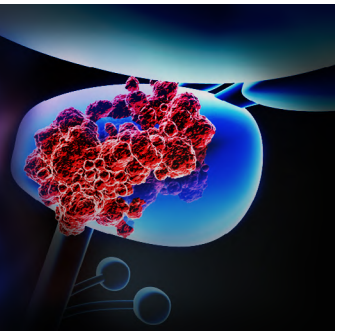
Prostate Cancer Research Review™



Making Education Easy

Issue 85 - 2025

In this issue:

Abbreviations used in this issue:

^{177}Lu = lutetium 177; **ADT** = androgen deprivation therapy; **CD** = cluster of differentiation; **CTLA-4** = cytotoxic T-lymphocyte antigen 4; **Gy** = Gray; **HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **ISUP** = International Society of Urological Pathology; **MRI** = magnetic resonance imaging; **mCRPC** = metastatic castration-resistant prostate cancer; **OS** = overall survival; **PD-1** = programmed cell death protein 1; **PD-L1** = programmed death ligand 1; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RARP** = robot-assisted radical prostatectomy; **SPP1hi-TAMs** = secreted phosphoprotein 1 transcripts.

Welcome to Issue 85 of Prostate Cancer Research Review.

First up we review a US study investigating the evolution of myeloid-mediated immunotherapy resistance in prostate cancer, which has discovered that *SPP1*^{hi}-TAMs are key mediators of ICI resistance in mCRPC through adenosine signalling. Following on, a dynamic risk model has effectively identified patients at low risk of prostate cancer reclassification during active surveillance, with the potential to reduce the burden of unnecessary biopsies. We conclude this issue with a study from Memorial Sloan Kettering suggesting that patients undergoing radical prostatectomy for prostate cancer should also receive extended pelvic lymph node dissection that includes the external iliac, obturator and hypogastric nodes.

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
niall.corcoran@researchreview.com.au

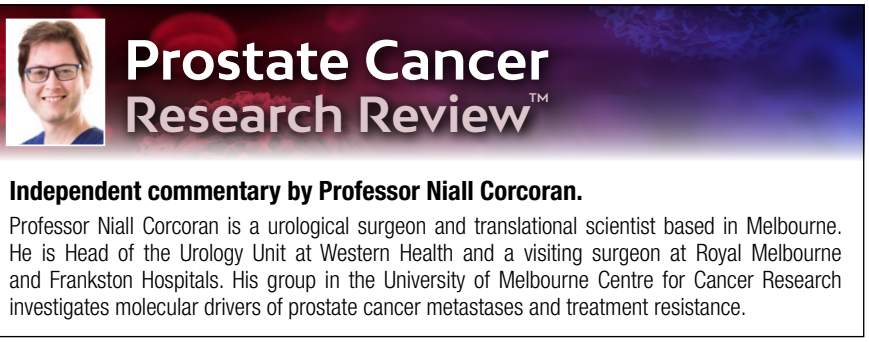
Evolution of myeloid-mediated immunotherapy resistance in prostate cancer

Authors: Lyu A et al.

Summary: This study used single-cell profiling of patient biopsies from prostate cancer patients and identified distinct populations of tumour-associated macrophages with elevated levels of secreted phosphoprotein 1 (*SPP1*) transcripts (*SPP1*^{hi}-TAMs) that become enriched during progression to advanced metastatic castration-resistant prostate cancer (mCRPC). In mice, a similar macrophage population suppresses *in vitro* CD8+ T cell activity and promotes immune checkpoint inhibitor (ICI) resistance *in vivo*. *SPP1*^{hi}-TAMs do not respond to anti-colony stimulating factor-1 receptor antibody treatments. A potential mechanism for *SPP1*^{hi}-TAM-mediated immunotherapeutic resistance is adenosine signalling, and pharmacological inhibition of adenosine A2A receptors reverses *SPP1*^{hi}-TAM-mediated immunosuppression and enhances CRPC responsiveness to PD-1 blockade in preclinical testing. Ciforadenant inhibition of A2ARs in combination with atezolizumab PD-L1 blockade produces clinical responses in mCRPC patients with a decrease in *SPP1*^{hi}-TAM abundance in CRPC, suggesting this pathway is involved in induction and downstream immunosuppression.

