cancer (average of typical LV doses in women with LV injury: left-sided, 8.3 Gy; right-sided, 0.6 Gy; left-minus-right dose difference, 7.7 Gy). The left-versus-right ratio did not vary significantly according to initial information on case-defining event, type of information documenting the injury location, or presence of cardiac risk factors at time of cancer diagnosis (P for heterogeneity $> .10$ for all three factors).

Average whole-heart doses were 6.9 Gy for left-sided radiotherapy and 3.2 Gy for right-sided radiotherapy. Exposure of the heart was nonuniform for all regimens, with substantial variation in doses received by different cardiac segments (Fig 2). For left-sided breast cancer, the LV apex received the highest doses for most regimens. For right-sided breast cancer, the entire LV was outside the fields for most regimens.

Ninety women had injury to the inferior LV segment after left-sided radiotherapy compared with 96 women after right-sided

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Table 1. Characteristics of 456 Women Who Underwent Radiotherapy for Breast Cancer and Subsequently Experienced a Cardiac Event and for Whom Information Was Available on the Location of the Cardiac Injury

Characteristic	Women With Documented Location of Left Ventricular Injury[a]				Women With Documented Location of Coronary Artery Disease[a]			
	Left (No.)[b]	Right (No.)[b]	Left-Versus-Right Ratio (95% CI)[c]	*P* for Heterogeneity	Left (No.)[b]	Right (No.)[b]	Left-Versus-Right Ratio (95% CI)[c]	*P* for Heterogeneity
Initial information on case-defining event				.49				.66
Hospital discharge register								
Myocardial infarction	218	158	1.38 (1.12 to 1.69)		40	28	1.43 (0.88 to 2.32)	
Coronary artery disease	20	9	2.22 (1.01 to 4.88)		34	23	1.48 (0.87 to 2.51)	
Death certificate only	5	4	1.25 (0.34 to 4.65)		6	2	3.00 (0.61 to 14.86)	
Information documenting location of injury[d]				.58				.10
Angiogram	—	—	—		80	53	1.51 (1.07 to 2.14)	
ECG[e]	218	158	1.38 (1.12 to 1.69)		—	—	—	
Echocardiogram	94	80	1.17 (0.87 to 1.58)		—	—	—	
Perfusion	4	3	1.33 (0.30 to 5.96)		—	—	—	
Multigated acquisition scan	2	1	2.00 (0.18 to 22.1)		—	—	—	
Autopsy	37	17	2.18 (1.23 to 3.87)		15	4	3.75 (1.24 to 11.30)	
Ventriculography	1	1	1.00 (0.06 to 16.0)		—	—	—	
Cardiac risk factors documented at time of breast cancer diagnosis				.97				.38
Previous diagnosis of ischemic heart disease[f]	21	15	1.40 (0.68 to 2.52)		11	6	1.83 (0.68 to 4.96)	
Any other cardiac risk factor[g]	118	81	1.46 (1.11 to 1.95)		38	20	1.90 (1.11 to 3.27)	
No known risk factor	104	75	1.39 (1.07 to 1.91)		31	27	1.15 (0.69 to 1.92)	
All women[h]	243	171	1.42 (1.17 to 1.73)		80	53	1.51 (1.07 to 2.14)	
Average of typical radiation doses to left ventricle/main coronary arteries, Gy	8.3	0.6	—		8.0	0.6	—	
Mean heart dose, Gy	6.9	3.2	—		6.9	3.2	—	

[a]Ninety-one women had evidence of both left ventricular injury and coronary artery disease with ≥ 70% stenosis.
[b]Numbers of women with injury after radiotherapy for left-sided and right-sided breast cancer.
[c]Ratio of the number of women with left-sided breast cancer to the number of women with right-sided breast cancer.
[d]Some women had information from more than one source. Information on the location of the left ventricular injury for 234 women was obtained from at least one of the following: echocardiogram, myocardial perfusion scan, multiple-gated acquisition scan, autopsy, or ventriculography. For the other 180 women, information on the location of the injury was available only from ECGs. Of these, 108 women had left-sided breast cancer and 72 had right-sided breast cancer, and the left-versus-right ratio was 1.50 (95% CI, 1.11 to 2.02).
[e]ECG only *v* all other women, *P* for difference = .64.
[f]Women with myocardial infarction or angina cited in their oncology record at the time of breast cancer diagnosis or for whom ischemic heart disease had been recorded as a primary diagnosis in the hospital discharge register before breast cancer diagnosis.
[g]The factors associated with subsequent risk of heart disease in women without a history of ischemic heart disease included factors for which the association was likely to be causal (eg, current smoker) and factors for which the association was indirect (eg, history of chronic obstructive pulmonary disease). Further details are given elsewhere.[8]
[h]Additional characteristics of the women are listed in the Data Supplement.

radiotherapy, giving a left-versus-right ratio of 0.94 (95% CI, 0.70 to 1.25; Fig 3C). The average typical inferior segment doses were 3.7 Gy for left-sided radiotherapy and 1.0 for right-sided radiotherapy, giving a left-minus-right difference of 2.7 Gy. For other segments, the left-versus-right ratios were as follows: lateral, 1.42 (95% CI, 1.04 to 1.95); septal, 2.09 (95% CI, 1.37 to 3.19); anterior, 1.85 (95% CI, 1.39 to 2.46); and apex, 4.64 (95% CI, 2.42 to 8.90); the corresponding left-minus-right differences in segment dose were 4.9, 7.2, 10.4, and 21.6 Gy, respectively (P_{trend} across all segments $< .001$).

Twenty radiotherapy techniques were used (Data Supplement). For the two most common (tangential and anterior electron or orthovoltage), the left-versus-right ratios of women with injury to individual LV segments increased with increasing left-minus-right segment dose difference (tangential, $P_{trend} = .005$; anterior electron or orthovoltage, $P_{trend} = .004$; Figs 3A and 3B; Data Supplement).

The left-versus-right ratio of injury increased with the left-minus-right difference in typical dose both for the 99 women irradiated after breast-conserving surgery ($P_{trend} = .05$; Fig 4A) and for the 315 women irradiated after mastectomy ($P_{trend} < .001$; Fig 4C). Ninety of the 99 women who underwent breast-conserving surgery received tangential radiotherapy, and in these women, the left-versus-right ratio of injury still tended to increase with the left-minus-right difference in typical dose ($P_{trend} = .06$; Fig 4B).

Coronary Artery Disease

Information on location of coronary artery stenosis was obtained for 221 segments in 133 women. The initial case-defining event was myocardial infarction in 51% of the women (68 of 133 women), coronary artery disease in 43% (57 of 133 women), and death certificate information in 6% (eight of 133 women; Table 1). Coronary angiography was available for all 133 women, and for 19 women, an autopsy report was also available. Eighty women were irradiated for left-sided cancer and 53 for right-sided cancer (left-versus-right ratio, 1.51; 95% CI, 1.07 to 2.14), with typical doses to the main coronary arteries combined of 8.0 and 0.6 Gy, respectively. As with LV injury, the left-versus-right ratio did not vary significantly according to the initial case-defining event information, type of information documenting location of injury, or

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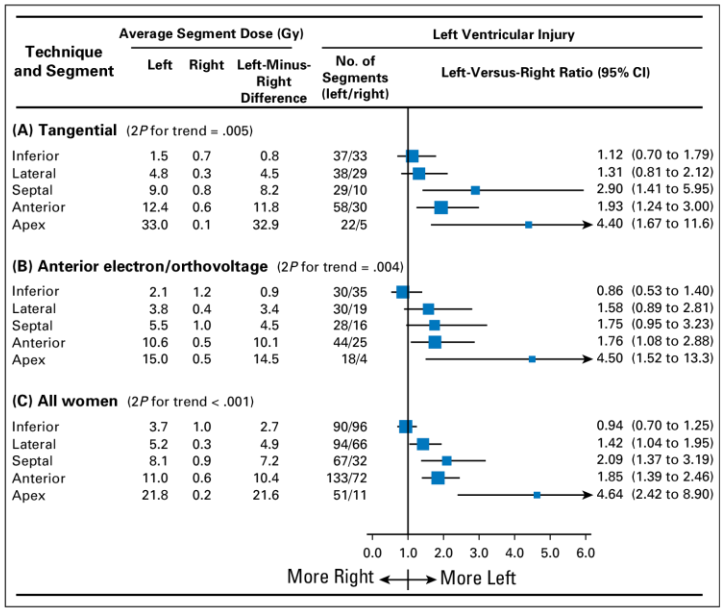


Fig 3. Left ventricular segment injury by radiotherapy technique. Average typical doses to ventricular segments in radiotherapy for left-sided and right-sided breast cancer and numbers of women with ventricular injury in left-sided and right-sided breast cancer are shown. In each panel, segments are listed in order of difference in the average of the typical segment doses received in left-sided and right-sided breast cancer for women with injury to the segment concerned (ie, left-minus-right difference). Some women had injury to more than one segment. Mean times to cardiac events were as follows: (A) tangential left, 10.8 years; tangential right, 12.4 years; (B) anterior electron or orthovoltage left, 14.2 years; anterior electron or orthovoltage right, 14.4 years; (C) all women left, 13.7 years; and all women right, 14.5 years.

presence of cardiac risk factors at breast cancer diagnosis (P for heterogeneity $\geq .10$ for all three factors).

