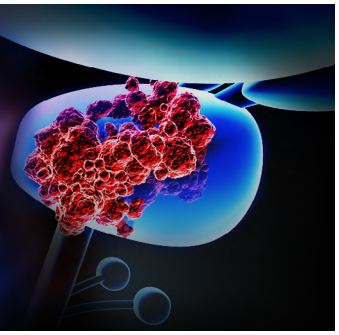
Prostate Cancer Research Review™



Making Education Easy

Issue 93 - 2026

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **ARPI** = androgen receptor pathway inhibitor; **BCR** = biochemical recurrence; **CI** = confidence interval; **HR** = hazard ratio; **HRR** = homologous recombination repair; **IHC** = immunohistochemistry; **mCSPC** = metastatic castration-sensitive prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer; **mpMRI** = multiparametric magnetic resonance imaging; **MRI** = magnetic resonance imaging; **OS** = overall survival; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **PTEN** = phosphatase and tensin homolog; **RCT** = randomised controlled trial; **rPFS** = radiographic progression-free survival; **RT** = radiotherapy; **SRT** = salvage radiotherapy.

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Welcome to Issue 93 of Prostate Cancer Research Review.

A Dutch study has investigated clinical parameters for the prediction of risk of biochemical recurrence in men with an undetectable PSA after surgery, creating a risk-adapted surveillance protocol that may reduce the number of unnecessary PSA tests, particularly in low-risk patients. In the AMPLITUDE trial, the combination of niraparib plus abiraterone acetate and prednisone significantly improved rPFS in patients with mCSPC harbouring *BRCA1*/*BRCA2* or other HRR gene alterations. We conclude this issue with a study investigating the use of early docetaxel and enzalutamide for metastatic hormone-sensitive prostate cancer.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Professor Niall Corcoran
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Risk-based prostate-specific antigen monitoring reduces follow-up burden after radical prostatectomy

Authors: Paulino Pereira LJ et al.

Summary: This nationwide study using data from the Netherlands Cancer Registry on 1043 men who had undergone radical prostatectomy between 2015 and 2016 for localised prostate cancer and who had undetectable PSA levels <6 weeks post surgery, investigated the use of an optimised, risk-adapted PSA monitoring schedule for the first 5 years. The schedule aimed to stratify patients into biochemical recurrence (BCR; PSA ≥0.1 ng/mL)-based risk groups, to reduce unnecessary PSA testing without compromising BCR detection rates. The average risk of BCR per PSA follow-up consultation outlined in the current European Association of Urology (EAU) schedule was used as a threshold to determine consultations needed. PSA at diagnosis, pT stage, pN stage, pathological International Society of Urological Pathology grade group, and positive surgical margins were identified as significant predictors for BCR. Based on HRs, risk stratification identified 43% low-risk (15% BCR), 42% intermediate-risk (36% BCR), and 15% high-risk (72% BCR) patients. Overall, the 5-year BCR-free survival rate was 62% (95% CI 58-66). Compared with the EAU schedule, risk stratification reduced consultations by 18% over the first 5 years, with 3% delayed BCR detection; low-risk patients required four, intermediate-risk patients required eight, and high-risk patients required 10 consultations in the revised schedule over this period.

Comment: Surveillance for BCR post prostatectomy is a significant burden in the resource restrained environment of the typical public hospital, particularly for patients at lower risk of recurrence. This study from the Dutch cancer registry investigated clinical parameters that predicted the risk of BCR in men with an undetectable PSA post surgery, creating a risk-adapted surveillance protocol. Men at low risk of recurrence (43% of the cohort) needed only four surveillance visits to detect BCR without a significant delay in diagnosis, a significant reduction compared to eight consultations recommended by the EAU. Surveillance for intermediate-risk patients was unchanged, whereas the authors propose an increase in surveillance for those at higher risk. Ultimately, the potential resource saving depends on the risk profile of patients being operated on, which in contemporary series may not include very many low-risk patients.