Comment: At last, maybe some insight into why responses to ICIs are relatively poor in metastatic prostate cancer. In this study the authors identify a specific subpopulation of tumour associated macrophages, which rise incrementally in biopsies from patients with increasingly progressive disease and show that they are associated with intra-tumoural immunosuppression by inducing cytotoxic T-cell exhaustion via adenosine-mediated signalling. Treatment of animal models with a drug (ciforadenant) that blocks adenosine receptors inhibits this immunosuppression and increases response rates to a PD-1 inhibitor. However, response rates to this combination in patients with mCRPC in the second-line setting were rather modest, so maybe some of the story, but not the whole one.

Reference: Nature 2025;637(8048):1207-1217
Abstract



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.

Personalized dynamic prediction model for biopsy timing in patients with prostate cancer during active surveillance

Authors: de Vos Il et al.

Summary: This analysis of data from the Prostate Cancer Research International: Active Surveillance (PRIAS) multicentre, prospective, web-based cohort study developed a dynamic prediction model for active surveillance based on 2512 patients with prostate cancer. A higher risk of prostate cancer reclassification was associated with increased age, higher PSA and velocity, lower prostate volume, suspicious MRI lesion, and no previous negative biopsy. The model had a negative predictive value of 86-97% depending on threshold and time point with a time-dependent area under the curve of 0.81-0.84. External validation, using the Movember Foundation's Global Action Plan Prostate Cancer Active Surveillance (GAP3) database including 3199 patients, suggested a time-dependent area under the curve of 0.52-0.90.

Comment: One of the priority areas in active surveillance research is to identify patients at the lowest risk of progression to enable safe de-escalation of surveillance intensity. This study uses data from patients with grade group (GG)1 disease enrolled in the PRIAS registry who underwent at least one follow-up biopsy, with the primary outcome being upgrading to ≥GG2, with external validation in Movember's GAP3 active surveillance cohort. Factors associated with a higher risk of upgrading were increased age, higher PSA and velocity, lower prostate volume, a suspicious lesion on MRI, and no previous negative biopsy. Most upgrading events occurred, as expected, in the first 24 months after diagnosis and likely reflect initial sampling error rather than true progression. However, taking these risk factors into account can safely reduce the number of routine 'interval' biopsies for patients at lower risk, something which many of us have already translated into our clinical practice.

Reference: JAMA Netw Open 2025;8(1):e2454366
Abstract

Comparison of two alternative sequences with cabazitaxel and ^{177}Lu-PSMA-617 in metastatic castration-resistant prostate cancer: A retrospective multicenter study (LuCaS)

Authors: Bolek H et al.

Summary: This retrospective, multicentre cohort study assessed the sequencing of cabazitaxel and ^{177}Lu-PSMA-617 on survival in 68 patients with mCRPC. Progression-free survival-2 (PFS-2) was similar in patients receiving ^{177}Lu-PSMA-617 first (LU-CA) versus cabazitaxel (CA-LU) first (10.8 vs 11.7 months; p = 0.422). Median overall survival (OS) was also similar in the LU-CA and CA-LU groups (16.6 vs 19.9 months). ^{177}Lu-PSMA-617 objective response rate (ORR) was 23.1% when used first versus 16.1% when used second, while the ORRs for cabazitaxel were 25.6% and 31.3%.

Comment: With multiple lines of systemic therapy now available for patients with metastatic disease, whether there is an ideal treatment sequence to maximise long-term outcomes, or it is largely irrelevant as long as the patients sees all treatment at some stage, is not yet clear. This small retrospective study suggests that at least for cabazitaxel and ^{177}Lu-PSMA-617, which agent is given first in the sequence did not impact long-term outcomes, with a similar time to second progression event as well as median OS observed. As expected, objective responses were more muted when each drug was second in the sequence compared to when it was first, as well as a greater reported toxicity.

Reference: Eur J Cancer 2025:217:115226
Abstract

Stereotactic radiation therapy for localized prostate cancer: 10-year outcomes from three prospective trials

Authors: Kennedy TAC et al.

