Prostate Cancer Research Review™

Making Education Easy

Issue 94 - 2026

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy
ARPI = androgen receptor pathway inhibitor
AUC = area under the curve
CI = confidence interval
CT = computed tomography
Gy = Gray
HR = hazard ratio
LUTS = lower urinary tract symptoms
mHSPC = metastatic hormone-sensitive prostate cancer
mpMRI = multiparametric magnetic resonance imaging
OR = odds ratio
OS = overall survival
PCSS = prostate cancer-specific survival
PET = positron emission tomography
PFS = progression-free survival
PI-RADS = Prostate Imaging-Reporting and Data System
PSA = prostate-specific antigen
PSMA = prostate-specific membrane antigen
RCT = randomised controlled trial
rPFS = radiographic progression-free survival
RT = radiotherapy

Welcome to Issue 94 of Prostate Cancer Research Review.

A phase III study published in the New England Journal of Medicine reports a significantly longer overall survival with the combination of enzalutamide plus leuprolide than with leuprolide alone among patients with prostate cancer with high-risk biochemical recurrence. In the WOLVERINE study, metastasis-directed therapy was associated with consistent and significant improvements in progression-free survival, radiographic progression-free survival and castration-resistance free survival in men with oligometastatic prostate cancer. We conclude this issue with a study investigating the impact of 5α-reductase inhibitors on multiparametric MRI characteristics and detection of 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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Improved survival with enzalutamide in biochemically recurrent prostate cancer

Authors: Shore ND et al.

Summary: This paper provides final OS data from the randomised, double blind, controlled, phase III EMBARK trial comparing enzalutamide plus leuprolide, leuprolide plus placebo, or enzalutamide monotherapy in 1068 patients with biochemically recurrent prostate cancer. The 8-year OS (α-controlled, key secondary endpoint) was 78.9% (95% CI 73.9-83.1) with enzalutamide plus leuprolide combination therapy versus 69.5% (95% CI 64.0-74.3) with leuprolide-alone (HR 0.60; 95% CI 0.44-0.80; p < 0.001); 8-year OS with enzalutamide monotherapy was 73.1% (95% CI 67.6-77.9) and did not differ from leuprolide alone (HR 0.83; 95% CI 0.63-1.10).

Comment: Given the success of ARPIs in prolonging OS in patients with mHSPC, it is reasonable to question if introducing them earlier in the disease can produce even greater survival benefits. This phase III study randomised patients with high-risk biochemically recurrent post-surgery or radiation (PSA doubling time ≤9months) with no evidence of metastatic disease on conventional imaging to either enzalutamide plus leuprolide (ADT) or ADT plus placebo (both blinded), or a parallel unblinded group who received enzalutamide monotherapy. The takeaway message is that ADT plus enzalutamide resulted in a significant improvement in both rPFS and OS compared to ADT plus placebo, which is perhaps not surprising given that most patients on the study likely had PSMA-PET detectable metastatic disease at baseline. This indication for enzalutamide is currently not reimbursed, so in patients without metastatic disease on PSMA-PET, use will be determined by commercial access programs and patient factors.

Reference: N Engl J Med. 2025;Oct 19 [Epub ahead of print]
Abstract

Metastasis-directed therapy and standard of care versus standard of care for oligometastatic prostate cancer (WOLVERINE): A systematic review and individual patient data meta-analysis from the X-MET collaboration

Authors: Tang C et al.

Summary: This systematic review and meta-analysis pooled individual patient data across seven phase II trials to assess the use of metastasis-directed therapy (MDT) plus standard of care (SOC) versus SOC in 472 patients with oligometastatic prostate cancer. Over a median follow-up time of 40.7 months, MDT was associated with improved trial-level PFS (HR 0.44; 95% CI 0.35-0.56; $p < 0.0001$), rPFS (HR 0.60; 95% CI 0.42-0.85; $p = 0.0039$) and castration resistance-free survival (HR 0.58; 95% CI 95% CI 0.37-0.92; $p = 0.019$), with similar improvements in patient level PFS (HR 0.45; 0.35-0.57; $p < 0.0001$), rPFS (HR 0.59; 95% CI 0.46-0.76; $p < 0.0001$) and castration resistance-free survival (HR 0.58; 95% CI 0.37-0.91; $p = 0.017$). MDT improvement in OS was not significant with an HR of 0.63 (95% CI 0.39-1.00; $p = 0.051$) in trial-level and HR 0.64 (95% CI 0.40-1.01; $p = 0.057$) in patient-level analyses.

