

Original Article

Reirradiation Options for Previously Irradiated Prostate Cancer: Is It Feasible to Randomise Between Treatment With Stereotactic Body Radiotherapy (SBRT) Versus High-Dose-Rate Brachytherapy?



J. Zhong^{ab*}, F. Slevin^{ac}, S. Brown^{d1}, M. Serra^e, P. Bownes^d, C. Thompson^d, R. Reed^f, K. Reeves^f, M. Dubec^{fg}, C. Eccles^{ef}, R. Chuter^{fg}, Y.M. Tsang^{hi}, N.J. Taylor^j, C.M.L. West^f, D. Buckley^k, R. Alonzi^l, A. Scarsbrook^{ab}, A. Choudhury^{ef}, P. Hoskin^{fl}, A.M. Henry^{ac}

^a Leeds Institute of Medical Research, University of Leeds, Leeds, UK

^b Department of Radiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

^c Department of Clinical Oncology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

^d Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK

^e Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK

^f Division of Cancer Sciences, University of Manchester, Manchester, UK

^g Department of Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, UK

^h Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

ⁱ Department of Radiation Oncology, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada

^j Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, UK

^k Biomedical Imaging, University of Leeds, Leeds, UK

^l Department of Clinical Oncology, Mount Vernon Cancer Centre, Northwood, UK

Abstract

Aims: Prostate cancer which recurs within the prostate following definitive radiotherapy can be treated again using radiation, known as reirradiation. Systematic reviews of cohort studies of salvage therapies suggest that reirradiation using brachytherapy (BT) or stereotactic body radiotherapy (SBRT) offers favourable disease control with acceptable toxicity. However, the optimal radiotherapy modality in this setting remains to be determined. The study aimed to establish feasibility of randomisation between HDR BT and SBRT.

Materials and methods: The reirradiation options for previously irradiated prostate cancer (RO-PIP) study is a randomised feasibility study of high-dose-rate BT (HDR BT) or SBRT for locally recurrent prostate cancer. The primary objective was to recruit 60 participants across three centres over a 24-month period. Secondary endpoints include other measures of feasibility, participant-reported outcomes, and clinician-reported acute and long-term toxicity.

Results: Between October 2022 and May 2025, 60 patients were screened and 18 (30%) were deemed ineligible. Of 42 eligible patients, 23 (54.8%) were randomised to HDR BT (n = 13) or SBRT (n = 10). One randomised participant withdrew prior to commencing treatment. One centre recruited 2 patients and the other centres recruited 9 and 12 patients, respectively. The most common reason for nonparticipation was treatment preference, with 10 patients preferring HDR BT (n = 7), SBRT (n = 2), or androgen deprivation therapy alone (n = 1). Six patients declined to participate for non-disclosed reasons. One patient declined participation due to distance from the treating site, 1 patient declined a biopsy, and 1 patient preferred observation.

Conclusion: Planned recruitment targets to a randomised multicentre study of BT or SBRT for treatment of locally recurrent prostate cancer were not achieved. A major barrier to participation was patient preference for a specific treatment. Future studies should be designed to allow patient, clinician, and/or centre preference for reirradiation options (either BT or SBRT), which could then be compared to standard of care.

© 2026 The Author(s). Published by Elsevier Ltd on behalf of The Royal College of Radiologists. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Key words: Brachytherapy; prostate cancer; Reirradiation; salvage; stereotactic body radiotherapy

Introduction

Prostate cancer is the second most diagnosed cancer worldwide, with approximately 1.4 million new cases annually [1,2]. Despite advances in radiotherapy for

Corresponding author. J. Zhong, Leeds Institute of Medical Research, University of Leeds, Leeds, UK.

E-mail addresses: j.zhong@leeds.ac.uk (J. Zhong), s.brown@leeds.ac.uk (S. Brown).

¹ Author responsible for statistical analysis.

primary treatment of non-metastatic prostate cancer, 3%–13% of patients are estimated to experience local disease recurrence within 10 years of treatment [3–7]. Local recurrence is increasingly being recognised as an important clinical entity, especially for patients initially treated for high-risk disease as it may be associated with increased risk of distant metastases and inferior survival [8].

