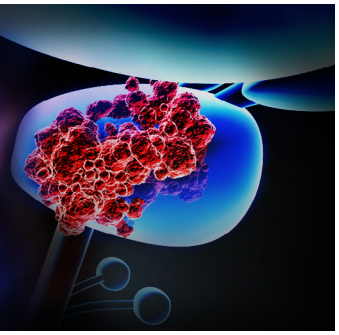
Prostate Cancer Research Review™



Making Education Easy

Issue 89 - 2025

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **ARPI** = androgen receptor pathway inhibitor; **CI** = confidence interval; **CT** = computed tomography; **FDG** = ^{18}Fluoro-2-deoxy-D-glucose; **GBq** = giga-becquerel; **GG** = grade group; **HR** =hazard ratio; **HRR** = homologous recombination repair; **ISUP** = International Society of Urological Pathology; **mCRPC** = metastatic castration-resistant prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer; **MRI** = magnetic resonance imaging; **NS** = not significant; **OR** = odds ratio; **OS** = overall survival; **PARP** = poly ADP-ribose polymerase; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RARP** = robot-assisted radical prostatectomy; **rPFS** = radiographic progression-free survival; **TRAE** = treatment-related adverse event.

Welcome to Issue 89 of Prostate Cancer Research Review.

According to findings from the TALAPRO-2 trial, combining talazoparib with enzalutamide significantly improves OS in patients with mCRPC. In the STAMPEDE trial, the addition of metformin to standard of care did not significantly improve OS in non-diabetic patients with mHSPC. A study from the Netherlands reports on the utility of minimum volume standards on surgical outcomes of radical prostatectomy. We conclude this issue with a study involving data from nine centres from the European Association of Urology Robotic Urology Section Scientific Working Group, reporting on outcomes of salvage robotic-assisted radical prostatectomy.

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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Talazoparib plus enzalutamide in men with metastatic castration-resistant prostate cancer: Final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial

Authors: Agarwal N et al.

Summary: The multinational, randomised, double-blind, placebo-controlled, phase III TALAPRO-2 trial examined the use of talazoparib plus enzalutamide in 805 patients with mCRPC unselected for HRR gene mutations. After a median follow-up of 52.5 months, OS (key secondary endpoint) was better with talazoparib plus enzalutamide versus enzalutamide plus placebo (HR 0.80; 95% CI 0.66-0.96; p = 0.016); median OS was 45.8 months (95% CI 39.4-50.8) versus 37.0 months (95% CI 34.1-40.4). OS was also better with talazoparib plus enzalutamide in 169 HRR-deficient patients (HR 0.55; 95% CI 0.36-0.83; p = 0.0035). Updated radiographic progression-free survival (rPFS; primary endpoint) was also better with talazoparib plus enzalutamide (HR 0.67; 95% CI 0.55-0.81; p < 0.0001); median rPFS 33.1 vs 19.5 months. Common grade ≥3 adverse events with talazoparib plus enzalutamide versus enzalutamide plus placebo were anaemia (49% vs 4%) and neutropenia (19% vs 1%)).

Comment: Final update from the TALAPRO-2 study, which reports on OS in men with mCRPC unselected for defects in HRR genes treated with enzalutamide +/- the PARP inhibitor talazoparib in the first-line setting. Consistent with previous findings of a significant increase in rPFS, the combination increased OS by about 20%. As expected, patients with HRR gene defects at study entry (21% in both groups) benefited the most, driven primarily by more rapid disease progression in this cohort with enzalutamide alone compared to other groups. However, benefits were also seen in patients without BRCA and other HRR gene defects, which although not all significant, suggests other unmeasured factors may select for PARP inhibitor sensitivity.

Reference: Lancet 2025;406(10502):447-460
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.

First-in-human results of terbium-161 [^{161}Tb]Tb-PSMA-I&T dual beta–auger radioligand therapy in patients with metastatic castration-resistant prostate cancer (VIOLET): A single-centre, single-arm, phase 1/2 study

Authors: Buteau JP et al.

Summary: The Australian, investigator-initiated, single-centre, phase I/II VIOLET trial evaluated the safety of Terbium-161 [^{161}Tb]Tb-PSMA-I&T in 30 patients with mCRPC. Dose escalation at three prespecified radioactivities (4.4 GBq, 5.5 GBq, and 7.4 GBq) did not identify any dose-limiting toxicities and the recommended phase II dose was 7.4 GBq. Pain and lymphopenia were the only types of grade 3 TRAEs (both 3%); there were no grade 4 TRAEs or treatment-related deaths.

