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Retreating localised prostate cancer with either repeat radiotherapy or brachytherapy

Submission date 30/05/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 01/07/2022	**Overall study status** Ongoing	
Last Edited 08/05/2025	**Condition category** Cancer	

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-further-treatment-prostate-cancer-has-come-back-prostate-after-previous-radiotherapy-ro-pip

Background and study aims
Prostate cancer is the most common UK male cancer. Radiotherapy is a type of cancer treatment that involves using radiation energy to kill cancer cells. The two ways to deliver radiation are from a machine outside the body (external beam radiation) or from internal sources placed within the body (brachytherapy) while the patient is asleep (requires a general anaesthetic).

Despite these treatments, in some patients, the cancer can come back and most of these cancers will come back within the prostate gland itself, which is called a local recurrence. Current research suggests treating the recurrence with a second course of radiation given using either brachytherapy or external beam may be better than other options (such as surgery) as there are fewer side effects. Brachytherapy and external beam radiotherapy for recurrence have not been directly compared and the side effects people experience after treatment have not been fully described.

External beam radiation can now be delivered so that more intense radiation doses are directed to the cancer in a more accurate way by using daily imaging. This new treatment is called ultra-hypofractionated or stereotactic ablative radiotherapy (SABR). Although it has been widely used for other indications, we do not know how effective it is for treating prostate cancer recurrence. We also have limited information on treatment side effects.

We want to check if participants are happy to be randomised to either treatment to see if a larger study may be possible. We also want to assess how the radiation treatment impacts on people’s long term quality of life by regular follow-ups and questionnaires. This means future patients will have better information when making treatment choices.

Who can participate?
Participation is by invitation only. Adult men with locally recurrent prostate cancer proven by biopsy will be invited to participate in the study.

What does the study involve?
Participants will receive one of two radiation treatments, either HDR Brachytherapy (HDR-BT) (standard of care) or ultra-hypofractioned external beam radiotherapy (EBRT). The treatment that a participant will receive will be decided at random (like tossing a coin).

For the participants receiving HDR-BT treatment, this will involve two separate visits to the hospital, as the treatment is carried out in two stages. These visits will be about 2 weeks apart. As each treatment requires a general anaesthetic, participants may need to stay in the hospital overnight after the treatment for observation.

For the participants receiving ultra-hypofractionated EBRT treatment, the participant will visit the hospital once for a planning CT scan and then on 5 separate occasions within a 2 week period to receive the radiation treatment. No general anaesthetic will be required for these treatment sessions. The participant will come for their treatment and leave on the same day.

Participants will be followed up by the study team for evaluation at 1, 3, 6, 12, and 24 months after treatment is completed.

What are the possible benefits and risks of participating?
We hope that the treatments will help participants and give them a better chance to get rid of their cancer. However, this cannot be guaranteed. The information we get from this study may help us to improve the future treatment of patients with prostate cancer as we will understand better the side effects so we can tailor treatments more effectively to patients.

By participating in this study, participants may have some extra tests, some of which are optional but others such as the MRI scan are required. Radiotherapy treatment, both external beam radiation treatment (EBRT) and brachytherapy, can cause side effects because of the healthy tissue around the cancer being exposed to the radiation. Bowel side effects (more common with EBRT) include increase in the frequency and urgency of bowel movements, lower abdominal discomfort, passing of mucus and bleeding from the back passage. Bladder side effects (more common with brachytherapy) include urinating more frequently and/or urgently, the need for a catheter (1 in 10 patients). Narrowing of the urethra, known as a stricture, can occur in 2 out of ten in the long term. In addition, fewer than 2 out of 10 men will experience slight blood loss whilst urinating during and after radiotherapy.

Where is the study run from?
University of Leeds (UK)

When is the study starting and how long is it expected to run for?
From March 2022 to June 2028

Who is funding the study?
Cancer Research UK (UK)

Who is the main contact?
Dr Ann Henry
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Contact information

Type(s)

Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05614700

Integrated Research Application System (IRAS)
297060

Central Portfolio Management System (CPMS)
51466

Protocol serial number
Grant code: 28832

Study information

Scientific Title
Reirradiation Options for Previously Irradiated Prostate cancer (RO-PIP): Feasibility randomised clinical trial investigating toxicity outcomes following reirradiation with ultra-hypofractionated external beam radiotherapy vs. high dose rate brachytherapy

Acronym
RO-PIP

Study objectives
Patients can be randomised to a trial comparing reirradiation with external beam radiotherapy and high-dose rate brachytherapy for locally recurrent prostate cancer.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 18/01/2022, Yorkshire & The Humber - Bradford Leeds Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, HRA Newcastle, NE2 4NQ; +44 (0) 2071048083; bradfordleeds.rec@hra.nhs.uk), ref: 21/YH/0305