Average whole-heart doses were 7.1 Gy for left-sided radiotherapy and 3.1 Gy for right-sided radiotherapy. For left-sided radiotherapy, part of the LAD coronary artery was included in the fields for most regimens, whereas part of the right coronary artery was usually irradiated in right-sided radiotherapy (Fig 2). Left-versus-right ratios of women with disease in any of the six individual coronary artery segments were as follows: proximal right, 0.48 (95% CI, 0.26 to 0.91); mid or distal right, 1.69 (95% CI, 0.85 to 3.36); proximal circumflex, 1.46 (95% CI, 0.72 to 2.96); distal circumflex, 1.11 (95% CI, 0.45 to 2.73); proximal LAD, 1.89 (95% CI, 1.07 to 3.34); and mid or distal LAD, 2.33 (95% CI, 1.19 to 4.59); the corresponding left-minus-right dose differences were −5.0, −2.5, 1.6, 3.5, 9.5, and 38.8 Gy respectively ($P_{trend} = .002$; Fig 5D).

When women given radiotherapy after breast-conserving surgery and mastectomy were considered separately, the left-versus-right ratio of segment injury increased with left-minus-right segment dose difference for both (breast-conserving surgery, $P_{trend} = .02$; mastectomy, $P_{trend} = .05$; Figs 5A and 5C). Notably, for radiotherapy after mastectomy, typical doses to the right coronary artery proximal segment were higher for right-sided than left-sided radiotherapy (left-sided dose, 10.8 Gy; right-sided dose, 15.1 Gy; left-minus-right dose difference, −4.3 Gy), and more women with right-sided than left-sided breast cancer had disease of this segment (left-versus-right ratio, 0.42; 95% CI, 0.20 to 0.87). Results for whole coronary arteries were similar (Data Supplement).

DISCUSSION

We have extended the commonly used technique of comparing the numbers of women with heart disease after radiotherapy for left-sided and right-sided breast cancer to provide insight into the effect of radiotherapy on individual segments of the LV and coronary arteries. We have shown that, for segments where there was little difference in the typical dose received from radiotherapy for left-sided and right-sided breast cancer, the left-versus-right ratios of the numbers of women with injury were close to 1. However, as the differences in typical segment dose between left-sided and right-sided cancer increased, so did the left-versus-right ratios of the numbers of women with injury to the segment concerned. Most increases were statistically significant when the left-minus-right difference in typical dose was greater than approximately 4 Gy. Notably, when the typical dose from right-sided radiotherapy was $>$ 4 Gy higher than from left-sided radiotherapy, the left-versus-right ratio of the number of women with injury was significantly lower than 1. Radiation-related increases in injury were seen throughout the cardiac structures studied, including the lateral, septal, anterior, and apex LV segments; the proximal right coronary artery segment; and the proximal and mid or distal LAD segments. These findings strongly suggest a close and direct relation between radiation exposure and injury to different segments of the LV and coronary arteries.

The 963 women eligible for this study formed the patient cases in a population-based case-control study. Any differences between the 456 women included in this study and the remaining 507

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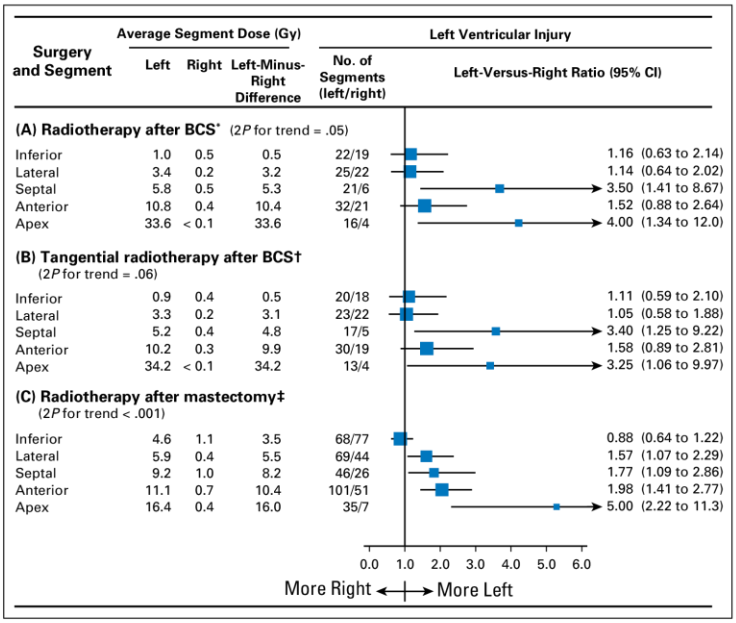


Fig 4. Left ventricular (LV) segment injury by type of surgery and radiotherapy technique. Average typical doses to ventricular segments in radiotherapy for left-sided and right-sided breast cancer and numbers of women with ventricular injury in left-sided and right-sided breast cancer are shown. In each panel, segments are listed in order of difference in the average of the typical segment doses received in left-sided and right-sided breast cancer for women with injury to the segment concerned (ie, left-minus-right difference). Some women had injury to more than one segment. (*) Radiotherapy after breast-conserving surgery (BCS) included tangential radiotherapy in 90 of 99 women and anterior electron or orthovoltage radiotherapy in nine of 99 women. (†) Tangents delivered after BCS involved smaller left-minus-right dose differences to most LV segments than tangents after mastectomy because the fields were not as wide, with the medial border typically midline rather than contralateral. (‡) Techniques included tangential in 76 of 315 women, anterior electron or orthovoltage in 136 of 315 women, cobalt chain in 66 of 315 women, and anterior megavoltage in 37 of 315 women. Mean times to cardiac events were as follows: (A) radiotherapy after BCS left, 7.6 years; radiotherapy after BCS right, 9.6 years; (B) tangential radiotherapy after BCS left, 7.5 years; tangential radiotherapy after BCS right, 9.7 years; (C) radiotherapy after mastectomy left, 15.6 years; and radiotherapy after mastectomy right, 16.0 years.

women who were not included are unlikely to have biased our results (Data Supplement). For the women studied, it is unlikely that breast cancer laterality affected the decision to give radiotherapy or the regimen used; in the population from which the women in our study were drawn, the ratio of the number of women irradiated for left-sided versus right-sided cancer was 1.1 (left breast cancer incidence is slightly higher than that of right breast cancer), and the characteristics of the women irradiated for left-sided and right-sided cancer were virtually identical, as was their subsequent mortality from all causes other than heart disease.[5] Hence, it is likely that the increases in segment injury reported are causally related to radiation.

A limitation of our study was that individual CT information was unavailable because the women were irradiated before the era of three-dimensional CT radiotherapy planning. Therefore, it was necessary to estimate cardiac doses retrospectively using a typical CT scan. Reassuringly, our cardiac dose estimates are similar to other estimates for these regimens.[15,16] Furthermore, we showed that dosimetric uncertainties had little effect on the use we made of our segment dose estimates (Data Supplement).

A second limitation is that for most women with LV injury, we did not have information on possible disease of the coronary artery supplying the segment concerned. Nevertheless, for 91 women with information on both coronary artery disease and LV injury, LV injury tended to occur in segments supplied by the diseased coronary arteries (Data Supplement). This may be a result of radiation-related coronary artery disease causing LV ischemia downstream. Alternatively, it may be a result of proximity of the coronary arteries to the LV segments they supply, resulting in similar radiation doses being received by both. Doses to many LV and coronary artery segments were highly correlated (Data Supplement). Hence, in our study, we could not tell whether radiation-related LV injury was caused directly by LV irradiation or indirectly by radiation-related coronary artery disease.

Myocardial perfusion defects (ischemic areas of the LV) after breast cancer radiotherapy have been demonstrated in studies involving a total of approximately 600 women. In some studies, women had cardiac imaging before and then months or years after left-sided radiotherapy, and each woman's pre- and postradiotherapy images were compared. In other studies, cardiac imaging was performed between 5 and 19 years after radiotherapy, and images of women given left-sided, right-sided, or no radiotherapy were compared.[17,18] The results of these studies are consistent with our study, although the clinical implications of the abnormalities are unknown. The myocardial perfusion studies did not provide segment doses, but several of them showed that the location of LV perfusion defects was determined by the borders of radiotherapy fields, rather than the distribution of major coronary vessels. This suggests defects were caused by damage to the myocardial microvasculature rather than coronary artery damage.[19] In two echocardiography studies including 70 women who received tangential radiotherapy, LV segment doses were related to subsequent segment function both before and a few weeks after