Reference: Eur Urol Oncol. 2025;8(5):1278-1285
Abstract

Prostate Cancer Research Review™

Independent commentary by Professor Niall Corcoran

Professor Niall Corcoran is a urological surgeon and translational scientist based in Melbourne. He is Head of the Urology Unit at Western Health and a visiting surgeon at Royal Melbourne and Frankston Hospitals. His group in the University of Melbourne Centre for Cancer Research investigates molecular drivers of prostate cancer metastases and treatment resistance.

Niraparib and abiraterone acetate plus prednisone for HRR-deficient metastatic castration-sensitive prostate cancer: A randomized phase 3 trial

Authors: Attard G et al.

Summary: In the phase III, double blind AMPLITUDE trial the utility of adding the poly (ADP-ribose) polymerase (PARP) inhibitor niraparib to abiraterone acetate and prednisone (AAP) in patients with mCSPC with homologous recombination repair (HRR) gene alterations was investigated. Patients (mean age 68 years; 56% had *BRCA1* or *BRCA2* alterations; 78% had high-volume metastases; and 16% had received docetaxel) were randomised to receive either niraparib plus AAP (n = 348) or placebo plus AAP (n = 348). Patients had received androgen deprivation therapy (ADT) at least 14 days and no longer than 6 months prior to randomisation and this was continued during study treatment. A significant improvement in radiographic progression-free survival (rPFS; primary endpoint) was seen first in the *BRCA* subgroup (median not reached at the time of analysis for the niraparib plus AAP group versus 26 months for the placebo plus AAP group; HR 0.52; 95% CI 0.37-0.72; p < 0.0001) followed by the intention-to-treat population (HR 0.63; 95% CI 0.49-0.80; p = 0.0001). Overall, grade 3 or 4 adverse events occurred in 75% of niraparib plus AAP recipients and 59% of placebo plus AAP recipients. The most frequent adverse events among niraparib plus AAP recipients were anaemia (29%) and hypertension (27%); 25% of patients required a blood transfusion. Death due to a treatment-emergent adverse event occurred in 14 niraparib plus AAP recipients and seven placebo plus AAP recipients.

Comment: PARP inhibitors (often in combination with an androgen receptor pathway inhibitor [ARPI]) are now well established in the treatment of mCRPC in men harbouring germline or somatic defects in HRR genes, particularly *BRCA2* and *BRCA1*. This phase III trial (AMPLITUDE) investigated the combination earlier in the disease, demonstrating that the PARP inhibitor niraparib in combination with abiraterone improves rPFS (the primary endpoint) compared to placebo plus abiraterone in men with HRR gene defects starting ADT. Time to symptomatic progression also favoured the combination, as did the trend in OS, although these data are currently immature. Grade 3/4 adverse events were more common with the niraparib combination (particularly anaemia requiring blood transfusion, and hypertension), although health-related quality of life was broadly similar in the longer term between the treatment arms. More mature OS data are awaited.

Reference: Nat Med. 2025;31(12):4109-4118
Abstract

A head-to-head comparison of sextant-systematic biopsy vs. extended-systematic biopsy for prostate cancer diagnosis in the era of MRI-targeted biopsy: SEXTANT-PRO non-inferiority randomized clinical trial

Authors: Deng R et al.

Summary: The head-to-head SEXTANT-PRO non-inferiority RCT compared novel combined MRI-targeted biopsy and sextant six-core systematic biopsy (TB + 6SB; n = 254) and classical TB + 12SB (n = 252) via the transperineal cognitive fusion technique for the diagnosis of prostate cancer in 506 biopsy-naïve men with a single suspicious lesion on prostate mpMRI. Baseline characteristics were similar between the two intervention groups. Compared with classical TB + 12SB, TB + 6SB exhibited a non-inferior clinically significant prostate cancer (grade group ≥2) detection rate (54.8% vs 54.3%, respectively); rate difference -0.5% (95% CI -9.2% to 8.3%). Rates of detection were also comparable between the two interventions in prostate cancer, high-grade prostate cancer, and clinically insignificant prostate cancer. A similar concordance in grade group between biopsy and radical prostatectomy whole-mount specimens was seen for both TB + 12SB (52.3%) and TB + 6SB (51.7%), p = 0.25. TB + 6SB was found to optimise procedural workflow efficiency and histopathology resource utilisation while significantly relieving discomfort during the procedure, reducing the post-biopsy pelvic pain, and significantly improving quality of life (p < 0.05).

