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PEARLS - a trial of radiotherapy in newly-diagnosed patients with lymph node positive prostate cancer

Submission date 20/05/2021	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 09/06/2021	**Overall study status** Ongoing	
Last Edited 04/06/2024	**Condition category** Cancer	

Plain English summary of protocol

Cancer Research UK lay summary: https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-intensity-modulated-radiotherapy-to-treat-prostate-cancer-pearls

Background and study aims
Prostate cancer is the most common cancer in men in the UK. It usually develops slowly, so there may be no signs for many years.
PEARLS aims to improve patient outcomes by treating patients whose cancer has spread to the lymph nodes with radiotherapy to an extended area than is currently used. The investigators think that by extending radiation to cover a wider area where recurrences can often occur may improve control of the cancer. There is currently no standard management for prostate cancer patients who present at diagnosis with cancer having spread to the lymph nodes in the abdomen. Previous studies have indicated that it is safe to treat the prostate and pelvic areas with radiotherapy. There have been no recent studies using modern radiotherapy technology to treat larger areas within the abdomen.

PEARLS will assess the differences in side effects for patients treated with standard or an extended radiotherapy area to make sure these are acceptable and if they are, we will include more patients in the study to see if the extended radiotherapy treatment helps to control the cancer better.

Who can participate?
Adult (18+ years) male patients with lymph node positive prostate cancer.

What does the study involve?
An interim review of safety in the first 150 patients will permit early stopping of the trial if toxicity associated with the extended radiotherapy area is unacceptable.

Patients will be randomised based on the extent of disease in their lymph nodes to either a standard area or an extended area including the lymph nodes in the abdomen. Radiotherapy will involve treatment over 20 fractions for all patients. Patients will be followed up at regular intervals.

Patients will be asked to complete quality of life questionnaires. In addition, patients may be asked to take part in optional sub-studies running within PEARLS, which will include donation of blood samples, stool samples and an additional PSMA PET-CT scan 6 months after the end of radiotherapy and recurrence.

What are the possible benefits and risks of participating?
All patients in the trial will be treated with high quality technical advanced radiotherapy designed by a group of leading experts in the field of prostate radiotherapy. It is hoped that there will be improved tumour control if radiotherapy of the para-aortic lymph nodes is more effective than just treating the prostate and pelvic lymph nodes. Improved tumour control might lead to a lower use of treatments for recurrent cancer and improved survival. The information we get from this study will help us to improve the future treatment of patients with prostate cancer. Although by taking part in the study, patients may not directly benefit, it will help to answer these questions and hopefully improve treatment for prostate cancer patients in the future.
Patients may receive an intravenous contrast agent to help design their radiotherapy and they are asked to let the radiographer know if they have ever had any problems after contrast injections. The para-aortic lymph node radiotherapy may have an increased risk of side effects (nausea, loose motions and diarrhoea), because more bowel will be exposed to radiotherapy compared to prostate/pelvic node radiotherapy. The investigators will try to minimise these risks, but treating larger areas can have more side effects.

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?
February 2020 to December 2032

Who is funding the study?
Cancer Research UK

Who is the main contact?
Ms Shama Hassan, PEARLS-icrctsu@icr.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Contact details
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Additional identifiers

Central Portfolio Management System (CPMS)
48429

Protocol serial number
Grant Codes: C70268/A29872

Study information

Scientific Title
A phase II/III trial of primary radiotherapy for androgen sensitive prostate cancer patients with lymph nodes

Acronym
PEARLS

Study objectives
Phase II: To determine whether moderately fractionated extended field intensity modulated radiotherapy (IMRT) is safe in node positive prostate cancer.
Phase III: To determine whether extended field IMRT improves metastasis-free survival (MFS) compared to standard field IMRT in patients with N1 M0 disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/04/2021, London - Central Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44(0)207 104 8225; londoncentral.rec@hra.nhs.uk), ref: 21/LO/0178

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Treatment

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

Interventions

Phase II aims to determine whether moderately fractionated extended field intensity modulated radiotherapy (IMRT) is safe in node positive prostate cancer. In the Phase III PEARLS aims to determine whether extended field IMRT improves metastasis free survival (MFS) compared to standard field IMRT in patients with N1 M0 disease.

Participants will be stratified by extent of lymph node disease into two cohorts: pelvic nodes or para-aortic +/- pelvic nodes and randomised to receive either:

- Control arm – standard field IMRT: 60 gray (Gy) to the prostate (and 44Gy to the pelvis with integrated boost of 51Gy to the involved lymph nodes in 20 fractions for patients with pelvic-node disease only)
- Experimental arm – extended field IMRT: 60Gy to prostate and 44Gy to pelvis and para-aortic region with integrated boost of 51Gy to the involved lymph nodes in 20 fractions.