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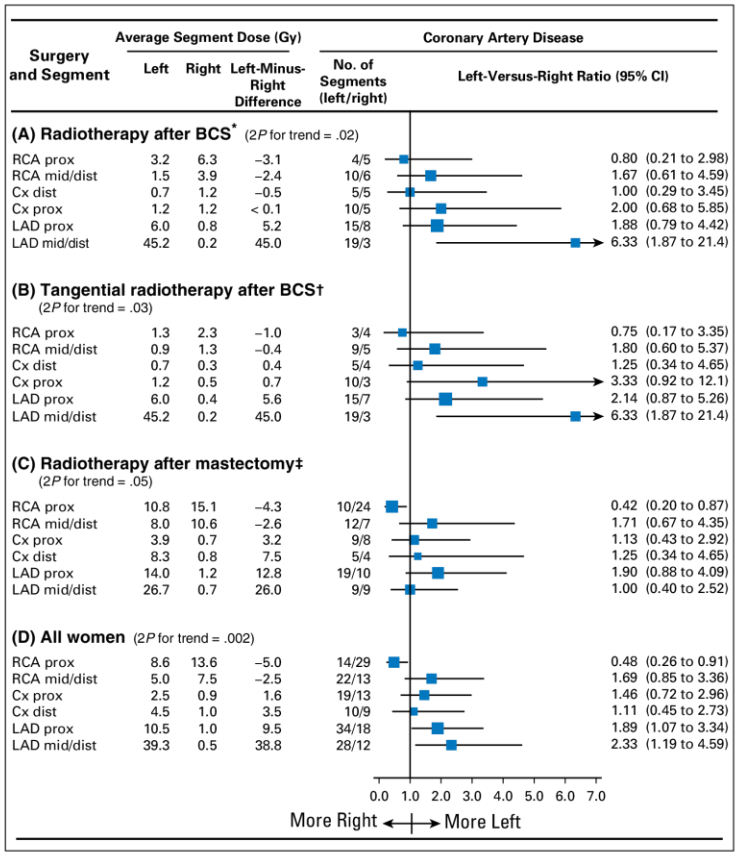


Fig 5. Coronary artery disease by type of surgery and radiotherapy technique. Average typical doses to arterial segments in radiotherapy for left-sided and right-sided breast cancer and numbers of women with coronary artery disease in left-sided and right-sided breast cancer are shown. Coronary artery disease was defined as ≥ 70% stenosis. In each panel, segments are listed in order of difference in the average of the typical doses received in left-sided and right-sided breast cancer for women with injury to the segment concerned (ie, left-minus-right difference). Some women had injury to more than one segment. One hundred twenty-eight women had information on diseased coronary artery segment and are included here. Five additional women had disease with known coronary artery location but not known segment. All 133 women are included in the Data Supplement. (*) Radiotherapy after breast-conserving surgery (BCS) included tangential radiotherapy in 48 of 53 women and anterior electron or orthovoltage radiotherapy in five of 53 women. (†) Tangents delivered after BCS involved smaller left-minus-right dose differences to most left ventricular segments than tangents after mastectomy because the fields were not as wide, with the medial border typically midline rather than contralateral. (‡) Techniques included tangential in 16 of 75 women, anterior electron or orthovoltage in 38 of 75 women, cobalt chain in 11 of 75 women, and anterior megavoltage in 10 of 75 women. Mean times to cardiac events were as follows: (A) radiotherapy after BCS left, 7.0 years; radiotherapy after BCS right, 9.8 years; (B) tangential radiotherapy after BCS left, 7.1 years; tangential radiotherapy after BCS right, 9.6 years; (C) radiotherapy after mastectomy left, 19.3 years; radiotherapy after mastectomy right, 17.2 years; (D) all women left, 13.5 years; and all women right, 14.7 years. Cx, circumflex; dist, distal; LAD, left anterior descending artery; prox, proximal; RCA, right coronary artery.

radiotherapy.[20,21] The LV apex received the highest doses from left tangential radiotherapy and had poorer function after radiotherapy than other segments. Function was significantly reduced in LV segments that received > 3 Gy.

Disease of the main coronary arteries has been demonstrated in three studies of patients referred for angiography some years after radiotherapy.[22-24] The studies, which were based on a total of 149 irradiated patients, found that coronary stenoses occurred preferentially in arterial segments likely to have received high radiation doses and are consistent with our findings.

In breast cancer radiotherapy, cardiac radiation doses have decreased over recent years. Women in the present study were irradiated between 1958 and 2001 and received mean heart doses of approximately 7 and 3 Gy for left-sided and right-sided breast cancer, respectively. In a systematic review of regimens in studies published from 2003 to 2013, average mean heart doses were 5.4 Gy (range, < 0.1 to 28.6 Gy) in 398 left-sided regimens and 3.3 Gy (range, 0.4 to 21.6 Gy) in 45 right-sided regimens.[11]

Currently, most women irradiated for breast cancer have tangential radiotherapy after breast-conserving surgery,[11] which is often considered risk free. However, in some countries, modern left tangential radiotherapy still delivers heart doses of several Gy,[11] and the LV apex and mid or distal LAD coronary artery segments are still in the radiation fields for some women.[12] In our study, the left-versus-right ratios for injury to these segments from tangential radiotherapy after breast-conserving surgery were approximately 3 for the LV apex and approximately 6 for the mid or distal LAD segment, indicating that irradiating these segments causes injury and that, where possible, they should be excluded from fields using cardiac-sparing techniques.[12,13]

In breast cancer, cardiac exposure from radiotherapy may increase in the future, because recent studies have shown that internal mammary radiotherapy improves breast cancer survival[25-27] and it is difficult to irradiate the internal mammary chain without incidentally irradiating the heart.[11] In addition, some women have unfavorable anatomy where incidental cardiac irradiation is unavoidable. In Hodgkin lymphoma, lung cancer,

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and esophageal cancer, the tumor can lie close to the heart,[10,13] rendering it difficult to achieve full tumor dose without exposing the heart. With modern three-dimensional CT-based radiotherapy planning, doses to small regions (eg, cardiac segments) can be modified by changing beam angles or using different techniques, so oncologists may have choice over exposure to individual structures. However, there is lack of consistency in radiotherapy guidelines on which cardiac structures are sensitive to radiation and should therefore be avoided. In radiotherapy for breast cancer and lymphoma, this is reflected by differing cardiac dose constraints. For example, in some countries, but not in others, the LAD coronary artery is considered a separate organ at risk, with more stringent dose constraints than the heart.[28-30] We demonstrated associations between radiation dose and injury for both LV and coronary artery segments. Therefore, the safest strategy, based on current knowledge, is to minimize dose to all segments.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cardiac Structure Injury After Radiotherapy for Breast Cancer: Cross-Sectional Study With Individual Patient Data

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ARTICLE
Clinical Study

Cardiovascular disease incidence after internal mammary chain irradiation and anthracycline-based chemotherapy for breast cancer

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BACKGROUND: Improved breast cancer (BC) survival and evidence showing beneficial effects of internal mammary chain (IMC) irradiation underscore the importance of studying late cardiovascular effects of BC treatment.
METHODS: We assessed cardiovascular disease (CVD) incidence in 14,645 Dutch BC patients aged <62 years, treated during 1970–2009. Analyses included proportional hazards models and general population comparisons.
RESULTS: CVD rate-ratio for left-versus-right breast irradiation without IMC was 1.11 (95% CI 0.93–1.32). Compared to right-sided breast irradiation only, IMC irradiation (interquartile range mean heart doses 9–17 Gy) was associated with increases in CVD rate overall, ischaemic heart disease (IHD), heart failure (HF) and valvular heart disease (hazard ratios (HRs): 1.6–2.4). IHD risk remained increased until at least 20 years after treatment. Anthracycline-based chemotherapy was associated with an increased HF rate (HR = 4.18, 95% CI 3.07–5.69), emerging <5 years and remaining increased at least 10–15 years after treatment. IMC irradiation combined with anthracycline-based chemotherapy was associated with substantially increased HF rate (HR = 9.23 95% CI 6.01–14.18), compared to neither IMC irradiation nor anthracycline-based chemotherapy.
CONCLUSIONS: Women treated with anthracycline-based chemotherapy and IMC irradiation (in an older era) with considerable mean heart dose exposure have substantially increased incidence of several CVDs. Screening may be appropriate for some BC patient groups.

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INTRODUCTION

Breast cancer (BC) survival has improved substantially in recent decades due to earlier diagnosis and treatment advances.[1–5] At present, both radiation therapy (RT) and anthracycline-based chemotherapy are commonly used. They cure many women of their cancer but both treatments have been associated with increased risks of cardiovascular disease (CVD).[6,7] Radiation-related CVDs include ischaemic heart disease (IHD) and valvular heart disease (VHD), with evidence for dose-dependency.[8–10] Previously, RT-related CVDs were thought not to emerge until 10 years after exposure.[11–15] Recently, however, increased risks have been observed within 5 years of exposure.[8,16] Anthracycline-based chemotherapy is associated with an increased, dose-dependent risk of cardiomyopathy (CMP) and heart failure (HF).[17–19] However, the reported cumulative HF incidence after anthracycline-based chemotherapy varies.[20–23]

Since the 1970s, thousands of women in the Netherlands have been treated with internal mammary chain (IMC) irradiation using techniques that deliver substantial radiation doses to the heart. Since the 1990s, many women in the Netherlands have also received anthracycline-based chemotherapy. The absolute heart disease risks for women treated in the past are currently unclear, and it is not known which women might benefit from surveillance for heart disease.

Recent randomised trials have reported a BC-specific survival benefit after nodal irradiation, including IMC irradiation.[24,25] This has re-opened the debate on the role of IMC irradiation in BC treatment.[26] Women given IMC radiotherapy today may still receive around 8 Gy,[27–30] but some cancer centres achieve much lower heart doses.[28,29,31] Many of these women also receive anthracycline-based chemotherapy. Identifying interactions between RT and anthracycline-based chemotherapy or

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established cardiovascular risk factors[8,11,32] is therefore relevant to women treated today.