Comment: Although commonly used in Australia, the evidence base for MDT in oligometastatic disease lacks robustness. This systematic review and meta-analysis used both trial and patient level data from six randomised phase II studies of MDT plus SOC versus SOC alone to estimate potential benefits. The use of MDT was associated with consistent and significant improvements in PFS, rPFS and castration-resistance free survival, and although there was a trend towards an improvement in OS this did not meet statistical significance. Given that it is still unclear which patients benefit from an MDT approach, the finding that higher baseline PSA was associated with a lack of improvement in rPFS with MDT whereas other pertinent variables (castration resistant prostate cancer status, number of metastatic lesions etc.) were not, gives some insights into appropriate patient selection for future studies.

Reference: Lancet Oncol. 2026;27(2):181-190
Abstract

Incidence and oncologic outcomes of patients with prostate-specific antigen persistence after radical prostatectomy

Authors: Lane BR et al.

Summary: This retrospective analysis examined whether patients with post-radical prostatectomy PSA persistence (PPP) constitute a unique, high-risk population based on data from the Michigan Urological Surgery Improvement Collaborative registry (MUSIC; n = 15,390; 11,019 no evidence of disease [NED], 1919 PPP, 2452 biochemically recurrent). PPP patients had clinically meaningful higher risk pre-radical prostatectomy and post-radical prostatectomy characteristics versus NED or biochemical recurrence patients. Patients who had PPP had higher PSA values before secondary treatment versus those with biochemical recurrence (median PSA 0.73 vs 0.28 ng/mL; $p < 0.001$). Five-year all-cause mortality rate was 2.5% (95% CI 2.1-2.9) for undetectable PSA (NED and biochemical recurrence combined) versus 5.7% (95% CI 4.3-5.7) in PPP patients ($p < 0.001$).

Comment: PPP after surgery commonly provokes a heart sinking feeling in both patients and clinicians as it becomes clear that prostatectomy has failed to control the disease and further treatment is likely necessary. This retrospective review from the MUSIC registry demonstrates that PPP is relatively common, occurring in 1 in 8 patients. PPP was associated with higher-risk features at the time of surgery compared to those who experienced traditional biochemical recurrence, including higher PSA, more advanced T stage and more frequent presence of nodal disease, but not the presence of positive surgical margins. Both primary PSA persistence and biochemical recurrence were associated with a significant increase in all-cause mortality compared to patients without recurrence, likely due to an increase in prostate cancer-specific survival (PCSS). The authors hypothesise that PPP represents a distinct clinical state compared to even early biochemical recurrence, but is likely just to be part of the same spectrum of undetected (micro)metastatic disease present at the time of surgery.

Reference: Cancer 2026;132(4):e70291
Abstract

Tumour-based epigenetic signatures as markers of prostate cancer aggressiveness after radical prostatectomy

Authors: Zhu Y et al.

Summary: This Australian study examined tumour DNA methylation-based signatures of aggressiveness and cell division in 293 patients with prostate cancer treated with radical prostatectomy. Most epigenetic signatures were associated with Gleason score, age, and tumour stage, but not serum PSA at diagnosis. After adjusting for clinicopathological variables, associations were observed with risk of PSA recurrence, with increased risks ranging from 1-17% per standard deviation for signatures of clinical variables and 17-33% for cell division scores; the strongest association was with the cell division score RepliTali.