There is uncertainty regarding the optimal management of patients with locally recurrent prostate cancer after previous radiotherapy but several salvage treatment options exist, including surgery, high-intensity focused ultrasound, cryotherapy, and delivery of further radiation. Reirradiation can use brachytherapy (BT) or stereotactic body radiotherapy (SBRT) [9,10]. There is increasing interest in reirradiation salvage treatments but no randomised evidence to guide treatment decisions. International expert panels have developed consensus regarding aspects of patient selection, diagnostic investigations, and therapeutic approaches using BT and SBRT [11,12]. Systematic reviews of cohort studies of salvage therapies suggest that BT and SBRT offer favourable disease control with acceptable toxicity profiles [5,13]. In these studies, 5-year relapse-free survival estimates following BT and SBRT are comparable to surgery or ablative therapies and range from 50% to 60% [5]. Severe combined urinary and bowel toxicity estimates with HDR BT and SBRT range from 4.2% to 8.0% and 0% to 1.5%, respectively. In contrast, 15%–23% of patients treated with salvage surgery or ablative therapies experience severe urinary toxicities. Despite these promising data from observational studies, efficacy and toxicity outcomes for BT and SBRT from randomised trials are lacking, with no evidence available on impact on patient-reported outcomes (PROs).

The reirradiation options for previously irradiated prostate cancer (RO-PIP) trial aimed to determine feasibility of recruitment to a randomised study of HDR BT or SBRT reirradiation for locally recurrent prostate cancer. This paper reports on the recruitment outcomes and other measures of feasibility from the trial.

Methods

Study Design and Participants

RO-PIP is a prospective, two-arm, open-label, randomised feasibility trial conducted across three UK tertiary oncology centres. The study received ethical approval from the Health Research Authority and Health and Care Research Wales (HCRW) Ethics Committee (Reference: 21/YH/0305) and was registered with ISRCTN (12238218). Full details of the study protocol were published previously [14]. A CONSORT checklist is shown in [Supplementary Material](#). Participants were identified through uro-oncology multidisciplinary team meetings and approached at uro-oncology outpatient clinics, after assessment of eligibility. All participants provided written informed consent.

Eligibility Criteria

The inclusion criteria is as follows:

- (1) Male individuals aged over 18 years.
- (2) Histologically confirmed locally recurrent prostate cancer (following radiation no less than 2 years previously).
- (3) No metastatic disease (confirmed on prostate-specific membrane antigen positron emission tomography–computed tomography [PSMA PET-CT]).
- (4) Able and willing to provide an informed consent to participate.
- (5) World Health Organization performance status: 0–2.
- (6) Reasonable urinary function (International Prostate Symptom Score [IPSS] <20 and Qmax >10 ml/s on flow tests).
- (7) Greater than 10-year life expectancy.

Randomisation

Participants were randomised by Leeds Cancer Research UK Clinical Trials Unit (CTU) on a 1:1 basis to receive either HDR BT or SBRT. Patients were randomised using permuted blocks, stratified by recruiting site and planned use of androgen deprivation therapy (ADT) therapy. Randomisation was performed centrally using a telephone randomisation system. Authorisation codes and personal identification numbers, provided by the CTU, were required to access the randomisation system.

Interventions

Eligible patients were randomised to receive either of the following:

1. HDR BT: 27 Gy in 2 fractions, delivered over up to 4 weeks apart.
2. SBRT: 36.25 Gy in 5 fractions, delivered alternate days over 2 weeks.

Planning guidelines containing full details on immobilisation, planning image acquisition, target volume and organ at risk contouring, treatment planning, treatment delivery, and quality assurance (QA) for HDR BT and SBRT were agreed by the coinvestigators prior to patient recruitment. All 3 centres are established BT and SBRT centres. No external QA processes were undertaken. ADT was used at the discretion of the treating clinician.

HDR BT Treatment Planning and Delivery

Gross tumour volume (GTV) was delineated on either transrectal ultrasound, CT, or magnetic resonance imaging (MRI) based on the intra-prostatic lesion defined using information from diagnostic MRI, PSMA PET-CT, and prostate biopsy. For patients where most or the entire prostate contained recurrent tumours, the entire prostate gland (excluding seminal vesicles) was contoured as GTV. For whole-gland treatments, CTV was defined as GTV (entire

prostate) with a 3 mm margin constrained to the rectum. For focal treatments, a margin of 3 mm constrained to urethra and rectum was used to define CTV. No margin was applied to generate planning target volume (PTV) ie, CTV = PTV. Organs at risk (OARs) included outer rectal wall and urethra as visualised from the urinary catheter. The prescription dose to the 100% PTV isodose was 27 Gy in 2 fractions delivered up to 4 weeks apart. Table 1 summarises target volume objectives and OAR constraints.

