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Proton beam therapy in patients with breast cancer: evaluating early and late effects

Submission date
04/05/2022

Recruitment status
Recruiting

Registration date
06/06/2022

Overall study status
Ongoing

Last Edited
20/11/2024

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims

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 the risks of side effects in normal tissues such as the heart. Researchers want to compare PBT with standard x-ray radiotherapy (RT) in breast cancer patients at a higher risk of side effects from RT. They aim to show that PBT reduces the predicted risk of long-term serious heart damage whilst not increasing other shorter term side effects such as skin changes.

Around 33,000 breast cancer patients/year need RT as part of their treatment. A proportion (around 500/year) are less well served by standard RT due to the need to treat lymph nodes near the breast-bone. A person's body shape can also make treatment difficult. This can result in a lower RT dose where it is needed (reducing the likelihood of cure), and/or an unwanted dose to healthy tissues such as the heart (increasing the risk of serious heart damage many years later).

PBT has been used in other countries to treat breast cancer, but numbers are small with no direct comparison with RT. PBT is different from RT as it delivers dose to a defined depth thereby giving better dose coverage where needed with a lower dose to the heart. Increased skin and rib side effects have however been reported around 2 years after treatment, although this is mostly with older PBT techniques delivered over 5 weeks. UK standard RT is delivered over 3 weeks as clinical trials have shown this to be as good as 5 weeks with fewer side effects.

The NHS has two PBT centres in Manchester (opened 2018) and London (opening 2021). We now have a unique opportunity to compare 3-week PBT with 3-week RT for this patient group with unmet need.

To confirm that PBT reduces rare but life-threatening side effects such as heart attacks compared with RT would need over 10,000 patients in a clinical trial lasting 15-20 years. This is not feasible and would mean large numbers of patients being exposed to less than optimal treatment in the meantime. The researchers plan an efficient clinical trial using average heart dose, a short term predictor for later heart damage, to deliver a result much earlier. They will invite breast cancer patients who have at least a 2 in 100 predicted lifetime risk of serious heart side effects from their planned RT to receive either PBT (Manchester/London) or RT (local centre). The choice of PBT or RT will be decided randomly by a computer to minimise bias. The researchers will compare the average heart dose received with PBT to that received with RT and

use symptoms reported by patients at 2 years after treatment to compare other side effects in and around the breast. Outcomes and side effects will be collected for 5 years and NHS databases will be used to collect even longer-term effects.

Who can participate?
Breast cancer patients aged 18 years and over who have at least a 2 in 100 predicted lifetime risk of serious heart side effects from their planned RT

What does the study involve?
Participants will be randomly allocated to receive either proton beam therapy at one of two UK NHS Proton Beam centres (The Christie Hospital, Manchester or University College Hospital, London) or optimal radiotherapy at their local centre. The choice of PBT or RT will be decided randomly by computer to minimise bias. The researchers will assess the average heart dose received with PBT compared with RT as a validated early measure predicting late heart RT damage. Patient-reported side effects in the treated breast will be compared between PBT and RT at 2 years. Outcomes and side effects will be collected for up to 5 years and NHS databases will be used for longer-term effects.

What are the possible benefits and risks of participating?
There is no guarantee that an individual will benefit directly from taking part in this study, although participants will be treated with either tailored RT, which is the most targeted and modern radiotherapy using x-rays available worldwide, or PBT. It is hoped that the information from the study will benefit people who develop breast cancer in the future.
Radiotherapy causes a number of short-term side effects. These effects will be similar to those experienced with standard radiotherapy outside this study. The risk of longer-term side effects on the heart and lungs from both tailored x-ray therapy and proton beam therapy is low, but the aim of this study is to be able to reduce these risks further. Radiotherapy and CT scans use radiation to inform images and provide treatment. This radiation may cause cancers to develop many years or decades after the exposure. These second cancer risks are very low and likely to be similar for both tailored x-ray therapy and proton beam therapy. The researchers will be monitoring this as part of the longer term follow-up in this study. All patients in the study will have a CT scan of the chest at 2 years, and may also have additional imaging during treatment in order to further improve the accuracy of the treatment. The radiation dose from all the additional scans will be small compared to the dose from the radiotherapy and will not significantly change the risk of developing cancer at a much later date. PBT treatment will take place at either The Christie NHS Foundation Trust in Manchester or University College Hospital in London rather than at a local radiotherapy centre. Which PBT centre allocated will depend on the participant's location and also which centre has availability for treatment. In some circumstances, this may not be the closest PBT centre.