Comment: Alterations in genome methylation affects gene expression is tissues which can often be detected as 'signatures' associated with numerous cellular processes such as cell division or senescence. This Victorian study leverages previously generated genome wide methylation data from a cohort of men who underwent prostatectomy to investigate the association of several previously generated methylation signatures and biochemical recurrence within 24 months. The strongest association was seen with a signature of cellular replication, which is consistent with other expression-based signatures (such as the cell cycle proliferation score, Prolaris) as well as clinical parameters such as PSA doubling time that show higher mitotic activity is associated with worse clinical outcomes. A more interesting and clinically relevant outcome would have been metastasis-free survival, although these data are not routinely collected in Prostate Cancer Outcomes Registry data.

Reference: Br J Cancer 2026;134(3):477-485
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.

Gallium-68-labeled prostate-specific membrane antigen positron emission tomography/computed tomography response in pelvic node-positive prostate cancer after definitive radiation therapy: Prognostic implications

Authors: Onal C et al.

Summary: This retrospective study examined the prognostic value of metabolic response assessed by Gallium-68 (^{68}Ga)-labelled PSMA PET/CT in 107 prostate cancer patients with pelvic lymph node metastases (PLNM) undergoing definitive RT and ADT. During a median 60.4-month follow-up, post-treatment ^{68}Ga-PSMA-PET/CT measured at a median of 4.1 months after RT showed maximum standardised uptake value (SUV_{max}) reductions in 98.1% of primary tumours and 93.5% of lymph nodes; there was a complete metabolic response (CMR) in 43.9% of primary tumours and 65.4% of lymph nodes. An association was seen between primary tumour CMR and improved 5-year distant metastasis-free survival (DMFS; 81.6% vs 61.4%; p = 0.006), PFS (72.2% vs 41.0%; p = 0.01), and PCSS; 96.4% vs 84.7%; p = 0.04). There was also an association between lymph node CMR and superior 5-year DMFS (87.3% vs 42.6%; p < 0.001), PFS (72.6% vs 25.9%; p < 0.001), and PCSS (97.5% vs 77.1%; p < 0.001). Multivariate analysis suggested improved DMFS PFS, and PCSS were associated with longer ADT duration (≥24 months) and lymph node CMR, while poorer DMFS was associated with Gleason score ≥8.

Comment: One potential role of PSMA-PET is to use it as read-out of treatment success in patients with locally advanced disease. This retrospective study investigated the potential prognostic role of metabolic response as measured by PSMA-PET in patients with N1 disease treated with EBRT to the primary and pelvic side walls with at least 18 months of ADT. Patients were rescanned ≈4 months after completion of radiotherapy, with significant reductions in the average SUV_{max} (>90%) observed in both the primary tumour as well as the nodal metastases. CMR (no detectable PSMA avidity) was observed in 43% of primary tumours and 65% of nodal sites, both of which were associated with improved DMFS, in addition to increases in PFS and PCSS. Interesting data that suggests it may be able to select patients for treatment intensification, although we would need changes to the reimbursement rules for the imaging.

Reference: Int J Radiat Oncol Biol Phys. 2025;123(5):1259-1268
Abstract

A prospective validation of the Decipher genomic classifier in men with early localized prostate cancer: The VANDAAM study

Authors: Yamoah K et al.

Summary: This multicentre, prospective, validation study sought to validate a genomic classifier (GC) of biopsy and/or radical prostatectomy tumour tissue for prediction of rapid-onset biochemical recurrence in 104 African American and 103 White men with low- or intermediate-risk prostate cancer. Overall, a high genomic-risk GC score was associated with 5.25-fold greater odds of rapid-onset 2-year biochemical recurrence compared with a low-risk GC score (OR 5.25; 95% CI 1.27-21.66; p = 0.021). In a surgical cohort subset (n = 74), biopsy- and radical prostatectomy-derived GC scores had a 77% concordance rate.

Comment: It is unclear if the more aggressive clinical course of prostate cancer in men of African ancestry is related to socio-economic factors or represents a distinct biology that may affect the performance of prognostic tests developed in predominantly White populations. This prospective study investigates the prognostic utility of the Decipher assay (a 22-gene transcriptional profile) in matched White and African American men with low- and intermediate-risk localised prostate cancer treated with curative intent. The Decipher assay performed numerically better in African American men compared to matched White patients in predicting biochemical recurrence within 2 years, with higher discriminatory ability. In an exploratory analysis using the whole transcriptome data that is provided by the test but not included in calculation of the genomic score, African American men were enriched for tumours with higher genomic immune markers and lower expression of DNA damage-repair markers, adding to data suggesting poorer outcomes related to a distinct genotype.