Here we report the separate and combined effects of various radiation fields, chemotherapy types and established cardiovascular risk factors on the long-term risks of IHD, VHD and HF in a large cohort of BC patients aged <62 years at diagnosis.

METHODS

Data collection procedures

Female BC patients (stages I–IIIA or ductal carcinoma in situ [DCIS]) were selected from the hospital-based registries of the Netherlands Cancer Institute, Amsterdam or the Erasmus MC - Cancer Institute, Rotterdam, the Netherlands. All patients were diagnosed during 1970–2009 and before the age of 62 years. Data collection procedures have been published previously.[11] In brief, patient and tumour characteristics, BC treatments (also locoregional recurrences and subsequent BCs) and CVD events were collected from registries and patient records. Patients were scored positive for hypertension, diabetes mellitus or hypercholesterolaemia if they received treatment for these conditions. Supplementary methods I shows detailed data collection procedures and patient eligibility criteria.

To complete information on CVD incidence, cardiovascular risk factors and causes of death, questionnaires were sent to general practitioners (GPs)[i] and, if applicable, cardiologists of all patients. ([i]In the Netherlands, all residents are expected to have a primary care physician. Medical correspondence from attending physicians is sent to the primary care physician. Such records are preserved by the primary care physicians throughout a patient's life and for at least 15 years after a patient's death). Date of death was acquired through the population-based municipal personal records database.

In the current study, women treated with trastuzumab or taxanes (with or without anthracycline-based chemotherapy) for their primary BC ($n = 979$) were excluded, since follow-up was short and the numbers of events were too small to examine the effects of these treatments on CVD risks. The total analytic cohort comprised 14,645 patients.

Treatment

A detailed description of the treatment modalities used in our cohort from 1970 to 1986 has been published previously.[11] During the 1970s, standard treatment for stage I–IIIa BCs consisted of mastectomy, with/without RT. In 1975, CMF (cyclophosphamide, methotrexate and fluorouracil) chemotherapy was introduced for premenopausal lymph node-positive patients. Breast-conserving surgery followed by whole breast irradiation was introduced in 1980. For women who underwent mastectomy, chest wall irradiation was indicated following incomplete resection or for extensive locoregional tumours. Regional nodal irradiation, including IMC irradiation, was used for women with positive axillary nodes and, in some cases, medial tumours. From the 1990s, anthracycline-based chemotherapy was used for most premenopausal, and later also for postmenopausal, lymph-node positive patients and for lymph-node negative patients with unfavourable tumour characteristics. Most common anthracycline dose was four times 60 mg/m^2 (doxorubicin equivalent) during the study period. DCIS was treated with either wide local excision followed by whole-breast RT or with mastectomy.

In previous decades, IMC irradiation usually consisted of direct photon beams, sometimes combined with electron beams, giving a total target dose of 36–54 Gy in 12–26 fractions. In the most recent treatment period, IMC irradiation consisting of a combination of oblique photon and electron beams giving a total target dose of 50 Gy (25 fractions) resulting in lower exposure of the heart was introduced.[33] Chest wall irradiation usually consisted of a direct electron beam giving a total target dose of 35–46 Gy (15–23 fractions). Whole breast irradiation usually consisted of tangential photon beams giving a total target dose of 44–52 Gy (22–26 fractions); most women also received a boost dose to the tumour bed.

Dosimetry

Dosimetry was performed to provide an indication of the typical level of cardiac exposure for women who received RT to different regions, according to laterality and IMC irradiation, during different time periods. Detailed information on the RT received was available for a sample of 683 women in the study cohort. Over 90% of these women were treated before the era of RT computed tomographic (CT) planning. Typical mean heart doses were estimated by reconstructing 44 different regimens on a "typical CT scan" (Supplementary methods II: Dosimetry). Dose distributions were generated for cobalt, electron and megavoltage beams using modern 3-dimensional CT treatment planning (Varian EclipseTM Treatment Planning System [TPS] version 10.0.39 [Varian Medical Systems, Palo Alto, USA]) and for orthovoltage fields using manual planning. A typical mean heart dose was allocated to each woman according to her regimen and total dose. Women were then categorised according to laterality and whether they received IMC irradiation. Within these categories, the typical doses were averaged. Given the large total number of women in the cohort, individual dosimetry was not undertaken and therefore no dose–response analyses have been performed.

Statistical analysis

BC treatments received throughout follow-up (including treatment for contralateral BCs and locoregional recurrences) were classified time-varyingly. Chemotherapy regimens were categorised as CMF-like or anthracycline-based regimens. Differences in the likely radiation exposure of the heart were accounted for by considering laterality and radiation fields (breast, chest wall, IMC).

Because collection of CVD incidence for patients treated during 1970–1986 was restricted to 10-year survivors,[11] time-at-risk started 10 years after BC diagnosis for patients diagnosed ≤1986 and 1 year after BC diagnosis for patients diagnosed >1986. Time-at-risk ended at date of event of interest, death, emigration, distant metastasis or date of last information, whichever came first.

General population comparisons. The incidence rate of myocardial infarction (MI) and HF (comprising congestive HF and CMP) in the cohort was compared with age-, sex- and calendar period-specific CVD incidence rates for the Dutch population.[34,35] No comparable reference rates were available for VHD and angina pectoris (AP). We calculated standardised incidence ratios (SIRs) and absolute excess risks and estimated 95% confidence intervals (CIs).[36]

Within-cohort comparisons. We assessed the association between treatments and CVD risk using proportional hazard models. A cardiovascular event was defined as a CVD diagnosis or death due to CVD. We estimated risks for any CVD (ICD-10 I20–52) and separately for IHD (MI and AP), VHD and HF. When analysing a specific CVD, the presence of any other CVD was treated as a time-dependent covariate. Additionally, age at BC, CVD history, risk factors at BC diagnosis (dichotomised into yes/no) and smoking were included in the models as main effects. Treatment-specific cumulative CVD incidence was estimated in patients above and below 50 years at BC diagnosis (to avoid mixing different age/treatment distributions), in the presence of death from causes other than CVD as a competing risk.[37] Model assumptions were verified using residual-based methods. Because the proportional hazard assumption did not hold for the IHD rate after IMC and chest wall irradiation, analyses are presented separately for <10

Table 1. Characteristics of hospital-based cohort of 14,645 breast cancer patients by year of breast cancer diagnosis

			Year of breast cancer diagnosis					
	Total		1970–1986		1987–1999		2000–2009	
Characteristic	No.	%	No.	%	No.	%	No.	%
Total no. of patients	14,645	100	3571	100	6626	100	4448	100
Age at diagnosis (years)								
Median (IQR)	47 (42–52)		47 (42–53)		46 (41–50)		51 (45–56)	
<35 years[a]	1010	6.9	236	6.6	562	8.5	212	4.8
35–40 years	1568	10.7	433	12.1	813	12.3	322	.2
40–49 years	6586	45.0	1600	44.8	3486	52.6	1500	33.7
50–61 years	5481	37.4	1302	36.5	1765	26.6	2414	54.3
Stage								
Ductal carcinoma in situ	929	6.3	40	1.1	318	4.8	571	12.8
I	4436	30.3	327	9.2	2168	32.7	1941	43.6
II	5251	35.9	433	12.1	3427	51.7	1391	31.3
IIIa	497	24.1	4	0.1	256	3.9	308	5.3
Unknown	3532	3.4	2767	77.5	457	6.9	237	6.9
Type of surgery[b]								
Mastectomy	8186	55.9	1139	31.9	4178	63.1	2869	64.5
Wide local excision	5127	35.0	2423	67.9	1639	24.7	1065	23.9
Type of surgery unknown	1332	9.1	9	0.3	809	12.2	514	11.6
Radiation therapy and chemotherapy[b]								
None	1663	11.4	439	12.3	578	8.7	646	14.5
Radiation therapy alone	8137	55.6	2513	70.4	3502	52.9	2122	47.7
Chemotherapy alone	406	2.8	19	0.5	216	3.3	171	3.8
Radiation therapy and chemotherapy	4439	30.3	600	16.8	2330	35.2	1509	33.9
Radiation fields[b]								
No radiation therapy	2069	14.2	458	12.8	794	12.0	817	18.4
Breast, no IMC	6301	43.0	621	17.4	3285	49.6	2395	53.8
Typical mean heart dose left/right (Gy)	4.8/0.6 Gy		4.3/0.6 Gy		4.8/0.7 Gy		1.5/0.3 Gy	
Chest wall, no IMC	796	5.4	337	9.4	382	5.8	77	1.7
Typical mean heart dose left/right (Gy)	5.8/2.8 Gy		4.0/2.8 Gy		6.3/2.8 Gy		1.5/0.3	
IMC, no chest wall or breast	2269	15.5	1164	32.6	850	12.8	255	5.7
Typical mean heart dose left/right (Gy)	14.7/8.9 Gy		12.2/8.9 Gy		16.5/9.9 Gy		16.1/9.4 Gy	
IMC and breast	1429	9.8	475	13.3	679	10.3	275	6.2
Typical mean heart dose left/right (Gy)	16.6/13.4 Gy		16.6/15.3 Gy		21.8/13.4 Gy		9.1/9.2 Gy	
IMC and chest wall	806	5.5	430	12.0	226	3.4	150	3.4
Typical mean heart dose left/right (Gy)	16.1/10.1 Gy		14.8/12.6 Gy		16.4/10.5 Gy		16.1/1.7 Gy	
Unknown	975	6.7	86	2.4	410	6.2	479	10.8
Chemotherapy regimen[b]								
No	9800	66.9	2952	82.7	4080	61.6	2768	62.2
CMF-like regimens	2029	13.9	619	17.4	1422	21.5	0	0
Anthracycline-based regimens[c]	2816	19.2	0	0	1124	17.0	1680	37.8
Endocrine therapy[b]								
No	12,205	83.3	3503	98.1	6.043	91.2	2659	59.8
Yes	2440	16.7	68	1.9	583	8.8	1789	40.2
Cardiovascular risk factors at breast cancer diagnosis[d]								
None known	10,908	74.5	1875	52.5	5132	77.5	3901	87.7
Hypertension, hypercholesterolemia or diabetes mellitus	671	4.6	355	9.9	186	2.8	130	2.9
Smoking[e]	2966	20.3	1265	35.4	1326	20.0	375	8.4
History of cardiovascular disease	484	3.3	315	8.8	82	1.3	97	2.0
Follow-up time (years)								
Median (IQR)	14 (9–20)		23 (17–28)		15 (9–19)		9 (6–11)	
1–4 years	1297	9.8	0	0	917	15.1	380	10.6