Comment: Interesting phase I/II study from Melbourne reporting on the first use of a dual beta radiation/Auger and conversion electron emitting terbium-161-PSMA radioligand in patients with progressive mCRPC after ARPI +/- chemotherapy. The beta radiation is like that produced by lutetium-177, whereas Auger and conversion electrons deliver much higher energy over shorter distances, theoretically improving lethality to single cells and small cell clusters. Encouraging PSA responses were observed, with a favourable short-term toxicity profile, although patients were carefully selected for both PSMA avidity and lack of PSMA/FDG discordance. Given its tolerability, further recruitment at a higher dose is planned. In memorium JV.

Reference: Lancet Oncol. 2025;26(8):1009-1017
Abstract

Metformin for patients with metastatic prostate cancer starting androgen deprivation therapy: A randomised phase 3 trial of the STAMPEDE platform protocol

Authors: Gillessen S et al.

Summary: The STAMPEDE multi-arm, multi-stage, randomised phase III trial recruited patients with high-risk locally advanced or metastatic adenocarcinoma of the prostate. This analysis investigated whether the addition of metformin 850 mg twice daily to standard of care (82% received ADT plus docetaxel and 3% received abiraterone, enzalutamide, or apalutamide) improves survival in non-diabetic patients with mHSPC (median age 69 years; median PSA 84 ng/mL) and reduces metabolic complications associated with ADT. Over a median of 60 months' follow-up, there were 473 deaths in the standard of care group (n = 938; median survival 61.8 months) versus 453 deaths in the metformin group (n = 936; median survival 67.4 months; HR 0.91; 95% CI 0.80-1.03; p = 0.15). Adverse events of grade 3 severity were reported in 52% of patients in the standard of care group and 57% of metformin recipients; 7% of patients in the standard of care group and 9% in the metformin group reported one or more grade 3 or worse gastrointestinal adverse events. Six drug-related deaths were reported in the standard of care group and one in the metformin group.

Comment: Previous small studies have suggested that metformin may have broad anti-cancer effects, including in prostate cancer. This latest analysis from STAMPEDE explored this by randomising non-diabetic mHSPC patients (94% de novo) to standard of care (ADT +/- radiation +/- docetaxel +/- ARPI) or standard or care plus open-label metformin, stratified by age, performance status and first-line treatment. Although the addition of metformin did not significantly improve OS (the primary endpoint) or prostate cancer-specific survival in the cohort, there was some evidence that metformin use may reduce PFS (and rPFS) specifically in patients with high-volume disease. Metformin use also significantly reduced the metabolic complications of ADT, including weight gain, improved lipid profiles and resulted in better glucose tolerance, which may be important in patients at high risk of cardiovascular events.

Reference: Lancet Oncol. 2025;26(8):1018-1030
Abstract

Pasritamig, a first-in-class, bispecific T-cell engager targeting human kallikrein 2, in metastatic castration-resistant prostate cancer: A phase I study

Authors: Stein MN et al.

Summary: This phase I study investigated the use of pasritamig, a first-in-class, T-cell-engaging bispecific antibody targeting human kallikrein 2 (KLK2) expressed on the surface of prostate cancer cells, in patients (n = 174) with mCRPC who had received ≥1 prior systemic therapy (median 4). SC pasritamig was escalated from 0.5 mg to 2000 mg and IV pasritamig from 150 mg to 900 mg at dosing frequencies ranging from once every week to once every 6 weeks, with different step-up dosing schedules. Overall, 82.8% of participants experienced TRAEs, with 9.8% experiencing grade ≥3 TRAEs. The recommended phase II dose was 3.5 mg (day 1), 18 mg (day 8), 300 mg (day 15), and then 300 mg IV once every 6 weeks. The most frequent TRAEs (all grade 1 or 2) in the recommended phase II dose safety population (n = 45) were infusion-related reactions (24.4%), fatigue (15.6%), cytokine release syndrome (8.9%, all grade 1), and lipase increase (8.9%). In the recommended phase II dose efficacy population (n = 33), median radiographic PFS was 7.85 (95% CI 2.89 to not estimable) months and a decrease of ≥50% in PSA from baseline was achieved in 42.4% of participants.

