CARDIAC EXPOSURES IN BREAST CANCER RADIOTHERAPY: 1950s–1990s

CAROLYN W. TAYLOR, F.R.C.R.,* ANDREW NISBET, PH.D.,† PAUL McGALE, PH.D.,* AND SARAH C. DARBY, PH.D.†

*Clinical Trial Service Unit, Oxford University, Oxford, United Kingdom; and †Department of Medical Physics, Royal Surrey County Hospital, University of Surrey, Surrey, United Kingdom

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

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

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

Conclusion: For most techniques, the greatest radiation doses were received by the anterior part of the heart and the left anterior descending coronary artery, a common site of atherosclerosis causing myocardial infarction. Irradiation of these structures might have contributed to the excess risk of death from heart disease seen after some past breast cancer RT regimens. © 2007 Elsevier Inc.

Breast radiotherapy, Heart disease, Long-term effects.

INTRODUCTION

Most women treated for early-stage breast cancer undergo primary surgery. This is often followed by adjuvant radiotherapy (RT), which reduces breast cancer mortality after breast-conserving surgery and after mastectomy in those with node-positive disease (1). Long-term follow-up of these women has, however, revealed that some past regimens led to an increased risk of death from heart disease, particularly ≥10 years after RT, presumably because of some unwanted irradiation of the cardiac structures.

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

The estimation of the cardiac risk of today’s breast RT requires the development of reliable dose–response relationships, which, in turn, require detailed cardiac dosimetry of past regimens given to women for whom we have long-term follow-up data. At present, few heart dosimetry data from breast cancer RT are available. Furthermore, it is unknown which quantitative measures of the heart dose or volume are most relevant to subsequent heart disease risk (2). Studies have used a variety of heart dose specifications, including the absorbed dose (5, 6), biologically effective

Acknowledgments—This work arose out of our involvement with the Early Breast Cancer Trialsists’ Collaborative Group. We thank the Early Breast Cancer Trialsists’ Collaborative Group secretariat and many collaborators for their comments; and also gratefully acknowledge Professor David Dodwell, Dr. Niall Moore, Professor John Hopewell, Dr. Giovanna Gagliardi, and Sir Richard Peto for their help with this work.

Received Feb 15, 2007, and in revised form May 14, 2007. Accepted for publication May 14, 2007.
Complex planning techniques might be justified to reduce based on their RT plan, thus identifying women for whom the development of treatment guidelines. In addition, for individual patients (e.g., those whose heart is included the radiation beam), it should allow the assessment of cardiac risk with these doses to derive dose–response relationships.

These should enable the prediction of the likely cardiac risk of current and future breast cancer RT regimens and facilitate the development of treatment guidelines. In addition, for individual patients (e.g., those whose heart is included the radiation beam), it should allow the assessment of cardiac risk based on their RT plan, thus identifying women for whom complex planning techniques might be justified to reduce the cardiac dose.

Methods and materials

General method

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

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

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

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

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

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

The cardiac dose distributions for several 250-kV regimens and iridium wire implants were also derived. This involved generating scaled hard copies of the appropriate CT slices on which isodose distributions for 250-kV X-rays or iridium wire implants were superimposed. Manual planning techniques incorporating lung correction were used to generate cardiac dose distributions. The physical density of lung was taken to be 0.25 g cm⁻³.

For the orthovoltage treatments, axial CT slices of the superior, middle, and inferior levels of the heart were used. For single direct fields, an applied dose was assumed. For tangential-pair RT, the use of tissue-equivalent bolus between the two applicators was assumed. The proportion of each cardiac structure included within each isodose line was calculated and used to plot dose–volume histograms. These were typically based on three CT slices per RT plan. For the heart, approximately 150 dose points per CT slice were used, and for the three coronary arteries, their small volumes meant that only one dose point per slice was used.

For all regimens, BEDs were calculated using the linear quadratic model. The estimated α/β ratios for radiation-related heart disease are 1–3 Gy (16, 17). For these calculations, an α/β ratio of 2 Gy was used. For orthovoltage RT, a correction factor of 1.1 was used to account for the enhanced biologic effectiveness of low-energy irradiation (7).

