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Original Article

The Dedicated Imaging Post-Prostatectomy for Enhanced Radiotherapy outcomes (DIPPER) trial protocol: a multicentre, randomised trial of salvage radiotherapy versus surveillance for low-risk biochemical recurrence after radical prostatectomy

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Background

Salvage radiation therapy (SRT) and surveillance for low-risk prostate-specific antigen (PSA) recurrence have competing risks and benefits. The efficacy of early SRT to the prostate bed with or without pelvic lymph nodes compared to surveillance in patients with PSA recurrence after radical prostatectomy and no identifiable recurrent disease evident on prostate specific membrane antigen-positron emission tomography/computer tomography (PSMA-PET/CT) is unknown.

Study Design

The Dedicated Imaging Post-Prostatectomy for Enhanced Radiotherapy outcomes (DIPPER) is an open-label, multicentre, randomised Phase II trial.

Endpoints

The primary endpoint is 3-year event-free survival, with events comprising one of PSA recurrence (PSA ≥0.2 ng/mL higher than baseline), radiological evidence of metastatic disease, or initiation of systemic or other salvage treatments. Secondary endpoints include patient-reported outcomes, treatment patterns, participant perceptions, and cost-effectiveness.

Eligibility Criteria

Eligible participants have PSA recurrence of prostate cancer after radical prostatectomy, defined by serum PSA level of 0.2–0.5 ng/mL, deemed low risk according to modified European Association of Urology biochemical recurrence risk criteria (International Society for Urological Pathology Grade Group ≤2, PSA doubling time >12 months), with no definite/probable recurrent prostate cancer on PSMA-PET/CT.

Patients and Methods

A total of 100 participants will be recruited from five Australian centres and randomised 1:1 to SRT or surveillance. Participants will undergo 6-monthly clinical evaluation for up to 36 months. Androgen-deprivation therapy is not permissible. Enrolment commenced May 2023.

Trial Registration

This trial has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN: ACTRN12622001478707).

Keywords

prostate neoplasm, radiotherapy, positron emission tomography-computed tomography, patient-reported outcome measures, prostate-specific antigen, clinical trial protocol, radical prostatectomy

Background

Around 30% of individuals with prostate cancer experience PSA recurrence after radical prostatectomy (RP), manifesting as a rise in serum PSA during follow-up [1]. Whereas adjuvant radiotherapy (RT) was historically administered after RP to reduce progression and potentially prolong survival, salvage RT (SRT) to the prostate bed with or without androgen-deprivation therapy (ADT) in the event of PSA recurrence has recently gained favour due to similar survival [2], lower toxicity, and importantly reduces unnecessary treatment [3].

However, controversy persists as to whether postoperative RT after RP is beneficial for all individuals, and if de-intensification is possible. Whilst SRT offers excellent biochemical control and local recurrence-free survival at the expense of short- and long-term toxicity [1,4–6], the impact of SRT on metastasis-free (MFS) and overall survival (OS) remains unclear [1,2,7]. Conversely, de-intensification to surveillance, consisting of regular clinical review and PSA testing, is a practiced alternative to SRT. Similar to 'active surveillance' for localised prostate cancer, surveillance permits avoidance of potentially unnecessary treatment and toxicity in up to one third of patients with PSA recurrence, in whom no further PSA progression is observed and who ultimately, enjoy equivalent survival to those who receive SRT [8]. To guide patient selection for SRT or surveillance, there is increasing interest in developing risk-stratification models [6,9].