Where is the study run from?
Institute of Cancer Research (UK)

When is the study starting and how long is it expected to run for?
November 2019 to February 2030

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
PARABLE Trial Team, parable-icrctsu@icr.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-proton-beam-therapy-for-breast-cancer-parable

Study website
https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/our-research/clinical-trials/parable

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Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
302709

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 52070, IRAS 302709

Study information

Scientific Title
PARABLE: Proton beam therapy in patients with breast cancer: evaluating early and late effects

Acronym
PARABLE

Study objectives
PARABLE aims to show that proton beam therapy (PBT) reduces the predicted risk of late serious heart toxicity with no increase in other shorter-term side effects compared with tailored photon radiotherapy (intensitymodulated arc therapy). PARABLE's specific objectives are to:
1. Change international practice for breast PBT early with a primary outcome analysis at 2 years' follow-up
2. Improve the understanding of PBT biological models through a mechanistic study with potential benefit for all cancer patients needing PBT.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 16/02/2022, West of Scotland Research Ethics Committee 3 (Ground Floor Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 314 0212; WoSREC3@ggc.scot.nhs.uk), ref: 21/WS/0171

Study design
Randomized; Interventional; Design type: Treatment, Radiotherapy

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Available on study website: https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/our-research/clinical-trials/parable

Health condition(s) or problem(s) studied
Breast cancer

Interventions
Participants will be recruited from selected sites across the UK. Potential participants will be identified by their clinical care teams and their suitability will be discussed at local multidisciplinary team meetings. Participants will be those undergoing adjuvant radiotherapy for breast cancer with ≥2% estimated absolute lifetime risk of radiation-induced late major cardiac events.

Eligible patients will predominantly be those requiring internal mammary node radiotherapy (RT) and will also include patients with unusual anatomy (e.g. pectus excavatum/sunken chest). These patients will be approached initially by a member of their clinical care team and provided with a PARABLE Introductory leaflet providing brief details of the trial, how the estimated lifetime risk of heart problems will be calculated and how it may be a suitable option for them if shown to be eligible.

Patients subsequently identified as having ≥2% estimated absolute lifetime risk of radiation-induced late major cardiac events will then be approached by a member of their clinical care team and will receive a verbal explanation of the trial, together with a PARABLE Main Patient Information Sheet which they will take home with them. They will be given sufficient time to make a decision about whether they would like to participate and will be able to discuss their options with friends, family or their GP. They will have the opportunity to raise questions about PARABLE with their clinical care or research team and these will be addressed prior to their decision about whether to participate. Should they choose to participate they will be asked to sign a consent form to record their informed consent.

The following assessments will be performed prior to randomisation into PARABLE:
1. Complete medical history (including specific risk factors for cardiovascular disease and RT toxicity)
2. Weight and height
3. Baseline signs and symptoms (Common Terminology Criteria for Adverse Events [CTCAE] v5.0, Radiation Therapy Oncology Group [RTOG])
4. Patient-reported outcomes (PRO) of health-related quality of life (QoL) including EORTC QLQ-C30 and QLQ-BR23, Body Image Scale, protocol-specific questions relating to breast changes resulting from cancer treatments, PRO-CTCAE items, EQ-5D-5L; healthcare resource usage (collected prior to the patient being aware of treatment allocation).
5. Biological sample collection (research bloods) for those patients providing optional consent

All participants will be randomised via the central randomisation service provided by the Clinical Trials and Statistics Unit at The Institute of Cancer Research (ICR-CTSU). Patients will be randomised in a 1:1 ratio to the following:
1. Experimental intervention: proton beam therapy (PBT) over 3 weeks
2. Control: tailored photon radiotherapy (RT) over 3 weeks.

Tailored photon RT will be delivered at patients' local RT centres and PBT in either Manchester or London depending on the proximity and availability of treatment slots within the required timeframe.

PARABLE on-treatment assessments:
Treatment will be delivered over a 3-week period, patients will be seen by their treating clinician at the end of each week and the following assessments performed:
1. Early skin and oesophageal toxicity (CTCAE v5.0) and adverse events (clinician-reported)
2. PRO of early toxicity and quality of life (QoL) including skin, breast pain and swelling, fatigue, insomnia, mouth/throat sores, cough and breathlessness, emotional functioning, cognitive functioning, sexual functioning and social functioning, EQ-5D-5L

PARABLE post-treatment assessments:
Early skin and oesophageal toxicity (CTCAE v5.0) and adverse events will be assessed from 2 weeks' post-treatment (5 weeks from the date treatment commenced) and then weekly until acute local symptoms (skin, breast, oesophageal and respiratory) ≤ grade 1 (clinician-reported). Assessments can be conducted remotely (i.e. via telephone) where patient attendance at clinic is not required.

