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Should patients requiring radiotherapy for breast cancer be treated with proton beam therapy?

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What you need to know

Standard x-ray radiotherapy reduces risk of breast cancer relapse with low risk of long-term side-effects in most patients.

Proton Beam Therapy (PBT) is a type of radiation therapy. It uses protons (high-energy charged particles) rather than x-rays to treat cancer. PBT can be more accurately targeted than x-rays potentially reducing risks of side-effects in organs such as the heart.

There are no randomised data supporting the routine use of PBT in patients with breast cancer.

There is a small population of breast cancer patients at higher-than-average lifetime risk of radiation-induced heart disease that may benefit from PBT. Randomised controlled trials are currently recruiting. These will evaluate the extent to which PBT can reduce heart doses in this patient population (mean heart dose being a predictor for the risk of late cardiac side-effects) whilst also comparing short to medium-term side-effects in PBT versus current standard-of-care x-ray techniques.

Introduction

According to the World Health Organisation, more than 2.3 million new cases of breast cancer were diagnosed worldwide in 2020. In the UK around 56,000 patients [https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer] are diagnosed with breast cancer each year, with around two-thirds of these receiving radiotherapy. X-ray radiotherapy for breast cancer reduces the risk of relapse by around half and, in many patients, improves survival with few long-term side-effects[1,2]. For example, in node positive patients, the use of radiotherapy reduced breast cancer mortality by 6% at 20 years[2]. In breast cancer radiotherapy, radiation dose is delivered to the target areas i.e. the breast (or chest wall) +/- regional lymph nodes (depending on the individual patient's situation) using x-ray beams. An international standard radiation dose to be delivered to the target areas in this setting is 40Gy in 15 fractions delivered over 3 weeks (the START trial having demonstrated

that this regimen is as effective as the previous standard of care of 50Gy in 25 fractions over 5 weeks but with lower risks of side-effects)..

Radiotherapy can also deliver small amounts of radiation dose to the surrounding organs including the heart, which can increase the risk of heart disease in proportion to the mean radiation dose to the heart (add Darby reference here). For many patients radiation doses to the heart will be very low but, particularly for patients requiring radiotherapy to the parasternally-located internal mammary nodes (IMN), radiation doses to the heart can be higher. Inclusion of the IMN in the radiotherapy field is based on data from a Danish prospective population cohort study which compared outcomes in 3089 patients treated with x-ray radiotherapy to breast/ chest wall and axillary nodes +/- the IMN. At a median follow-up of 15 years, this demonstrated a 4.7% overall survival advantage from including the IMN in the radiotherapy target volume (95% CI 0.77 to 0.96; p= 0.007)[3]. The largest benefits were seen in patients with higher stages of lymph nodes involvement and/or primary cancers located in the medial aspects of breast tissue. In the majority of patients, even those requiring radiotherapy to the IMN, it is possible to deliver radiotherapy with a 1% or lower risk of long-term cardiac side-effects and a 0.1% risk of other significant side-effects such as second cancers. This is because, breath-hold techniques (in which patients take a breath in and hold it thereby moving the heart away from the radiotherapy beam during treatment) can be used with (or without) dose-shaping techniques (such as volumetric modulated arc therapy (VMAT)) to minimise radiation doses to the heart. However, in a small population of younger patients and/or patients with cardiac risk-factors requiring IMN radiotherapy and/ or in whom the heart sits particularly close to the chest wall due to anatomical variations such as pectus excavatum, it is difficult to deliver radiation dose where it is needed without increasing a patient's risk of long-term radiation-induced heart disease to unacceptable levels (2% or higher long-term risk of long-term radiation-associated major coronary events).