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

Specific techniques reconstructed

The RT details for >60 trials of RT for early breast cancer (1950s–1990s) were collated using trial publications and protocols, textbooks (18–21), and discussions with radiotherapists who had worked in various countries from 1950 onwards. Using this information, RT techniques commonly used to treat the chest wall, breast, and associated lymphatics were reconstructed. Descriptions of the target volumes, clinical definition of the field borders, field
arrangements and beam energies are given in Table 1 and illustrated in Fig. 2. The focus-to-skin distance was 100 cm for all fields; wedges and compensators were not used. The tangential pair beams were 180° opposed.

Variation in patient anatomy

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

RESULTS

Dose estimates for the representative patient

The mean doses to the coronary arteries and the maximum dose, mean dose, and mean BED to the heart for the representative patient are summarized in Table 2. Appendix Tables 1 to 8 (online only) give additional details, including the percentage volume of each structure irradiated to various doses and the mean BED and maximum dose.

Heart dose from chest wall or breast irradiation

For breast or chest wall RT (Figs. 2a–c), the mean heart dose varied between 0.9 and 14 Gy for left-sided and between 0.4 and 6 Gy for right-sided RT (Table 2). The largest doses resulted from orthovoltage (250-kV) irradiation. For example, for standard left tangential RT (Fig. 2a), the mean heart dose...
<table>
<thead>
<tr>
<th>Target</th>
<th>Field arrangement</th>
<th>Definition of field borders</th>
<th>Beam energy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest wall/breast (a, b)</td>
<td>Tangential pair (18–20)</td>
<td>Superior—sternal notch Inferior—1 cm below inframammary fold Medial—midline or matched to internal mammary chain field Lateral—midaxillary line</td>
<td>6 MV</td>
<td>Tissue equivalent bolus between applicators for 250 kV</td>
</tr>
<tr>
<td>Chest wall (c)</td>
<td>Direct anterior (19, 22)</td>
<td>Superior—inferior border of supraclavicular fossa field Inferior—xyphoid–sternal junction Medial—midline Lateral—midaxillary line</td>
<td>10-MeV electrons</td>
<td></td>
</tr>
<tr>
<td>Chest wall and internal mammary nodes (d)</td>
<td>Tangential pair (19)</td>
<td>Superior—sternal notch Inferior—1 cm below inframammary fold Medial—1 cm to contralateral side of midline Lateral—midaxillary line</td>
<td>6 MV</td>
<td>Medial tangential beam angled 10° downward</td>
</tr>
<tr>
<td>Chest wall and internal mammary nodes McWhirter fields (e)</td>
<td>Tangential pair (23)</td>
<td>Superior—sternal notch Inferior—1 cm below inframammary fold Medial—sternal border on contralateral side Lateral—midaxillary line</td>
<td>250 kV</td>
<td>Tissue equivalent bolus between applicators</td>
</tr>
<tr>
<td>Internal mammary nodes (f)</td>
<td>Direct anterior (18, 20, 24)</td>
<td>Superior—sternal notch Inferior—xyphoid–sternal junction Medial—midline Lateral—6 cm from medial border</td>
<td>6 MV</td>
<td>Usual size: 17 × 6 cm</td>
</tr>
<tr>
<td>Internal mammary nodes (similar to f)</td>
<td>Direct anterior (19)</td>
<td>Superior—sternal notch Inferior—xyphoid–sternal junction Medial—1 cm contralateral to midline Lateral—7 cm from medial border</td>
<td>10-MeV electrons</td>
<td>Usual size: 17 × 7 cm</td>
</tr>
<tr>
<td>Mastectomy scar boost</td>
<td>Direct anterior (25, 26)</td>
<td>5 × 14 cm Strip covering the approximate position of mastectomy scar</td>
<td>60Co</td>
<td>Placement of field approximate</td>
</tr>
<tr>
<td></td>
<td>Brachytherapy (27, 28)</td>
<td>Two plane, five-wire iridium implant</td>
<td>10-MeV electrons</td>
<td></td>
</tr>
<tr>
<td>Supraclavicular fossa (g)</td>
<td>Direct anterior (18, 19)</td>
<td>Superior—cricothyroid groove Inferior—middle of second costal cartilage Medial—1 cm to contralateral side of midline Lateral—crosses acromioclavicular joint</td>
<td>6 MV</td>
<td>Usual size 10 × 16 cm beam tilted 15° laterally</td>
</tr>
<tr>
<td>Posterior axilla (h)</td>
<td>Direct posterior (19)</td>
<td>Superior—spine of scapula Inferior—inferior border of supraclavicular fossa field Medial—follows the lateral wall of bony thorax Lateral—bisects the humeral head</td>
<td>6 MV</td>
<td>Lead used to shape medial border</td>
</tr>
</tbody>
</table>

