

Abstract

Aims: To measure cardiac tissue doses in left-sided breast cancer patients receiving supine tangential field radiotherapy with multileaf collimation (MLC) cardiac shielding of the heart and to assess the impact on target volume coverage

Materials and methods: Sixty seven consecutive patients who underwent adjuvant radiotherapy to the left breast (n=48) or chest wall (n=19) in 2009/10 were analysed. Heart, left anterior descending coronary artery (LAD), whole breast and partial breast clinical target volumes (WBCTV and PBCTV) were outlined retrospectively (the latter only in patients who had undergone breast conserving surgery (BCS)). Mean heart and LAD $*NTD_{mean}$ and maximum LAD doses (LAD_{max}) were calculated for all patients ($*NTD_{mean}$ is a biologically weighted mean dose normalised to 2Gy fractions using a standard linear quadratic model). Coverage of WBCTV and PBCTV by the 95% isodose was assessed (BCS patients only).

Results: Mean heart NTD_{mean} (SD) was 0.8 (0.3) Gy, mean LAD NTD_{mean} 6.7 (4.3) Gy and mean LAD_{max} 40.3 (10.1) Gy. Coverage of the WBCTV by 95% isodose was <90% in 1 in 3 patients and PBCTV coverage <95% (range 78-94%) in 1 in 10 BCS patients.

Conclusion: The use of MLC cardiac shielding reduces doses to cardiac tissues at the expense of target tissue coverage. Formal target volume delineation in combination with an assessment of the likelihood of local relapse (LR) is recommended in order to aid decisions regarding field and MLC placement.

Keywords: Breast cancer; cardiac dose; cardiac shielding; radiotherapy; target tissue coverage.

Introduction

The current UK standard for adjuvant breast radiotherapy in women who have undergone breast conserving surgery (BCS) or mastectomy uses tangential fields to treat the whole breast and chest wall respectively. Data from the Early Breast Cancer Trialists' Collaborative Group most recent meta-analysis suggest that adjuvant radiotherapy for breast cancer nearly halves a woman's relative risk of breast cancer recurrence [1]. In addition, there is an absolute reduction in breast cancer mortality at 15 years of about 4%. However, standard tangential breast radiotherapy fields risk giving unwanted irradiation to cardiac tissues. This problem is particularly significant in women receiving left breast radiotherapy, for whom the radiation dose received by cardiac tissues is greater than for those who receive right breast radiotherapy [2]. Consequently women who receive left breast radiotherapy have an increase in cardiac morbidity [3] and mortality [4] relative to right-sided patients. Increased awareness of late cardiac toxicity coupled with improvements in radiotherapy techniques has helped drive down the dose of radiation received by cardiac structures [5], but recent work suggests that mean heart dose (Gy) would need to be reduced to zero to eliminate the risk of late cardiac effects altogether [6].

An approach used in many UK radiotherapy centres currently is to shield cardiac tissues using multileaf collimation (MLC) [2012 Royal College of Radiologists audit]. However, the use of MLC to shield the heart risks simultaneously shielding target tissue (see Figure 1). Most UK radiotherapy centres do not formally define a whole or partial breast clinical target volume for the purpose of whole breast radiotherapy field placement unless the patient is being treated within a clinical trial, and as such the compromise between target tissue coverage and heart dose is assessed visually, taking into account known patterns of local relapse and rates of cardiac morbidity [7].

In this study we set out to determine mean doses delivered to the heart and LAD using standard tangents with MLC shielding and to determine the proportion of women in whom a compromise is made between target and normal tissue irradiation. We also wanted to ascertain whether there was a relationship between the cardiac doses, operation type (BCS or mastectomy) and the position of the tumour bed within the breast.

Materials and methods

The study was approved by The Royal Marsden Hospital Audit Committee. Sixty-seven consecutive patients with left-sided breast cancer who underwent adjuvant radiotherapy to the breast or chest

wall between November 2009 and February 2010 were identified. The majority of patients who underwent BCS had titanium clips inserted into the tumour bed at the time of surgery [8].

Patient positioning, image acquisition radiotherapy planning and treatment

All patients were scanned supine on a breast board, with arms extended above the head in supports (Med-Tec, Iowa, USA). Markers were placed bilaterally 1-2cm posterior to the mid-axillary line and aligned axially with a midline marker using lateral lasers. CT data (Philips Medical Systems, UK) was acquired without contrast in free-breathing from C6 to below the diaphragm.