The European Association of Urology (EAU) Guideline panel [6] has recommended stratification of patients with PSA recurrence into low- and high-risk groups utilising clinicopathological factors such as pathological Gleason Score or International Society for Urological Pathology (ISUP) Grade Group (GG), and post-RP PSA doubling time (PSA-DT):

- Low risk: PSA-DT >1 year AND pathological Gleason Score <8 (OR ISUP GG <4)
- High risk: PSA-DT ≤1 year OR pathological Gleason Score 8–10 (OR ISUP GG 4–5)

Using these definitions, a validation cohort of 1040 individuals with PSA recurrence after RP demonstrated a 5-year MFS of 99.7% (95% CI 99.0–100%) and 86.7% (95% CI 83.4–90.1%) in EAU low- and high-risk cohorts, respectively [10], supporting the stratification. Whilst ~50% of individuals in either cohort received SRT (D. Tilki, personal communication, 2019), the timing of SRT, either 'early' at detection of PSA recurrence, or 'late' following biochemical persistence/progression, did not confer a statistically significant difference in MFS or cancer-specific survival, further emphasising the uncertainty regarding optimal management of this condition.

Prostate-specific membrane antigen-positron emission tomography (PSMA-PET)/CT may improve risk stratification and is increasingly used in the evaluation of prostate cancer across the disease spectrum due to detection of additional metastases and change in management [1,7]. It has recently been publicly subsidised in Australia as a standard-of-care investigation following PSA recurrence/persistence after RP or definitive RT [11]. Notably, PSMA-PET/CT detects a higher rate of metastases in patients with EAU high-risk disease than low-risk disease [12,13] and ligand uptake is associated with prognostic factors including PSA, ISUP GG and PSA-DT in the setting of PSA recurrence [14]. Preliminary data evaluating the relationship between PSMA-PET/CT characteristics and SRT outcomes support the assertion that low or absent ligand expression is associated with enhanced favourable biology and clinical outcomes [15,16], representing a truly low-risk cohort of patients in whom surveillance may be preferable.

Comparative data between SRT and surveillance since PSMA-PET/CT has been adopted into clinical practice are sparse. Thus, observational data and anecdotal experience have already influenced clinical practice, with surveillance being

exercised by clinicians in 32–46% of cases of PSA recurrence where PSMA-PET/CT does not show discernible prostate cancer [8,17]. In one study of individuals entering surveillance after PSA recurrence, 34% did not experience PSA progression during a median of 3.2 years of follow-up [8]. In a subgroup analysis of this study, SRT did improve event-free survival (EFS) over surveillance in both EAU low- (hazard ratio [HR] 0.18, $P = 0.04$) and high-risk (HR 0.3, $P = 0.23$) groups when PSMA-PET/CT showed no active disease, or only locally recurrent prostate cancer [18]. However, among individuals who underwent surveillance, neither EAU risk group (HR 1.42, 95% CI 0.55–3.69; $P = 0.73$) or PSMA-PET/CT findings (HR 1.28, 95%CI 0.45–3.63; $P = 0.47$) predicted EFS [18]. Importantly, surveillance permits nuanced treatment recommendations with further PSA progression recurrence depending on pattern of spread according to PSMA-PET/CT, where recurrence may occur outside radiation fields (in up to 50% who recur after surveillance) and SRT and RT-related toxicity can therefore be avoided.

Trial Feasibility

To assess more widely whether equipoise was present, we distributed an on-line survey to prostate cancer clinicians, consisting of primarily urologists and radiation oncologists [19]. We received 53 responses (58% urology, 40% radiation oncology) of diverse practice experience (median [range] 15 [8–22] years). In all, 81% of those surveyed were supportive of 'de-intensification' as a concept for management of PSA recurrence following RP. Also, 83% (44/53) of respondents reported they would be comfortable to randomise to surveillance or SRT in those with a negative PSMA-PET/CT on a clinical trial. Furthermore, whilst urologists were mixed in their opinions regarding systemic therapy, they were generally not supportive of ADT use after PSA recurrence. Some radiation oncologists expressed a preference to use ADT whenever giving SRT, a recommendation that was strengthened when PSMA-PET/CT demonstrated metastases, whilst others felt systemic therapy in this low-risk population was over-treatment.