Comment: Bispecific T-cell engagers (BITEs) are a type of immunotherapy that simultaneously bind targets on both cancer cells and T cells, encouraging T-cell–mediated lysis of target-expressing tumour cells. This phase I study in men with treatment-resistant mCRPC targets KLK2, a protein intimately related to PSA (KLK3), which has previously been thought to be either cytoplasmic or secreted, but has recently been shown to have significant cell surface expression with a distribution essentially limited to prostate tissue. Overall tolerability appears better that other BITE therapies, which may relate to better on-target/off tumour binding profile, with at least some hints of efficacy. Although widely used in the treatment of haematological malignancies, use in solid organ tumours has been more challenging, although it is a rapidly evolving area.

Reference: J Clin Oncol. 2025;43(22):2515-2526
Abstract

Earn CPD

Royal Australasian College of Physicians (RACP) MyCPD participants can claim the time spent reading and evaluating research reviews as CPD in the online MyCPD program. Please contact MyCPD@racp.edu.au for any assistance.

Royal Australian & New Zealand College of Radiologists (RANZCR) members can claim reading related to their practice as a CPD activity under the category 'journal reading and web based no certificate *reflection required'. More info.

Earn CPD

Nursing and Midwifery Board of Australia (NMBA) Journal reading and watching videos (including Research Reviews) may be considered a self-directed activity set out in the NMBA Registration Standard: Continuing Professional Development. One hour of active learning will equal one hour of CPD. Details at NMBA CPD page.

The importance of multiparametric magnetic resonance imaging, positron emission tomography/computed tomography, and biopsy for identifying and delineating the extent of intraprostatic radiorecurrent prostate cancer: A secondary analysis of the F-SHARP clinical trial

Authors: Venkatesulu B et al.

Summary: This secondary analysis of 62 patients with prostate cancer with intraprostatic radiorecurrence (IPRR) after curative-intent prostate cancer radiation enrolled in a phase II trial, compared the impact of multiparametric MRI, PET/CT, and biopsy on identifying IPRRs and defining the extent of prostatic involvement for target salvage local therapy (SLT) delineation. For detecting IPRR, MRI had a sensitivity of 91.8% and PET/CT a sensitivity of 85.5%. In the majority of patients, biopsy-proven cancer lay outside of the MRI-defined (70.5%) and PET/CT-defined (73.8%) target. The authors concluded that in 63.9% of patients, delineating the brachytherapy target using imaging only would have missed the full extent of recurrence.

Comment: Accurate identification of intraprostatic recurrence following definitive radiotherapy is increasingly important as the suite of focal salvage options continues to expand. This retrospective analysis compared the accuracy of pre-biopsy MRI and CT/PET (predominantly fluciclovine) to identify the localisation and extent of recurrence in a small phase I/II study of high-dose salvage therapy in this setting. Using a systematic prostate biopsy at the ground state truth, MRI was marginally more sensitive than PET/CT in identifying the site of recurrence, although over two-thirds of patients had recurrent disease on biopsy that lay outside the lesion location on imaging. Given the sampling error with biopsy, perhaps whole gland salvage therapy may be the better oncological option.

Reference: Int J Radiat Oncol Biol Phys. 2025;122(5):1186-1191
Abstract

Evaluation of short term surgical outcomes of radical prostatectomy in the decade following the introduction of minimum volume standards in the Netherlands

Authors: van der Starre CM et al.

Summary: This study from the Netherlands evaluated the effects of implementing a minimum volume standard (MVS) on the extent of care centralisation and short-term surgical outcomes in men undergoing radical prostatectomy between 2014 and 2022; an MVS of 20 radical prostatectomies per institution per year was implemented in the Netherlands in 2014 and raised to 50 radical prostatectomies in 2018, and 100 in 2019. According to data from the nationwide Netherlands Cancer Registry, 24,576 radical prostatectomies were performed between 2014 and 2022, with the number of hospitals performing such therapy decreasing from 40 to 14, while the median number of radical prostatectomies per hospital per year increased from 85 to 189. Multivariable logistic regression analysis revealed that between 2014 and 2022, the positive surgical margin rate decreased from 51.6% to 45.7% for pT3-4 (OR 0.95; 95% CI 0.93-0.98) and from 23.6% to 17.6% for pT2 (OR 0.93; 95% CI 0.91-0.96) prostate cancer. Furthermore, there was a decline in PSA persistence from 14.0% to 7.7% (OR 0.84; 95% CI 0.82-0.87), and in the grade ≥3 complication-rate from 3.9% to 3.0% (OR 0.94; 95% CI 0.90-0.98).