Comment: Systematic biopsies in addition to targeted cores marginally increase the detection rate of grade group ≥2 cancers compared to targeted cores alone, but at a cost of increased time, resource utilisation and complications. So, if you perform systematic biopsies, how many cores should you take? This Chinese study randomised biopsy-naïve men with a single PIRADS ≥3 lesion on MRI to a targeted transperineal biopsy under local anaesthetic using cognitive-fusion (x3 cores) with either a 6- or 12-core sextant systematic biopsy (1 or 2 cores from each segment). They show fewer systematic biopsies was non-inferior for the detection of any, clinically significant and higher-grade tumours compared to the extended template, but was better tolerated both during the procedure and in the immediate postop period. With the more limited template, the median procedure time was shorter (2.5 minutes!) and cheaper (~30%), important considerations when operating at volume!

Reference: EClinicalMedicine 2025;90:103630
Abstract

Prostate-specific membrane antigen PET-guided intensification of salvage radiotherapy after radical prostatectomy: A phase 2 randomized clinical trial

Authors: Belliveau C et al.

Summary: This phase II RCT evaluated whether intensification of salvage radiotherapy (SRT) guided by PSMA-PET (PSMAiSRT) is associated with improved failure-free survival (FFS) in men with biochemical recurrence following radical prostatectomy. A total of 128 men (median age 71 years; median PSA at enrollment 0.3 ng/mL) received either standard-of-care SRT to the prostate bed, with or without elective pelvic RT, with or without adjuvant hormonal therapy (controls), or PSMA-PET/CT-guided SRT, intensified to detected sites of disease; 52% of PSMAiSRT recipients received intensified SRT, with addition of pelvic RT (25%), metastasis-directed RT (3%), lymph node boost (30%), or prostate bed boost (23%). Both groups had similar rates of adjuvant hormone therapy (controls 86% vs PSMAiSRT recipients 84%). PSMAiSRT improved both FFS and eugonadal FFS at a median of 37 months of follow-up (HRs 0.50; 95% CI 0.27-0.94; p = 0.04 and 0.45; 95% CI 0.21-0.96; p = 0.03, respectively); the greatest benefit was seen in the subgroup with PSA ≥0.3 ng/mL (HR 0.17; 95% CI 0.04-0.79; p = 0.01). Patients in the PSMAiSRT group received fewer next-line treatment events than controls (4 vs 12; HR 0.32; 95% CI 0.11-1.02; p = 0.04). Quality of life and rates of toxic effects did not differ between groups.

Comment: Detection of avid lesions by PSMA-PET in the BCR post prostatectomy setting can change how salvage radiation is delivered, but it is yet unclear if this improves patient outcomes. In this phase II study, patients with BCR were randomised to receive a PSMA-PET scan and subsequent guided salvage radiation intensification (PSMAiSRT) with RT boost to detectable disease, or no PSMA-PET with standard of care salvage radiation (prostate bed +/- elective pelvic lymph nodes +/- ADT at the discretion of the treating radiation oncologist). Patients with a negative PSMA-PET underwent standard-of-care salvage radiation. Radiation was intensified in over half of patients in the PMSAiSRT arm (predominantly to pelvic lymph nodes and avid local recurrences, but also a small number with oligometastses). Patients in the PSMAiSRT arm had a significant improvement in FFS (the primary endpoint) with no increase in toxicity. Still need larger cohorts and more mature data, but good to see the evidence catching up with current Australian practice.