Proton beam therapy (PBT) uses high-energy charged particles rather than x-rays to treat cancer. PBT is able to deliver radiation dose to a defined depth thereby giving better dose coverage where needed with least dose to surrounding normal tissues. In breast cancer patients, PBT can therefore reduce radiation doses to the heart, lung and other breast [figure 1]. It is estimated, based on the proportion of women fulfilling eligibility criteria IMN radiotherapy and the proportion of patients likely to incur higher

mean heart doses, that there are around 500 women per year in the UK that could benefit from PBT over standard x-ray radiotherapy techniques in terms of reduced risks of long-term cardiac effects. There is a theoretical concern that biological effects at the end of the PBT beam may increase side-effects in skin (temporary redness), rib (fractures) and lung (subclinical changes) compared to x-ray radiotherapy albeit this has not been the case with more modern PBT techniques. Nonetheless patient focus group discussions suggest that patients want to optimise both their medium-term and long-term side-effect risks.

What is the evidence of the uncertainty?

No "high certainty" evidence exists on the clinical benefits of PBT in patients requiring locoregional radiotherapy for breast cancer in relation to either cardiac late-effects and/or cosmetic outcomes. A guide to GRADE evidence ratings is shown in box 1.

In-silico dosimetric studies (in which radiation dose distributions from different radiotherapy techniques are modelled using radiotherapy planning CT scans from individual patients) have demonstrated that PBT can reduce mean radiation doses to the heart, lung and contralateral breast in patients undergoing radiotherapy to the IMN, compared with standard x-ray radiotherapy[4-11] leading to moderate certainty around the cardiac dose-reducing properties of PBT albeit the clinical extent of the benefits remains to be determined. In patients with pectus excavatum for example[12] heart dose

Box 1: GRADE Working Group grades of evidence

- High certainty—we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate certainty—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low certainty—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
- Very low certainty—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

is reduced by more than 50% in many cases which is likely to halve a patient's long-

term cardiac risks depending on age and cardiac risk factor status. A systematic search for published clinical studies was undertaken according to the criteria in box 2.

There are no published randomised controlled trials comparing PBT against highest quality standard x-ray radiotherapy in breast cancer patients. In terms of other clinical outcomes, small non-randomised prospective cohort studies, mainly from the US, have demonstrated that a 5-week course of PBT to the breast/ chest wall and regional LNs is safe, can reduce heart doses (to <1 Gy in the majority of patients[13]) and has comparable short-to medium-term side-effects to 5-week standard x-ray radiotherapy with low rates of local and distant relapse[5,14-20] albeit there are no studies with median follow-up beyond 5 years. Most of the data on normal tissue effects from PBT relate to the historical 5-week fractionation. Given that a 3-week course of radiotherapy for breast cancer has been an international standard of care for over a decade[21] more recently designed randomised controlled trials compare 3-week PBT against 3-week standard radiotherapy.

A recently published international consensus statement[13] also describes the lack of high-level evidence for the use of PBT in locoregionally advanced breast cancer and encourages recruitment of patients into ongoing randomised controlled trials. In summary, there is moderate certainty that non-cardiac normal tissue outcomes are equivalent for PBT and standard x-ray radiotherapy but this needs to be established in randomised controlled trials.

Is ongoing research likely to provide relevant evidence?

As PBT enables delivery of full dose to breast and nodes whilst aiming to reduce mean heart dose (MHD), it can be concluded that long-term cancer outcomes will be, at least, maintained using PBT, if not improved. Given the low event rates for breast cancer relapse, it isn't feasible to test this endpoint within a RCT of PBT against x-ray radiotherapy. The key research question remains whether, in the subpopulation of patients undergoing radiotherapy for breast cancer who are at higher risk of radiation-induced heart disease, PBT can reduce the risk of long-term serious heart damage

without increasing other short-term side-effects such as skin changes compared to standard x-ray radiotherapy.

Worldwide, there are three ongoing randomised controlled trials currently recruiting to address this question, the US RADCOMP trial, the Danish (DBCG) Breast PBT Trial, and the UK PARABLE trial (see box 3). Two trials (RADCOMP and DBCG) have 10-year rates of cardiac complications as the primary endpoint. In PARABLE, mean heart dose, as a predictor of the risk of long-term radiation-induced heart damage, is used as a co-primary endpoint, allowing for a much shorter follow-up period and smaller sample size. These RCTs should provide high certainty around the population of patients in whom PBT will provide the greatest benefits in terms of reduced risks of late cardiac side-effects. High certainty around the effects of PBT on other normal tissues compared with standard x-ray radiotherapy will also be provided.