Therefore, current practice suggests both SRT and surveillance can be considered appropriate standards of care and equipoise is evident [19]. Whilst SRT offers enhanced local control and higher cure or remission rates to limit follow-up intensity, enhanced survival outcomes have not been consistently observed (despite higher level evidence) and there is potential for significant morbidity. Conversely, surveillance may be safe in low-risk patients who opt for delayed treatment and may limit morbidity, thus resulting in surveillance being commonly practiced. This equipoise underpins the design of the Dedicated Imaging Post-Prostatectomy for Enhanced Radiotherapy outcomes (DIPPER) clinical trial.

Patient-Reported Outcomes

Patient-reported outcomes (PROs) are recognised as key outcome measures in clinical trials, including in prostate cancer. In prior studies, SRT resulted in significantly poorer recovery of urinary, bowel, and erectile function when evaluated using the European Organisation for Research and Treatment Quality-of-Life Questionnaire-Cancer 30 (EORTC QLQ-C30) [20]. Additionally, fear of cancer recurrence is also reported among patients in follow-up following RP, with higher scores observed for younger individuals and those who received adjuvant RT [21]. PROs are important in the comparison of SRT and surveillance for patients experiencing PSA recurrence, particularly with respect to potential differences on impacts such as fear of recurrence and avoidance of RT-related toxicities.

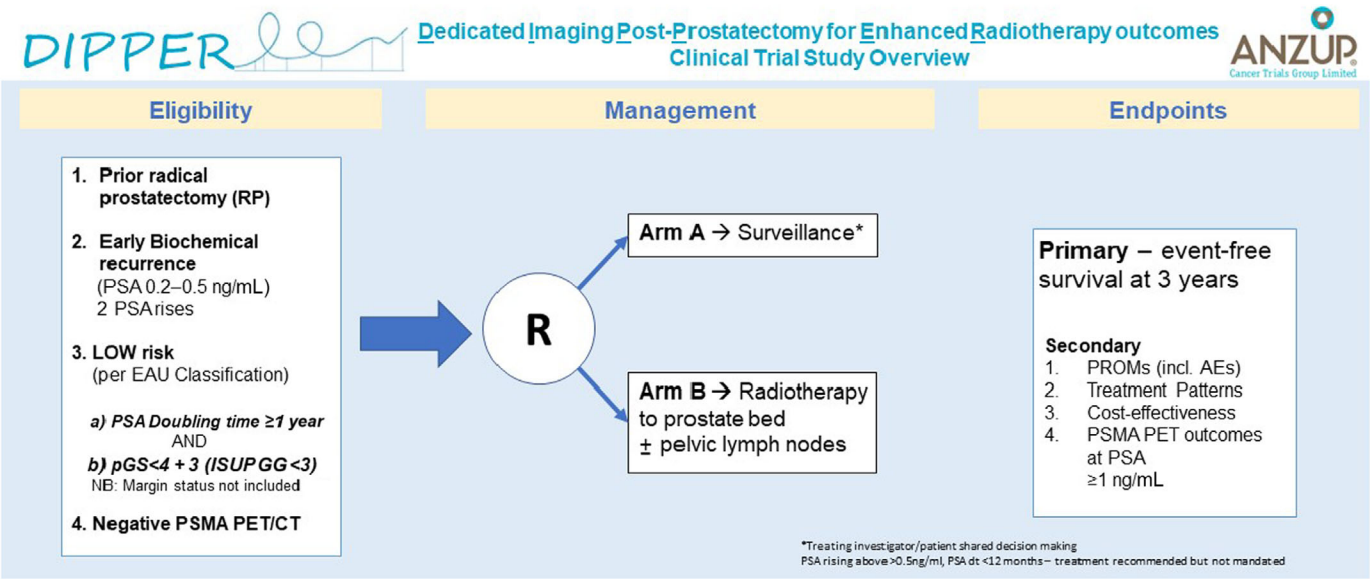
Study Design

The DIPPER is an open-label, multicentre, randomised Phase II trial, designed to determine the effectiveness of early SRT compared to surveillance in individuals with early PSA recurrence after RP, who have low-risk features according to the modified EAU Guidelines criteria and no evidence of recurrence according to PSMA-PET/CT. Eligible participants will be randomised in a 1:1 ratio to surveillance (Arm A) or SRT to the prostate bed with or without pelvic lymph node RT (PLNRT) (Arm B; Fig. 1).