Table 1 continued

Characteristic	Total		Year of breast cancer diagnosis					
			1970–1986		1987–1999		2000–2009	
	No.	%	No.	%	No.	%	No.	%
5–9 years	2604	19.7	0	0	723	11.9	1881	52.6
10–19 years	5816	44.0	1344	37.7	3154	52.0	1318	36.8
20–29 years	2979	22.5	1702	47.7	1277	21.1	0	0
≥30 years	523	4.0	523	14.7	0	0	0	0
Vital status								
Alive	10,064	68.7	1889	52.9	4240	64.0	3935	88.5
Deceased	4580	31.3	1682	47.1	2385	36.0	513	11.5

IQR interquartile range, *IMC* internal mammary chain. [a]Median age for patients aged <35 years at diagnosis was 32 years, with an interquartile range of 30–34 years. [b]Mutually exclusive treatment groups, taking into account primary treatment only. [c]Including either epirubicin or doxorubicin. [d]335 patients had more than one of the mentioned cardiovascular risk factors at breast cancer diagnosis and these patients are listed more than once. The most frequent combinations involved current or previous smoking. [e]Smoking defined as quit shortly before breast cancer diagnosis, smoker at breast cancer diagnosis or smoker during follow-up. 17.5 % of the cohort had never smoked. Smoking information was missing for 62.3% of the cohort

and ≥10 years after treatment.

We evaluated whether the observed data were consistent with an additive or a multiplicative model for the joint effect of two risk factors A and B by likelihood ratio tests of $\gamma = 0$ in models HR$(A,B) = 1 + \beta_1 A + \beta_2 B + \gamma A{\times}B$ and HR$(A,B) = \exp(\alpha + \beta_1 A + \beta_2 B + \gamma A{\times}B)$.[38] Analyses were performed using Stata/SE 13.0 (StataCorp LP, College Station, TX) and EPICURE 1.8 (Hiro Soft International Inc, Seattle, WA). The study was approved by the review board of the Netherlands Cancer Institute.

RESULTS

The median follow-up duration of our cohort ($n = 14{,}645$) was 14 years, with 3486 patients followed ≥20 years. Median age at BC diagnosis was 47 years. Eighty six percent of patients received RT, of whom 36% had IMC irradiation. One third of the patients received chemotherapy (58% anthracycline-based). Few patients were treated for cardiovascular risk factors at BC diagnosis (4.6%), but >20% were current or past smokers (Table 1). A statistically significant but small difference in CVD history was observed between left- and right-sided BC patients (left-sided: 3.6%, right-sided: 3.0%). Other characteristics, including treatments, did not differ significantly by laterality (data not shown). BC treatment (including the receipt of IMC irradiation and anthracycline-based chemotherapy) was not associated with socioeconomic status, cardiovascular history at BC diagnosis or cardiovascular risk factors. (Supplementary table 7)

General population comparisons

Compared to the general population, our cohort had a higher MI rate (SIR = 1.4 95% CI 1.3–1.6), whereas the HF rate was not increased overall (SIR = 1.0 95% CI 0.9–1.1) (Table 2). While for HF the highest SIRs were seen for young ages at BC diagnosis, MI rates were increased only for older ages at diagnosis (Table 2). Subdividing the entire cohort by follow-up duration and treatment period, an increased HF rate was observed 1–9 years after treatment in patients treated ≥1987 (SIR = 1.4 95% CI 1.1–1.9 for 1987–1999 and 1.5 95% CI 1.0–2.0 for 2000–2009). In contrast, the increases in the MI rate were greatest in the longest follow-up intervals.

Among patients treated with neither RT nor chemotherapy, the MI rate was not increased (SIR = 0.8 95% CI 0.5–1.1) and the HF rate was decreased (SIR = 0.5 95% CI 0.4–0.8) compared with the general population. Increased MI rates were observed after RT (e.g. SIR = 1.5 95% CI 1.4–1.7 for patients treated with RT and without chemotherapy), while HF rates were increased after anthracycline-based chemotherapy (SIR = 4.6 95% CI 3.7–5.7).

Within-cohort comparisons

For women treated with RT, the lowest typical mean heart doses were for those who received right-sided breast irradiation without IMC (0.6 Gy, interquartile range (IQR) 0.3–0.7) (Table 1, Supplementary table 1). Compared to this group, women who received IMC irradiation (either left- or right-sided, average of mean heart doses for typical IMC irradiation 12.2 Gy, IQR 8.7–16.5) had significantly increased rates of all four cardiovascular outcomes: any CVD (hazard ratio (HR) = 1.56 95% CI 1.35–1.84), IHD (HR = 2.36 95% CI 1.74–3.22), VHD (HR = 1.63 95% CI 1.18–2.24) and HF (HR = 1.82 95% CI 1.27–2.63, based on inclusion of multiple CVDs per woman) (Summary model, Table 3). Increases were observed after both left- and right-sided IMC (Table 3) and with/without additional breast or chest wall radiation (Supplementary table 2). Increased rates of any CVD and of IHD were also seen after left chest wall irradiation (average of typical mean heart doses 5.8 Gy, IQR 3.8–5.3) when compared to right breast irradiation (HRs were 1.83 95% CI 1.39–2.40 and 2.57 95% CI 1.61–4.11, respectively). In the entire cohort, no significant increases were observed in women with left breast irradiation (average of mean heart doses 4.7 Gy, IQR 1.5–4.8) compared to those treated with right breast irradiation (HR for IHD 1.38 95% CI 0.96–1.99, Supplementary table 2); yet, for women treated at age ≤50 years an increased rate of IHD was observed (HR = 1.70 95% CI 1.03–2.80) (Supplementary table 3). Additional analyses considered just the first cardiovascular event and found the following (very similar) HRs for women who received IMC irradiation compared with women who received right-sided breast irradiation without IMC: any CVD (HR = 1.49 95% CI 1.25–1.77), IHD (HR = 2.51 95% CI 1.70–3.72), VHD (HR = 1.57 95% CI 1.02–2.44) and HF (HR = 1.71 95% CI 0.99–2.94) (Supplementary table 4).

Women treated with anthracycline-based chemotherapy had increased rates of VHD (HR = 1.75 95% CI 1.16–2.65) and HF (HR = 4.32 95% CI 3.07–6.07) compared to no chemotherapy (Table 3, based on inclusion of multiple CVDs per woman). When just the first cardiovascular diagnosis was considered, the increase in HF was slightly reduced (HR = 3.93 95% CI 2.49–6.22) (Supplementary table 4). When including VHD events diagnosed on the same day as IHD/HF, the anthracycline-based chemotherapy-associated risk of VHD was still increased (HR = 1.70 95% CI 1.09–2.65), but when excluding such VHD events the HR dropped to 1.11 (95% CI 0.62–2.00). Additional stratification by treatment

Table 2. Comparison of myocardial infarction and heart failure rates with the general population