Reference: JAMA Oncol. 2025;11(12):1431-1438
Abstract

Active monitoring, surgery, and radiotherapy for cribriform-positive and cribriform-negative prostate cancer: A secondary analysis of the PROTECT randomized clinical trial

Authors: Sushentsev N et al.

Summary: These authors retrospectively analysed results from the PROTECT RCT to establish the association between cribriform-positive and cribriform-negative prostate cancer and 15-year risk of metastasis (bony, visceral, or lymph node metastases on imaging or PSA >100 ng/mL) among 712 men (mean age 62 years) who underwent active monitoring, surgery, or RT. A total of 93 (13.1%) men had cribriform-positive disease and 42 (5.9%) developed metastasis. Cribriform-positive disease significantly increased the risk of metastasis (HR 3.61; 95% CI 1.60-8.11; p = 0.003) in the intention-to-treat analysis. A significantly reduced risk of metastasis was seen in those who had received RT with neoadjuvant ADT (HR 0.35; 95% CI 0.16-0.78; p = 0.04); 15-year cumulative incidence in patients with cribriform-positive disease, 8%. Compared with active monitoring, surgery delayed metastasis but did not significantly improve long-term outcomes (HR 0.52; 95% CI 0.25-1.08; p = 0.09); 15-year cumulative incidence in patients with cribriform-positive disease, 25% for active monitoring versus 26% for surgery. Results were similar with per-protocol analyses.

Comment: Cribriform growth is characterised by a sieve-like appearance of tumour cell clusters. Although it is classified as Gleason pattern 4 it has a more aggressive natural history than the more commonly found 'poorly formed and fused glands'. This retrospective analysis of patients enrolled in the PROTECT study found that the presence of cribriform growth (for this study defined as cribriform and/or intraductal growth pattern, present in 13% of patients) increased the risk of metastasis over three-fold compared to patients with no cribriform growth. Upfront treatment with RT/ADT resulted in a significant reduction in metastatic events in these patients at 15 years compared to patients initially randomised to active monitoring. In contrast, while surgery delayed the onset of metastatic disease the cumulative incidence was the same at 15 years, suggesting that early ADT is possibly important in suppressing micro metastatic disease at diagnosis. Interestingly patients with non-cribriform Gleason 4 growth patterns and 3+4 disease did not benefit from treatment, reinforcing their eligibility for active surveillance.

Reference: JAMA Oncol. 2025;11(12):1512-1517
Abstract

^{177}Lu-prostate-specific membrane antigen neoadjuvant to stereotactic ablative radiotherapy for oligorecurrent prostate cancer (LUNAR): An open-label, randomized, controlled, phase II study

Authors: Kishan AU et al.

Summary: The single-centre, randomised, open-label, controlled phase II trial LUNAR trial assessed whether the addition of neoadjuvant PSMA-targeting radioligand therapy to stereotactic ablative radiotherapy (SBRT) would improve outcomes for men with oligorecurrent hormone-sensitive prostate cancer. Following stratification by stage (N1/M1a v M1b) and lesion count (1 v 2-3 v 4-5), patients received either SBRT to all lesions or two cycles of ^{177}Lu-PNT2002 (6.8 GBq/cycle, 2 weeks apart) followed by SBRT to all lesions. Analysis, undertaken in 87 evaluable patients (SBRT n = 42 and ^{177}Lu + SBRT n = 45) revealed that at a median follow-up of 22 months, the addition of ^{177}Lu to SBRT significantly improved PFS (17.6 months; 95% CI 15 months to not reached vs 7.4 months; 95% CI 6.0-13.5 months); HR 0.37; 95% CI 0.22-0.61, p < 0.0001. Grade 3 adverse events included lymphopenia in two SBRT recipients and three ^{177}Lu + SBRT recipients.