* Regimens a–h illustrated in Fig. 2.
dose was 4.7 Gy for megavoltage and 14 Gy for orthovoltage irradiation. This was partly explained by lateral scatter and partly by the depth–dose characteristics of an orthovoltage beam. To deliver 42 Gy at the mid-plane point on the central axis, a given dose of approximately 42 Gy multiplied by 1.8 is needed from each tangential 250-kV beam. The resulting dose distribution within the breast/chest wall and within normal tissue nearby is inhomogeneous, with hot spots of up to 125% of tumor dose (53 Gy) within the heart for left-sided RT.

Where tangential beams were matched to a direct IMC field (Fig. 2b), the medial tangential border was 6 cm from the midline. The heart was, therefore, several centimeters from the posterior field edges and received low radiation doses from the tangential beams. The mean heart dose was

![Radiotherapy techniques reconstructed for cardiac dose estimations. See Table 1 for additional details, including definitions of field borders. IMC = internal mammary chain; Co-60 = 60Co.](image-url)
<table>
<thead>
<tr>
<th>Target</th>
<th>Field arrangement</th>
<th>Beam energy</th>
<th>Typical dose and fractionation</th>
<th>Mean dose (Gy)</th>
<th>Maximum dose (Gy)</th>
<th>Mean BED (Gy)</th>
<th>LAD</th>
<th>RCA</th>
<th>CCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest wall/breast (a)</td>
<td>Tangential pair(^1)</td>
<td>6 MV/(^{60})Co</td>
<td>50 Gy in 25</td>
<td>4.7</td>
<td>1.5</td>
<td>49.2</td>
<td>4.8</td>
<td>7.0</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 kV(^3)</td>
<td>42 Gy in 20</td>
<td>14</td>
<td>6</td>
<td>60</td>
<td>19</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Chest wall/breast medial border matched to internal mammary field (b)</td>
<td>Tangential pair(^2)</td>
<td>6 MV/(^{60})Co</td>
<td>50 Gy in 25</td>
<td>0.9</td>
<td>0.9</td>
<td>13.1</td>
<td>1.6</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 kV(^3)</td>
<td>42 Gy in 20</td>
<td>5</td>
<td>1</td>
<td>32</td>
<td>5</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Chest wall (c)</td>
<td>Direct anterior</td>
<td>10-MeV electrons</td>
<td>50 Gy in 25</td>
<td>2.8</td>
<td>1.5</td>
<td>27.8</td>
<td>20.0</td>
<td>3.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Chest wall and internal mammary nodes (d, e)</td>
<td>Tangential pair(^3)</td>
<td>6 MV/(^{60})Co</td>
<td>50 Gy in 25</td>
<td>13.5</td>
<td>2.4</td>
<td>50.3</td>
<td>44.1</td>
<td>21.7</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250 kV(^3)</td>
<td>36 Gy in 20</td>
<td>14</td>
<td>9</td>
<td>48</td>
<td>41</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>Internal mammary nodes (f)</td>
<td>Direct anterior</td>
<td>6 MV/(^{60})Co</td>
<td>50 Gy in 25</td>
<td>16.7</td>
<td>10.5</td>
<td>48.4</td>
<td>47.6</td>
<td>27.8</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-MeV electrons</td>
<td>50 Gy in 25</td>
<td>15.0</td>
<td>9.3</td>
<td>44.1</td>
<td>43.0</td>
<td>21.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Mastectomy scar boost</td>
<td>Direct anterior</td>
<td>(^{60})Co</td>
<td>10 Gy in 5</td>
<td>0.9</td>
<td>0.2</td>
<td>8.1</td>
<td>6.8</td>
<td>1.2</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-MeV electrons</td>
<td>10 Gy in 5</td>
<td>0.3</td>
<td>0.2</td>
<td>5.1</td>
<td>2.9</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Brachytherapy</td>
<td>(^{192})Ir(^4)</td>
<td>10 Gy in 5</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 Gy</td>
<td>1</td>
<td>—</td>
<td>7</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Supraclavicular fossa (g)</td>
<td>Direct anterior</td>
<td>6 MV/(^{60})Co</td>
<td>50 Gy in 25</td>
<td>0.8</td>
<td>—</td>
<td>1.4</td>
<td>—</td>
<td>1.1</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 Gy in 25</td>
<td>0.4</td>
<td>—</td>
<td>1.3</td>
<td>—</td>
<td>0.6</td>
<td>—</td>
<td>0.5</td>
</tr>
<tr>
<td>Posterior axilla (h)</td>
<td>Direct posterior</td>
<td>6 MV/(^{60})Co</td>
<td>50 Gy in 25</td>
<td>0.5</td>
<td>—</td>
<td>0.8</td>
<td>—</td>
<td>0.8</td>
<td>—</td>
</tr>
</tbody>
</table>