Standard tangential fields (inferior border of the clavicle (superior), 1cm below the inframammary fold (inferior), midline (medial) and anterior border of serratus anterior (lateral)) were applied in order to encompass breast or chest wall tissues. The depth of lung tissue included in the tangential fields was constrained to ≤ 2 cm. Where cardiac tissues were present within the tangential fields, MLC leaves were positioned manually in order to shield cardiac tissue. Each attending clinician approved the positioning of the tangential fields and used clinical judgement (based on risks of local relapse versus risk of late effects) to decide whether or not the MLC leaves should be retracted to increase coverage of target (breast or chest wall) tissues. Plans were produced which fulfilled ICRU 62 criteria [9]. Patients were treated using 6 or 10 MV photons with either 50 Gy in 25 fractions over 5 weeks or 40 Gy in 15 fractions over 3 weeks.

Delineation of target tissues and organs-at-risk

Partial and whole breast target volumes are not formally outlined in patients receiving standard off-study whole breast or chest wall radiotherapy at our institution. This study, therefore, retrospectively delineated target tissues and organs-at risk (OAR). The whole breast clinical target volume (WBCTV) encompassed breast tissue visualised on CT (limited by pectoral fascia and 5mm from skin). In the majority of patients, titanium clips were inserted at the time of surgery and one or two clips were used to mark each of the six excision boundaries, according to a national protocol [8]. The tumour bed was defined using the tumour bed clips, and included any associated seroma or distortion of breast architecture. This volume was then expanded by 15mm in all directions (limited by the WBCTV) to form the partial breast clinical target volume (PBCTV). In patients without tumour bed clips, a tumour bed was only outlined if a seroma was present. The whole heart was outlined to the extent of the pericardial sac, in accordance with the UK National Cancer Research Institute

Intensity Modulated and Partial Organ RadioTherapy (IMPORT) study criteria [10]. The major blood vessels and the inferior vena cava were excluded. The LAD was outlined according to previously published criteria [5], including the left main coronary artery; where the LAD was difficult to visualise, its location was inferred from the course of the anterior interventricular groove. In accordance with current practice, the LAD was then expanded by 10mm to account for uncertainty in delineation, and movement related to respiration and the cardiac cycle [11]. All volumes were drawn by the same radiation oncologist, and the volumes of patients selected at random verified by a second radiation oncologist.

Analysis

All analysis was performed on the original clinical plans. Mean heart $*NTD_{mean}$ and LAD NTD_{mean} and their standard deviations (SD) and range were calculated ($*NTD_{mean}$ is a biologically weighted mean dose normalised to 2Gy fractions using a standard linear quadratic model [12], $\alpha/\beta=3Gy$ [13,14]). The mean maximum LAD dose (LAD_{max}), SD and range were calculated from dose volume histogram (DVH) data and normalised to 2Gy fractions. Spearman's rank correlation coefficient was calculated to assess the relationship between mean heart NTD_{mean} , LAD NTD_{mean} and LAD_{max} .

Using DVH data, the percentage coverage of both the WBCTV and PBCTV by the 95% isodose was calculated. Target volume coverage was assessed according to previously published criteria [15], such that $\geq 90\%$ of the WBCTV and $\geq 95\%$ of the PBCTV should be covered by the 95% isodose. The data were analysed to determine in what proportion of patients these constraints were met. Where PBCTV coverage constraints were not met, the individual plans were reviewed to assess the scope for improving PBCTV coverage (although not assessed formally by replanning).

In patients who underwent BCS, the quadrant in which the tumour bed was located (the "index quadrant") was noted and one-way ANOVA tests performed to compare the 95% isodose coverage, mean heart NTD_{mean} , mean LAD NTD_{mean} and mean LAD_{max} of these groups. The Mann-Whitney U test was used to compare the 95% isodose coverage, mean heart NTD_{mean} , mean LAD NTD_{mean} and mean LAD_{max} of upper and lower half tumours and inner and outer half tumours in BCS patients (central tumours were excluded from the analysis).

Results

48 (72%) patients underwent BCS and 19 (28%) underwent mastectomy. Cardiac shielding with MLC was used in 58% of patients. For all patients, mean heart NTD_{mean} (SD) and [range] were 0.8 (0.3) [0.0 – 2.1] Gy, mean LAD NTD_{mean} 6.7 (4.3) [1.2 – 22.6] Gy and mean LAD $_{max}$ 40.3 (10.1) [4.6 – 51.3] Gy. Spearman correlations for mean heart and LAD NTD_{mean} ($r = 0.4$, $p = 0.03$), mean heart NTD_{mean} and LAD $_{max}$ ($r = 0.3$, $p = 0.03$) and mean LAD NTD_{mean} and LAD $_{max}$ ($r = 0.7$, $p < 0.01$).