Patient pathway

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 have lymph node positive prostate cancer on PSMA PET-CT who opt to have radiotherapy as part of their management plan.

Participants will be approached by a member of their clinical care team and will receive a verbal explanation of the trial, together with a 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 and their GP. They will have the opportunity to raise any questions about PEARLS with their clinical care or research team and these will be addressed prior to their decision about whether to participate. Should they chose to participate they will be asked to sign a consent form to record their informed 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). Participants will be randomised using a computer generated minimisation technique which ensures balance between the treatment groups. Using this technique, the treatment allocation for each participant depends on the characteristics of the participants already involved, thus minimising imbalance across any factors that might predict outcome.

The following assessments will be performed prior to randomisation.

- Complete medical history.
- DRE and physical examination (both only if clinically indicated).
- PSA test prior to the commencement of ADT.
- Diagnostic PSMA PET-CT to be ideally performed prior to starting ADT or within 4 weeks of commencing bicalutamide/LHRHa therapy.
- Full blood count, biochemistry inclusive of urea & electrolytes, liver function tests, bone ± glucose (within 6 weeks prior to randomisation).
- Assessment of performance status, using WHO scale.
- Baseline symptoms will be assessed using RTOG bladder and bowel toxicity scoring and Common Toxicity Criteria for Adverse Event Reporting (CTCAE) version 5 (within 4 weeks prior to randomisation).
- If the patient has consented to the PRO sub study, completion of the following questionnaires (within 4 weeks prior to randomisation):
  - International Prostate Symptom Score (IPSS)
  - Expanded Prostate Index Composite-26 (EPIC-26) Short Form questionnaire

- Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).
- EQ-5D.

PEARLS pre-treatment assessments (after randomisation):
• Assessment of pre-treatment symptoms (RTOG, CTCAE v5)
• PSA and testosterone (2- 4 months after starting ADT).
• FBC (for patients taking part in T-cell – blood sample collection) sample to be taken at same time as sub- study blood.

PEARLS during treatment assessments:
Treatment will be given over 4 weeks, patients will be seen at the end of each week and the following assessments will be performed:
• Acute toxicity assessment (RTOG, CTCAE v5).
• Bloods – FBC (for patients taking part in T-cell – blood sample collection) sample to be taken at same time as substudy blood – at end of week 2.
• Bloods- FBC, biochemistry (renal profile only) – at end of week 4 only.
• Quality of life questionnaire [PRO-CTCAE, EPIC-26, IPSS, EQ-5D-5L] - at end of week 4 only.

PEARLS follow-up
Patients will be seen at the following timepoints from start of radiotherapy treatment: 6, 8, 12, 18 weeks, and then at 6, 12, 18, 24, 30, 36, 42, 48 and 60 months. After this patients will be seen on an annual basis. The following assessments will be performed:
6, 8 and 12 weeks from first external beam radiotherapy fraction:
• Acute toxicity assessment (RTOG, CTCAE v5).
18 weeks from first external beam radiotherapy fraction:
• Acute toxicity assessment (RTOG, CTCAE v5).
• Quality of life questionnaire [PRO-CTCAE, EPIC-26, IPSS, EQ-5D-5L].
• Bloods- FBC, biochemistry (renal profile ONLY).
• Bloods- PSA.
6, 12, 18, 24, 30, 36, 48, 42 and 60 months (from first radiotherapy fraction)
• Bloods- FBC, biochemistry (renal profile ONLY) (at month 6, 18 and 24 only).
• Bloods – FBC (for patients taking part in T-cell – blood sample collection) sample to be taken at same time as substudy blood – at month 12.
• Bloods- PSA.
• Bloods - Testosterone (at months 36, 48, 60 only).
• Toxicity Assessment – RTOG and CTCAE (v5).
• Quality of Life questionnaire [PRO-CTCAE, EPIC-26, IPSS, EQ-5D-5L] (at month 6, 12, 18, 24 only).
Annual visits after 60 months: Patients will not be required to undergo any trial specific investigations, however data will be requested annually from standard follow visits relating to patients disease status, survival and health resource usage assessment.