Primary study design
Interventional

Study design
Interventional randomized feasibility study

Study type(s)
Treatment

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

Interventions
Phase 1- Recruitment and registration:
This two-arm randomised (1:1) feasibility study will aim to prospectively recruit 30 patients over 24 months into each treatment arm (BT and SABR) giving a total of 60 patients in the study. This accounts for any dropouts resulting in incomplete data sets.
Suitable patients meeting the inclusion criteria for the study will be identified via the Leeds, the Christie, and Mount Vernon Hospital Prostate MDT meetings which encompass the local surrounding district general hospitals. Suitable trial patients will be invited to take part in the study during their routine clinical appointment with the treating clinical oncologist and provided with written patient information sheets and if the patient is willing to take part they will be consented to join the trial. After being given verbal and written information about the study in the routine outpatient clinic, potential participants will be given sufficient time to consider participation (at least 24 h). A member of the research team will call the patient in the following week after the initial outpatient clinic to follow-up whether the patient would like to take part. If the patient wants to take part, a physical consent form will be sent out to the patient for them to sign and send back. A telephone or face to face appointment will also be offered to the patient if they want to discuss the study involvement in greater detail.
Prior to the trial recruitment stage, all patients will have received standard of care prostate MRI scans and a prostate biopsy to confirm they have local recurrence of their prostate cancer. As part of the standard care, all patients will also have baseline blood tests including prostate specific antigen (PSA) and testosterone levels.
Once a participant is deemed eligible for the study, they will be registered and given sequential ID numbers. These ID numbers will be used to identify all collected samples. The ID is in the form of an alphanumeric code.

Phase 2 - Randomisation:
Following confirmation of written consent and eligibility, patients will be randomised using a 9 am to 5 pm telephone and web-based system based at the Leeds Institute of Clinical Trials Research Unit (Leeds, UK). Patients will be randomised using stratified permuted blocks to receive either external beam radiotherapy (EBRT) or high-dose rate brachytherapy (HDR-BT) (1:1), stratified by recruiting site and previous androgen deprivation therapy (hormone therapy). Patient randomisation will take place as close to the intervention start date as possible and, in line with NHS guidelines, is aimed to be done no more than 31 days prior to treatment start date.

Phase 3 – Intervention:
The patient will receive one of two radiation treatments, either HDR Brachytherapy (HDR-BT) (standard of care) or ultra-hypofractioned external beam radiotherapy (EBRT).
For the HDR-BT treatment arm, this will involve two separate visits to the hospital as the treatment is carried out in two stages. These visits will be about 2 weeks apart. As each treatment requires a general anaesthetic, patients may need to stay in the hospital overnight after the treatment for observation.
For the ultra-hypofractionated EBRT arm, the patient will visit the hospital once for a planning CT scan and then on 5 separate occasions within a 2 week period to receive the radiation treatment. No general anaesthetic will be required for these treatment sessions. The patient will come for their treatment and leave on the same day.

Phase 4 – Imaging with PROMs Assessment and translational components:
Changes in patient-reported Health-Related Quality of life (HRQoL)/PROMs will be assessed by the EPIC-26, EORTC QLQ-C30, and IPSS questionnaires. All three questionnaires are validated questionnaires for assessing quality of life, urinary symptoms, and treatment-related toxicity/ side effects following prostate-specific treatment. We have gathered feedback on all these questionnaires from the Leeds Radiotherapy Patient and Public Involvement Group. The feedback was positive, with patients understanding the questions and being able to complete them in a timely manner without assistance (approximately 30 min to complete all three questionnaires). Physical copies of the questionnaires will be sent to all recruited patients for completion and these can be posted back or given in at the time of any routine face to face clinic appointments.
The specific time points for these evaluations are:
1. Baseline assessment (prior to salvage treatment)
2. 1 month post treatment completion
3. 3 months post treatment completion
4. 6 months post treatment completion
5. 12 months post treatment completion
6. 24 months post treatment completion
Further follow-up will be permissible and encouraged where possible as part of routine clinical care.
All patients will be consented to have two to three additional multiparametric MRIs (specific sequences can be found in the separate imaging protocol) which will be paired with PROMs assessments at the same timepoints (at baseline and then post-treatment at 1 month and 1 year). These MRI scans are in addition to their routine clinical follow-up.
All patients will already have had a prostate biopsy in their base hospital prior to being approached for this study as one inclusion criteria is that they need to have biopsy proven local recurrence. These samples will be stored in the pathology laboratories of the participant's base hospital. The plan is to arrange for transfer of these already collected prostate biopsy samples to the Manchester University Cancer Research Centre Biobank for processing and analysis.
All patients will also be given the option to donate additional blood and urine samples at baseline and then 1, 3 and 6 months after radiation treatment. This will allow urine/ blood proteomic and cytokine signatures to be measured and determine the impact of re-irradiation on such parameters.
For the EBRT treatment arm, the total number of research visits is 10.
For the brachytherapy treatment arm, the total number of research visits is 7.
This includes the treatment visits (5 for EBRT and 2 for the brachytherapy arm). The number of treatment visits and follow-up visits would be the same without participating in the study as these are the standard time points for clinical follow-up. With this study there are more face to face visits for the additional blood samples and MRI scans because if the patient was not on the study then their 1, 3, 6, 12, 18, 24-month follow-up appointments could be conducted remotely.