WBCTV 95% isodose coverage was <90% in 17 (35%), range 73-100%. The PBCTV 95% isodose coverage was <95% in 10% of patients (range 78-100%). Three out of 5 patients in whom PBCTV coverage was <95% also had WBCTV coverage <90%. Reasons for compromised PBCTV coverage included shielding cardiac tissue, seroma close to skin (compromising dose in the build-up region) and large separation leading to difficulties with chest wall coverage, suggesting that factors in addition to cardiac shielding may play a part in PBCTV compromise.

Figure 2 shows the BCS patients categorised according to the index quadrant of their tumour. Over 50% of patients had tumours that were situated within the upper outer quadrant. No statistically significant difference was detected between index quadrant groups for 95% isodose coverage, mean heart NTD_{mean} , mean LAD NTD_{mean} and mean LAD $_{max}$ (see Table 1). 60% of patients who underwent BCS had tumours were situated in the upper half of the breast, 21% in the lower half and 19% were centrally located. No statistically significant difference was noted between the 95% isodose coverage, mean heart NTD_{mean} , mean LAD NTD_{mean} and mean LAD $_{max}$ of patients with upper half vs lower half tumours nor inner vs outer half tumours, although mean LAD NTD_{mean} and LAD $_{max}$ were greater in patients with lower and inner half tumours (see Tables 2 and 3).

There was no statistically significant difference in mean heart NTD_{mean} (Gy) between patients who underwent BCS and those who underwent mastectomy: 0.8 (0.2) vs 0.8 (0.4), $p=0.6$. However, mean LAD NTD_{mean} and LAD $_{max}$ (Gy) were significantly greater for patients who underwent mastectomy: 5.9 (3.6) vs 8.7 (5.3), $p=0.04$ and 38.2 (11.3) vs 45.5 (3.6), $p < 0.01$.

Discussion

This study quantifies the doses to the heart and LAD of left-sided breast cancer patients receiving tangential field radiotherapy with MLC at this centre in 2010. It also assesses the impact of this cardiac shielding on target tissue coverage. Our data demonstrate a further reduction in cardiac doses from those reported by Taylor et al. in 2006 [11], and fit with the progressive reduction in doses seen since the 1970s (see Table 4), reflecting both the increased awareness of the need to

reduce cardiac doses in left breast radiotherapy, coupled with improvements in radiotherapy techniques (none of these historical studies used cardiac shielding).

Although both mean heart and LAD doses are lower in this study than has previously been reported, the reduction in mean heart dose (65%) has been more dramatic than for mean LAD dose (12%). This phenomenon can be explained by the way in which MLC cardiac shielding is positioned. Although MLC leaves were used to shield the myocardium, the LAD frequently lies outside the shielded region a) because it is not routinely identified as an organ at risk and b) because it is the most anteriorly placed cardiac substructure. The net effect of this is that much of the LAD may sit in the penumbra region of the radiation field (see Figure 3), thus giving higher and more heterogeneous mean LAD doses than might be anticipated. Reducing the radiation dose to cardiac tissues in left-sided breast cancer patients frequently necessitates a trade-off between the treatment of target tissue and avoidance of OAR: a judgement which clinicians make on a routine basis. There are two main factors which need to be considered in order to weigh up this trade-off: the risk of local relapse (LR) and the risk of radiation-related heart disease (RRHD). The risk of LR is increased by factors such as young age [16-19], high tumour grade [19], the presence of extensive ductal carcinoma in situ (DCIS) [17] and negative ER status [20], and particular caution should be used when compromising target tissue coverage in these groups of patients. To help with this problem, nomograms have been developed to assess the risk of ipsilateral breast recurrence, such as that from the EORTC 22881-10882 boost versus no boost trial [21]. A key question, however, is 'What is the effect of reducing target tissue coverage on the risk of LR?'. Data strongly suggest that the majority of LRs in BCS patients occur in the vicinity of the original tumour [22-25], and therefore compromising PBCTV coverage is likely to have a proportionately greater effect on the risk of LR than compromising WBCTV. Data from the START Trial A generated a γ value for tumour control of 0.2 (the γ value represents the percent increase in effect per percent increase in total dose delivered in 2Gy fractions) [26], suggesting that low level underdosing of target tissue in breast patients may not have a measurable impact on local control. Although partial external beam breast irradiation is being investigated in a number of ongoing trials (IMPORT LOW, NSABP B-39, RAPID), whole breast radiotherapy nevertheless remains the current standard after BCS. Patterns of LR after mastectomy are much less well understood, and in view of this there is currently insufficient evidence to support any compromise of target tissue coverage in patients requiring chest wall radiotherapy. This restriction on compromising target tissue coverage when irradiating the chest wall would be expected to lead to higher mean heart and LAD doses, and our data support this.