Patient reported outcomes
PEARLS participants will be asked to join the Quality of Life substudy. This is an optional substudy which collects details of bowel, bladder and sexual function symptoms participants are experiencing and the impact of these on their daily lives. Those who agree to participate will be asked to complete a patient reported outcomes questionnaire before radiotherapy, at the end of radiotherapy and at 18 weeks. Further questionnaires will be at 6, 12, 18, 24 and 60 months. The initial questionnaires will be handed to patients at clinic visits and those from 6 months onwards will be posted directly to patients' homes. The questionnaires should take no more than 30 minutes to complete.

Quality assurance, training and patient safety
Detailed technical radiotherapy planning and delivery guidelines will be in place for PEARLS. These will set out exactly how the radiotherapy should be given. They will include details of the safety margins to be added around the prostate, pelvic nodes and tumour for each treatment group, mandatory limits relating to the proportion of the total radiotherapy dose to which normal tissue can be exposed (dose constraints), how participants should be prepared to receive treatment. Similar technical radiotherapy document has been used with success to standardise treatment between centres in other ICR-CTSU radiotherapy trials, including CHHiP, PACE, PIVOTAL and PIVOTALboost (all also in prostate cancer).

In addition to the technical radiotherapy guidelines, a comprehensive quality assurance programme led by the National Clinical Research Institute Radiotherapy Clinical Trials Quality Assurance (NCRI RTTQA) group will be put in place to ensure quality and consistency of radiotherapy delivery to participants within and between PEARLS centres. Centres will have to pass components of this programme before they are approved to recruit PEARLS participants.

PEARLS trial teams at participating sites will also receive training from the PEARLS trial manager on the trial protocol and logistics at a site initiation meeting prior to commencing recruitment. Only when a centre has satisfactorily completed the pre-trial quality assurance and training, will they be able to invite patients to participate in PEARLS. Quality assurance processes will be ongoing throughout PEARLS. Adherence to the radiotherapy planning and delivery guidelines will be monitored throughout the trial.

Patient safety will be monitored by the Independent Data Monitoring Committee (IDMC) who will review all safety and efficacy data by treatment group.

Central trial management will be conducted by the ICR-CTSU, a UKCRC registered NCRI cancer clinical trials unit.

Participants will be recruited to PEARLS at participating sites for approximately 78 months. It is planned that the primary publication will be prepared within 60 months of recruitment closure, which will allow time for data cleaning and analysis. The Phase II publication will be published ahead of this. Where possible, follow up data will continue to be collected for all trial participants from routine clinic visits until their death, to contribute to the planned secondary endpoint analyses which will be published as data becomes available. Analysis of all primary and secondary endpoints will be conducted by ICR-CTSU. A Trial Management Group (TMG) will be set up and will have responsibility for day to day management of the trial. It will include the Chief Investigator, ICR-CTSU Scientific Lead, Co-investigators and identified collaborators, the Trial Statistician and Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups membership will include a lay/consumer representative.

The independent Trial Steering Committee (TSC) will meet annually throughout PEARLS to oversee the study's progress on behalf of the sponsor and funder. The IDMC will meet in confidence, at least annually, to review the data and make recommendations as appropriate to the TSC and TMG.

Intervention Type
Procedure/Surgery

Primary outcome(s)

Phase II: Acute lower gastrointestinal (GI) toxicity at week 18 from the start of radiotherapy measured using Radiation Oncology/Toxicity grading (RTOG)
Phase III: Metastasis-free survival (MFS) defined as the time from randomisation to the first detection of distant metastasis on imaging or death from any cause, whichever occurs first, measured using patient records. Distant metastasis defined as extra-pelvic lymphadenopathy, bone and visceral metastases

Key secondary outcome(s)
Phase II
1. Toxicity will be measured at the following time points: 18 week, 6, 12, 18, 24 months and then annually for 5 years (excluding FBC after 24 months) using RTOG, CTCAE v5 GI, genitourinary (GU), blood/bone marrow (FBC)
2. Ability to deliver 44Gy in 20 fractions to the pelvic and para-aortic lymph nodes with an integrated boost to the involved lymph nodes of 51Gy in 20 fractions within organ at risk dose constraints using the varying radiotherapy planning techniques and delivery systems at participating centres
3. Patient Reported Outcomes at end of radiotherapy and week 18 follow up:
3.1. Prostate cancer related quality of life (EPIC-26)
3.2. Prostate symptoms (IPSS)
3.3. Symptomatic toxicity (PRO-CTCAE)
3.4. Quality of life (EQ-5D-5L)
4. Late RTOG and CTCAE v5 GI, GU at 6, 12, 18 and 24 months