	Myocardial infarction[a]				Heart failure[a]			
	Observed	SIR	95% CI	AER	Observed	SIR	95% CI	AER
Total	394	1.4	1.3–1.6	8	396	1.0	0.9–1.1	0
Age at breast cancer diagnosis (years)								
<35	5	0.9	0.3–2.1	0	12	2.7	1.4–4.7	7
35–40	17	1.1	0.7–1.8	1	20	1.4	0.9–2.2	4
40–49	180	1.5	1.3–1.7	8	179	1.1	1.0–1.3	3
50–61	192	1.4	1.2–1.6	12	185	0.8	0.7–1.0	−8
Calendar period of breast cancer diagnosis and follow-up interval								
1970–1986								
10–19 years	128	1.3	1.1–1.5	21	91	0.8	0.7–1.0	−16
20+ years	120	2.1	1.7–2.5	210	127	0.9	0.7–1.0	−63
1987–1999								
1–9 years	41	0.7	0.5–1.0	-6	57	1.4	1.1–1.9	8
10–19 years	54	1.7	1.3–2.2	15	64	1.1	0.8–1.4	3
20+ years	8	1.7	0.7–3.4	24	9	0.8	0.4–1.5	−17
2000–2009								
1–9 years	26	1.5	1.0–2.2	7	36	1.5	1.0–2.0	9
10+ years	6	2.0	0.7–4.3	23	12	2.6	1.3–4.5	58
Radiation therapy and chemotherapy								
None	29	0.8	0.5–1.1	−5	33	0.5	0.4–0.8	−16
Radiation therapy alone	264	1.5	1.4–1.7	12	233	0.9	0.7–1.0	−5
Chemotherapy alone	6	2.6	0.9–5.5	13	8	2.7	1.2–5.3	16
Radiation therapy and chemotherapy	75	1.7	1.4–2.2	9	122	2.1	1.7–2.5	16
Radiation fields[b]								
Breast (no IMC)	87	1.2	0.9–1.4	2	81	0.8	0.6–1.0	−3
Chest wall (no IMC)	34	1.5	1.0–2.0	14	42	1.0	0.7–1.3	−1
IMC	203	1.9	1.6–2.1	23	205	1.2	1.0–1.4	6
Chemotherapy regimens								
CMF-like regimens	59	1.7	1.3–2.2	11	44	1.0	0.8–1.4	0
Anthracycline-based regimens[c]	22	1.5	0.9–2.2	3	86	4.6	3.7–5.7	33
Cardiovascular risk factor at BC diagnosis[d]								
None known	342	1.3	1.2–1.5	6	347	1.0	0.9–1.1	−1
At least one	52	2.3	1.7–3.0	42	49	1.3	1.0–1.8	17
Smoking								
Never	110	1.1	0.9–1.3	3	115	0.8	0.6–0.9	−10
Currently or previous	174	2.3	2.0–2.7	28	141	1.4	1.2–1.6	11
Unknown	110	1.0	0.8–1.2	0	140	0.9	0.8–1.1	−1

SIR standardised incidence ratio, *CI* confidence interval, *AER* absolute excess risk, *IMC* internal mammary chain. [a]Expected numbers were calculated using age-, sex- and calendar period-specific CVD incidence rates for the Dutch population. Myocardial infarction and heart failure incidence data from the Continuous Morbidity Registration Nijmegen of General Practices were used as reference rates for the years 1971–1999 and from the Netherlands Institute for Health Services Research Primary Care Database from 2000 onwards. Myocardial infarction included diagnoses I21–22 International Classification of Diseases, 10th revision. Heart failure included both cardiomyopathy and congestive heart failure; diagnoses I42 and I50 International Classification of Diseases, 10th revision. These were the only two cardiovascular diseases for which general population data were available. Just as in the general population registries, each individual patient in our cohort could have had a diagnosis of both myocardial infarction and heart failure. [b]Mutually exclusive treatment categories. [c]Including either epirubicin or doxorubicin. [d]Hypertension, hypercholesterolaemia or diabetes mellitus

period did not affect the estimates (results not shown). No increased CVD rates were observed comparing patients treated with endocrine therapy to no endocrine therapy.

The joint effects of IMC irradiation, anthracycline-based chemotherapy, cardiovascular risk factors at BC diagnosis and smoking were compatible with either an additive or a multiplicative relation for all CVDs (Supplementary table 6). For HF, however, the combined effect of IMC irradiation and anthracycline-based chemotherapy seemed more than additive ($p = 0.06$). A more than nine-fold increase was observed among patients treated with both IMC irradiation and anthracycline-based chemotherapy (HR = 9.23 95% CI 6.01–14.18), whereas the separate HRs were 2.14 (95% CI 1.55–2.96) and 5.10 (95% CI 3.12–8.34), respectively, all compared to either IMC or anthracycline-based chemotherapy (Table 3).

When analysing IHD rates by time since treatment, no significant increases were seen in the first 10 years (Fig. 1, Supplementary table 5). IMC irradiation during 1970–1986 or

Table 3. Within-cohort comparison of cardiovascular disease rates after breast cancer by treatment

	Any cardiovascular event			Ischaemic heart disease ≥10 years after breast cancer treatment[a]			Valvular heart disease			Heart failure[b]		
	n/*N*[d]	HR	(95% CI)	*n*/*N*[d]	HR	(95% CI)	*n*/*N*[d]	HR	(95% CI)	*n*/*N*[d]	HR	(95% CI)
Multivariable model[c]												
Radiation field[f]												
Breast, right-sided (no IMC)	230/2562	1.00	Ref.	48/1684	1.00	Ref.	51/2519	1.00	Ref.	40/2520	1.00	Ref.
Chest wall, right-sided (no IMC[e])	61/315	1.24	0.93–1.65	24/244	1.73	1.05–2.85	10/349	0.51	0.25–1.03	23/350	1.68	0.98–2.88
IMC, right-sided (+/− breast/chest wall)	344/1804	1.50	1.26–1.78	180/1478	2.54	1.84–3.52	97/1824	1.26	0.88–1.79	90/1824	1.78	1.21–2.61
Breast, left-sided (no IMC)	272/2761	1.11	0.93–1.32	70/1821	1.37	0.95–1.98	56/2797	1.00	0.69–1.47	41/2798	0.87	0.56–1.35
Chest wall, left-sided (no IMC[e])	71/302	1.83	1.39–2.40	96/226	2.57	1.61–4.11	16/352	0.91	0.50–1.62	20/352	1.42	0.80–2.50
IMC, left-sided (+/− breast/chest wall)	413/1963	1.66	1.41–1.97	190/1621	2.20	1.59–3.04	162/2002	2.00	1.44–2.78	118/2002	1.94	1.33–2.82
No radiation therapy	221/1825	1.21	1.00–1.46	72/1222	1.50	1.04–2.17	44/1738	0.78	0.52–1.18	44/1741	1.22	0.79–1.89
Chemotherapy[f]												
No chemotherapy	1258/8238	1.00	Ref.	506/6112	1.00	Ref.	336/8296	1.00	Ref.	274/8301	1.00	Ref.
CMF-like regimen	240/1727	1.00	0.87–1.16	105/1363	1.07	0.85–1.33	72/1751	1.15	0.88–1.50	44/1749	0.89	0.64–1.24
Anthracycline-based regimen	193/2252	1.51	1.25–1.82	21/1107	1.00	0.61–1.64	43/2262	1.75	1.16–2.65	84/2263	4.32	3.07–6.07
Endocrine therapy												
No endocrine therapy	1518/10201	1.00	Ref.	605/7614	1.00	Ref.	406/10283	1.00	Ref.	345/10286	1.00	Ref.
Endocrine therapy	173/2016	0.97	0.80–1.17	27/968	0.85	0.55–1.29	45/2026	1.22	0.83–1.79	57/2027	0.93	0.65–1.31
Summary model[h]												
Breast, right-sided (no IMC)	230/2562	1.00	Ref.	48/1684	1.00	Ref.	51/2519	1.00	Ref.	40/2520	1.00	Ref.
IMC (left- or right-sided, +/− breast/chest wall)	757/3629	1.56	1.35–1.84	370/3099	2.36	1.74–3.22	259/3826	1.63	1.18–2.24	208/3826	1.82	1.27–2.63
Joint effects of treatments[f,g]												
Breast RT (no IMC), no anthracyclines	441/4475	1.00	Ref.	111/3102	1.00	Ref.	97/4423	1.00	Ref.	59/4312	1.00	Ref.
IMC RT, no anthracyclines	690/3113	1.54	1.35–1.75	361/2697	2.00	1.50–2.66	242/3159	1.74	1.35–2.25	165/2993	2.14	1.55–2.96
Breast RT (no IMC), anthracyclines	61/848	1.52	1.16–1.99	7/402	1.88	0.90–3.93	10/893	1.24	0.64–2.40	20/941	5.10	3.12–8.34
IMC RT, anthracyclines	67/654	2.09	1.62–2.69	9/402	2.32	1.19–4.55	17/667	2.86	1.76–4.65	31/683	9.23	6.01–14.18
Test for departure from additivity/multiplicativity		$p = 0.70/0.74$			$p = 0.57/0.27$			$p = 0.51/0.96$			$p = 0.06/0.68$	