The trial was designed by the authors, in conjunction with the Sponsor, the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP). Funding has been sourced from the ANZUP Discretionary Funding Initiative, ANZUP Below the Belt Research Fund, and Mundipharma Pty. Ltd. (Sydney, NSW, Australia), as well as salary funding for the principal investigator (M.J.R.) from Metro North Health. The trial was first registered with the Australian Clinical Trials Registry (ACTRN12622001478707) on 24 November 2022. Central ethical approval was obtained from St Vincent's Human Research Ethics Committee (HREC 2022/ETH01222) in 2022. Local ethical and governance approval has been or will be obtained for five participating sites. The study is being conducted in accordance with the Declaration of Helsinki, the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research 2007 and the NHMRC Australian Code for Responsible Conduct of Research. All participants will provide written informed consent.

The primary objective of the study is to determine the efficacy of early SRT to the prostate bed with or without PLNRT compared to surveillance in people who have experienced PSA recurrence following RP and have no definite or probable recurrent prostate cancer evident on PSMA-PET/CT.

Fig. 1 DIPPER study schema.



Endpoints

The primary endpoint is the 3-year EFS, where an 'event' is defined by the following composite outcome (Table 1):

1. PSA recurrence defined as serum PSA ≥0.2 ng/mL higher than the baseline (including post-SRT nadir) followed by any other rise at least 14 days apart; or,
2. Metastatic disease on either PSMA-PET/CT, CT, or bone scan (if CT or bone scan, needs to be confirmed on another modality); or,
3. Initiation of systemic treatments (ADT or other) or additional salvage therapies (e.g., stereotactic body RT) per participant/clinician preference.

The secondary objectives and endpoints (Table 1) are to determine:

- Differences in PROs between treatment arms,
- Treatment patterns, specifically use of PLNRT in a low-risk population; and,
- The cost-effectiveness of SRT compared with surveillance in patients with rising PSA after RP, expressed as the cost per quality-adjusted life years (QALYs).

A future exploratory analysis of clinical and imaging characteristics utilising archival histopathological specimens and molecular analyses will be considered.

Table 1 Study endpoints.

Primary endpoint
1. 3-year EFS defined by at least one of the following composite outcomes:
a. PSA recurrence defined as serum PSA ≥ 0.2 ng/mL higher than the baseline (including post-SRT nadir) followed by any other rise at least 14 days apart; OR
b. Metastatic disease on either PSMA-PET/CT, CT or bone scan (if CT or bone scan, needs to be confirmed on another modality); OR
c. Initiation of systemic treatments (ADT or other) or additional salvage therapies (e.g., stereotactic body RT) per patient/clinician preference
Secondary endpoints
1. Patient-reported outcome measures (PROMs)
a. Quality of life—EORTC QLQ-C30 and EORTC QLQ-PR25
b. Fear of cancer recurrence—FCRI-SF
2. Treatment patterns
a. Use of PLNRT in low-risk population
3. Participant perceptions
a. Expectations according to the ETS
b. Preference for treatment pathway
4. The cost-effectiveness of SRT compared with surveillance in patients with rising PSA after RP, expressed as the cost per QALYs

Eligibility Criteria

The target population for the DIPPER trial is adults with prostate adenocarcinoma who experience PSA recurrence after RP, who are considered low risk using the modified EAU Guidelines criteria and in whom there is no evidence of locally recurrent or distant metastatic disease according to PSMA-PET/CT. Prospective participants will be screened for eligibility according to the inclusion and exclusion criteria outlined in Table 2.

Methods

After providing informed consent, all eligible participants will be randomised, via a secure centralised system assigning participants in a 1:1 ratio to surveillance (Arm A) or RT (Arm B). Randomisation will be stratified by recruiting site

Table 2 Eligibility criteria.