Weekly (from week 4 until week 12) patients will be asked to record Patient-Reported Outcomes (PRO) of early toxicity and QoL including skin, breast pain and swelling, fatigue, insomnia, mouth /throat sores, cough and breathlessness, emotional functioning, cognitive functioning, sexual functioning and social function, with the addition of EQ-5D-5L and healthcare resource use at the 12 week time point.

Patients will be provided with questionnaire booklets to take home and record details weekly until week 12 post-treatment

PARABLE post-treatment follow-up:
After treatment, clinical follow up should follow local guidelines. The following assessments will be conducted:

3, 6 and 12 months post-treatment:
Cough and breathlessness assessment (RTOG)

A 12-month assessment will only be required if the patient experienced symptoms at 3 and/or 6 months. Patients with confirmed pneumonitis will be followed up as per local protocol, with status documented at 12 months.

6, 12, 24 and 60 months post-treatment:
PRO of late toxicity and QoL, including EORTC QLQ-C30, QLQ-BR23, Body Image Scale, protocol-specific questions relating to breast changes resulting from cancer treatments, EQ-5D-5L; healthcare resource use.
Patients will be sent PRO questionnaires directly to their homes by the ICR-CTSU PARABLE team. Specific consent to provide contact details will be
requested at the time of trial entry.

24 months post-treatment:
1. Chest CT scan (non-contrast for comparison with RT planning CT) for mechanistic study
2. Biochemistry profile (thyroid function test)

12, 24, 36, 48 and 60 months post-treatment:
1. Clinician-reported late toxicity
2. Assessment for recurrence and survival

At disease recurrence/relapse or diagnosis of new primary cancer routine clinical, histological and imaging information will be collected. Tumour tissue (diagnostic and/or recurrence) will be requested subject to patients' written informed consent. Associated information, including imaging scans carried out at the time of any relapse as part of standard care will also be requested.

Clinical follow-up to 5 years after randomisation will be in accordance with patients' local RT centres guidelines for both PBT and RT groups. Information collected from NHS databases via routine data linkage may also be used. Patients will provide specific consent for this at the time of trial entry.

Intervention Type
Other

Primary outcome measure
1. Mean heart dose (in Gy) using widetangent field placement in deep inspiration breath hold (DIBH) at baseline
2. Patient-reported normal tissue toxicity in the breast measured using the EORTC QLQ-BR23 breast symptoms score at 2 years

Secondary outcome measures
1. Mean lung and contralateral breast doses measured from the treatment plan (PBT or volumetric modulated arc therapy [VMAT]) at baseline
2. Early and late toxicity: skin and oesophageal toxicities assessed by clinicianrecorded CTCAE v5. 0 weekly on treatment, 2 weeks postRT then weekly until acute reaction graded as 0 (none) or 1 (mild). Cough and breathlessness will be assessed by clinicianrecorded RTOG at 3, 6 and 12 months.
3. Healthrelated quality of life: late toxicity and healthrelated quality of life will be assessed by patients using PRO including EORTC QLQC30, QLQBR23, Body Image Scale and items capturing breast changes resulting from cancer treatments (established in previous trials). Questionnaires will be administered at baseline, 6, 12, 24, and 60 months.

4. Health economic consequences: analysis will utilise the healthcare resource use questionnaire developed for the trial and the EuroQol fivedimensional questionnaire (EQ5D5L). These will be collected at baseline, 3, 6, 12, 24 and 60 months.
5. Changes to the planned RT pathway (including delays and replanning) will be defined as the proportion of patients with a delay to RT or PBT exceeding 4 weeks' overall treatment time and the proportion requiring replanning.
6. Second primary cancers (including contralateral breast, lung and oesophagus), defined as proportion of patients with confirmed diagnosis up to 5 years' follow-up
7. Recurrence and survival, defined as cumulative incidence rates up to 5 years' follow-up
8. Incidence of major cardiac events will be reported, defined as proportion of patients at 5 years' follow-up with atherosclerotic coronary heart disease or other heart disease death, myocardial infarction, coronary revascularisation, or hospitalisation for major cardiovascular event (heart failure, valvular disease, arrhythmia, or unstable angina)

