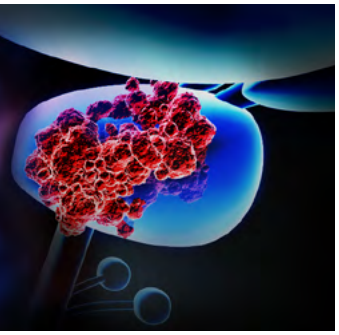
Prostate Cancer Research Review™



Making Education Easy

Issue 78 - 2024

In this issue:

Abbreviations used in this issue:

ADT = androgen-deprivation therapy; **AS** = active surveillance; **AUC** = area under the receiver operating characteristic curve; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **IL** = interleukin; **Lu** = lutetium; **mCRPC** = metastatic castration-resistant prostate cancer; **mpMRI** = multiparametric magnetic resonance imaging; **OR** = odds ratio; **OS** = overall survival; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **PI-RADS** = Prostate Imaging-Reporting and Data System.

Welcome to Issue 78 of Prostate Cancer Research Review.

According to the findings of the phase II ENZA-p trial, the addition of [[177]Lu]Lu-PSMA-617 to enzalutamide improved PSA progression-free survival in men with metastatic castration-resistant prostate cancer. In a large US study, we learn that while AS is the preferred management strategy for low-risk prostate cancer, not everyone takes it up. We conclude this issue with a study on the impact of genomic biomarkers on a clinical risk prediction model for upgrading/upstaging among men with favorable-risk 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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[[177]Lu]Lu-PSMA-617 plus enzalutamide in patients with metastatic castration-resistant prostate cancer (ENZA-p): An open-label, multicentre, randomised, phase 2 trial

Authors: Emmett L et al.

Summary: This open-label, randomised, controlled phase II trial assessed the use of enzalutamide plus adaptive-dosed [177]Lu-PSMA-617 versus enzalutamide alone in 162 patients with mCRPC. After a median follow-up of 20 months, 32 (39%) enzalutamide plus [177]Lu-PSMA-617 and 16 (20%) enzalutamide alone recipients remained on treatment. Median PSA progression-free survival (PFS) was 13.0 months (95% CI 11.0-17.0) with enzalutamide plus [177]Lu -PSMA-617 and 7.8 months (95% CI 4.3-11.0) with enzalutamide alone (HR 0.43; 95% CI 0.29-0.63; p < 0.0001). The most common all grade adverse events were fatigue (75%), nausea (47%), and dry mouth (40%) in the enzalutamide plus 177Lu-PSMA-617 group and fatigue (70%), nausea (27%), and constipation (23%) in the enzalutamide alone group; grade 3-5 adverse events occurred in 40% versus 41%. Grade 3 events occurring only in enzalutamide plus [177]Lu-PSMA-617 recipients included anaemia (4%) and decreased platelet count (1%).

Comment: Androgen receptor inhibition can increase PSMA expression in prostate cancer cells, suggesting potential synergy between agents directed against both targets. This is tested in this Australian open-label phase II study which randomised men with mCRPC to either enzalutamide alone or in combination with 2-4 doses (depending on persistence of PSMA-PET positive disease after 2 doses) of [177]Lu-PSMA-617 in the first-line setting. Eligible patients had PSMA-PET-positive disease with at least 2 risk factors for early progression with enzalutamide monotherapy. Combination treatment significantly improved PSA-PFS (the primary endpoint) with consistent positive effects across key secondary endpoints. However, given that more and more patients are being exposed to novel hormonal agents in the hormone sensitive phase of the disease it will be important to establish efficacy at this point.

Reference: Lancet Oncol. 2024;25(5):563-571
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.

Determinants of active surveillance uptake in a diverse population-based cohort of men with low-risk prostate cancer: The Treatment Options in Prostate Cancer Study (TOPCS)

Authors: Xu J et al.

Summary: This US study examined determinants of uptake of active surveillance (AS) over definitive treatment among 1688 men with low-risk prostate cancer. Overall, 57% of patients chose AS (51% Black participants, 61% White), with unadjusted patient factors associated with initial AS uptake including older age, White race, and higher education. After adjustment for covariates, none of these factors predicted AS uptake. The strongest determinant was a recommendation by a urologist (adjusted prevalence ratio 6.59; 95% CI 4.84-8.97). Other factors included a shared patient-physician treatment decision, greater prostate cancer knowledge, and residence in metro-Detroit versus Georgia. Men who thought of their diagnosis as more serious were less likely to choose AS.

Comment: Although AS is the preferred management strategy for low-risk prostate cancer, not everyone takes it up, particularly in the US. This large cohort study explored factors associated with higher uptake in an ethnically diverse population. Almost 60% of men chose AS (with the remainder proceeding to definitive treatment), with by far the strongest influence being urologist treatment recommendation. This makes sense, as it is likely a surrogate for other clinical/pathological factors not measured in the study (number of cores involved, maximum linear length, MRI findings), which might influence the clinical recommendation. Of those factors that decrease adoption of AS, lack of understanding about risk of progression and over-estimating the 'curative' benefits of treatment were independently significant, suggesting better education and counselling could increase AS uptake even further.

Reference: Cancer 2024;130(10):1797-1806
Abstract

A prospective study of birth weight and prostate cancer risk and mortality in the Health Professionals Follow-up Study

Authors: Liu Q et al.