Meanwhile, consideration must be given to factors which increase the risk of RRHD, including dose [6,27,28], young age [27,29] and pre-existing ischaemic heart disease [3,6]. There is also evidence that conventional cardiac risk factors such as hypertension, diabetes, cholesterol and smoking may increase risk [6,30-32]. However, although there have been clear reductions in the doses of radiation delivered to the heart and LAD during tangential radiotherapy over the past 40 years, recent evidence suggests that there is no threshold dose to the heart below which the risk of RRHD ceases to exist [6]. In addition, hypofractionated breast radiotherapy regimens are now standard in the UK [2012 Royal College of Radiologists audit], but some have questioned whether the larger fraction sizes used in these schedules will have a negative impact on cardiac toxicity in view of the presumed low α/β ratio of the heart. Recent work suggests, however, that these fears are unfounded and that the most popular hypofractionated regimens in fact spare heart tissue relative to 2Gy schedules, assuming an α/β ratio for the heart of $\geq 1.5\text{Gy}$ and assuming late cardiac effects are not sensitive to total treatment time [33]. Remaining unanswered questions include which cardiac substructure is the most radiosensitive (and therefore which should be used for evaluating tolerance doses) and the effect of cardiotoxic systemic therapies on RRHD in breast cancer patients.

The absence of a threshold dose implies that all patients can benefit from reducing heart doses in breast radiotherapy. As such, it is important that the target vs OAR trade-off is optimised. A first step towards accomplishing this would be routine outlining of target tissues and OAR in breast radiotherapy. We intend to modify our practice firstly by introducing routine outlining of the tumour bed (and expansion to a PBCTV). We propose to do this in all patients regardless of tumour bed position as our findings suggest that cardiac doses are not simply a function of the position of the tumour bed within the breast. In addition, the use of alternative radiotherapy techniques (such as breath-hold or prone treatment) makes it possible to reduce cardiac doses without the need to compromise target tissue coverage. Prone breast radiotherapy may reduce cardiac doses in larger breasted women [15], however, questions remain over its reproducibility [34]. Deep inspiratory breath-hold techniques significantly reduce the dose to cardiac structures [35-37], and although their use across Europe continues to increase [7], there is currently only very limited UK uptake [2012 Royal College of Radiologists audit]. Treating a smaller target volume (partial breast irradiation), using either external beam radiotherapy or intraoperative treatment, is being investigated in a number of Phase III clinical trials [38], and these techniques may further reduce cardiac doses. Finally, it is only by avoiding adjuvant breast radiotherapy altogether that there can be no risk of RRHD and there may be a population of patients in whom the recurrence risk is so low that radiotherapy after BCS can be omitted. This is being investigated in the PRIME trial [39] and long-term recurrence and survival data from this study are awaited.

We acknowledge that our study has limitations. Patient numbers were small, however, consecutive patients were analysed to minimise the effect of this and improve representativeness. The imbalance in patient numbers when stratified by index quadrant hindered subgroup analysis. Steps were taken to minimise delineation errors. For LAD outlining we used a standard method, as defined by Taylor et al [5], and additionally all volumes were drawn by the same radiation oncologist and random cases verified by a second radiation oncologist. Uncertainty in tumour bed delineation was minimised by routine placement of tumour bed clips at surgery.

Conclusion

This study demonstrates a continued reduction in radiation doses to cardiac tissues through the use of MLC. However, this fall in cardiac doses has led to target tissue coverage being compromised. We recommend the use of formal target volume definition in combination with individualised assessments of the risk of LR in order guide the placement of field borders and the use of MLC. Techniques which minimise the need for a compromise between target tissue and OAR coverage (such as breath-holding) should be pursued as a matter of priority.

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Figure 1: Digitally rendered radiograph (DRR) demonstrating how multileaf collimation (MLC) used for shielding cardiac tissue risks simultaneously shielding target tissue.