Comment: Although metastasis-directed therapy can delay progression in oligorecurrent disease, patients eventually develop recurrence usually in out-of-treatment field sites. As this likely represents the presence of undetectable micro-metastatic disease at the time of treatment, there is considerable interest in combining metastasis-directed therapy with systemic therapies to further improve outcomes. This phase II study randomised patients with oligorecurrent disease post prostatectomy or RT to two cycles of neoadjuvant ^{177}Lu-PSMA radioligand therapy followed by SBRT to all PSMA-PET detectable lesions or SBRT alone, stratified by tumour location and lesion count. Combination therapy significantly improved PFS compared to MDT alone, indicating that ^{177}Lu-PSMA radioligand therapy had a therapeutic effect on micrometastatic disease. Results may be even better using an alpha particle and/or auger electron emitter which can target smaller lesions.

Reference: J Clin Oncol. 2025;43(36):3812-3821
Abstract

Metformin active surveillance trial in low-risk prostate cancer

Authors: Fleshner NE et al.

Summary: In the multicenter, randomised, double-blind, placebo-controlled phase III Metformin Active Surveillance Trial (MAST) the utility of metformin, a commonly prescribed antidiabetic agent with demonstrated anti-tumour activity, in delaying the progression of low-risk localised prostate cancer managed with active surveillance was investigated. Participants received either metformin 850 mg twice daily (n = 205) or placebo (n = 203). At 36-months' follow-up, there was no significant difference in rates of therapeutic and/or pathologic progression (70 metformin vs 74 placebo recipients) nor PFS (HR 1.09; 95% CI 0.79-1.52; p = 0.59). There was also no significant difference between groups in negative biopsy rates at 36 months (metformin 41.0% vs 31.1%; p = 0.181). Prespecified subgroup analysis revealed that metformin was associated with increased pathologic progression among obese patients (BMI ≥30; HR 2.36; 95% CI 1.21-4.59; p = 0.0092).

Comment: Metformin is great for diabetes but does nothing for prostate cancer. After two decades of research, thousands of patients and millions of dollars, it's time to stop pushing this rock uphill.

Reference: J Clin Oncol. 2025;43(34):3662-3671
Abstract

Capivasertib plus abiraterone in PTEN-deficient metastatic hormone-sensitive prostate cancer: CAPItello-281 phase III study

Authors: Fizazi K et al.

Summary: The CAPItello-281 study investigated the efficacy of capivasertib versus placebo plus abiraterone, prednisone/prednisolone, and ADT in patients with phosphatase and tensin homolog (PTEN)-deficient mHSPC (diagnostic cut-off: ≥90% viable malignant cells with no specific cytoplasmic PTEN IHC staining). A statistically significant improvement in rPFS (primary endpoint) was observed with capivasertib plus abiraterone (n = 507, median 33.2 months) versus placebo plus abiraterone (n = 505, 25.7 months); HR 0.81; 95% CI 0.66-0.98; p = 0.034. Post hoc rPFS analyses for loss of PTEN cut-offs of ≥95%, ≥99%, and 100% revealed that while the placebo plus abiraterone arm performed progressively worse as the cut-off for the degree of PTEN loss was increased, capivasertib plus abiraterone performed consistently across cut-offs, resulting in a numerically improved treatment effect. Overall, the HR for OS (26.4% maturity) was 0.90 (95% CI 0.71-1.15; p = 0.401). Thirty-six (7.2%) patients died due to an adverse event associated with capivasertib plus abiraterone and 26 (5.2%) due to abiraterone and placebo plus abiraterone. The most common adverse events associated with capivasertib plus abiraterone were diarrhoea (51.9%), hyperglycaemia (38.0%) and rash (35.4%), and these occurred in 8%, 12.9%, and 7.0% of placebo plus abiraterone recipients, respectively.