SBRT Treatment Planning and Delivery

Target volume delineation utilised CT ± MRI with GTV defined using information from diagnostic MRI, PET-CT, and prostate biopsy. For patients where most or the entire prostate contained recurrent tumours, the entire gland (excluding seminal vesicles) was contoured. For focal treatment, a margin of 3 mm constrained to the prostate capsule was used to define CTV. For whole-gland treatments, no additional margin to CTV was applied. The PTV was defined as CTV +5 mm margin on conventional linear accelerators (linacs) or CTV +3 mm margin on MR linacs. A minimum PTV diameter of 2.5 cm was recommended. The following OARs were contoured: rectum, bladder, penile bulb, urethra (if MR ± catheter used for planning), bowel loops (if likely to be in or within 1 cm of the PTV), and separate right and left femoral heads. The prescription dose to PTV and GTV was 36.25 Gy in 5 fractions and 40 Gy in 5 fractions, respectively, delivered alternate days over 2 weeks. Table 2 summarises target volume objectives and OAR constraints. If the OAR constraints could not be met whilst planning for optimal GTV and PTV coverage criteria, the centres were instructed to achieve the mandatory OAR constraints for rectum, bladder, and bowel loops accepting under-coverage of PTV ± GTV. For bladder and rectum, OAR constraints were chosen to allow a cumulative equivalent dose in 2 Gy fractions of 120 Gy to bladder and 110 Gy to rectum [15].

Table 1
HDR BT target coverage objectives and OAR constraints

Target or organ	Focal HDR BT	Whole-gland HDR BT
D90 PTV	>12.1Gy per fraction	>12.1Gy per fraction
GTVprostate	Not applicable	
V100%		>90%
V150%		<45%
V200%		<15%
Urethra ^a		
D10%	<12.1Gy per fraction	<10.1Gy per fraction
D30%		<8.7Gy per fraction
Rectum		
V100%	0	0
D1cc	<10.1Gy per fraction	<10.1Gy per fraction
D2cc	<8.7Gy per fraction	<8.7Gy per fraction

Abbreviations: D90 PTV, minimum dose covering 90% of the PTV; GTV, gross tumour volume; OAR, organ at risk; PTV, planning target volume.

^a Note urethral constraints may not be achieved if full retreat or if focal PTV is close to the urethra. For these cases, it may be justified to increase the Urethra D10% but this must not exceed 110%.

Table 2

SBRT target coverage objectives and organs at risk (OARs) constraints

Target or organ	Limit	Optimal	Mandatory
PTV	V36.25Gy	≥85%-95%	None
PTV	V34.4Gy	≥98%	None
GTV	Maximum percentage dose	105%-130%	130%
GTV	V40Gy	≥95%	None
Rectum	V23.4Gy	None	<1 cc
Bowel loops	V18.1Gy	<5 cc	None
Bowel loops	V30Gy	None	<1 cc
Bladder	V27Gy	<10 cc	<15 cc
Femoral heads	V14.5Gy	<5%	None

Abbreviations.

GTV, gross tumour volume; PTV, planning target volume.

Outcomes

Primary Outcome

The primary objective of the study was feasibility and to quantitatively evaluate recruitment rates ie, the number of participants providing consent for randomisation into the study, regardless of uptake of their randomised treatment procedure. The recruitment target was to enrol 60 participants over 24 months from when the last study site opened (accounting for differences in set-up study time).

Secondary Outcomes

Secondary outcomes included additional feasibility endpoints, including numbers of patients screened, treatment compliance, withdrawal rate, and reasons for nonparticipation. Toxicity endpoints included PROs, evaluated using the Expanded Prostate Cancer Index Composite-26, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30, and the IPSS questionnaires, and incidence of clinician-reported toxicities, evaluated using clinician-reported toxicity (Common Terminology Criteria for Adverse Events version 5.0. Evaluations were made at the baseline (prior to HDR BT or SBRT) and at 1, 3-, 6-, 12- and 24-months posttreatment. Toxicity and PROs will be reported once all participants have completed a minimum of 24 months follow-up posttreatment.

Sample Size and Statistical Analysis

RO-PIP is an exploratory feasibility study and, therefore, a formal statistical power calculation was not conducted. The purpose was to determine feasibility of recruitment and to estimate specific parameters such as toxicity to inform sample size calculations for future studies. Based on published guidance regarding feasibility studies, it was considered that recruitment of 60 participants across 3 centres over 24 months would be sufficient [16]. Descriptive and summary statistics were used to summarise recruitment rates, eligibility, and randomisation outcomes. No formal hypothesis testing was conducted, consistent with the feasibility nature of the study.