Reference: J Natl Compr Canc Netw. 2025;24(1):e257089
Abstract

Patient-reported quality of life in PROFIT, a phase 3 randomized clinical trial evaluating moderately hypofractionated radiotherapy for intermediate-risk prostate cancer

Authors: Sanmamed N et al.

Summary: This analysis of the multinational, randomised phase III clinical PROFIT trial examined differences in long-term patient-reported outcomes (PROs) between moderately hypofractionated (HF; 60 Gy in 20 fractions over 4 weeks) and conventional fractionated (CF; 78 Gy in 39 fractions over 8 weeks) radiotherapy. American Urological Association Symptom Scores (AUASS) did not differ between treatments and were stable over time in both arms (median 5 points); there were no differences in urinary, bowel, sexual, or hormonal domains or subdomains at any time point (p > 0.02). The largest decline with time occurred in sexual domain (decrease ≥10 points from baseline to 24 months in both arms). Short Form Health Survey 12-item (SF-12) mean scores for both physical component summary (PCS) and a mental component summary (MCS) did not differ between treatments and remained stable at all time points. The only differences in minimally important difference (MID) were in bowel subdomains at 48 months, with MID reductions favouring HF for bowel summary (53% vs 44%; p = 0.01) and bowel function (51% vs 39%; p = 0.001) scores. Overall treatment satisfaction (satisfied or extremely satisfied) was ≥88% of patients in both groups.

Comment: Patients with clinically localised intermediate-risk disease are likely to live a long time even without treatment. Maintenance of quality of life in the long term is therefore an important consideration for patients if upfront radical therapy is contemplated. This study reports on patient-reported outcome measures from subjects enrolled in the PROFIT study (an RCT comparing conventional versus moderate hypofractionation). Out to 48 months, there was no difference between treatment schedules for urinary, bowel or sexually related domains, although there was a decline in all measures (particularly sexual function) from baseline. Re-enforces the appropriateness of moderate hypofractionation in this patient group.

Reference: Eur Urol Oncol. 2026;9(1):26-36
Abstract

PSA response to predict progression in metastatic hormone-sensitive prostate cancer (mHSPC) patients. When is the optimal time point?

Authors: Martínez-Corral R et al.

Summary: This retrospective (2017-24) multicentre study examined the most informative time point for PSA response to predict disease progression in 599 patients with mHSPC receiving ADT plus ARPI. Over a median follow-up of 24 months, biochemical recurrence rates at 3, 6, and 9 months were 48%, 60%, and 53%, respectively. The highest predictive accuracy of PSA response for progression at 18 months came from the 9-month cut-off (AUC = 0.87); negative predictive value (NPV) was high at all time points (0.92, 0.95, and 0.97), while positive predictive value (PPV) was limited (0.44, 0.38, and 0.38). Kaplan-Meier analysis suggested a longer PFS in biochemical complete response (PSA ≤0.2 ng/mL) versus non-response (NR; PSA >0.2 ng/mL) groups at 6 and 9 months (p < 0.0001). Independent predictors of progression were high-volume disease and NR status.

Comment: Secondary analyses of mHSPC ADT based therapy trials show that shorter time to PSA nadir as well as achieving an undetectable level are prognostic markers of clinical response. However, it has yet to be defined when the optimal time point is for landmark analysis of 'time to PSA nadir'. This retrospective study of patients undergoing ARPI doublet therapy investigated the predictive utility of PSA measured at different timepoints for disease progression within 18 months. They find that PSA response at 9 months (<0.22 ng/mL) had the highest discriminative ability for progression, with a high negative predictive value. This adds to a growing body of evidence supporting the use of PSA response at 9 months to select patients for de-escalation.

Reference: Urol Oncol. 2026;44(2):124.e9-124.e15
Abstract

Utility of MRI perilesional biopsy in prostate cancer: Impact of the Prostate Imaging-Reporting and Data System and biopsy history

Authors: Cannoletta D et al.