Mechanistic endpoints:
1. Change in median lung Hounsfield Units per Gy on CT from baseline to 2 years for PBT versus photon RT
2. In patients randomised to PBT, correlation of RBEweighted dose maps for the three selected variable and standard RBE 1.1 models with radiological changes in lungs and ribs at 2 years
3. Differences in planned versus accumulated mean heart dose for PBT versus photon RT will be calculated using deformable image registration and compared with dose from the planning CT in order to calculate the percentage difference in dose at baseline

Overall study start date
27/11/2019

Completion date
01/02/2030

Eligibility

Key inclusion criteria
Current inclusion criteria as of 20/11/2024:

1. Age ≥18 years, female or male
2. Histologically proven invasive breast carcinoma treated with:
2.1. Breast conservation surgery with axillary surgery (biopsy or dissection) OR
2.2. Mastectomy with axillary surgery (biopsy or dissection)OR
2.3. In the case of an occult breast primary, axillary surgery (biopsy or dissection) only is permissible
3. Recommended to undergo RT to the breast/chest wall +/- axilla +/- IMN
4. Estimated lifetime risk of radiation-induced late cardiac toxicity around 2% or higher*
* Calculated from tables of mean heart dose, age and cardiovascular risk factors (pre-existing cardiac disease, other circulatory diseases, diabetes, chronic obstructive pulmonary disease, smoking, body mass index >30 kg/m2)(10).
N.B. Mean heart dose is estimated using wide-tangent field placement in deep inspiration breath hold (DIBH)) as this is the commonest technique for IMN RT in the UK and can be carried out quickly to ensure an efficient patient pathway.
5. Ability to provide written informed consent to participate in PARABLE

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Previous inclusion criteria:

1. Age ≥18 years, male or female
2. Histologically proven invasive breast carcinoma treated with wide local excision or mastectomy, and any type of axillary surgery
3. Recommended to undergo RT to the breast/chest wall + internal mammary node (IMN) RT; or if pectus excavatum, recommended to undergo RT to the breast/chest wall +/- IMN RT
4. Estimated lifetime risk of radiation-induced late cardiac toxicity ≥2%*

*calculated from tables of mean heart dose, age and cardiovascular risk factors (pre-existing cardiovascular disease, diabetes, chronic obstructive pulmonary disease, active smoker, body mass index > 30kg/m2, chronic pain medication, use of anthracycline chemotherapy).

N.B. mean heart dose is calculated from radiotherapy plan using wide tangents in deep inspiration breath hold (DIBH) as this is the most common technique for IMN RT in the UK and can be planned relatively quickly to ensure an efficient patient pathway.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 192; UK Sample Size: 192

Key exclusion criteria
Current exclusion criteria as of 20/11/2024:

1. Definitive clinical or radiological evidence of metastatic disease.
2. Prior RT to the ipsilateral chest wall, breast and thorax.
3. Connective tissue disorders requiring active medical therapy. (Patients with a history of connective tissue disorders in whom a multidisciplinary team has agreed that the benefits of radiotherapy outweigh the risks may be included. Methotrexate and/or other immune therapies must be stopped during RT or PBT).
4. Concomitant TDM1 or capecitabine is not permitted.
5. Breast tissue expander implants with integrated metallic injection ports are contraindicated and not permitted within PARABLE.

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Previous exclusion criteria:

1. Definitive clinical or radiological evidence of metastatic disease
2. Prior RT to the ipsilateral chest wall, breast and thorax

3. Connective tissue disorders requiring active medical therapy (Patients with a history of connective tissue disorders in whom a multidisciplinary team has agreed that the benefits of radiotherapy outweigh the risks may be included. Methotrexate and/or other immune therapies must be stopped during RT or PBT)
4. Concomitant TDM1 or capecitabine is not permitted

Date of first enrolment
08/06/2022

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal Marsden Hospital
Royal Marsden Hospital
Downs Road
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Study participating centre
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Study participating centre
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Study participating centre

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United Kingdom
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor type
Research organisation

Website
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ROR
https://ror.org/043jzw605

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR131120

Results and Publications

Publication and dissemination plan
Results will be presented at international conferences and published in peer-reviewed medical journals; the researchers will produce lay summaries with PPI partners. The researchers anticipate publishing the trial protocol within the first 18 months of the start of recruitment. Results publication estimated in 2027, primary analysis expected after the last patient recruited has completed 1 year of follow-up and incorporating time for data cleaning and analysis.

Intention to publish date
31/12/2027

Individual participant data (IPD) sharing plan
The datasets generated during and analysed during the current study will be available upon request.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Protocol (other)	v4.0	22/02/2024	20/11/2024	No	No