Patient and Public Involvement

The study was discussed with the Leeds Cancer Centre Oncology Patient and Public Involvement and Engagement Group and their feedback was used to shape the trial protocol and participant information sheet.

Results

Between October 2022 and May 2025, 60 patients were screened. A summary of participant flow is shown in Figure 1. Of 60 patients who were screened, 18 (30%) were deemed ineligible. The most common reasons for ineligibility were presence of metastatic disease on PET-CT or large volume of locally recurrent disease considered unsafe to treat with BT or SBRT. Of 42 eligible patients, 23 participants (54.8%) were randomised to BT (n = 13) or SBRT (n = 10). One centre only recruited 2 patients and the other centres recruited 9 and 12 patients, respectively. One participant randomised to BT subsequently withdrew prior to treatment. A summary of clinicopathological and treatment characteristics of randomised participants is shown in Table 3.

In screening logs, the most common reason for nonparticipation was treatment preference, with 10 eligible patients (24.4%) preferring either BT (n = 7), SBRT (n = 2) or ADT alone (n = 1). Six eligible patients declined to participate for non-disclosed reasons. One patient declined participation due to distance from treating site, 1

patient declined to undergo a biopsy, and 1 patient preferred to undergo observation.

Discussion

To the authors' knowledge, RO-PIP is the first study randomising between BT and SBRT for treatment of locally recurrent prostate cancer. Twenty-three participants were randomised to HDR BT or SBRT, although recruitment of the planned 60 participants at three centres within the 24-month recruitment window was not feasible.

Despite not meeting its primary endpoint, the RO-PIP study adds value to the evidence base for salvage BT and SBRT. There have been several previous prospective observational and single-arm clinical trials. Much of the evidence to date is derived from retrospective studies of limited quality, which introduces bias that may overestimate treatment effect sizes [5,14,17–24]. In this context, RO-PIP provides important insights, especially for the toxicity and quality of life data, which will be reported later. RO-PIP is also complementary to 2 ongoing phase I/II trials, which are currently in progress. GETUG AFU 31 is currently evaluating salvage SBRT in a single-arm phase II trial following publication of phase I toxicity results for 21 participants [25,26]. F-SHARP is a similar phase I/II trial but is evaluating HDR BT [14]. Taken together with RO-PIP, these studies will help inform future trials of salvage therapies for locally recurrent prostate cancer.

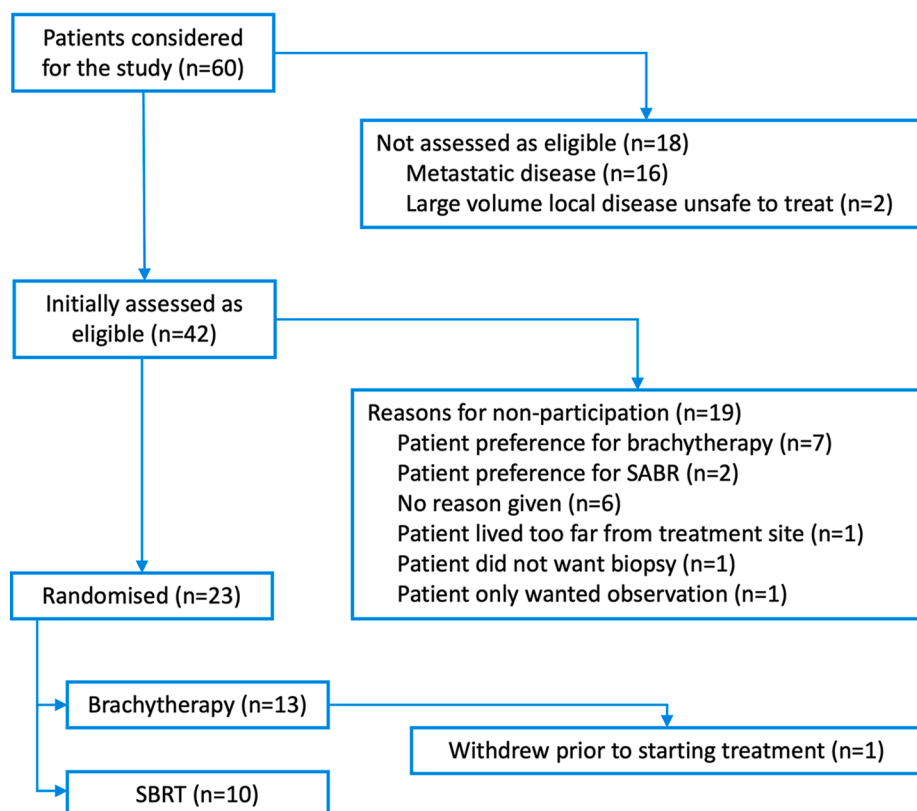


Fig 1. CONSORT diagram of participant flow.