Inclusion criteria	Exclusion criteria
1. Individuals aged ≥18 years, with pathological diagnosis of adenocarcinoma of the prostate previously treated with RP 2. Post-RP PSA recurrence (PSA 0.2–0.5 ng/mL) with two documented consecutive PSA rises taken at least 14 days apart 3. Low-risk features according to modified EAU Guidelines criteria (Gleason score ≤3 + 4 or ISUP GG ≤2 AND PSA-DT >12 months) 4. No evidence of locally recurrent or metastatic disease according to PSMA-PET/CT scan (or in event of equivocal report, the Principal Investigator considers that there is no evidence of prostate cancer) within 3 months of randomisation 5. Willing to complete PROMs and cost-effectiveness questionnaires (unless is unable to complete because of literacy or limited vision) 6. ECOG performance status 0–1 7. Estimated life expectancy >7 years 8. Willing and able to comply with all study requirements, including treatments such as SRT, and available for follow-up 9. Has provided signed, written informed consent to participate	1. Prior PSMA-PET/CT scan for investigation of early biochemical recurrence suggestive of local recurrence, regional nodal or distant metastasis 2. Prior pelvic RT that would impact delivery of the protocol RT 3. Contraindications to RT (including active inflammatory bowel disease) 4. Prior or current ADT or systemic therapy for prostate cancer 5. Bilateral orchidectomy 6. Positive regional nodal disease (pN1) at RP 7. Evidence of metastatic disease on any imaging modality 8. History of another malignancy within 5 years prior to randomisation except for those malignancies treated with curative intent with a predicted risk of relapse of <10% including but not limited to cutaneous non-melanoma carcinoma; or adequately treated, non-muscle-invasive urothelial carcinoma of the bladder 9. Concurrent illness, including severe infection that might jeopardise the ability of the participant to undergo the procedures outlined in this protocol with reasonable safety 10. Participation in other clinical trials of investigational agents for the treatment of prostate cancer or other diseases

ECOG, Eastern Cooperative Oncology Group.

using a random combination of permuted blocks of size two and four within each stratum.

Participants randomly assigned to the surveillance group (Arm A) will undergo surveillance with clinical review and PSA evaluation performed every 6 months for up to 36 months or until an event occurs. Additionally, participants will complete PRO questionnaires every 12 months during follow-up. For participants whose PSA progresses to ≥ 0.5 ng/mL and continues to rise (with two consecutive rises recorded at least 14 days apart), clinicians may consider SRT as part of shared decision-making with the participant.

Participants randomly assigned to the RT group (Arm B) will commence SRT to the prostate bed with or without pelvic nodes within 8 weeks of randomisation. The dose delivered to the prostate bed will be 64–70 Gy in 1.8–2 Gy per fraction, according to standard practice, where the prostate bed clinical target volume (CTV) is adapted from the Faculty of Radiation Oncology Genito-Urinary Group (FROGG) consensus guidelines and planning target volume (PTV) is defined by the addition of a 5–10 mm margin to the CTV. PLNRT is optional according to clinician discretion, reflecting variation in clinical practice, and should be delivered using a simultaneous integrated technique to a total dose of 50–56 Gy (or an equivalent dose using an alpha/beta ratio of 1.5 Gy), where applicable. The pelvic nodal CTV should be defined using the NRG Oncology updated international consensus atlas and pelvic nodal PTV defined by adding a 5–8 mm margin to the CTV. Following completion of RT, participants will be evaluated every 6 months (from randomisation), identical to participants assigned to Arm A.

The following concomitant therapies are prohibited in all patients: ADT (including LHRH analogue or antagonists), androgen pathway inhibitors (such as abiraterone or enzalutamide), cytotoxic chemotherapy, immunotherapy including sipuleucel-T and/or continuous use of systemic corticosteroid with a dose equivalent >10 mg prednisolone/prednisone. Commencement of systemic treatments will trigger recording of an event as per the primary outcome definition, and discontinuation of the patient from the trial.