n/N number of events/number at risk, *HR* hazard ratio, *CI* confidence interval, *IMC* internal mammary chain, *Ref.* reference category. The analyses shown in this table include all diagnoses of cardiovascular disease, e.g. if a patient was diagnosed with ischaemic heart disease and then later with valvular heart disease, then both are listed. Analyses considering just the first diagnosis of cardiovascular disease are in Supplementary Table 4. [a]Because the proportional hazard assumption did not hold for the ischaemic heart disease rate after internal mammary chain and chest wall irradiation, results are shown here for ≥10 years after breast cancer treatment. No increased ischaemic heart disease rates were seen in the period <10 years after treatment. These results are presented in Supplementary Table 5. [b]Heart failure included both cardiomyopathy and congestive heart failure; diagnoses I42 and I50 International Classification of Diseases, 10th revision. [c]Hazard ratios estimated using one multivariable model containing radiation fields (right breast, right-sided chest wall, right-sided internal mammary chain field, left breast, left-sided chest wall, left-sided internal mammary chain field, no radiation therapy, unknown radiation fields), chemotherapy (no chemotherapy, CMF-like regimen, anthracycline-based regimen), endocrine therapy (no, yes), age at breast cancer treatment (<40, 40–49, 50–61 years), cardiovascular risk factor at breast cancer diagnosis yes/no (hypertension, hypercholesterolemia or diabetes), smoking (ever, never or unknown) and other cardiovascular diseases (time-dependent). Hazard ratios for the covariates, estimates for patients with unknown radiation fields and estimates for patients irradiated to the internal mammary chain separately for patients additionally irradiated to the breast/chest wall are shown in Supplementary Table 2. [d]Analyses included all patients with at least 1 day of cardiovascular follow-up after start of time at risk ($n = 12,355$). Patients with a specific cardiovascular diagnosis before start of time at risk were excluded from analysis with that specific diagnosis as end point ($n = 138$ for any cardiovascular event (including also 27 diagnoses of arrhythmia and 3 of pericarditis), $n = 50$ for ischaemic heart disease, $n = 18$ for valvular heart disease and $n = 36$ for heart failure). Numbers at risk differs by end point due to time-dependency of the treatment variables. [e]For some women who were treated with direct electrons with the chest wall as the target, the internal mammary chain received a therapeutic dose. [f]Mutually exclusive treatment categories, taking into account primary treatment, as well as treatment for (loco)regional recurrences and second breast cancers. [g]Hazard ratios estimated using one multivariable model containing one variable for the joint effect of radiation therapy and anthracycline-based chemotherapy (breast irradiation without anthracycline-based chemotherapy, internal mammary chain irradiation without anthracycline-based chemotherapy, breast irradiation with anthracycline-based chemotherapy, internal mammary chain irradiation with anthracycline-based chemotherapy), age at breast cancer (<40, 40–50, 50–61 years), cardiovascular risk factor at breast cancer diagnosis yes/no (hypertension, hypercholesterolaemia or diabetes), smoking (ever, never or unknown) and other cardiovascular diseases (time-dependent). Patients not irradiated to either the breast or internal mammary chain were excluded from these analyses. [h]Hazard ratios estimated using one multivariable model containing radiation fields (right breast, right-sided chest wall, left breast, left-sided chest wall, internal mammary chain (left- or right-sided), no radiation therapy, unknown radiation fields), chemotherapy (no chemotherapy, CMF-like regimen, anthracycline-based regimen), endocrine therapy (no, yes), age at breast cancer treatment (<40, 40–49, 50–61 years), cardiovascular risk factor at breast cancer diagnosis yes/no (hypertension, hypercholesterolemia or diabetes), smoking (ever, never or unknown) and other cardiovascular diseases (time-dependent)

1987–1999 was associated with increased IHD rates ≥10 years after treatment (Fig. 1, Table 4); the HR for 0–9 years after IMC irradiation compared to breast irradiation only during 1987–1999 was 1.32 (95% CI 0.74–2.37), while for 10+ years the HRs were 1.64 (95% CI 1.19–2.25) and 1.72 (95% CI 1.17–2.53) for 1970–1986 and 1987–1999, respectively. In the period 2000–2009, numbers were too small to detect or reject a risk increase for either 0–9 or ≥10 years after IMC irradiation (Table 4). HF rates after anthracycline-based chemotherapy were increased compared to no chemotherapy during the period 1–4 years after diagnosis (HR = 6.80 95% CI 2.75–16.82) and remained increased until at least 10–15 years after treatment (HR = 4.03 95% CI 2.70–6.00).

Among women diagnosed before age 50 years during 1987–1999, the cumulative incidence of IHD twenty years after BC treatment was 11.3% (95% CI 6.8–17.1) for those who received IMC irradiation and had a cardiovascular risk factor (including smoking) at diagnosis compared to 6.4% (95% CI 4.5–8.7) for those who had a cardiovascular risk factor but did not receive IMC irradiation (Fig. 2). For VHD and HF, the cumulative 20-year incidences were also considerably higher for women who received IMC radiation and had a cardiovascular risk factor compared with those who had a cardiovascular risk factor but no IMC radiation. Results for age 50+ years are in Supplementary Figure 1. Cumulative incidences of IHD, VHD and HF by anthracycline-based treatment and IMC irradiation for women aged ≤50 years are given in Supplementary Figure 2.

Women treated more recently (1990–2006) had a lower cumulative MI risk than women treated in earlier years (1970–1989) (Supplementary Figure 3). In addition, the absolute increase in cumulative MI risk compared to the population-expected risk was notably smaller for those treated during 1990–2006 than for those treated before 1990. When compared with women receiving right breast RT only, the HR for all other RT regimens was 2.82-fold (95% CI 1.48–5.37) for the period 1980–1989 and 1.84 (95% CI 0.83–4.05) for the period 1990–2006 (10-year survivors only; $p_{difference} = 0.41$).

DISCUSSION

Our study shows that, in women treated for BC in the Netherlands between 1970 and 2009, IMC irradiation was associated with an increased incidence of IHD, VHD and HF. Risk increases were seen not only after left-sided but also after right-sided IMC irradiation, and importantly, the proportional increase in the risk of IHD was greatest in the period >20 years after treatment. Anthracycline-based chemotherapy was associated with increased incidence of HF. The combination of IMC irradiation and anthracycline-based chemotherapy was associated with a nine-fold increased incidence of HF relative to patients who received only breast RT and no anthracycline-based chemotherapy.

Anthracycline-based chemotherapy (received by women in our cohort after 1990) was associated with increased HF incidence up to 15 years after treatment; there was insufficient follow-up to assess risk beyond this. Our estimate of the proportional increase in the rate (HR = 4.32) is somewhat higher than previously reported in population-based studies.[21,39,40] A possible explanation is the young age of the women in our cohort, as we observed an even larger increases in patients treated ≤50 years (HR = 5.23 95% CI 3.41–8.01).

The increased VHD rate after anthracycline-based chemotherapy when multiple CVD diagnoses per woman are considered is a new finding in BC patients. Our detailed analysis, however, excluding VHD events diagnosed at the time of HF/IHD diagnosis suggests that the anthracycline-based chemotherapy-associated VHD risk in this cohort may be caused by anthracycline-based chemotherapy-related HF, rather than a direct effect of anthracycline-based chemotherapy. An anthracycline-related

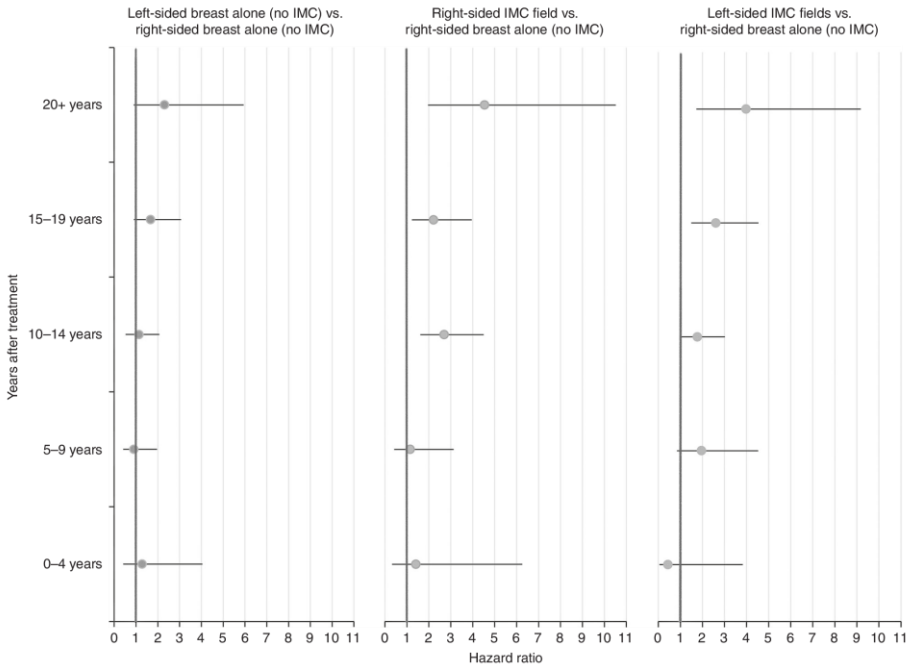


Fig. 1 Within cohort comparison of ischemic heart disease rates by time since treatment and radiation therapy in patients diagnosed during 1970-1999. The analyses shown in this figure include all diagnoses of ischemic heart disease, e.g. including patients diagnosed with valvular heart disease or heart failure prior to ischemic heart disease. For women diagnosed with breast cancer during 1970-86, data on cardiovascular disease were available only for the period 10+years after treatment. IMC, internal mammary chain.Cox proportional hazard model including the following variables: radiation fields (right-), age at breast cancer treatment (<40, 40-49, 50-61 years), chemotherapy (none, CMF-like, anthracycline-based chemotherapy), cardiovascular risk factor at breast cancer diagnosis yes/no (hypertension, hypercholesterolemia, or diabetes), smoking (ever, never, or unknown), and other cardiovascular diseases diagnoses (time-dependent).In the period 2000-2009 follow-up duration was too short for reliable estimates (see Table 4)