Table 3
Participant clinicopathological and treatment characteristics

	HDR BT	SBRT	Total
Patient numbers	13	10	23
Age (Years)			
Median (range)	71 (66-77)	72 (63-77)	72 (63-77)
Primary treatment Gleason Score			
3+3	3 (23%)	2 (20%)	5 (22%)
3+4	7 (54%)	0	7 (30%)
4+3	2 (15%)	5 (50%)	7 (30%)
4+4	0	1 (10%)	1 (4%)
4+5	1 (8%)	2 (20%)	3 (13%)
Baseline PSA (ng/ml)			
Median (range)	10.2 (4.7-89)	24.65 (4.3-210.0)	15 (4.3-210)
TNM group			
T1c	1 (8%)	0	1 (4%)
T2a	4 (31%)	1 (10%)	5 (22%)
T2b	1 (8%)	1 (10%)	2 (9%)
T2c	1 (8%)	1 (10%)	2 (9%)
T3a	5 (38%)	3 (30%)	8 (35%)
T3b	1 (8%)	4 (40%)	5 (22%)
RISK group			
Low	0	1 (10%)	1 (4%)
Intermediate	8 (62%)	0	8 (35%)
High	5 (38%)	9 (90%)	14 (61%)
Previous radiotherapy (dose/number of fractions)			
HDR BT (19/1)	3 (23%)	0	3 (13%)
LDR BT (145/1)	2 (15%)	1 (10%)	3 (13%)
EBRT (57/19)	1 (8%)	0	1 (4%)
EBRT (60/20)	1 (8%)	2 (20%)	3 (13%)
EBRT (76/37)	2 (15%)	0	2 (9%)
EBRT (74/37)	4 (31%)	5 (50%)	9 (39%)
EBRT (46/23) + HDR BT (15/1)	0	1 (10%)	1 (4%)
EBRT (37.5/15) + HDR BT (15/1)	0	1 (10%)	1 (4%)
Previous ADT			
NO	5 (38%)	1 (10%)	6 (26%)
YES	8 (62%)	9 (90%)	17 (74%)
IF yes, median (range) duration (months)	15 (6-46)	24 (6-36)	24 (6-46)
Recurrence PSA (ng/ml)			
Median (range)	4.3 (1.39-13.1)	2.7 (0.78-10.2)	4 (0.78-13.1)
IPSS			
Median (range)	4 (0-16)	7 (2-9)	7 (0-16)
Qmax (ml/s)			
Median (range)	17.3 (15.8-22.4)	25.1 (23.0-27.3)	22 (15.8-27.3)
WHO performance status			
0	12 (92%)	10 (100%)	22 (96%)
1	1 (8%)	0	1 (4%)
ACE-27			
0	11 (85%)	8 (80%)	19 (83%)
1	2 (15%)	2 (20%)	4 (17%)

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; ADT, androgen deprivation treatment; BT, brachytherapy; EBRT, external beam radiotherapy; HDR, high dose rate; IPSS, International Prostate Symptom Score; LDR, low dose rate; PSA, prostate-specific antigen; Qmax, maximum urine flow rate, WHO, World Health Organization.

Several factors may explain why recruitment to the primary endpoint in RO-PIP was not feasible. Screening logs indicated that a major barrier to participation for patients who were eligible for RO-PIP appeared to be patient preference for a specific treatment. It is possible that the need for participants allocated to BT to be suitable for general anaesthesia and an invasive procedure could also have influenced patient (and clinician) perspectives regarding the randomisation. This means that a future phase III trial will need to allow participant/clinician choice of salvage therapy, for example HDR BT, low-dose-rate BT, SBRT, or even other ablative treatments such as high-intensity focused ultrasound/cryotherapy, to maximise opportunities for participant recruitment, which reflects the wider patient population. There were additional challenges to recruitment in RO-PIP. Protocols employed in 1 site where only 2 patients were recruited for follow-up after primary prostate radiotherapy (and hence identification of patients with early biochemical recurrence who had isolated local recurrence of prostate cancer) may have restricted identification of potentially eligible patients. RO-PIP was also affected by the Covid-19 pandemic and ongoing recovery, which impacted staff availability, clinical trial deliverability, follow-up pathways, access to PET-CT, and deferral of non-urgent radiotherapy.