Comment: Loss of the tumour suppressor PTEN is relatively common in prostate cancer and results in the downstream activation of a number of androgen receptor-independent pathways involved in cell proliferation and resistance to cell death, including PI3K/Akt. This phase III study investigates the efficacy of an oral pan-Akt inhibitor (capivasertib) in combination with abiraterone and ADT in patients with PTEN-deficient (≥90% of malignant cells negative by IHC) de novo mHSPC. Patients randomised to the Akt inhibitor arm had a 7.5-month improvement in rPFS (primary endpoint) compared to the placebo arm, with data on key secondary endpoints including OS still maturing. Encouraging results as patients with PTEN-deficient tumours commonly have a poorer prognosis and a more limited response to ADT/ARPI compared to patients with PTEN intact disease.

Reference: Ann Oncol. 2026;37(1):53-68
Abstract

An online treatment decision aid for men with low-risk prostate cancer eligible for active surveillance and their partners increases the uptake of active surveillance: The Navigate randomised controlled trial

Authors: Schofield P et al.

Summary: This Australian, multicentre, parallel-group, prospective, RCT assessed the impact of an online decision aid (Navigate) on active surveillance uptake, quality of life, and decision-making in 302 patients with low-risk prostate cancer. More men self-reported active surveillance versus another treatment when using Navigate versus usual care (90.6% vs 79.0%; p = 0.008). In addition, Navigate participants reported greater decision-making preparedness (p < 0.001). Partners could also enrol and there was no difference between those allocated to Navigate (n = 70) or usual care (n = 49).

Comment: Navigating treatment choices in localised prostate cancer can be difficult for patients, particularly in lower-risk disease where the prospect of benefit from upfront radical intervention is low. This Australian trial investigated the impact of randomisation to either an online decision aid (Navigate) or the Prostate Cancer Foundation of Australia website (usual care) on uptake of active surveillance, decision satisfaction and quality of life. Patients randomised to Navigate had a higher uptake of active surveillance as an initial management strategy than those receiving usual care as well as a greater degree of decision preparedness. There was no impact on other secondary endpoints including decision regret, anxiety or quality of life, likely due to the high uptake of active surveillance in both arms. Anything that assists patient decision-making in this space is welcome, although it does not appear to be publicly available at the current time.

Reference: Eur Urol Oncol. 2025;8(5):1227-1236
Abstract

Target trial emulation of early docetaxel and enzalutamide for metastatic hormone-sensitive prostate cancer

Authors: Soon YY et al.

Summary: This study used a trial emulation method based on data from the randomised controlled "ENZAlutamide in first line androgen deprivation therapy for METastatic prostate cancer" (ENZAMET) trial in 1125 patients with mHSPC to estimate the effects of adding early docetaxel to enzalutamide. The emulation, based on a pre-randomisation plan to use or not use early docetaxel, compared docetaxel plus enzalutamide, enzalutamide without docetaxel, docetaxel without enzalutamide, and no docetaxel or enzalutamide. Propensity score matching of 987 matched participants (87.7%), found no difference with or without planned use of early docetaxel (HR 1.02; 95% CI 0.92-1.12), with effect modification by enzalutamide use (p = 0.02). In those receiving enzalutamide, OS did not differ with or without planned use of early docetaxel (HR 1.18; 95% CI 0.94-1.49), regardless of disease volume. In those not receiving enzalutamide, OS was longer in those who planned use of early docetaxel (HR 0.90; 95% CI 0.82-0.98), especially in those with high-volume disease (p = 0.006).

Comment: The use of triplet therapy in mHSPC remains somewhat controversial given the lack of RCT data directly comparing docetaxel plus ARPI/ADT vs ARPI/ADT alone. This Australian study used patient level data from the ENZAMET trial to emulate an RCT where 'randomisation' was achieved by propensity score matching clinically relevant baseline characteristics. The headline result is that in patients randomised to receive enzalutamide, planned early docetaxel use did not appear to affect OS irrespective of disease volume, whereas in patients randomised not to receive enzalutamide, docetaxel improved OS in patients with high-volume disease, consistent with the results from CHAARTED. Although these insightful data do not support triplet therapy, at least with enzalutamide use as the ARPI, propensity matching cannot truly mimic randomisation given the potential for unmeasured confounders.

Reference: BJU Int. 2026;137(1):173-180
Abstract