Key: Orange wireframe – heart; small coloured dots – tumour bed clips; large yellow dot – isocentre

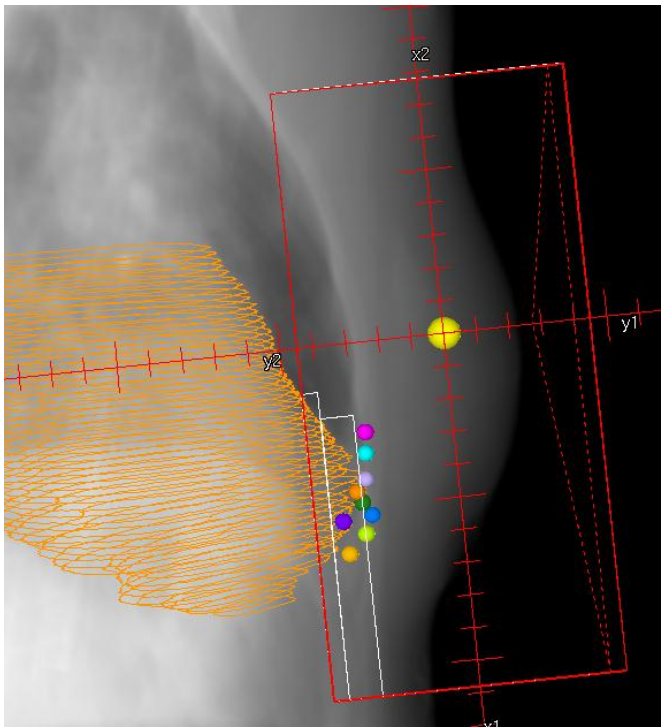


Figure 2: BCS patients categorised according to index quadrant of tumour

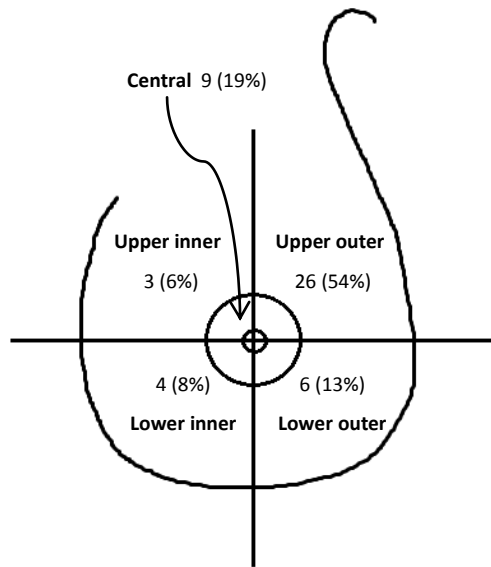


Figure 3: Axial CT slice demonstrating LAD sitting within penumbra region of left breast tangential radiotherapy fields