Biochemical recurrence following prior radiotherapy is common but the natural history is variable. Many patients may experience prolonged survival prior to development of metastatic disease or have competing risks for mortality, whereas others are at increased risk of prostate cancer-specific mortality (PSCM) [27]. This means that patient selection is important when considering investigations and management. Several factors have been identified as increasing risk of PSCM, including higher initial Gleason grade, shorter time from initial treatment to recurrence and shorter prostate-specific antigen (PSA) doubling time [28]. Use of PSMA PET-CT during early biochemical recurrence provides an additional method to stratify patients, including identification of local recurrence, which could benefit from salvage therapies [29]. Nevertheless, despite the increasing interest in salvage treatment of locally recurrent prostate cancer, there remains no clear standard of care [9,10]. Other options may include observation or ADT. The recently published EMBARK trial also demonstrated the metastasis-free survival benefit from addition of the androgen receptor pathway inhibitor (ARPI) enzalutamide, with/without concurrent ADT, for patients with 'high-risk' biochemical recurrence following previous radical treatment, defined in EMBARK as a PSA doubling time of ≤ 9 months and a PSA ≥ 1 ng/ml post radical prostatectomy and $\geq$ nadir +2 ng/ml post radiation therapy, respectively [30]. These results are likely to inform a 'standard care' treatment arm within a future phase III trial of salvage therapies for locally recurrent prostate cancer, but this does also present a valuable opportunity to understand the additional benefit that local disease control might provide [31].

Future studies of salvage therapies, including reirradiation, therefore, need to clearly consider which patients are

most likely to benefit from salvage treatment and who needs additional systemic anticancer therapies such as ADT and ARPI therapies. Given the strong influence of patient preference for specific treatments in RO-PIP, it is crucial that patients are fully involved in the design of these studies, to ensure that their perspectives can shape the eligibility criteria, randomisation and interventions and the endpoints which are used. An ongoing National Institute for Health and Care Research Programme Development Grant (NIHR206942) at Leeds Cancer Centre in the UK has a focus on Public and Patient Involvement and Engagement to shape future clinical trials in reirradiation. Patients treated with reirradiation for locally recurrent prostate cancer are included in this work and their perspectives regarding the potential benefits and harms of treatment will be invaluable when considering future studies.

Conclusion

Recruitment to a randomised study of BT or SBRT for treatment of locally recurrent prostate cancer did not appear feasible. A major barrier to participation was patient preference for a specific treatment. Future studies should be designed to allow patient, clinician, and/or centre preference for reirradiation options (either BT or SBRT), which could then be compared to the standard of care.

Funding Statement:

The RO-PIP study translational work is part funded by a Leeds Hospitals Charity grant (award number A2002239).

Author contributions1.

Jim Zhong, Finbar Slevin, and Ann Henry contributed as guarantor of integrity of the entire study.2.

Jim Zhong, Finbar Slevin, Ann Henry, Sarah Brown, Ananya Choudhury, and Peter Hoskin contributed to study concepts and design.3.

All authors contributed to literature research.4.

All authors contributed to clinical studies.5.

Jim Zhong, Finbar Slevin, and Ann Henry contributed to experimental studies/data analysis.6.

Sarah Brown, Jim Zhong, Finbar Slevin, and Ann Henry contributed to statistical analysis.7.

All authors contributed to manuscript preparation.8.

All authors contributed to manuscript editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jim Zhong reports a relationship with Cancer Research UK that includes funding grants.

Ann Henry, Sarah Brown, Ananya Choudhury, Peter Hoskin, and Andrew Scarsbrook reports a relationship with Cancer Research UK that includes funding grants. Finbar Slevin reports a relationship with the National Institute for Health and Care Research that includes funding grants. Given her role as Deputy Editor of Clinical Oncology (AH), she had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor. Given his role as Junior Assistant Editor of Clinical Oncology (FS), he had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Research data are stored in an institutional repository and will be shared upon reasonable request to the RO-PIP Trial Management Group after the final trial results are published.

Acknowledgements

CT would like to acknowledge Cancer Research UK funding for the Leeds Radiotherapy Research Centre of Excellence (RRCOER-Jun24/100004).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clon.2026.104085>.