Summary: This was an analysis of long-term outcomes, pooled data from three Canadian clinical trials that included 267 patients with low- and intermediate-risk localised prostate cancer who received stereotactic ablative radiotherapy (SABR). After a median follow-up of 10.3 years the 10-year biochemical failure rate was 7.7% (95% CI 3.9-11.5) with a 10-year OS rate of 84.1% (95% CI 79.3-89.1), a prostate cancer-specific survival rate of 99.2% (95% CI 98.1-100), and a freedom from metastasis rate of 98.8% (95% CI 97.5-100). A second malignancy occurred in 10.1% of patients with 22.2% rated as likely or possibly related to prior radiation therapy; 10-year freedom from second malignancy was 89.2%.

Comment: Stereotactic radiotherapy for localised prostate cancer is very convenient for patients and potentially more cost-effective from a healthcare payer's perspective. This report summarises patient level data from three Canadian prospective clinical trials. All patients had low-/intermediate-risk disease and were treated with SABR to the prostate of 35 to 40 Gy in five fractions. The rate of biochemical control at 10 years was 92.3%, with a metastasis-free survival rate exceeding that of the radiation arm in ProtecT at the same time point (acknowledging the inclusion of some higher-risk patients in the latter study), suggesting good cancer control. The rate of incidence of secondary malignancy likely or possibly related to SABR was 2.2%, which is still a concern, but may still be less than other radiotherapy techniques.

Reference: Int J Radiat Oncol Biol Phys. 2025;121(2):325-330
Abstract

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.

Earn CPD

CPD Home. Subscribers can claim the time spent reading and evaluating research reviews as an Educational Activity: Professional Reading in the CPD Tracker. Please Contact Us for support.

Follow us at:

Natural history of PIRADS-2 lesions on serial multiparametric magnetic resonance imaging: Real-life data from an Academic Center

Authors: Esen B et al.

Summary: This retrospective, single-centre analysis of serial multiparametric (mp) MRI scans aimed to evaluate the natural history of Prostate Imaging Reporting and Data System (PIRADS) score 2 lesions in 172 biopsy-naive patients to identify the rates of mpMRI upgrade. Overall, mpMRI progression occurred in 31.4% of patients after 1 year, 37 were upgraded to PIRADS-3, 16 to PIRADS-4, and one to PIRADS-5. Multivariate analysis suggested that a PSA increase of ≥25% during follow-up was predictive of mpMRI upgrade (OR: 2.384; p = 0.019). A prostate biopsy was undertaken in 30 of 54 patients and prostate cancer was detected in 15 patients (5 ISUP grade 1, 10 grade 2)

Comment: Is it safe to discharge patients with a PIRADS-2 lesion on their MRI back to their general practitioner without a biopsy? This study examined the natural history of PIRADS-2 lesions in men referred for an elevated PSA/abnormal digital rectal exam over a 10-year period. All baseline and repeat MRI were re-reported using PIRADSv2.1 system, with the decision to proceed to a repeat MRI based on clinical assessment, most commonly for a rising PSA. Just under a third of patients were upgraded, ~70% to PIRADS-3 and ~30% to PIRADS-4/5, more commonly due to the appearance of a new lesion rather than a change in the pre-existing one and was associated with higher changes in PSA from baseline. Prostate cancer was subsequently diagnosed in 30/53 patients who underwent biopsy, all of whom had GG1/GG2 disease. Given that this study over-estimates the risk (as patients with a PIRADS-2 lesion who did not have an indication for repeat MRI were excluded), it suggests it is safe to discharge to GP follow-up if the PSA is monitored.

Reference: Urol Oncol. 2025;43(1):65.e9-65.e15
Abstract

Irreversible electroporation of localised prostate cancer downregulates immune suppression and induces systemic anti-tumour T-cell activation – IRE-IMMUNO study

Authors: Geboers B et al.