Comment: Volume-based centralisation of complex surgical procedures has long been advocated to reduce the risk of mortality and morbidity and improve patient outcomes. Much of the supporting evidence comes from complex gastrointestinal cancer surgery, but how it applies to more commonly performed and certainly less risky procedures such as surgery for prostate cancer is less clear. This registry-based study evaluated the impact of the introduction of progressively increasing institutional minimum volume standards on short-term outcomes in patients undergoing radical prostatectomy. Although the number of hospitals performing surgery more than halved, the impact on positive surgical margin rate and complications was much more modest. Importantly, how these improvements impact long-term patient quality of life and metastasis-free survival is unclear.

Reference: Urol Oncol. 2025;43(7):445.e1-445.e10
Abstract

Long-term outcomes of active surveillance for Grade Group 1 prostate cancer and the impact of the use of MRI on overtreatment

Authors: de Vos II et al.

Summary: These authors report on the long-term outcomes of 8910 men from 169 centres worldwide with GG1 prostate cancer, included in the multicentre, prospective, web-based Prostate Cancer Research International Active Surveillance (PRIAS) study. At 15 years post-diagnosis, the cumulative incidence of definitive treatment was 55% (95% CI 53-57), of metastasis it was 2.7% (95% CI 1.5-4.4), and of prostate cancer-specific mortality was 0.23% (95% CI 0.09-0.54). The use of MRI during the first 18 months of active surveillance was associated with a significantly higher risk of reclassification to ≥GG2. Men with a positive MRI prior to diagnosis had a higher risk of reclassification to GG2, but not to ≥GG3. Compared to men who had GG1 prostate cancer on last biopsy during active surveillance, those with GG2 prostate cancer on MRI-targeted re-biopsy who underwent definitive treatment did not show a statistically significant higher risk of 5-year disease recurrence.

Comment: Updated results from the PRIAS study report on the long-term outcomes of men with GG1 prostate cancer treated initially with active surveillance. The headline result is the confirmation of oncological safety of the approach, with a 15-year incidence of metastases and prostate cancer mortality of 2.7% and 0.23% respectively, which is lower than that of an aged-matched population without cancer! 50% of patients however progressed to radical treatment (mostly within the first 5 years) indicating overtreatment in this group is still occurring, suggesting what defines meaningful progression needs to be given more consideration. All men who died of prostate cancer underwent definitive treatment within 1-2 years, generally for "grade progression", or more likely initial sampling error, which may be ameliorated with pre-biopsy MRI.

Reference: BJU Int. 2025;136(2):245-253
Abstract

Perioperative complications of focal therapy for prostate cancer: Results from the GeRmAn Nationwide inpatient Data (GRAND) study

Authors: Pyrgidis N et al.

Summary: This German study used GeRmAn Nationwide inpatient Data from 2005 to 2023 on 10,544 patients with prostate cancer to compare the perioperative complications of the most common focal therapy modalities including high-intensity focused ultrasound (HIFU), hyperthermia, irreversible electroporation of the prostate, cryotherapy, vascular photodynamic therapy of the prostate (VTP), and transurethral ultrasound ablation. In addition, the role of concomitant transurethral resection of the prostate (TURP) on perioperative complications, and the complication rate of focal therapy versus brachytherapy and RARP were assessed. The majority of patients (92%) received HIFU. Between 2005 and 2023, there was a steady annual decline in the number of focal therapy cases performed. Overall, urinary tract infection (UTI; 9.6%) was the most prevalent complication of focal therapy (HIFU 10%, hyperthermia 6.2%, cryotherapy 6.8%, VTP 3.9%); haematuria was observed in 3.6% of all cases. Compared with non-HIFU procedures, HIFU was associated with higher rates of UTIs (10% vs 5.2%, $p < 0.001$), but lower rates of haematuria (3.4% vs 5.5%, $p < 0.001$) and admission to the intensive care unit (0.7% vs 2.2%, $p < 0.001$). There was an association between concomitant TURP and higher rates of transfusion ($p < 0.001$), haematuria ($p < 0.001$), sepsis ($p = 0.001$), and urinary retention ($p = 0.03$).