Key: Orange colourwash – LAD, dark green colourwash – LAD plus 1cm margin

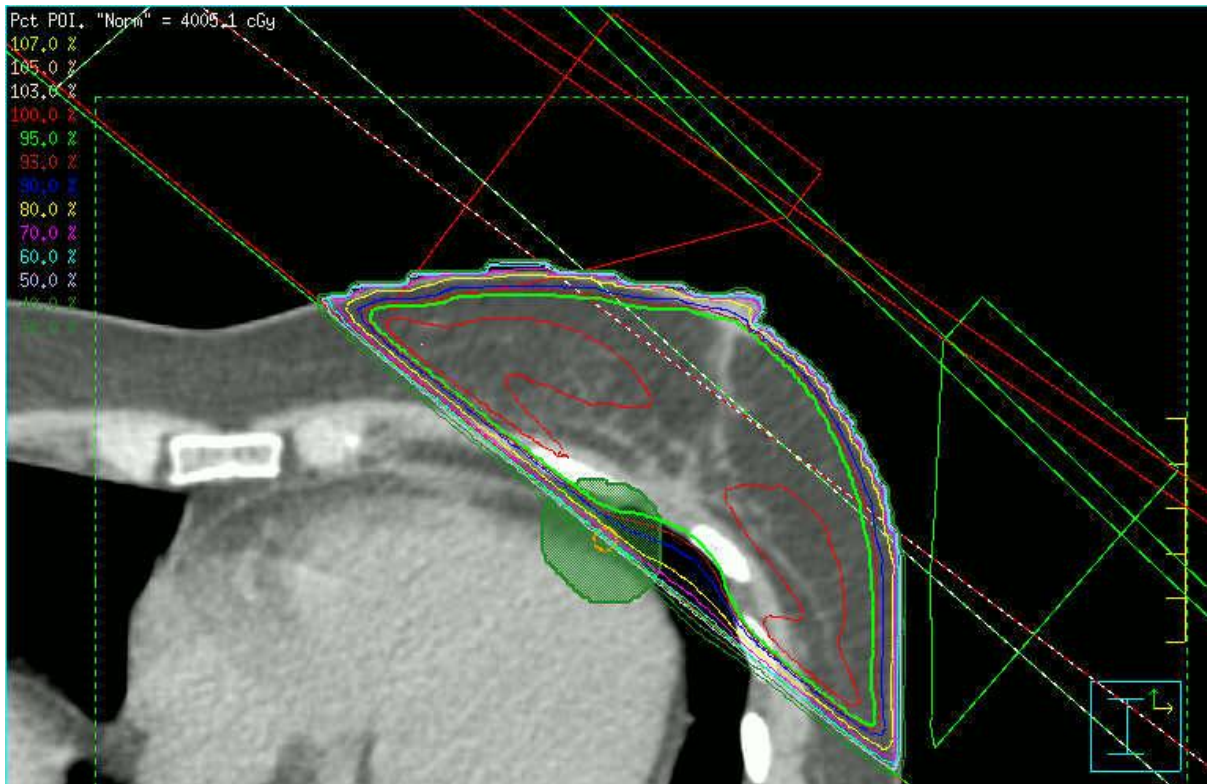


Table 1

Target volume isodose coverage (%) and cardiac dose parameters (Gy) stratified according to index quadrant of tumour (standard deviations in brackets).

Tumour quadrant	WBCTV V95%	PBCTV V95%	Heart NTD _{mean}	LAD NTD _{mean}	LAD _{max}
Central <i>n</i> =9	89 (9)	95 (7)	0.8 (0.2)	5.2 (3.5)	33.5 (14.8)
Lower inner <i>n</i> =4	86 (8)	99 (1)	0.8 (0.3)	5.7 (1.4)	43.0 (1.2)
Lower outer <i>n</i> =6	91 (6)	99 (1)	0.8 (0.2)	8.1 (2.9)	42.6 (6.6)
Upper inner <i>n</i> =3	85 (2)	97 (2)	0.9 (0.4)	6.0 (2.9)	39.3 (5.3)
Upper outer <i>n</i> =26	90 (5)	97 (5)	0.7 (0.3)	5.6 (4.1)	38.0 (11.7)
<i>p</i>	0.46	0.67	0.87	0.62	0.53

Table 2

Target volume isodose coverage (%) and cardiac dose parameters (Gy) stratified according to index half of tumour (upper vs lower) (standard deviations in brackets).

Tumour half	WBCTV V95%	PBCTV V95%	Heart NTD _{mean}	LAD NTD _{mean}	LAD _{max}
Upper <i>n=29</i>	89 (5)	97 (4)	0.8 (0.3)	5.7 (3.9)	38.1 (11.1)
Lower <i>n=10</i>	89 (7)	99 (1)	0.8 (0.2)	7.2 (2.6)	42.7 (5.0)
<i>p</i>	0.84	0.82	0.71	0.09	0.42

Table 3

Target volume isodose coverage (%) and cardiac dose parameters (Gy) stratified according to index half of tumour (outer vs inner) (standard deviations in brackets).

Tumour half	WBCTV V95%	PBCTV V95%	Heart NTD _{mean}	LAD NTD _{mean}	LAD _{max}
Outer <i>n</i> =25	90 (5)	97 (4)	0.8 (0.4)	6.6 (4.9)	39.9 (10.8)
Inner <i>n</i> =13	88 (6)	98 (1)	0.8 (0.3)	7.2 (2.8)	43.1 (5.1)
<i>p</i>	0.41	0.84	0.62	0.16	0.83

Table 4

Cardiac doses (Gy) in left breast radiotherapy since the 1970s (standard deviations in brackets, where available).

Period	Mean heart dose	Mean LAD dose	LAD _{max}
1970s (Sweden) [5]	13.3	31.8	52.0
1990s (Sweden) [5]	4.7	21.9	51.5
2006 (UK) [11]	2.3 (0.7)	7.6 (4.5)	35.2 (8.8)
2010 (UK)	0.8 (0.3)	6.7 (4.3)	40.3 (10.1)