Summary: This prospective study compared systemic anti-tumour immune responses in peripheral blood samples after irreversible electroporation (IRE; n = 20) or RARP (n = 10) in patients with localised intermediate-risk prostate cancer. IRE depleted systemic regulatory T cells (p = 0.0001) and increased activated CTLA-4 positive (+), CD4+ (p < 0.001) and CD8+ (p = 0.032) T cells; effects that were positively correlated with tumour volume or ablation size. IRE induced expansion of prostatic acid phosphatase (PSAP) and/or New York oesophageal squamous cell carcinoma 1- (NY-ESO-1) specific T-cell responses in four of eight immune-competent patients. Activated myeloid derived suppressor cell frequencies were temporarily increased after RARP (p = 0.047).

Comment: This interesting study from Sydney looked at the effect of IRE on systemic anti-tumour immune response in patients with intermediate-risk disease. Compared to patients undergoing RARP, patients treated with IRE showed greater evidence of systemic immune activation as measured by a drop in regulatory T cells (immunosuppressive) and significant increases in CTLA-4 expression on circulating cytotoxic and helper T cells (indicating immune activation), correlating with treated tumour volume. However, it is not clear if this is specifically a mono/oligo-clonal anti-tumour cell response, or represents activation against antigens related to 'tissue damage'. Certainly, does not seem sufficient to eradicate tumour outside the treated field by itself, but perhaps may prime tumours to anti-CTLA-4 checkpoint inhibitors.

Reference: BJU Int. 2025;135(2):319-328
Abstract

Refining risk stratification of high-risk and locoregional prostate cancer: A pooled analysis of randomized trials

Authors: Ravi P et al.

Summary: This pooled analysis of data from 3604 patients with high-risk localised/locoregional prostate cancer (HRLPC; median PSA 24 ng/mL) across 10 trials assessed outcomes after radiotherapy and long-term ADT (18-36 months). Variables associated with poorer metastasis-free survival (MFS) included Gleason score ≥8 (HR 1.45), cN1 disease (HR 1.86), cT3-4 disease (HR 1.28), and PSA >20 ng/mL (HR 1.30). Poorer OS outcomes were associated with Gleason score ≥8 (HR 1.42), cN1 disease (HR 1.77), cT3-4 disease (HR 1.22), and PSA >20 ng/ml (HR 1.21). Adjusted 5-year MFS rate for patients with one risk factor was 83% while for those with 2-3 risk factors it was 78%; 10-year MFS rates were 63% and 53%. 10-year adjusted OS rates were 67% and 60%. Among cN1 patients, adjusted 5- and 10-year MFS rates were 67% and 36% with a 10-year OS rate of 47%.

Comment: In counselling patients about natural history and treatment options, many clinicians reference the original D'Amico three tier system (low, intermediate, high) or more commonly a derivation (separating intermediate risk into favourable and unfavourable) based on PSA, clinical stage and biopsy findings. However, forcing continuous/ordinal data into categories always results in information loss. This is exemplified by this study investigating the impact of accumulating 'high-risk' features on MFS and OS in men with high-risk disease treated with radiotherapy and long-term ADT across 10 trials. Somewhat intuitively, the more independent high-risk features a patient has the worse their MFS and OS, with the worst outcomes observed for patients with N1 disease, which identifies groups who may benefit most from treatment intensification. The obvious caveat is that all patients were staged by conventional imaging.

Reference: Eur Urol. 2025;87(2):217-224
Abstract

Impact of gene expression classifier testing on adjuvant treatment following radical prostatectomy: The G-MINOR prospective randomized cluster-crossover trial

Authors: Morgan TM et al.

Summary: This prospective, randomised, controlled, cluster-crossover trial examined the use of a tissue-based genomic classifier (GC; n = 175) or usual care (n = 168) on adjuvant treatment after radical prostatectomy. After 18 months, GC recipients received adjuvant treatment 9.7% of the time versus 8.7% in usual care recipients (difference 0.99%; 95% CI -7.6 to 9.6). After controlling for Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score, higher GC scores did not increase the likelihood of adjuvant treatment (odds ratio [OR] 1.35 per 0.1 increase in GC score; 95% CI 0.98-1.85). Using the GC risk groups, after CAPRA-S adjustment a high GC risk was associated with higher odds of receiving adjuvant treatment (OR 6.9; 95% CI 1.8-26; p = 0.005).