Phase III
5. Acute toxicity RTOG, CTCAE v5 GI, genitourinary (GU), blood/bone marrow (FBC) up to 18 week follow-up
6. Late RTOG and CTCAE v5 GI, GU, blood/bone marrow (FBC) toxicity at 6, 12, 18 and 24 months and then annually for 5 years (excluding blood/bone marrow (FBC) toxicity from 24 months)
7. Patient-Reported Outcomes at end of radiotherapy, week 18, month 6, 12, 18, 24 and 60:
7.1. Prostate cancer related quality of life (EPIC-26)
7.2. Prostate symptoms (IPSS)
7.3. Symptomatic toxicity (PRO-CTCAE)
7.4. Quality of life (EQ-5D-5L)
8. Time to biochemical progression defined as time (in days) from randomisation to 1st biochemical progression (Phoenix definition: 2ng/ml increase in PSA over the nadir achieved after completion of radiotherapy treatment) measured using patient records
9. Time to radiographic progression defined as time (in days) from randomisation to radiographic progression measured using patient records
10. Failure-free survival defined as the time (in days) from randomisation to first biochemical failure, recommencement of androgen deprivation therapy, local recurrence, lymph node/pelvic recurrence, distant metastases or death due to prostate cancer measured using patient records
11. Overall survival defined as the time (in days) from randomisation to death from any cause measured using patient records

Completion date
06/12/2032

Eligibility

Key inclusion criteria

1. Histologically confirmed adenocarcinoma of the prostate (histological confirmation can be based on tissue taken at any time, but a re-biopsy should be considered if the biopsy is more than 12 months old).
2. Any T stage, N1, M0; any T stage, N1, M1a (limited to para-aortic region); or any T stage, N0, M1a (limited to para-aortic region) on PSMA PET-CT imaging done at time of diagnostic staging (stage IV disease).
3. Age at least 18 years.
4. Patient on LHRH analogue therapy.
5. Adequate renal and bone marrow function.
6. WHO Performance status of 0-2.
7. Written informed consent.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Male

Key exclusion criteria
1. Prior radiotherapy to the prostate or pelvis; prior bilateral orchiectomy; radical prostatectomy.
2. For those patients who have received docetaxel chemotherapy or are receiving androgen receptor targeted therapy, there should be no ongoing CTCAE grade 2 or greater GI toxicity relating to this systemic therapy.
3. Medical conditions (non-prostate cancer related) expected to limit life expectancy to < 5 years.
4. Bilateral hip prostheses or any other implants/hardware that would introduce substantial CT artefacts and would make pelvic node planning more difficult.
5. Medical conditions likely to make radiotherapy inadvisable e.g. inflammatory bowel disease, intractable urinary symptoms, previous colorectal surgery.
6. Previous malignancy within the last 2 years (except basal cell carcinoma or squamous cell carcinoma of the skin or small renal masses under surveillance), or if previous malignancy is expected to significantly compromise 5 year survival.
7. Any other contraindication to external beam radiotherapy to the para-aortic and/or pelvic region.

Date of first enrolment
30/06/2021

Date of final enrolment
31/12/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Royal Marsden Hospital
Fulham Road
Chelsea
London
United Kingdom
SW3 6JJ

Study participating centre
Lister Hospital
Coreys Mill Lane
Hertfordshire
Stevenage
United Kingdom
SG1 4AB

Study participating centre
St Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
University College London Hospital
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Clatterbridge Cancer Centre
Clatterbridge Road

Bebington
Wirral
United Kingdom
CH63 4JY

Study participating centre
Maidstone Hospital
Maidstone and Tunbridge Wells NHS Trust
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Study participating centre
John Radcliffe Hopsital
Headley Way
Oxford
United Kingdom
OX3 9DU

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Freeman Hospital
Newcastle Upon Tyne Hospital Trust
Freeman Road
High Heaton
Newcastle
United Kingdom
NE7 7DN

Study participating centre
The Christie Hospital
Wilmslow Road
Withington

Manchester
United Kingdom
M20 4BX

Study participating centre
Queen Elizabeth Hospital Birmingham
University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
Bristol Royal Infirmary
University Hospitals Bristol and Weston NHS Foudnation Trust
Marlborough Street
Bristol
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BS1 3NU

Study participating centre
Walsgrave General Hospital
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Study participating centre
Derriford Hospital
Derriford Road
Crownhill
Plymouth
United Kingdom
PL6 8DH

Sponsor information

Organisation

Institute of Cancer Research

ROR
https://ror.org/043jzw605

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
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		24/09/2022	04/06/2024	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 3.0	24/05/2022	04/06/2024	No	No