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

\(^1\) BED calculated using \(\alpha/\beta\) ratio of 2.

\(^2\) Arm elevated on T-bar rest.

\(^3\) Regimens a–h illustrated in Fig. 2.

\(^4\) Doses for low-energy regimens given to nearest Gray because of uncertainties involved in manual planning; all other doses given to 1 decimal place.
0.9–5 Gy for left-sided and 0.4–1 Gy for right-sided irradiation.

For wide tangential RT (Figs. 2d and 2e), the medial border was 1 cm contralateral to the midline. Hence, relatively large heart volumes were irradiated: $\geq 10$ Gy was received by 44.8–53% and 3.0–29% of the heart for left- and right-sided irradiation, respectively (Appendix Tables 1 and 5), and mean heart dose was 13.3–14 Gy and 2.3–9 Gy for left- and right-sided irradiation, respectively.

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

**Heart dose from IMC irradiation**

The IMC is located anteriorly, in the intercostal spaces, close to the heart. Therefore, IMC RT generally led to greater mean heart doses than irradiation of other targets, particularly for left-sided treatment. IMC RT, using either direct anterior (Fig. 2f) or wide tangential (Figs. 2d and 2e) fields, delivered a mean heart dose of 2.7–16.7 Gy for left-sided and 2.3–10.5 Gy for right-sided RT (Table 2), with the greatest doses resulting from left direct anterior 6-MV irradiation (Fig. 4b). The heart volume irradiated was also considerable, particularly for direct anterior photon fields, which delivered $\geq 10$ Gy to around 40% and around 20% of the heart for left- and right-sided fields, respectively. In contrast, direct electron IMC irradiation resulted in a lower mean heart doses of around 2 Gy and lower heart volumes of around 7% receiving $\geq 10$ Gy (for both left- and right-sided RT), owing to the rapid decrease in dose beyond the 90% isodose.

Direct anterior megavoltage IMC RT (Figs. 2f and 4) resulted in irradiation of different parts of the heart for left- and right-sided treatment. For a right-sided field, doses of $\sim 35$ Gy were received by the right atrium, but, for a left-sided field, similar doses were received by the left ventricle.

**Heart dose from scar boost irradiation**

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

The heart dose from boost RT was small relative to the dose from the chest wall or breast RT because of the low given dose. For example, a patient who received 50 Gy MV tangential left chest wall RT, followed by 10 Gy electron scar boost would receive a total mean heart dose of 5.0 Gy:
Combinations of different regimens

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

Heart dose from supraclavicular fossa and axillary irradiation

The supraclavicular fossa (SCF) and axillary fields were distant from the heart, which received scattered radiation alone. The mean dose was 0.3–0.8 Gy for left-sided fields. The right-sided SCF and axillary fields are even farther from the heart, therefore, the cardiac doses are likely to be lower.