References

- [1] Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. *Eur Urol* 2020;77(1):38–52.
- [2] International Agency for Research on Cancer, W.H.O. Data visualization tools for exploring the global cancer burden in. 2025], <https://gco.iarc.fr/today/home>.
- [3] Bolla M, Maingon P, Carrie C, Villa S, Kitsios P, Poortmans PMP, et al. Short androgen suppression and radiation dose escalation for intermediate-and high-risk localized prostate cancer: Results of EORTC trial 22991. *J Clin Oncol* 2016;34(15):1748–1756.
- [4] Ma TM, Chu F-I, Sandler H, Feng FY, Efstathiou JA, Jones CU, et al. Local Failure Events in Prostate Cancer Treated with Radiotherapy: A Pooled Analysis of 18 Randomized Trials from the Meta-analysis of Randomized Trials in Cancer of the Prostate Consortium (LEVIATHAN). *Eur Urol* 2022;82(5):487–498.
- [5] Valle LF, Lehrer EJ, Markovic D, Elashoff D, Levin-Epstein R, Karnes RJ, et al. A Systematic Review and Meta-analysis of

- Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). *Eur Urol* 2021;80(3):280–292.
- [6] Zelefsky MJ, Kollmeier M, McBride S, Varghese M, Mychalczak B, Gewanter R, et al. Five-Year Outcomes of a Phase 1 Dose-Escalation Study Using Stereotactic Body Radiosurgery for Patients With Low-Risk and Intermediate-Risk Prostate Cancer. *Int J Radiat Oncology*Biophysics* 2019;104(1):42–49.
 - [7] Zumsteg ZS, Spratt DE, Romesser PB, Pei X, Zhang Z, Kollmeier M, et al. Anatomical Patterns of Recurrence Following Biochemical Relapse in the Dose Escalation Era of External Beam Radiotherapy for Prostate Cancer. *J Urol* 2015;194(6):1624–1630.
 - [8] Kishan AU, Chu FI, King CR, Seiferheld W, Spratt DE, Tran P, et al. Local Failure and Survival After Definitive Radiotherapy for Aggressive Prostate Cancer: An Individual Patient-level Meta-analysis of Six Randomized Trials. *Eur Urol* 2020;77(2):201–208.
 - [9] European Association of Urology. Prostate cancer. 2024], <https://uroweb.org/guidelines/prostate-cancer>.
 - [10] National Comprehensive Cancer Network. NCCN Guidelines Version 4.2024 Prostate Cancer. 2024], https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
 - [11] Corkum MT, Buyyounouski MK, Chang AJ, Chung HT, Chung P, Cox BW, et al. Salvage prostate brachytherapy in radio-recurrent prostate cancer: An international Delphi consensus study. *Radiother Oncol* 2023;184.
 - [12] Jerezek-Fossa BA, Marvaso G, Zaffaroni M, Gugliandolo SG, Zerini D, Corso F, et al. Salvage stereotactic body radiotherapy (SBRT) for intraprostatic relapse after prostate cancer radiotherapy: An ESTRO ACROP Delphi consensus. *Cancer Treat Rev* 2021;98:102206.
 - [13] Zhong J, Slevin F, Scarsbrook AF, Serra M, Choudhury A, Hoskin PJ, et al. Salvage Reirradiation Options for Locally Recurrent Prostate Cancer: A Systematic Review. *Front Oncol* 2021;11:681448.
 - [14] Zhong J, Brown S, Serra M, Shuttleworth P, Bownes P, Thompson C, et al. Reirradiation Options for Previously Irradiated Prostate cancer (RO-PIP): Feasibility study investigating toxicity outcomes following reirradiation with stereotactic body radiotherapy (SBRT) versus high-dose-rate brachytherapy (HDR-BT). *BMJ Open* 2022;12(11):e068580.
 - [15] Abusaris H, Hoogeman M, Nuytens JJ. Re-irradiation: outcome, cumulative dose and toxicity in patients retreated with stereotactic radiotherapy in the abdominal or pelvic region. *Technol Cancer Res Treat* 2012;11(6):591–597.
 - [16] National Institute for Health and Care Research. Guidance on applying for feasibility studies. 2025], <https://www.nihr.ac.uk/guidance-applying-feasibility-studies>.
