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Overview

Cardiac Side-effects From Breast Cancer Radiotherapy

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Abstract

Breast cancer radiotherapy reduces the risk of cancer recurrence and death. However, it usually involves some radiation exposure of the heart and analyses of randomised trials have shown that it can increase the risk of heart disease. Estimates of the absolute risks of radiation-related heart disease are needed to help oncologists plan each individual woman's treatment. The risk for an individual woman varies according to her estimated cardiac radiation dose and her background risk of ischaemic heart disease in the absence of radiotherapy. When it is known, this risk can then be compared with the absolute benefit of the radiotherapy. At present, many UK cancer centres are already giving radiotherapy with mean heart doses of less than 3 Gy and for most women the benefits of the radiotherapy will probably far outweigh the risks. Technical approaches to minimising heart dose in breast cancer radiotherapy include optimisation of beam angles, use of multileaf collimator shielding, intensity-modulated radiotherapy, treatment in a prone position, treatment in deep inspiration (including the use of breath-hold and gating techniques), proton therapy and partial breast irradiation. The multileaf collimator is suitable for many women with upper pole left breast cancers, but for women with central or lower pole cancers, breath-holding techniques are now recommended in national UK guidelines. Ongoing work aims to identify ways of irradiating pan-regional lymph nodes that are effective, involve minimal exposure of organs at risk and are feasible to plan, deliver and verify. These will probably include wide tangent-based field-in-field intensity-modulated radiotherapy or arc radiotherapy techniques in combination with deep inspiratory breath-hold, and proton beam irradiation for women who have a high predicted heart dose from intensity-modulated radiotherapy.

Key words: Breast cancer radiotherapy; cardiac-sparing breast radiotherapy; long-term effects; radiation-related heart disease

Statement of Search Strategies Used and Sources of Information

This paper reflects expert opinion and current literature accessed by the authors; no formal search was carried out.

Introduction

In most developed countries, radiotherapy is received by around half of women with breast cancer [1]. It has been shown to reduce the risk of cancer recurrence and death and it has undoubtedly saved the lives of many women [2,3]. However, breast cancer radiotherapy inevitably involves some radiation exposure of the normal tissues within the thorax, including the heart. Analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) including around 40 000 women in 78 randomised trials have shown that the beneficial effect of radiotherapy was offset by a 30% increase in the heart disease death rate, with most of these deaths being due to ischaemic heart disease [4].

The excess of heart disease after radiotherapy has been confirmed by a number of observational studies in populations of women irradiated for breast cancer. In observational data where the women receiving radiotherapy have not been selected at random, comparison of irradiated and unirradiated women may give misleading answers [5]. However, a comparison of heart disease rates between women irradiated for left-sided versus right-sided breast cancers can provide information on the differing cardiac risks of higher versus lower cardiac radiation dose. Heart disease after breast cancer radiotherapy has been studied in this way in more than 20 observational studies including around a quarter of a million women irradiated worldwide

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between 1968 and 2004 [6,7]. The left versus right ratios of incident or fatal heart disease were greater than one in most of these studies, and the increase was statistically significant in around a third of them. The most commonly reported excesses were ischaemic heart disease and myocardial infarction.

Cardiac Risks for Women Today

Estimates of the absolute risks of radiation-related ischaemic heart disease are needed to help oncologists plan each individual woman's treatment. These risks can then be balanced against the absolute benefits of radiotherapy [2–4]. Estimation of each woman's absolute radiation-related cardiac risk needs: (i) the percentage increase in the ischaemic heart disease rate per unit cardiac radiation dose, (ii) her estimated cardiac radiation dose from her radiotherapy plan and (iii) her background risk of ischaemic heart disease in the absence of radiotherapy.

Risk Per Unit Dose

There are two dose–response relationships for heart disease after breast cancer radiotherapy based on around 1000 cardiac events each. The first, based on population-based data, included individual patient information on the regimen used and cardiac outcome data [8]. In these data, the rate of incident major coronary events increased by 7.4% per Gy (95% confidence interval 2.9–14.5) mean heart dose. The second dose–response relationship is based on data from women irradiated in randomised trials over the past half a century [6]. In both these studies, there was no evidence of a threshold dose below which no risk occurs, but risks after cardiac doses below around 2 Gy could not be estimated precisely so the possibility of a threshold could not be excluded. There are several differences between these two dose–response relationships. The first is based on incident events; it included major coronary events and individual patient dose estimates. The second is based on deaths; it included all heart disease and trial-based dose estimates. Nevertheless these two dose–response relationships in two different data sets are consistent with each other and provide strong evidence that the risk of heart disease does indeed increase linearly with increasing cardiac radiation dose, and that the quantitative estimates of the risks per Gy are roughly correct. The population-based dose–response relationship (7.4% per Gy) [8] is probably more relevant than the dose–response relationship in randomised data because it included individual patient information on the regimen used, on cardiac outcomes and cardiac risk factors before radiotherapy. It is this dose–response relationship that is most useful in predicting risks for women in the clinic today.

In both of these studies a number of different dose measures were considered, e.g. mean and maximum doses to the left anterior descending, right and circumflex coronary arteries and percentage volume of the heart irradiated to different dose levels. The left anterior descending coronary artery is of particular interest because it is sometimes included in left breast cancer radiotherapy fields. In both studies, estimated mean doses to the left anterior descending coronary artery and the heart were highly correlated. The mean dose of radiation to the heart was a better predictor of radiation-induced heart disease than any of the other cardiac dose measures, including mean left anterior descending coronary artery dose.

Cardiac Radiation Dose

Exposure of the heart from breast cancer radiotherapy has reduced substantially over the past few decades. Recent estimates suggest that the mean heart dose from breast cancer radiotherapy worldwide may be around 5 Gy in left-sided radiotherapy and 3 Gy in right-sided [9], but with considerable variation according to country, patient anatomy and technique.

Most women in the UK receive tangential radiotherapy, which delivers mean heart doses of around 1–2 Gy from left-sided and 1 Gy from right-sided radiotherapy [10,11]. In right-tangential radiotherapy, the heart usually receives scattered irradiation only. In left-tangential irradiation, part of the heart may be included in the fields for some women. The method of estimating heart dose for such women varies. In some cancer centres, each woman's three-dimensional computed tomography radiotherapy plan, including her cardiac contour, is used to calculate her mean heart dose. In other centres this has not yet been implemented routinely and mean heart dose from left-tangential radiotherapy may be roughly estimated using the maximum heart distance, i.e. the maximum distance that the heart protrudes into the radiotherapy fields [12].

Risk of Ischaemic Heart Disease in the Absence of Radiotherapy

Each woman's radiation-related risk approximately multiplies her pre-existing ischaemic heart disease risk (i.e. her risk in the absence of radiotherapy). So women with cardiac risk factors tend to have higher absolute risks than other women.

The dose–response relationship of 7.4% per Gy mean heart dose has been applied to recent data on the rates of death from ischaemic heart disease for the 15 Westernmost countries of the European Union [8]. Detailed predictions of cardiac risk, subdivided according to mean heart dose, presence or absence of pre-existing cardiac risk factors and age at irradiation are available in the online supplementary material of the paper. They may be used in combination with the risks of breast cancer recurrence and of death from breast cancer and other diseases to predict risk for individual women in the clinic.

Relevance to Radiotherapy Practice

In breast cancer radiotherapy today, the radiation dose received by the heart varies from woman to woman, as does

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