Coronary artery doses

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

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

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

Patient-to-patient variability in heart dose

The doses in Tables 2 and Appendix Tables 1–8 are estimates for a representative patient of average weight and build. The dose received by any individual patient will vary from these, depending on her individual characteristics, including breast size, extent of breast surgery, and sternal length, and on the circumstances of her RT (e.g., the linear accelerator used). These sources of variability would, in most cases, apply to any method of estimating cardiac dose retrospectively. The magnitude of their likely effect on cardiac dose is described below.

Variation in patient anatomy

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

Presence of breast tissue

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

**Variation in patient position**

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

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

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

**Difficulty identifying field borders**

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

**Variability in boost position**

Cobalt-60 and iridium wire boosts were reconstructed, first centered on the nipple, second moved 2 cm superiorly, and third, 2 cm inferiorly. Table 4 shows the resulting differences in mean heart dose. In reality, the position of the scar and, therefore, of the boost, could well vary more than $\pm 2$ cm; therefore, the heart dose measurements are subject to a high degree of uncertainty. In general, the farther inferior the boost, the greater the heart dose. However, the heart dose from boost irradiation is always low relative to other techniques because of the low given dose of 10–20 Gy.

**Use of different models of treatment unit**

For axillary and SCF irradiation, two different makes of linear accelerator with, nominally, the same energy (6 MV) were used. These fields were chosen, because they are usually distant from the heart; therefore, the heart dose is largely from scattered irradiation originating in the machine treatment head and can vary according to the machine used. The mean heart dose varied between 0.8–1.4 Gy for supraclavicular and between 0.5–0.9 Gy for axillary fields. Thus, the use of different RT machines made little difference to the heart dose. To enable a comparison between different regimens (Table 1), for each beam energy, the data from only one machine were used.

**Effect of changing source-to-skin distance for cobalt-60 beams**

Direct IMC and tangential pair 60Co fields were set up using source-to-skin distances of 70 and 100 cm. This difference in the source-to-skin distance resulted in differences in the mean heart dose of only 0.2 Gy for IMC and 0.1 Gy for tangential pair irradiation.

**DISCUSSION**

We have presented dose estimates for breast cancer RT regimens that were in widespread use worldwide from the 1950s to the 1990s. There were considerable variations in the cardiac doses according to the regimen used. For example, 6-MV direct IMC RT delivered 17-Gy heart dose and

<table>
<thead>
<tr>
<th>Target</th>
<th>Field arrangement</th>
<th>Mean heart dose (Gy)</th>
<th>Field(s) in standard position</th>
<th>Field(s) moved superiorly by 1 cm</th>
<th>Field(s) moved inferiorly by 1 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest wall/breast</td>
<td>Tangential pair</td>
<td></td>
<td>Left 4.7</td>
<td>Right 1.2</td>
<td>Left 4.1</td>
</tr>
<tr>
<td>Chest wall and internal mammary chain</td>
<td>Tangential pair</td>
<td></td>
<td>Left 13.3</td>
<td>Right 2.3</td>
<td>Left 12.1</td>
</tr>
<tr>
<td>Internal mammary chain</td>
<td>Direct anterior</td>
<td></td>
<td>Left 15.0</td>
<td>Right 9.3</td>
<td>Left 12.6</td>
</tr>
</tbody>
</table>

* Variability likely to be minimal because dose mainly from scattered radiation.
25-Gy LAD dose, whereas electron IMC irradiation delivered 3-Gy heart dose and 6-Gy LAD dose, while still delivering therapeutic tumor dose. Such differences are likely to have resulted in a wide variation in the cardiac doses worldwide, during the past few decades, owing to the diversity in RT practice. This will be useful when deriving dose–response relationships. Our estimates include coronary artery and heart doses for a wide variety of different regimens and are consistent with the few published CT-based estimates (Table 5). The techniques available for comparison were wide and standard left tangential irradiation (22, 30) and direct IMC irradiation (2, 24). The estimates of irradiated heart volumes were usually consistent with our estimates to within ±3% of volume and were never more than ±11%.