Comment: This study investigates the impact of a genomic classifier (Decipher, Veracyte) on decision making regarding the use of adjuvant therapy (radiation +/- ADT in the absence of a biochemical recurrence) in patients with high-risk features (T3/4, positive margins) and an undetectable PSA post prostatectomy. In the GC arm, patients with a high GC score were more likely to undergo adjuvant treatment independent of clinical and pathological risk as measured by the CAPRA-S score, indicating that the test impacts treatment decision making. However, whether this change in treatment impacts long-term cancer outcomes needs more follow-up.

Reference: Eur Urol. 2025;87(2):228-237
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.

Evaluating biparametric versus multiparametric magnetic resonance imaging for diagnosing clinically significant prostate cancer: An international, paired, noninferiority, confirmatory observer study

Authors: Twilt JJ et al.

Summary: This multinational study assessed the noninferiority of biparametric MRI (bpMRI) to mpMRI in diagnosing clinically significant prostate cancer using 62 readers assessing 400 MRIs. bpMRI and mpMRI had similar area under the receiver operating curve (AUROC) values of 0.853 (95% CI 0.819-0.887) and 0.859 (95% CI 0.826-0.893). Prostate Imaging Reporting and Data System (PI-RADS) scores ≥3 indicated that bpMRI and mpMRI had sensitivities of 88.6% (95% CI 84.8-92.3) and 89.4% (95% CI 85.8-93.1), and specificities of 58.6% (95% CI 52.3-63.1) and 57.7% (95% CI 52.3-63.1). Using alternative risk thresholds, mpMRI increased sensitivity but reduced specificity. Dynamic contrast-enhanced (DCE) MRI gave the greatest net benefit for an mpMRI pathway in cancer-averse scenarios, bpMRI had a greater benefit for biopsy-averse scenarios.

Comment: Omitting intravenous contrast makes prostate MRI faster, cheaper and safer, but what effect does it have on cancer detection? This international multicentre study compared the relative performance of bpMRI and mpMRI sequences from a retrospective cohort of individual patients to predict the presence of ≥GG2 disease on a subsequent biopsy. The headline result is that at a PI-RADS threshold of ≥3, both modalities had similar test performance, with 91% of patients having concordant lesion grading. mpMRI was marginally more sensitive for clinically significant cancers, whereas bpMRI was marginally more specific, so in most low-risk patients bpMRI may be the preferred technique.

Reference: Eur Urol. 2025;87(2):240-250
Abstract

Pelvic lymph node dissection in prostate cancer: Update from a randomized clinical trial of limited versus extended dissection

Authors: Touijer KA et al.

Summary: This clinically integrated randomised trial comparing limited (external iliac nodes) versus extended pelvic lymph node dissection (PLND; (external iliac, obturator, and hypogastric nodes) in 1432 patients undergoing radical prostatectomy. At a median follow-up of 4.2 years biochemical recurrence (BCR) rates did not differ between treatment arms (HR 1.05; 95% CI 0.97-1.13). At a median follow-up of 5.4 years, there was a protective effect of extended PLND against metastasis (any metastasis HR 0.82; 95% CI 0.71-0.93; p = 0.003; distant metastasis HR 0.75; 95% CI 0.64-0.88; p < 0.001).

Comment: To dissect the pelvic lymph nodes or not to dissect them at the time of prostatectomy is the debate that refuses to die. In this latest instalment, investigators from Memorial Sloan Kettering report an updated analysis of their single-centre cluster randomised trial of limited versus extended lymph node dissection in men with predominantly intermediate-risk disease. Again, there was no difference in the BCR rates between the two groups (the primary endpoint) but with longer follow-up metastasis free survival (both any metastasis and distant metastasis) was increased in the extended PLND group. The absolute difference is 3% at 10 years, and although there are caveats in interpreting secondary endpoints, the magnitude of treatment effect is hard to dismiss. Infamously the difference in node counts between the limited and extended dissection was rather modest, perhaps suggesting that a more complete disruption of upstream lymphatic connections rather than better clearance of nodal micrometastases is key.

Reference: Eur Urol. 2025;87(2):253-260
Abstract