Treatment (or Observation) Discontinuation

Reasons for discontinuation on trial include patient choice, disease progression, unacceptable toxicity, intercurrent illness or other factors that prevent further treatment or compliance with the protocol (including dose constraints for RT).

Assessments

Clinical assessments including serum PSA, will be performed at baseline and every 6 months for patients assigned to both Arm A and Arm B, and will continue for up to 36 months until the primary endpoint or other study discontinuation criteria are met (Table 3). Adverse events, concomitant therapies, and documentation of any additional PSMA-PET/CT will be recorded at each visit.

Patient-Reported Outcomes and Participant Perceptions

The PROs data will be collected from participants in DIPPER at the time of randomisation and during follow-up to evaluate the impacts that surveillance and early SRT have on PROs. The ANZUP Consumer Advisory Panel, which comprises a group of engaged consumer representatives, was involved in the selection of PRO measures (PROMs) and the

Table 3 Schedule of assessments (according to the Standard Protocol Items: Recommendations for Interventional Trials [SPIRIT] statement).

Trial stages	Pre-treatment	Treatment	Follow-up				
Assessment description	**Baseline/ randomisation**	**6 -months post-randomisation**	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**	**Follow-up 4**	**Follow-up 5**
Time since randomisation	**Time = 0**	**+6 months**	**+12 months**	**+18 months**	**+24 months**	**+30 months**	**+36 months**
Visit type	**Clinic/study visit**	**Study visit 1**	**Study visit 2**	**Study visit 3**	**Study visit 4**	**Study visit 5**	**Study visit 6**
Visit window	**within 3 months of PSMA PET/ CT +4 weeks for only questionnaires**	**±4 weeks[‡]**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**	**±4 weeks**
Enrolment							
Eligibility assessment	×						
Informed consent	×						
Reasons for non-participation	×						
Assessments							
Clinic assessment (PSA, adverse events, concomitant therapy, additional PSMA-PET)		×	×	×	×	×	×
RT plan		×[§]					
Patient-specific resource use	×	×					
PRO questionnaires*	×	×	×		×		×
Participant perceptions[†]	×						
Event/exit questionnaire		×[¶]	×[¶]	×[¶]	×[¶]	×[¶]	×[¶]

**Inclusive of EORTC QLQ- C30, EORTC-QLQ-PR25, and the FCRI-SF. [†]Using the ETS and participation perceptions. [‡]For PRO and participant perceptions only. [§]Only for participants assigned to Arm B. [¶]If 'event' endpoint met.*

development of the DIPPER protocol and participant recruitment materials, including the participant information and consent form.

Three commonly used instruments will be used to evaluate PROs in DIPPER: (i) the EORTC QLQ-C30, version 3 [22], is a comprehensive and reliable tool with discriminatory validity evaluating functional domains and symptoms in people with a cancer diagnosis; (ii) the EORTC-QLQ-Prostate Cancer 25 (PR25) [23] evaluates cancer- and treatment-specific symptoms in individuals with a diagnosis of prostate cancer; and (iii) the short-form Fear of Cancer Recurrence Inventory severity subscale (FCRI-SF) evaluates peoples' fear or cancer progression and has demonstrated reliability in this setting [24]. If collection of PROs data is not completed, site staff will be asked to complete the Patient-Reported Outcome Completion and Missing Data (PRO-CoMiDa) Form [25].

Additionally, participant perceptions will be evaluated using the Expectation of Treatment Scale (ETS), which is a five-item scale assessing factors related to expected outcomes of treatment [26].

Resource Use

Healthcare resource use will be assessed for the conduct of SRT (including planning, simulation, delivery of RT, and participant travel for SRT), and treatment of metastases and the use of systemic therapies, where applicable for both arms. Healthcare resource use will be assessed using study specific case report forms based on the completion of scheduled treatments as required. In addition, patient-specific resource to access healthcare, e.g., travel time, will be collected from participants at the first study visit after randomisation. Resource use associated with the complications arising from each study arm will be captured in study specific case report forms to further inform cost-effectiveness.