Summary: Despite limited evidence, the European Association of Urology guidelines recommend combining MRI-targeted biopsies with perilesional biopsies as an alternative to systematic biopsies. These authors investigated the diagnostic performance of perilesional biopsies compared to other biopsy strategies, assessing the impact of the Prostate Imaging-Reporting and Data System (PI-RADS) score and biopsy history in 2852 patients with a visible lesion at mpMRI of the prostate and a Prostate Imaging-Reporting and Data System (PI-RADS) score ≥3 who underwent MRI-targeted biopsies plus perilesional biopsies as an alternative to systematic biopsies. Perilesional biopsies were defined as those taken from sectors next to the mpMRI lesion. Overall, 48% of patients had clinically significant prostate cancer, with MRI-targeted biopsies plus systematic biopsies having a higher detection rate than MRI-targeted biopsies plus perilesional biopsies (50% vs 45%, p = 0.03); this was especially evident for patients undergoing active surveillance (46% vs 40%, p = 0.04) and those with PI-RADS 3 lesions (26% vs 21%, p = 0.02; no significant differences were found between groups for PI-RADS 4 or 5 lesions).

Comment: In patients with an MRI visible lesion, targeted biopsy including additional perilesional cores is recommended as an alternative strategy to targeted biopsy with systematic gland sampling. This retrospective cohort study compared the two strategies in men with ≥PI-RADS 3 lesions undergoing routine targeted and systematic biopsy, with systematic cores taken from sectors adjacent to lesions labelled as 'perilesional'. For PI-RADS 4/5 lesions both techniques were equivalent, though the systematic biopsies picked up more 'clinically significant' cancers in patients with PI-RADS 3 lesions. Whether these additional tumours are really 'clinically significant', however, is debatable, and systematic biopsies certainly pick up significantly more low-grade tumours.

Reference: BJU Int. 2026;137(2):282-288
Abstract

Prostate zonal impact of 5α-reductase inhibitors on multiparametric MRI characteristics and detection of prostate cancer

Authors: Das A et al.

Summary: This retrospective analysis using data on 1108 PI-RADS version 2 score 3-5 lesions in 718 patients across a multi-institutional cohort assessed the impact of 5α-reductase inhibitors on mpMRI features of such lesions and their influence on the detection of clinically significant prostate cancer. Ninety (8%) of lesions were in patients who had received 5α-reductase inhibitor therapy for ≥3 months prior to mpMRI. There was a significantly reduced odds of detecting clinically significant prostate cancer on targeted biopsy in patients who had received 5α-reductase inhibitors (OR 0.32; 95% CI 0.18-0.57). While there was no difference in odds of detection of clinically significant prostate cancer in transition zone lesions (OR 0.38; 95% CI 0.11-1.18), there was a pronounced reduction in detection in peripheral zone lesions (OR 0.20; 95% CI 0.05-0.68). Upon blinded review in a subset of 66 lesions in patients receiving 5α-reductase inhibitors and matched non-users, higher mean apparent diffusion coefficient values in peripheral zone lesions (869 vs 765 mm^2/s; p = 0.04) and lower lesion conspicuity (p = 0.027) were observed in 5-ARI recipients.

Comment: Men being evaluated in the clinic for an elevated PSA are often either already on or are prescribed dutasteride/tamsulosin for concomitant LUTS, but how this affects the performance of prostate MRI for cancer detection remains to be clarified. This retrospective study measured the rates of ≥Grade Group 2 cancer stratified by zonal location in men treated with or without a 5α-reductase inhibitor. Overall, the rate of diagnosis of clinically significant prostate cancer was lower in men taking 5α-reductase inhibitors than those without for lesions in the peripheral zone, but not the transition zone, even when matched by lesion PI-RADS rating and other relevant clinical features. Further analysis showed 5α-reductase inhibitors led to changes in apparent diffusion coefficient within the peripheral zone, which could increase the rates of false-positive lesion detection. Important to remember in interpreting MRI/biopsy discordance.

Reference: BJU Int. 2026;137(2):332-338
Abstract

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