Table 4. Within-cohort comparison of ischaemic heart disease ratios for different radiation fields by time since treatment and treatment period

Treatment period	Time since treatment								
Radiation field[a]	0–9 years			10–19 years			20+ years		
	n/N	HR	(95% CI)	*n/N*	HR	(95% CI)	*n/N*	HR	(95% CI)
1970–1986									
Breast only (no IMC)	0/0	—		44/1162	1.00	Ref.	11/402	1.00	Ref.
IMC[b]	0/0	—		318/3899	1.35	0.93–1.96	144/1455	2.51	1.35–4.67
1987–1999									
Breast only (no IMC)	37/3345	1.00	Ref.	66/3432	1.00	Ref.	10/784	1.00	Ref.
IMC[b]	20/1524	1.32	0.74–2.37	48/1340	1.68	1.09–2.57	9/261	2.11	0.85–5.25
2000-2009									
Breast only (no IMC)	34/2,028	1.00	Ref.	8/686	1.00	Ref.	0/0	—	
IMC[b]	5/544	0.62	0.23–1.62	4/290	0.90	0.26–3.05	0/0	—	

n/N number of events/number at risk, *HR* hazard ratio, *CI* confidence interval, *IMC* internal mammary chain, *Ref.* reference category. [a]Patients were time-dependently categorised based on the treatment they received throughout follow-up into irradiation of the breast without internal mammary chain irradiation (either left or right breast), internal mammary chain irradiation (left- of right-sided) with or without radiation of additional fields and no/other radiation fields (estimates not shown). [b]Irradiation of the left- or right-sided internal mammary chain, with or without additional irradiation of the breast or chest wall

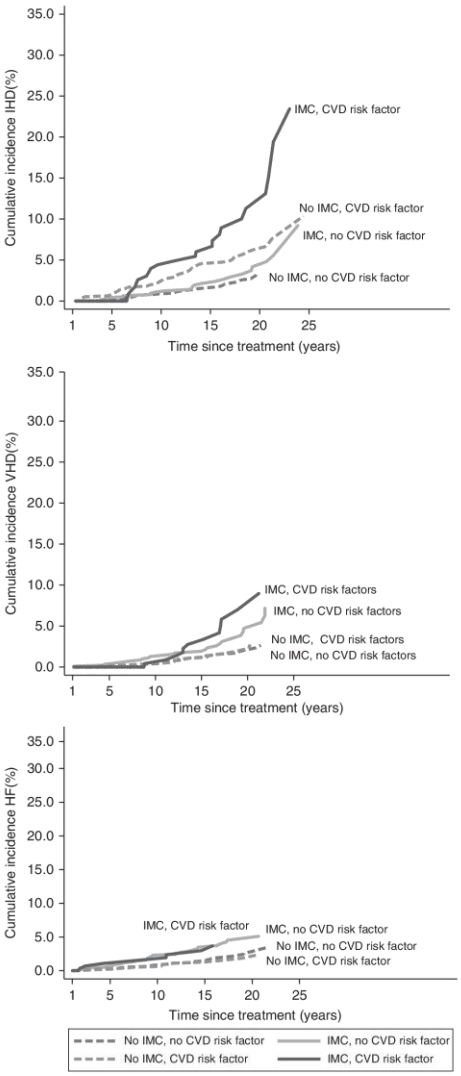


Fig. 2 Cumulative risk of cardiovascular diseases in patients diagnosed during 1987-1999 and aged 50 years or younger at breast cancer diagnosis, by internal mammary chain irradiation and cardiovascular disease risk factors (including smoking) at breast cancer diagnosis. IMC, internal mammary chain; CVD, cardiovascular disease; CHD, ischemic heart disease; VHD, valvular heart disease; HF, heart failure. The analyses of ischemic heart disease, valvular heart disease, and heart failure shown in this figure include all diagnoses of cardiovascular disease, e.g. if a patient was diagnosed with ischemic heart disease and then later with valvular heart disease then both events are counted. Patients with a specific cardiovascular diagnosis before start of time at risk were excluded from analysis with that specific diagnosis as endpoint (n=50 for ischemic heart disease, n=18 for valvular heart disease, and n=36 for heart failure)

increase in the diagnosis of VHD as a first CVD event has previously been observed in Hodgkin lymphoma patients.[41,42]

In a recent case–control study, the risk of a major coronary event increased by 7.4%/Gy mean heart dose.[8] Although not statistically significant, our HR of 1.38 for left breast (~5 Gy typical mean heart dose) versus right breast RT (~0.6 Gy typical mean heart dose) is consistent with these results. In our large, population-based cohort of early BC patients,[43] we studied hospitalisation for CVD and also found an increased rate of IHD comparing left- versus right-sided breast irradiation (without IMC irradiation) (HR = 1.24 95% CI 1.01–1.52). These findings, together with the increased rate we observed in patients treated at age ≤50 years in the current study, suggest that left breast irradiation does slightly increase IHD risk. Also in line with Darby and colleagues' results are our IHD HRs of 1.77–2.78 for women who received typical heart doses of ~9–15 Gy from IMC RT compared with women with right breast RT. The effect of cardiovascular risk factors on radiation-related cardiac risk in the two studies is also consistent. In both studies, cardiovascular risk factors prior to RT did not significantly increase *relative* risk of radiation-related CVD but did increase the *absolute* risk due to RT. Our study included patients up to the age of 61 years at BC diagnosis. Older patients generally have more cardiovascular risk factors. Hence, the absolute risks of treatment-related CVD may be higher in older patients. Additionally, the presence of cardiovascular risk factors might influence the onset of treatment-related CVD. Future studies should focus also on older BC patients and the onset of the increased CVD rates among these older patients.

Our results are relevant to a large number of BC survivors treated with older IMC regimens, who may remain at an elevated CVD risk for an extensive period. Follow-up in our study was too short to detect or reject an IHD risk increase associated with IMC irradiation during 2000–2009. Recent studies showing improved BC survival after IMC irradiation[24,25,44] still have insufficient follow-up (≤10 years) to detect an increased CVD risk which, as we report, continues into the third decade after treatment. For women who receive BC treatment today, the predicted absolute risks of IMC RT are expected to be substantially lower than for the women in our study. This is partly because the IHD risk in the general population has decreased substantially since the 1970s (Supplemental Figure 3). A recent systematic review of heart dose estimates from BC RT during 2003–2013 showed that heart dose from IMC regimens varied according to technique and was typically ~8 Gy in left-sided RT[27], which is lower than the average of ~13 Gy in our study. Modern radiotherapy techniques, including intensity-modulated radiotherapy and deep-inspirational breath hold, can deliver mean heart doses of <4 Gy even for IMC radiotherapy in left-sided tumours and their use is strongly recommended.

Our results suggest that the combined effects of radiation and anthracycline-based chemotherapy may be greater than their individual effects on the heart. This finding needs confirmation as in several countries guidelines recommend both IMC RT and anthracycline-based chemotherapy sequentially for women with poor prognostic features, such as nodal involvement.

Strengths of our study include data on RT fields and type of chemotherapy, GP- and cardiologist-reported CVD incidence and cardiovascular risk factors and long and near-complete follow-up. Surveillance bias in our study population is unlikely, as there are no recommendations concerning CVD screening in the nation-wide to BC follow-up guidelines in the Netherlands, which are adhered to closely.

A potential limitation that we have considered is whether the increased CVD risk associated with BC treatment might be due to a less favourable cardiovascular risk profile among women who received IMC radiation or anthracycline-based chemotherapy and this in turn might be associated with higher BC stage and lower socioeconomic status. However, in our relatively young BC cohort from two cancer centres, BC treatment was not associated with

socioeconomic status, cardiovascular history at BC diagnosis or cardiovascular risk factors. Data on other risk factors for CVD, such as family history of CVD, body mass index and chronic obstructive pulmonary disease, were, unfortunately, not collected. However, in the Netherlands, BC treatment guidelines do not recommend taking CVD risk factors into account and, accordingly, no differences in prevalence were observed between the treatment categories for the CVD risk factors that were collected. Therefore, missing information on other CVD risk factors is unlikely to have affected our estimates. Another potential limitation is the possibility of unreported events. Because, inherent to a retrospective study design, we rely on the registration of events in medical records, it is possible that some CVD events might have gone unreported. This might have caused our estimates to be slightly underestimated. Lastly, our study did not include patients treated with trastuzumab or taxanes, nor were we able to consider the different types of endocrine therapy. CVD rates after these modern systemic therapies should be evaluated in future studies.

In conclusion, anthracycline-based chemotherapy and irradiation using regimens with substantial mean heart doses (9–17 Gy) were associated with increased incidence of several types of CVDs. The predicted absolute risks of IMC RT are lower for women today, and for most women, the benefits will exceed the risks. However, the risks may be greater for some subgroups, e.g. women with left-sided BC who receive both IMC irradiation and anthracycline-based chemotherapy or who have cardiovascular risk factors. For BC survivors, our results are also relevant as subgroups may benefit from cardiac surveillance.[45]

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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