Phase 5 – Reporting:
Feasibility and safety data will be reviewed by the trial management group on a regular basis. No formal interim analysis will take place however a study report will be produced for review by the independent data monitoring and ethics committee (DMEC) approximately midway through the study. The aim of the report is to evaluate and monitor the key study objectives (i.e. recruitment rates, number of participants taking up their treatment allocation), as well as expected adverse events (AEs) and serious adverse events (SAEs) and the delivery time of HDR-BT or hypofractionated EBRT post-randomisation. The research team will have the opportunity to raise any concerns with the trial progression/ running allowing the trial team to improve processes going forward.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Feasibility measured using overall, and recruitment site-specific recruitment rates collected monthly over the 24-month recruitment period

Key secondary outcome(s)
1. Toxicity following salvage ultra-hypofractionated external beam radiotherapy (EBRT) or high-dose rate brachytherapy (HDR-BT) to inform future RCT design will be measured using:
1.1. Patient-reported outcome measures (PROMs) in terms of impact on quality of life and urinary, bowel, and sexual function using the EPIC-26, EORTC QLQ-C30, and IPSS questionnaires at baseline, 1, 3, 6, 12, and 24 months
1.2 Clinician-reported toxicity outcomes collected using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 at baseline, 1, 3, 6, 12, 18, and 24 months
2. Identification of MRI biomarkers that may be predictive of genitourinary and gastrointestinal toxicity (measured by PROMs as detailed above) using multiparametric MRIs at baseline and at 1-month and 1-year post-treatment
3. Image quality and repeatability of prostate functional imaging for detecting hypoxia measured using the diffusion coefficient (D), perfusion fraction (f), and pseudo-diffusion coefficient (D*) on IVIM sequences and the rate of relaxation per second (R2*) on BOLD sequences at 1-month and 1-year post-treatment
4. Changes in a hypoxia-associated gene signature and proteomic/cytokine signatures following primary radiation (and exploration of the prognostic value of such changes) measured using blood and urine samples collected at baseline and 1, 3, and 6 months after radiation treatment

Completion date
01/06/2028

Eligibility

Key inclusion criteria
1. Aged ≥18 years
2. Biopsy-proven locally recurrent prostate cancer
3. T1-3 N0 M0 Any Gleason/ISUP grade group adenocarcinoma prostate with most recent PSA <50 ng/ml
4. Baseline plasma testosterone level required
5. Willing and able to provide informed consent
6. Primary prostate cancer treatment must have been with external beam radiotherapy (EBRT)

or brachytherapy (BT)
7. Biochemical recurrence at least 2 years after primary radiation treatment completed
8. Performance status WHO 0-2
9. Reasonable urinary function (IPSS <20 and Qmax >0 ml/s on flow tests)
10. > 10-year life expectancy
11. No metastatic disease (PET-CT - any of choline/fluciclovine/PSMA)
12. No prior prostatectomy (TURP >3 months before randomisation is acceptable)
13. No history of inflammatory bowel disease
14. Suitable for procedure under general anaesthesia
15. Androgen Deprivation Therapy may be initiated at the discretion of the treating oncologist but this must be started at the time of the first salvage radiotherapy treatment (at first fraction of EBRT or at HDR-BT)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Male

Key exclusion criteria
1. Not compliant with any inclusion criteria
2. Do not have a prostate biopsy confirming locally recurrent prostate cancer or who are unfit for a prostate biopsy
3. Unfit for a general anaesthetic due to other comorbidities
4. Contraindications to MRI
5. Clinical or radiological evidence of metastatic prostate disease
6. Medical or psychiatric condition that impairs their ability to give informed consent

Date of first enrolment
30/07/2022

Date of final enrolment
31/05/2026

Locations

Countries of recruitment
United Kingdom

Study participating centre

Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre
East and North Hertfordshire NHS Trust
Lister Hospital
Coreys Mill Lane
Stevenage
United Kingdom
SG1 4AB

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)

CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
All of the individual participant data collected during the trial will be available for sharing, after de-identification and completion of the current study and after publication of the study results. The de-identified datasets (imaging and clinical data) used and analysed in the current study will be available from the corresponding author Dr Ann Henry (ann.henry2@nhs.net) on reasonable request. Consent has been obtained for this.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		08/11/2022	10/11/2022	Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes