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## PEARLS – A multicentre phase II/III trial of extended field radiotherapy for androgen sensitive prostate cancer patients with PSMA-avid pelvic and/or para-aortic lymph nodes at presentation

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### ABSTRACT

PEARLS is a multi-stage randomised controlled trial for prostate cancer patients with pelvic and/or para-aortic PSMA-avid lymph node disease at presentation. The aim of the trial is to determine whether extending the radiotherapy field to cover the para-aortic lymph nodes (up to L1/L2 vertebral interspace) can improve outcomes for this patient group.

### Introduction/rationale

Prostate cancer is the most frequently diagnosed cancer in men in over one-half of the countries of the world. In 2020, there were an estimated 1.4 million new prostate cancer cases and 375,000 deaths [1,2]. Stage IV prostate cancer includes patients whose cancer has spread to regional lymph nodes (N1) or to non-regional or distant lymph nodes (M1a), or to the bone (M1b) or visceral sites (M1c). In 2019, around 20 % of patients diagnosed with prostate cancer in England presented with stage IV disease [3].

There is a lack of prospective data guiding treatment decisions in patients presenting with node-positive (N1 and M1a) prostate cancer. For a long time, patients with pathologically-involved lymph nodes at presentation were considered to harbour systemic disease and thus palliative androgen deprivation therapy (ADT) was considered the treatment of choice. More recent randomised phase III data have shown a significant overall survival benefit by adding docetaxel, abiraterone, enzalutamide, and apalutamide to ADT [4–6]. However, several reports have challenged the notion that pelvic lymph node involvement is always systemic by demonstrating a benefit from maximizing local control

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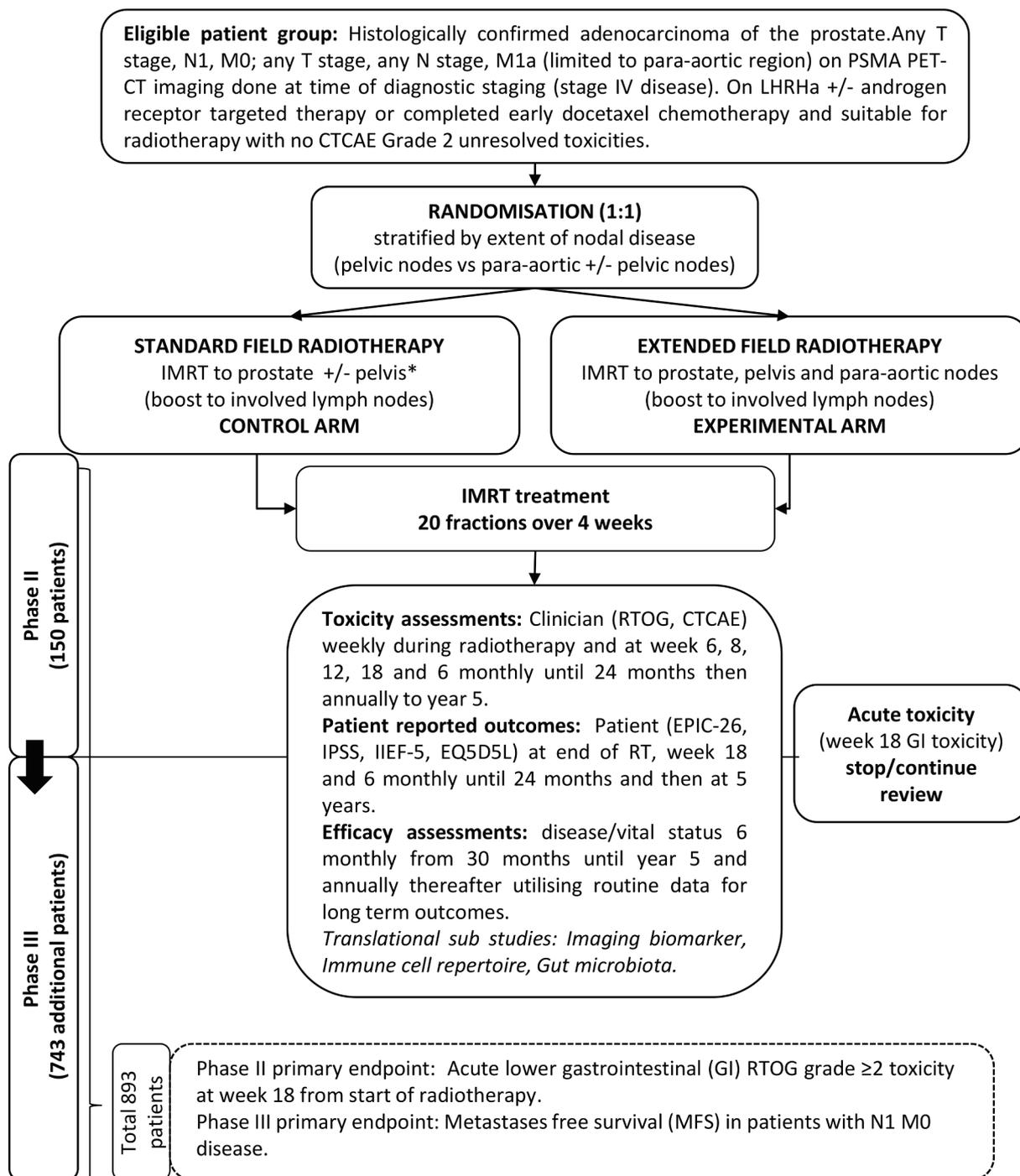
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with radical surgery and adjuvant radiotherapy [7,8] or ADT and radiotherapy [9,10].

In STAMPEDE [10], 58/71 (82 %) N1 patients received radiotherapy to both the prostate and pelvic lymph nodes but the treatment field did not include the para-aortic lymph nodes. In addition, within the Royal Marsden phase I/II IMRT trial [9], 74 (17 %) patients had pelvic lymph node disease at presentation on conventional imaging and the biochemical/clinical failure-free rate was 71 % (95 % CI 66 %–75 %) at 5 years for the whole group. In the absence of randomised data,

extrapolation from this data showing a favourable effect on failure free survival, prostate and pelvic radiotherapy should be considered a standard of care in N1 patients.

On review of patterns of recurrence after pelvic radiotherapy, a predominant site for lymph node recurrence is within the para-aortic lymph node region. Sites of recurrence are rarely seen within irradiated pelvic lymph node field [11,12]. These findings form the basis of the hypothesis being tested in the PEARLS trial – i.e., that encompassing the para-aortic lymph nodes will have a favourable effect on metastasis



\* Standard field size in the control group is defined by extent of nodal disease: participants with pelvic lymph node disease receive IMRT to the prostate + pelvic lymph nodes; participants with para-aortic node disease receive IMRT to the prostate

Fig. 1. PEARLS Trial schema.

free survival (MFS). In addition, patients currently presenting with para-aortic lymph node involvement (M1a) are managed with palliative intent including systemic therapy [4–6] and prostate radiotherapy [13]. There may be a group of patients where inclusion of the involved lymph nodes may offer a curative treatment option, as is seen in patients with cervical cancer [14].

Molecular imaging with PSMA PET-CT has led to a better understanding of the lymph drainage pattern of prostate cancer and patterns of nodal recurrence. Uptake of molecular imaging in recent years has been characterised by early and frequent use outside of clinical trials with lack of prospective evaluation [15]. We can try to prospectively embed these imaging modalities into therapeutic studies to fully quantify their impact [16]. We expect that there will be an increase in identification of node-positive prostate cancer patients using PSMA PET-CT. With the increased sensitivity of PSMA PET-CT over conventional imaging for prostate cancer lymph node staging, all patients entering PEARLS will have radiologically defined pelvic and/or para-aortic lymph node-positive disease on PSMA PET-CT imaging.

There is international variation as to the optimal superior border for pelvic lymph node radiotherapy. In the updated NRG Oncology international consensus atlas on pelvic lymph node volumes, the superior border is at the aortic bifurcation [17]. However, prostate regional lymph nodes are defined as nodes of the true pelvis, which are the pelvic nodes below the bifurcation of the common iliac arteries. Historically, prostate radiotherapy trials have defined the superior border for elective pelvic radiotherapy in relation to the vertebral interspaces, typically L5/S1, therefore excluding part of the common iliac artery territory. In PEARLS, patients who have PSMA avid lymph nodes at, or inferior to the L4/L5 interspace will be included in the pelvic lymph node cohort encompassing the nodes of the true pelvis. Patients with PSMA avid lymph nodes superior to the L4/L5 interspace up to the L1/L2 interspace, which is usually the level of the renal veins will be included in the para-aortic lymph node cohort.

The primary aim of this clinical trial is to assess the clinical feasibility of treating patients with radiographically suspicious lymph nodes within the pelvis and/or para-aortic region with radical radiotherapy using treatment fields that cover the “at-risk” nodal volume. The hypothesis is that adding this “local” treatment to standard systemic therapy will extend the envelope of cure.

## Design

PEARLS is a seamless phase II/III multi-stage randomised controlled trial (Fig. 1). Men with histologically confirmed prostate cancer with PSMA-avid nodal disease within the pelvis and / or para-aortic region receiving androgen deprivation therapy +/- androgen receptor (AR) targeted therapy or docetaxel chemotherapy are eligible. PEARLS is registered [ISRCTN:36344989].

### Study objectives

#### Primary objective

Phase II: To determine whether moderately fractionated extended field IMRT is safe in patients diagnosed on functional imaging with pelvic and/or para-aortic lymph node positive prostate cancer.

Phase III: To determine whether extended field IMRT improves metastasis-free survival (MFS) when compared to standard field radiotherapy in patients with pelvic lymph node only disease.

#### Secondary objectives

Secondary objectives are to assess (and in phase III to compare between extended field and standard field groups):

Phase II.

- Acute bowel, bladder and bone marrow toxicity of extended field prostate radiotherapy up to 18 weeks.

- Feasibility of delivery and compliance of randomised treatments at participating centres.
- Patient reported outcomes at 18 weeks.

#### Phase III

- Acute and late toxicity.
- Patient reported outcomes.
- Time to biochemical progression.
- Time to and pattern of radiographic progression.
- Failure-free survival.
- Overall survival.

#### Exploratory objectives

- Out of radiotherapy field MFS.
- Time to symptomatic skeletal event.
- Time to castration resistance.
- Dosimetry of prostate, seminal vesicles, lymph nodes and organs at risk.

#### Eligibility

All patients provide written informed consent to participate. Inclusion and exclusion criteria are as follows:

#### 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, any N stage, 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 (clinical decision)
6. WHO Performance status of 0–2.

#### Exclusion criteria

- Prior radiotherapy to the prostate or pelvis; prior bilateral orchiectomy; radical prostatectomy.
- For those patients who have received docetaxel chemotherapy or are receiving AR targeted therapy, there should be no ongoing CTCAE grade 2 or greater GI toxicity relating to this systemic therapy.
- Medical conditions (non-prostate cancer related) expected to limit life expectancy to <5 years.
- Bilateral hip prostheses or any other implants/hardware that would introduce substantial CT artefacts and would make pelvic node planning more difficult.
- Medical conditions likely to make radiotherapy inadvisable e.g., inflammatory bowel disease, intractable urinary symptoms, previous colorectal surgery.
- 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.
- Any other contraindication to external beam radiotherapy to the para-aortic and/or pelvic region.

#### Treatment allocation

Allocation of radiotherapy field size to either standard field IMRT or extended field IMRT uses a 1:1 allocation ratio. Within each cohort,

treatment allocation is by minimisation with a random element. Balancing factors include radiotherapy centre, systemic treatment beyond LHRHa (any vs none) and start of ADT in relation to PSMA PET scan ( $\leq 4$  weeks vs  $> 4$  weeks).

Two cohorts of patients will be recruited: Those with nodal disease limited to the pelvic lymph nodes and those with nodal disease in the para-aortic region.

#### Treatment description

At entry into the study, all patients will be receiving LHRHa (either luteinizing hormone-releasing hormone agonist or antagonist) +/- AR targeted therapy (abiraterone/prednisolone, enzalutamide, apalutamide) or docetaxel chemotherapy in accordance with standard clinical practice at their centre.

Consenting patients are randomised in a 1:1 ratio to either:

- Control arm of standard field image-guided intensity-modulated radiotherapy (IMRT) with 60 Gray (Gy) to the prostate (and 44 Gy to the pelvis with integrated boost of 51 Gy to the involved lymph nodes for patients with pelvic-node disease only).
- Experimental arm of extended field image-guided IMRT with 60 Gy to the prostate and 44 Gy to the pelvis and para-aortic region with an integrated boost of 51 Gy to the involved lymph nodes. All randomised patients will receive IMRT given in 20 fractions over 4 weeks.

Details of the schedule of assessments and follow-up are shown in [Table 1](#).

#### Radiotherapy Quality Assurance (RT QA)

A comprehensive QA programme for the PEARLS trial has been designed and implemented by the National Radiotherapy Quality Assurance (RTQA) Group including pre-trial and on-trial components. The QA processes for the PEARLS trial have been streamlined for centres that have already completed the QA programme for the PIVOTALboost [ISRCTN:80146950] or PACE [ISRCTN:17627211] trials.

For pre-trial QA, centres must complete the following prior to site activation: 1) Facility questionnaire, 2) benchmark outlining case and 3) benchmark planning case.

On-trial QA includes prospective and/or retrospective case reviews, independent review of staging PSMA PET-CT imaging and report, dosimetry site visit (subject to prior RTQA dosimetry accreditation) and Digital Imaging and Communications in Medicine (DICOM) data collection for all patients.

Radiotherapy planning and delivery guidelines are provided in appendix 2.

In addition to the planning and radiotherapy treatment guidelines, a pelvic lymph node, extended field and nodal boost contouring atlas has been developed (see appendix 3). Several webinars were held to ensure consensus approval of these documents amongst the UK prostate radiotherapy community prior to their release.

#### Translational research

There are three separate translational research sub-studies in PEARLS.

##### Immune cell repertoire

This sub-study ( $n = 30$ ) aims to compare changes in the immune cell repertoire during and after radiotherapy to the prostate alone versus radiotherapy to the prostate with pelvic and/or para-aortic lymph nodes.

##### PSMA PET-CT biomarker imaging response

The primary aim of this sub-study ( $n = 26$ ) is to determine whether

PSMA PET-CT can be used as an imaging biomarker in node-positive prostate cancer. It is unclear when lesions lose their PSMA uptake after radiation or whether residual PSMA uptake is associated with residual tumour viability. Additional inclusion criteria for patients considering the optional PSMA PET-CT sub-study is three or more PSMA avid lymph nodes on the diagnostic PSMA PET-CT staging scan.

##### Gut microbiome

The objective of this translational work ( $n = 110$ ) within PEARLS is to determine how intestinal microbial populations change during treatment in relation to field size and to study associations with bowel toxicity and treatment efficacy. Comparisons will be performed at each time point to assess relevant associations between the microbiota and treatment outcomes.

##### Safety reporting

Serious Adverse Events (SAEs) are reportable after commencement of study treatment i.e., after fiducial marker insertion or first fraction of radiotherapy if no fiducials are used, and up to 30 days after end of study treatment. In addition, RTOG grade  $\geq 3$  acute or late radiation side effects, i.e., related to study treatment (except erectile dysfunction), occurring within 5 years after radiotherapy treatment are reported as SAEs.

##### Endpoints

###### Primary endpoints

Phase II: Acute lower gastrointestinal (GI) RTOG G2+ toxicity at week 18 from start of radiotherapy.

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, where distant metastasis is defined as extra-pelvic lymphadenopathy, bone or visceral metastases.

###### Secondary endpoints

Phase II: Acute and late toxicity, compliance to treatment dose constraints and patient reported outcomes.

Phase III: Acute and late toxicity, patient reported outcomes, time to biochemical progression, time to and pattern of radiographic progression, failure-free survival and overall survival.

###### Patient reported outcomes endpoints

Participants are asked to take part in a quality of life study. This includes patient reported outcomes collected using the following questionnaires: Expanded Prostate Index Composite-26 (EPIC 26) Short Form [18], International Prostate Symptom Score (IPSS) [19], The NCI Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Measurement System [20] and the EQ-5D-5L [21].

##### Statistical considerations

PEARLS is a trial with separate primary endpoints and sample sizes calculated for each phase. All patients recruited during phase II will contribute to phase III. Recruitment to phase III will continue whilst phase II primary endpoint data mature. Phase II has a toxicity primary endpoint and the principal analysis will combine data from extended field IMRT patients from both the pelvic node and para-aortic node cohorts. Phase III is powered to evaluate the primary endpoint of MFS in the pelvic node cohort of patients.

##### Sample size

Phase II requires 75 patients to be treated with extended field IMRT. With 1:1 treatment allocation ratio the total sample size for phase II is 150 patients. The primary endpoint in phase II is acute lower GI toxicity

**Table 1**  
Schedule of assessments.

Visit/Assessment	Screening (pre-randomisation)	Pre-treatment	During RT Treatment				Follow-up (timed from start of radiotherapy)														Recurrence			
			End week 1	End week 2	End week 3	End week 4	Week 6	Week 8	Week 12	Week 18	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 60	Year 6–10 (annual)				
Informed consent	X																							
Histological confirmation of prostate cancer	X																							
Complete history and physical examination (physical examination & DRE if clinically indicated).	X																							
Radiological assessment (PSMA PET-CT +/- multi-parametric MRI scan)	X																							
Bloods – full blood count (FBC)	X	X <sup>1</sup>		X <sup>1</sup>		X			X	X	X <sup>1</sup>	X	X											
Bloods – biochemistry (renal profile only)						X			X	X		X	X											
Bloods – biochemistry (glucose, liver function, bone profile, renal profile)	X																							
Bloods – PSA	X	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bloods – testosterone		X																			X	X		
Toxicity Assessment – RTOG and CTCAE (v5)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life questionnaire [PRO CTCAE EPIC-26, IPSS, EQ-5D]	X					X			X	X	X	X	X								X			
<b>Optional sub-studies</b>																								
PSMA PET (26 patients)						X					X													X
T-cell – blood sample collection (London centres ONLY – 30 patients) – 6 timepoints		X		X		X			X	X	X													
T-cell – diagnostic tumour collection		X																						
Gut microbiota – stool sample collection (110 patients) – 6 timepoints		X				X			X	X	X			X										

<sup>1</sup> FBC ONLY at these time-points for patients taking part in the T-cell blood sample collection.

at 18 weeks from the start of radiotherapy. The RTOG G2+ toxicity-free rate at 18 weeks, which if true could imply that the experimental arm does not warrant further investigation, is set at 82 %, i.e., ruling out a G2+ acute GI toxicity rate of 18 % or higher. The RTOG G2+ toxicity-free rate at 18 weeks in the experimental arm is expected to be 92 %. Using a Fleming single-stage design (with 5 % alpha and 80 % power), if at least 68/75 patients receiving extended field IMRT are toxicity-free, it would be considered sufficient to continue to phase III. The phase II stop/continue decision will be based on the toxicity experience of patients receiving extended field radiotherapy both in the pelvic node and para-aortic node cohorts, as the experimental treatment is the same for both the cohorts. The assessment of toxicity will focus on radiotherapy-related events only. The sample size was calculated using the Sample Size Tables for Clinical Studies software.

The primary endpoint for phase III is MFS and the time point of primary interest is 5 years. This endpoint was chosen as it is a non-PSA based failure-free survival endpoint and has been found to be predictive of overall survival in localized prostate cancer [22]. The power calculation for phase III is based on the pelvic node cohort and requires 693 pelvic node patients. It is assumed that the control arm 5-year MFS rate in the pelvic node cohort will be 80 %. This is based on extrapolation from two radiotherapy trials [6,7] in patients with known pelvic lymph node disease on conventional imaging. The phase III trial has a superiority design and is powered to detect a 7 % difference in 5-year MFS from 80 % to 87 %, corresponding to detecting a hazard ratio of 0.62. This will require a total of 161 events (85 % power and a 5 % two-sided significance level). The target number of events would be anticipated to accrue in 693 pelvic node patients recruited over 6.5 years of staggered recruitment with a minimum of 5 years follow up on all patients. This assumes that 6 % of all patients will be recruited in the first year, 8 % in the second year, 12 % in the third, 16 % in the fourth, 22 % in the fifth year, and 36 % in the remaining one and a half years. To allow for 3 % loss to follow up at the time of the primary endpoint analysis (based on the experience in CHHiP [23], the target sample size is 714 pelvic node patients (357 standard field IMRT; 357 extended field IMRT). The sample size is based on the log-rank test using the ‘artsurv’ command in STATA.

The phase III sample size is driven by the number of events in the pelvic node cohort but allowing for concurrent enrolment to the para-aortic node cohort. With the expectation that recruitment of patients with para-aortic disease will be one quarter the rate of patients with pelvic node only disease, we estimate there will be 179 para-aortic patients recruited after 6.5 years giving an estimated total sample size of 893 patients.

#### Interim analyses and stopping rules

The trial is designed with stages to assess feasibility and safety during phase II and efficacy in phase III. Recruitment will be closely monitored by the Trial Management Group (TMG) and Trial Steering Committee (TSC). An Independent Data Monitoring Committee (IDMC) will review the accumulating data at regular intervals at least annually.

#### Planned timeline

PEARLS recruited its first patient on 25th June 2021 and is currently open in 12 UK centres (as of 31/08/22). International participation is planned for phase III to support a planned recruitment timeline of approximately 6.5 years.

#### Discussion

PEARLS investigates an “orphan” prostate cancer patient group, for which there have been no prospective randomised trials evaluating the effect of radiotherapy. This may, in part, be due to the limited diagnostic performance of conventional imaging. However, with molecular imaging providing a higher detection rate for lymph node disease, the

optimal radiotherapy treatment strategy for this patient group needs to be determined. PEARLS complements the completed CHHiP [22] [ISRCTN:97182923] and PACE [ISRCTN:17627211] trials, currently recruiting PIVOTALboost [24] [ISRCTN:80146950], recently opened PACE-NODES [ISRCTN/Clinical Trial.gov pending] and STAMPEDE2 (Arm S) prostate cancer radiotherapy trials in the UK.

#### Ethics approval

PEARLS was approved by the London – Central Research Ethics Committee (21/LO/0178).

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#### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JM and AT declare funding from Cancer Research UK (RadNet C7224/A28724). JM declares honoraria/travel assistance from Astellas, Bayer, Ferring, Janssen. TB declares honoraria from Elekta and AstraZeneca. DC declares Vice Chair of Advisory Group Digestive Cancers Europe – Chair of the Patient Advisory Group and Vice Chair of the Board. AM declares IDMC payment to institution research fund. LP declares CRUK Clinical Trials Fellowship funding. AR declares honoraria/travel assistance from Janssen, Astellas and AstraZeneca. IS declares honoraria from Bayer, Bristol Myers Squibb, Janssen. AT declares research funding from Elekta, Varian and Accuray and honoraria/travel assistance from Elekta and Accuray. AW declares funding from Prostate Cancer UK, honoraria with travel/accommodation funded by AACR 2022, ESTRO, ImmunoRad 21 and 22 and co lead of TGFbeta working group. EH declares grants from Varian Medical Systems Inc., Astra Zeneca, Janssen-Cilag, Bayer, Roche Products LTD, Merck Sharp & Dohme received by the Institution of Cancer Research. EH declares funding from Cancer Research UK for the central coordination of the PEARLS trial.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2022.09.003>.

#### References

- [1] Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries Hyuna Sung PhD CA: A Cancer Journal for Clinicians Volume 71, issue 3 pages 209-249.
- [2] Wang L, Lu B, He M, Wang Y, Wang Z, et al. Prostate cancer incidence and mortality: global status and temporal trends in 89 countries from 2000 to 2019. *Front Public Health* 2022;10:811044.
- [3] <https://crukcanerintelligence.shinyapps.io/EarlyDiagnosis/> (accessed 7<sup>th</sup> September 2022).
- [4] James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, et al. STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term

- hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multi-arm, multistage, platform randomised controlled trial. *Lancet* 2016;387(10024):1163–77.
- [5] James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, et al. STAMPEDE investigators. abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med* 2017 Jul 27;377(4):338–351.
- [6] Attard G, Murphy L, Clarke NW, Cross W, Jones RJ, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet* 2022;399:447–60.
- [7] Jegadeesh N, Liu Y, Zhang C, Zhong J, Cassidy RJ, Gillespie T, et al. The role of adjuvant radiotherapy in pathologically lymph node-positive prostate cancer. *Cancer* 2017 123(3):512–520.
- [8] Motterle G, Ahmed ME, Andrews JR, Karnes RJ. The role of radical prostatectomy and lymph node dissection in clinically node positive patients. *Front Oncol* 2019;9:1395.
- [9] Reis Ferreira M, Khan A, Thomas K, Truelove L, McNair H, et al. Phase 1/2 Dose-escalation study of the use of intensity modulated radiation therapy to treat the prostate and pelvic nodes in patients with prostate cancer. *Int J Radiat Oncol Biol Phys* 2017 Dec 1;99(5):1234–1242.
- [10] James ND, Spears MR, Clarke NW, Dearnaley DP, Mason MD, et al. STAMPEDE investigators. failure-free survival and radiotherapy in patients with newly diagnosed nonmetastatic prostate cancer: data from patients in the control arm of the STAMPEDE Trial. *JAMA Oncol* 2016;2(3):348–57.
- [11] Liskamp CP, Donswijk ML, van der Poel HG, Schaake EE, Vogel WV. Nodal recurrence patterns on PET/CT after RTOG-based nodal radiotherapy for prostate cancer. *Clin Transl Radiat Oncol* 2020;22:9–14.
- [12] Van Hemelryk A, De Meerleer G, Ost P, Poelaert F, De Gerssem W, et al. The outcome for patients with pathologic node-positive prostate cancer treated with intensity modulated radiation therapy and androgen deprivation therapy: a case-matched analysis of pN1 and pN0 patients. *Int J Radiat Oncol Biol Phys* 2016;96(2):323–32.
- [13] Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *The Lancet* 2020;392:2353–66.
- [14] Pötter R, Tanderup K, Kirisits C, de Leeuw A, Kirchheiner K, et al. EMBRACE Collaborative Group. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. *Clin Transl Radiat Oncol* 2018;11(9):48–60.
- [15] Murray JR, Kopka K, Afshar-Oromieh A. Imaging and radiotherapy for recurrent prostate cancer: An evolutionary partnership. *Radiother Oncol* 2018;129(2):387–8.
- [16] Vapiwala N, Hofman MS, Murphy DG, Williams S, Sweeney C. Strategies for evaluation of novel imaging in prostate cancer: putting the horse back before the cart. *J Clin Oncol* 2019;37(10):765–9.
- [17] Hall WA, Paulson E, Davis BJ, Spratt DE, Morgan TM, et al. NRG oncology updated international consensus atlas on pelvic lymph node volumes for intact and post-operative prostate cancer. *Int J Radiat Oncol Biol Phys* 2021;109(1):174–85.
- [18] Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology* 2000;56:899–905.
- [19] Barry MJ, Fowler Jr FJ, O’Leary MP, Bruskewitz RC, Holtgrewe HL, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992;148(5):1549–57.
- [20] Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, et al. Development of the National Cancer Institute’s patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst* 2014;106(9).
- [21] Buchholz I, Janssen MF, Kohlmann T, Feng YS. A systematic review of studies comparing the measurement properties of the three-level and five-level versions of the EQ-5D. *Pharmacoeconomics* 2018;36(6):645–61.
- [22] Xie W, Regan MM, Buyse M, Halabi S, Kantoff PW, et al. Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. *J Clin Oncol* 2017;35(27):3097–104.
- [23] Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;17(8):1047–60.
- [24] Syndikus I, Cruickshank C, Staffurth J, Tree A, Henry A, et al. PIVOTALboost: A phase III randomised controlled trial of prostate and pelvis versus prostate alone radiotherapy with or without prostate boost (CRUK/16/018). *Clin Transl Radiat Oncol* 2020;1(25):22–8.