Comment: As focal therapy becomes more widely available, there is ongoing interest in both long-term efficacy and the risk of complications. This nationwide database study reports on immediate complications following focal therapy in all patients treated in Germany, based on hospital coding data submitted for remuneration over an 18-year period. HIFU, which was the focal therapy of choice in 92% of patients, was associated with an in-hospital UTI rate of 10%, which was twice that of non-focal therapies, but with comparably lower rates of haematuria or admission to ICU. The analysis is significantly limited by the lack of follow-up outside the immediate post-procedural inpatient stays, so long-term complications (stricture rates, re-treatment rates etc.) are not reported. Interestingly the median length of stay for focal therapy was 4 days, which may say more about the intricacies of the German remuneration system, given that it was 7 days for an RARP over the say time period!

Reference: BJU Int. 2025;136(2):306-313
Abstract

Magnetic resonance imaging-led risk-adapted active surveillance for prostate cancer: Updated results from a large cohort study

Authors: Englman C et al.

Summary: This clinical cohort study assessed outcomes of MRI-led risk-adapted active surveillance in 1150 patients over a median follow-up of 64 months. At baseline, 36% had Gleason score (GS) 3+4, 55% had MRI-visible lesions, and 17% had MRI-visible GS 3+4 disease. The 5-year event-free survival rate for non-visible GS 3+3 was 91% (95% CI 88-94), for MRI-visible GS 3+3 was 71% (95% CI 65-78), for non-visible GS 3+4 was 70% (95% CI 63-78), and for MRI-visible GS 3+4 was 44% (95% CI 35-54). Overall, 487 patients received follow-up biopsies, and histological upgrade to GS ≥4+3 was uncommon (n = 67). Progression to nodal or bone metastases occurred in 10 patients who had declined follow-up MRI and/or biopsies; 30 patients chose treatment despite stable characteristics.

Comment: Active surveillance protocols continue to evolve towards a risk-adapted approach, with planned interval biopsies increasingly omitted if PSA and MRI findings are stable. This updated report from University College London Hospitals, where patients undergo an MRI at baseline, 12 months +/- 24 months along with regular PSA measurements and re-biopsy is only considered for radiological progression or rising PSA density, finds that an estimated 43% of patients will progress to definitive treatment and/or upgrading to ISUP grade group 3 (GG3) disease by 10 years. Radiological progression was much more common (59% at 10 years), whereas progression to ISUP GG3 disease was only 10% over the same period, with rates for both being highest in those with MRI visible GG2 tumour at baseline. Metastases were very uncommon and there were no prostate cancer deaths, suggesting even with this approach too many men are treated without benefit.

Reference: Eur Urol. 2025;88(2):167-175
Abstract

Outcomes of salvage robotic-assisted radical prostatectomy: High-volume multicentric data from the European Association of Urology Robotic Urology Section Scientific Working Group

Authors: Moschovas MC et al.

Summary: This retrospective (2008-23) multicentre study using data from the European Association of Urology Robotic Urology Section Scientific Working Group examined the outcomes of salvage RARP in 397 patients with recurrent prostate cancer after prostate-preserving therapy (radiation therapy [RT], whole gland ablation [WG], and focal gland ablation [FG]). After a median follow-up of 38 months for RT, 20 months for FG, and 24 months for WG ($p < 0.001$), only four (1%) patients experienced intraoperative complications with <2% experiencing Clavien grade ≥3 complications after surgery. Overall, 5-year cumulative biochemical recurrence incidence rates were 35% for RT, 45% for FG, and 23% for WG (NS), 3-year cumulative continence incidence rates were 67%, 92%, and 71% ($p < 0.001$), 5-year cumulative potency incidence rates were 16%, 11%, and 5.3% (NS), and 5-year OS rates were 95%, 94%, and 100% (NS).

Comment: In the recent past, salvage prostatectomy was much more commonly spoken about than performed, due to the perceived risk of rectal injury and complete urinary incontinence. However, as the detection of intraprostatic recurrence following radiation or ablation has improved, urologists are more frequently being asked to consider salvage surgery. This multicentre retrospective review of salvage prostatectomy outcomes over a 15-year period finds that although feasible to perform salvage RARP safely (1 rectal injury in the cohort), the functional outcomes are worse than in the primary setting, even in experienced hands. However, they were not dire, as about 70% of patients achieved continence (better if only prior focal therapy), although the ability to perform a nerve-sparing procedure was significantly compromised, and potency rates were correspondingly low. Did patients benefit oncologically? Hard to know.

Reference: Eur Urol. 2025;88(1):103-113
Abstract