Statistical Considerations

Based on the Memorial Sloan-Kettering Cancer Centre nomogram using SRT without ADT [27], a 6-year progression-free survival rate utilising conventional imaging of ~70% is expected. With use of PSMA-PET/CT, adjustment for enhanced sensitivity to detect additional 20% distant metastases [8,18], an adjusted 3-year failure-free survival rate for a population receiving SRT (Arm B) is expected to approximate 84–87%. EFS in the surveillance group (Arm A) is expected to be ~60%, based on prior studies (38%) [18] with adjustment for patient selection (ISUP GG 1 and 2 only).

A study with 100 participants provides 90% power to detect a 25% absolute difference (60% in Arm A vs 85% in Arm B) in the proportion of patients with 3-year EFS between the surveillance and SRT groups, respectively. This calculation is based on a log-rank test of time to event with a two-sided alpha of 5% and allows for 10% loss to follow-up over 3 years.

Analysis Plan

Demographic information and baseline clinical characteristics (including baseline PSA) will be summarised descriptively

using minimum, maximum, median, interquartile range, mean and standard deviation for quantitative variables, where applicable. Categorical variables will be described in tabular form.

Point estimates for EFS will be estimated using the Kaplan–Meier method and log-rank test comparing survival times between study arms at key timepoints, including 3 years, using an intention-to-treat analysis. A secondary analysis of EFS on a per-protocol basis will also be performed. Sensitivity analyses for EFS adjusting for prognostic factors will be conducted using Cox regression. The primary analysis dataset will be locked once the final participant registered has completed 3 years of follow-up. A formal statistical analysis plan will be developed and submitted to a public archive prior to dataset lock and biostatistician unblinding.

Secondary PROs will be analysed using hierarchical linear models with site as a random effect. The secondary treatment pattern outcome of use of PLNRT in a low-risk population will be analysed using a log-binomial or logistic hierarchical model with a random effect at site level. The ETS and treatment pathway preference question will also be summarised descriptively. Analyses will be based on complete case records but the implementation of multiple imputation of missing values will be considered according to the proportion and patterns of missingness.

A prospectively defined cost-effectiveness analysis will also be conducted to assess the cost per QALY for SRT compared with surveillance in individuals with EAU low-risk PSA recurrence and no discernible prostate cancer on PSMA-PET/CT. Costs included in the analysis will focus on those for the conduct of SRT (including planning, simulation, delivery of RT, and participant travel for SRT), and treatment of metastases and the use of systemic therapies, where applicable for both arms. Healthcare service use will be valued based on publicly available sources, such as those published through the Medicare Benefits Schedule (MBS) for publicly funded services in Australia. Resource use associated with the complications arising from each study arm will be captured in study specific case report forms to further inform cost-effectiveness.

For the purposes of the economic evaluation, responses from the EORTC QLQ-C30 will be expressed as quality-of-life weights in order to estimate QALYs using the EORTC Quality of Life Utility Measure-Core 10 dimensions (QLU-C10D) algorithm [28]. This will adjust the time observed on trial in varying health states, e.g., time free from progression, by the corresponding quality of life weights for those health states to estimate the mean QALYs associated with the two treatment arms. The incremental cost-effectiveness ratio (ICER) will be expressed as the cost per QALY. Analyses will be subject to deterministic and probabilistic sensitivity analyses as a means of investigating the robustness of the ICER estimates, with a nominated threshold of AU$50000 per QALY.

Results

The study was opened to enrolment in May 2023.