**Sources of variability for a given regimen**

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

Some uncertainty existed in locating the three main coronary arteries because arterial contrast was not used for CT planning. However, these arteries were visible on some CT slices, and their course tends to follow the interventricular and atrioventricular grooves, which are identifiable on CT. In addition, the accuracy of CT-based estimates is limited by normal movement of the heart, lungs, and thoracic cage. These movements will tend to slightly change the position of the heart relative to the radiation beams. However, the CT planning scan used for these reconstructions was acquired during several minutes (including many breathing cycles), and the original RT would also have been delivered during several minutes. Therefore, the CT images are likely to illustrate the changing position of the heart relative to the treatment fields during the original RT, thus averaging the variation in dose caused by such changes.

For some regimens, heart dose is affected by patient position. Treatment position for tangential irradiation in the 1950s to 1990s varied. In some regions, the ipsilateral arm was elevated using a T-bar rest, in others it was abducted to 90°. For left tangential RT, lowering the ipsilateral arm (from the T-bar position to 90°) changed the mean heart dose from 2 to 3.4 Gy in our volunteer, which represents a 70% increase. Similar systematic changes in heart dose have been reported for 11 other patients (29). For our

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

<table>
<thead>
<tr>
<th>Technique</th>
<th>Typical dose and fractionation</th>
<th>Field or implant in standard position</th>
<th>Field or implant moved superiorly by 2 cm</th>
<th>Field or implant moved inferiorly by 2 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachytherapy using ¹⁰³Ir wire implant</td>
<td>20 Gy</td>
<td>0.6</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Direct anterior ⁶⁰Co beam</td>
<td>10 Gy in 5</td>
<td>0.9</td>
<td>0.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Technique/field description</th>
<th>Beam energy</th>
<th>Laterality</th>
<th>Measure of dose/volume</th>
<th>Published estimate of volume (%)</th>
<th>Present estimate of volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gyenes 1997 (30)</td>
<td>Wide tangential pair to breast and internal mammary chain</td>
<td>⁶⁰Co</td>
<td>Left</td>
<td>Percentage of volume of heart receiving &gt;50% of dose</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Tangential pair</td>
<td>6 MV</td>
<td>Left</td>
<td>Percentage of volume of heart receiving &gt;50% of dose</td>
<td>5.7</td>
<td>5.5</td>
</tr>
<tr>
<td>Gagliardi 1996 (2)</td>
<td>Direct internal mammary chain field</td>
<td>⁶⁰Co</td>
<td>Left</td>
<td>Percentage of volume of heart receiving &gt;30% of dose</td>
<td>55†</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Direct internal mammary chain field</td>
<td>⁶⁰Co</td>
<td>Right</td>
<td>Percentage of volume of heart receiving &gt;46% of dose</td>
<td>30†</td>
<td>27</td>
</tr>
</tbody>
</table>

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

†Reported doses estimated from published dose–volume histograms and converted from dose in equivalent 2-Gy fractions; thus, a greater degree of uncertainty is present.
representative patient (T-bar position), 6-MV left tangential irradiation delivered a 4.7 Gy mean heart dose (Table 2). If she had undergone irradiation in the 90° arm position, her heart dose might have been around 8 Gy (assuming a 70% dose increase for a change from the T-bar to 90° arm position). We speculate that the mean LAD dose could have been >70% greater, because it is close to the radiation beams. The right and circumflex coronary arteries are distant from the tangential beams, and their doses were probably little affected by arm position. Our dose estimates for left tangential irradiation are applicable to patients treated in the T-bar position but are likely to systematically underestimate the heart and LAD doses for patients irradiated with the ipsilateral arm lower (e.g., at 90°).

Irradiation of LAD coronary artery

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

Need for dose–response relationship

To reliably assess the cardiac risks of current and future RT regimens, relationships between the cardiac doses and subsequent cardiac morbidity and mortality are needed. This study has successfully quantified the cardiac doses and volumes irradiated for most common breast cancer RT regimens used between the 1950s and 1990s and demonstrated a wide range of cardiac doses. These estimates were derived to enable the development of cardiac dose–response relationships using data from the Early Breast Cancer Trialists’ Collaborative Group trials and data from other women for whom information on RT technique, tumor laterality, and outcome are available.

REFERENCES