 - [17] Bergamin S, Eade T, Kneebone A, Booth J, Hsiao E, Schembri GP, et al. Interim Results of a Prospective Prostate-Specific Membrane Antigen-Directed Focal Stereotactic Reirradiation Trial for Locally Recurrent Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2020;108(5):1172–1178.
 - [18] Chitmanee P, Tsang Y, Tharmalingam H, Hamada M, Alonzi R, Ostler P, et al. Single-Dose Focal Salvage High Dose Rate Brachytherapy for Locally Recurrent Prostate Cancer. *Clin Oncol* 2020;32(4):259–265.
 - [19] Corkum MT, Morton G, Loblaw DA, Tseng CL, Murgic J, Ravi A, et al. A Prospective Study of Magnetic Resonance Imaging-guided Focal Salvage High-dose-Rate Brachytherapy for Radiorecurrent Prostate Cancer: Updated Results of 30 Patients. *Pract Radiat Oncol* 2022;12(6):e531–e537.
 - [20] Crook J, Rodgers JP, Pisansky TM, Trabulsi EJ, Amin MB, Bice W, et al. Salvage Low-Dose-Rate Prostate Brachytherapy: Clinical Outcomes of a Phase 2 Trial for Local Recurrence after External Beam Radiation Therapy (NRG Oncology/RTOG 0526). *Int J Radiat Oncol Biol Phys* 2022;112(5):1115–1122.
 - [21] Fuller D, Wurzer J, Shirazi R, Bridge S, Law J, Crabtree T, et al. Retreatment for Local Recurrence of Prostatic Carcinoma After Prior Therapeutic Irradiation: Efficacy and Toxicity of HDR-Like SBRT. *Int J Radiat Oncology*Biophysics* 2020;106(2):291–299.
 - [22] Maenhout M, Peters M, van Vulpen M, Moerland MA, Meijer RP, van den Bosch M, et al. Focal MRI-Guided Salvage High-Dose-Rate Brachytherapy in Patients With Radio-recurrent Prostate Cancer. *Technol Cancer Res Treat* 2017;16(6):1194–1201.
 - [23] Murgic J, Morton G, Loblaw A, D'Alimonte L, Ravi A, Wronski M, et al. Focal Salvage High Dose-Rate Brachytherapy for Locally Recurrent Prostate Cancer After Primary Radiation Therapy Failure: Results From a Prospective Clinical Trial. *Int J Radiat Oncol Biol Phys* 2018;102(3):561–567.
 - [24] Yamada Y, Kollmeier MA, Pei X, Kan CC, Cohen GN, Donat SM, et al. A Phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. *Brachytherapy* 2014;13(2):111–116.
 - [25] Pasquier D, Lacornerie T, Supiot S, Pommier P, Quivrin M, Simon JM, et al. The Safety and Efficacy of Salvage Stereotactic Radiation Therapy in Patients with Intraprostatic Tumor Recurrence After Previous External Radiation Therapy: Phase 1 Results from the GETUG-AFU 31 Study. *Eur Urol Oncol* 2023;6(4):399–405.
 - [26] Pasquier D, Le Deley M-C, Tresch E, Cormier L, Duterque M, Nenau S, et al. GETUG-AFU 31: a phase I/II multicentre study evaluating the safety and efficacy of salvage stereotactic radiation in patients with intraprostatic tumour recurrence after external radiation therapy—study protocol. *BMJ Open* 2019;9(8):e026666.
 - [27] Falagarino UG, Abbadi A, Remmers S, Björnebo L, Bogdanovic D, Martini A, et al. Biochemical Recurrence and Risk of Mortality Following Radiotherapy or Radical Prostatectomy. *JAMA Netw Open* 2023;6(9):e2332900.
 - [28] Van den Broeck T, van den Bergh RCN, Arfi N, Gross T, Moris L, Briers E, et al. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. *Eur Urol* 2019;75(6):967–987.
 - [29] Mazzone E, Thomson A, Chen DC, Cannoletta D, Quarta L, Pellegrino A, et al. The Role of Prostate-specific Membrane Antigen Positron Emission Tomography for Assessment of Local Recurrence and Distant Metastases in Patients with Biochemical Recurrence of Prostate Cancer After Definitive Treatment: A Systematic Review and Meta-analysis. *Eur Urol* 2025 Aug;88(2):129–141.
 - [30] Freedland SJ, Luz MdA, Giorgi UD, Gleave M, Gotto GT, Pieczonka CM, et al. Improved Outcomes with Enzalutamide in Biochemically Recurrent Prostate Cancer. *New Engl J Med* 2023;389(16):1453–1465.
 - [31] Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet* 2018;392(10162):2353–2366.