Discussion

The latest randomised evidence is supportive of early SRT as an alternative to adjuvant RT for management of PSA recurrence and has stimulated appetite for safe treatment avoidance, whilst maintaining oncological control and reducing morbidity. The EAU guidelines have offered valuable prognostic information to help guide decision-making for patients experiencing PSA recurrence [1]. However, inaccurate prediction of oncological outcomes based on clinical variables, and limited prospective data on oncological outcomes informed by PSMA-PET/CT produces considerable uncertainty in the optimal management of PSA recurrence. As PSMA-PET/CT emerges as a routine component of clinical care for patients with PSA recurrence [12,13], combination with clinical variables may permit identification of a truly low-risk population who will derive the least potential oncological benefit from SRT, specifically those with no metastases on PSMA-PET/CT and of low EAU risk.

Whilst SRT treatment offers valuable local control for some individuals [8,10], a lack of consistent MFS and OS benefits [1,2,7] coupled with increasing evidence relating to potential morbidity and deleterious impacts on PROs [20] has seen a trend away from early SRT in favour of observation, both in practice and in consensus guidelines [29]. Additionally, there is uncertainty regarding the additive value of PLNRT in addition to prostate bed RT [30,31], with variability in uptake and use of concomitant ADT [7]. The benefit of ADT alongside SRT is unclear, with decision-making strongly influenced by likelihood of systemic disease (indicated by PSA-DT and pathological Gleason Score) as well as patient anxiety and risk of short- and long-term treatment-related morbidity [29]. Regardless, the addition of either (or both) treatments to prostate bed SRT is likely to raise potential morbidity and negatively impact PROs, making a prospective trial of treatment de-intensification in patients with low-risk PSA recurrence even more important.

Whilst trials are underway to assess whether randomisation to PSMA-PET/CT-informed decision making improves oncological outcomes [32], widespread use of PSMA-PET/CT in Australia following public subsidisation of the instrument for this indication and other countries, means these studies are not feasible as the technology is already part of routine clinical care. Therefore, leveraging the EAU risk stratification and incorporating routine PSMA-PET/CT imaging in the face of clinical equipoise for low-risk PSA recurrence, the DIPPER

clinical trial will help establish the efficacy of SRT and surveillance in patients with low-risk PSA recurrence following RP. We hypothesise that the 3-year EFS will be higher in eligible participants assigned to SRT than those receiving surveillance; however, an important proportion of individuals assigned to surveillance will not have an 'event' during follow-up and difference in PROMs and QALYs are likely to favour surveillance in this selected population.

The DIPPER trial commenced in May 2023 and aims to complete recruitment within 2 years. The data derived from the trial will contribute valuable information to the field.

Conclusion

The DIPPER trial will provide the first prospective evidence relating to oncological outcomes between SRT and surveillance in EAU low-risk PSA recurrence following RP utilising contemporary imaging techniques. We anticipate the results will inform larger trials and provide clinicians and patients with meaningful and holistic information to help guide management of early PSA recurrence.

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Disclosure of Interests

None declared.

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Abbreviations: ADT, androgen deprivation therapy; ANZUP, Australian and New Zealand Urogenital and Prostate Cancer Trials Group; CTV, clinical target volume; DIPPER, Dedicated Imaging Post-Prostatectomy for Enhanced Radiotherapy outcomes; EAU, European Association of Urology; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EORTC QLQ-(C30)(PR25), European Organisation for Research and Treatment Quality-of-Life Questionnaire-(Cancer 30) (Prostate Cancer 25); ETS, Expectation of Treatment scale; FCRI-SF, short-form Fear of Cancer Recurrence Inventory severity subscale; GG, Grade Group; HR, hazard ratio; ISUP, International Society of Urological Pathology; ICER, incremental cost-effectiveness ratio; MFS, metastasis-free survival; NHMRC, National Health and Medical Research Council; OS, overall survival; PRO(Ms), patient-reported outcome (measures); PSA-DT, PSA doubling time; PSMA-PET, prostate specific membrane antigen-positron emission tomography; PTV, planning target volume; QALYs, quality-adjusted life years; RP, radical prostatectomy; (PLN)(S)RT, (pelvic lymph node) (salvage) radiotherapy.