What should we do in the light of the uncertainty?

In the majority of patients, radiation doses to the heart can be kept low with a simple breath-hold technique being able to keep mean heart doses well under 2Gy even in left-breast affected patients. In patients requiring radiotherapy to the IMN and/or patients with pectus excavatum, breath-hold can be combined with dose-shaping techniques (such as VMAT) to keep normal tissue doses low. In patients in whom the risk of radiation-induced heart disease is higher (due to higher mean radiation dose to the heart, pectus excavatum, young age and/or cardiac risk factors), patients should, where possible, be offered the possibility of entering a RCT of PBT against standard x-ray radiotherapy. Where a clinical trial is unavailable, given the absence of data demonstrating a clear benefit of PBT over standard x-ray radiotherapy, patients should be offered optimal x-ray radiotherapy (breath-hold and dose-shaping techniques). It is particularly important in such cases for clinicians and patients to weigh up the benefits versus side-effects of treatment. In most patients the survival advantages of radiotherapy will far outweigh the long-term cardiac risks.

Box 3: Ongoing randomised controlled trials

Ongoing clinical studies of PBT in breast cancer were identified from the ClinicalTrials.gov website, the World Health Organisation International Clinical Trials Registry Platform, and the Cochrane Central Register of Controlled Trials using the search terms 'breast cancer' AND 'proton'. Trials of partial breast PBT and reirradiation as well as those without a cardiac primary endpoint were excluded. Three randomised controlled trials are currently recruiting as per the table below.

Trial, Location	**Link**	**N, eligibility**	**Randomisation**	**Primary endpoint**
Pragmatic randomised trial of proton vs. photon therapy for patients with non-metastatic breast cancer: a radiotherapy comparative effectiveness (RADCOMP) consortium trial, US	https://clinicaltrials.gov/ct2/show/NCT02603341	1278, for breast cancer patients aged ≥ 21 years requiring RT to internal mammary chain	1:1 PBT versus photon therapy (Treatment 5 days per week for 5-7 weeks)	Major cardiovascular events at 10 years after RT
The Danish Breast Cancer Collaborative Group (DBCG) Proton Trial: Photon versus Proton Radiation Therapy for Early Breast Cancer, Denmark	https://clinicaltrials.gov/ct2/show/NCT04291378	1502, for breast cancer patients in whom RT is indicated and in whom standard planning shows mean heart dose of 4Gy or more and/or V20 lung of ≥ 37%	1:1 PBT versus photon therapy (Treatment 5 days per week for 3-5 weeks)	Radiation-associated ischaemic and valvular heart disease at 10 years after RT
Proton beam therapy in patients with breast cancer: evaluating early and late effects (PARABLE), UK	https://doi.org/10.1186/ISRCTN14220944	192, for breast cancer patients aged ≥18 years who have around a 2% or higher predicted lifetime risk of serious heart side-effects from their planned RT	1:1 PBT versus standard tailored RT (intensity-modulated arc therapy and breath-hold) (Treatment 5 days per week for 3 weeks)	Co-primary endpoints: i) Mean heart dose; ii) patient-reported normal tissue toxicity in the breast (EORTC QLQ-BR23 breast symptoms score) at 2 years after RT

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PPI statement

MM is the PPI representative and co-investigator on the UK PARABLE trial (Proton beAm theRApy in patients with Breast cancer: evaluating early and Late Effects). As such she has led on PPI input into the design and delivery of a proton trial in breast cancer patients including participating in patient focus groups informing decisions around eligible population, trial endpoints and patient acceptability. MM has contributed, using this experience base, to the writing of this manuscript.

Competing interests statement

The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: none.
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