Summary: This analysis of data from the Health Professionals Follow-up Study assessed the association between self-reported birth weight and aggressive prostate cancer risk in 19,889 men. Overall, 2520 men were diagnosed with prostate cancer, with 643 having higher-grade/advanced stage disease, 296 with lethal disease, and 248 with fatal disease. There was no association between birth weight and overall prostate cancer, or lower-grade or organ-confined disease. There was a borderline trend for risk of higher-grade and/or advanced-stage prostate cancer with increasing birth weight (adjusted HR [aHR] per pound 1.05; 95% CI 0.99-1.11; p = 0.08); there were no associations with risk of lethal (aHR 0.99; 95% CI 0.91-1.08) or fatal (aHR 0.99; 95% CI 0.90-1.08) disease.

Comment: Higher birth weight is linked with an increased incidence of a range of different cancers, particularly breast cancer, by adversely impacting a number of different growth pathways during organ development. Similar biological mechanisms are hypothesised to be active during prostate organogenesis, with a number of small studies reporting an increase in the risk of both prostate cancer incidence as well as the development of clinically significant disease. This large and well-powered prospective cohort study nested within the larger Health Professionals Follow-up Study investigated the association between self-reported birth weight and subsequent development of prostate cancer over 22 years of follow-up. No significant association was observed between higher birth weight and any measure of future aggressive cancer, comprehensively putting this one to bed.

Reference: Br J Cancer 2024;130(8):1295-1303
Abstract

Impact of circulating tumor cell-expressed prostate-specific membrane antigen and prostate-specific antigen transcripts in different stages of prostate cancer

Authors: Cho H et al.

Summary: This prospective study examined whether a circulating tumour cell (CTC)-based transcript platform assessing mRNA expression of six transcripts (PSMA, PSA, AR, AR-V7, EpCAM, and KRT 19 mRNA) could identify potential prognostic markers in 21 healthy individuals and 247 prostate cancer patients (localised prostate cancer n = 94; metastatic hormone-sensitive prostate cancer [mHSPC] n = 44; mCRPC n = 109). CTC detection rates for localised prostate cancer, mHSPC, and mCRPC were 75.5%, 95.3%, and 98.0%. In localised prostate cancer, expression of PSMA (HR 3.35; p = 0.028) and PSA (HR 1.42; p = 0.047) mRNA were associated with biochemical recurrence. Patients with mHSPC with high PSMA (HR 4.26; p = 0.020) and PSA (HR 3.52; p = 0.042) mRNA expression had worse mCRPC-PFS rates than those with low PSMA and PSA expression. Increased PSA and PSMA expression was associated with shorter PSA-PFS and radiological PFS in patients with mCPRC, suggesting a possible drug resistance association.

Comment: CTC enumeration has been found to have prognostic relevance in advanced prostate cancer, however, CTCs are rarely detected in localised disease. In this context, this interesting Korean study reports CTC levels in various stages of prostate cancer, reporting positive detection in 73% of patients with localised disease, a third of whom had low-grade disease. It is likely that their highly sensitive method is detecting normal circulating prostate cells rather than tumour cells per se, as CTCs were also detected in healthy donors at a lower level, albeit not significantly different to patients with both localised prostate cancer and mHSPC. As such the observed interaction with PSA and PSMA expression probably reflects detection of 'true' CTC, suggesting a possible prognostic role in early disease with this assay.

Reference: Clin Cancer Res. 2024;30(9):1788-1800
Abstract

Annual mpMRI surveillance: PI-RADS upgrading and increasing trend correlated with patients who harbor clinically significant disease

Authors: Greenberg JW et al.

Summary: This prospective, single-centre study assessed the utility of annual multiparametric mpMRI in 208 patients on AS, using radiologic upgrading and PI-RADS trends to identify clinically significant disease identified by subsequent biopsy. Men with a PI-RADS score of 3 and 5 at first mpMRI had similar biopsy Gleason grade reclassification-free survival to counterparts. However, men with an initial PI-RADS score of 4 had a shorter 5-year Gleason grade reclassification-free survival versus those with a PI-RADS score of 1-2. In a subset of 70 patients with ≥2 mpMRIs, those experiencing increasing mpMRI scores had a greater risk of Gleason grade reclassification, and a 35.4% difference in 5-year Gleason grade reclassification-free survival probability.

Comment: Traditional AS programs rely on regular interval prostate resampling to detect evidence of tumour progression even if other clinical parameters (PSA, clinical stage) remain stable. As evidence accumulates of the reliability of prostate MRI to detect evidence of progression, increasingly clinicians are opting to replace interval biopsies with interval MRIs. Further supporting this approach is this small prospective study from the US which found that men in whom the PI-RADS lesion score increased over time had a much greater risk of upgrading on subsequent biopsy than those in whom it decreased or remained stable. Good news for patients, and radiologists.

Reference: Urol Oncol. 2024;42(5):158.e11-158.e16
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.

During the COVID-19 pandemic 20 000 prostate cancer diagnoses were missed in England

Authors: Lemanska A et al.

Summary: This analysis of the English OpenSAFELY-TPP dataset (n =24 million) assessed the effect of the COVID-19 pandemic on prostate cancer incidence, prevalence, and mortality from January 2015 to July 2023. Recorded incidence declined by 4772 (31%) cases in 2020 (15,550 vs 20,322; 95% CI 19,241-21,403) and by 3148 cases in 2021 (18%; 17,950 vs 21,098; 95% CI 19,740-22,456). In 2022, incidence had returned to expected levels. Age at diagnosis shifted towards older men, from 71.6 years (95% CI 71.5-71.8) in 2020 and 71.8 years (95% CI 71.7-72.0) in 2021 versus 71.3 years (95% CI 71.1-71.4) in 2019.

Comment: It was predicted that the reduction in routine cancer screening during the COVID-19 pandemic would lead to a delay in diagnosis and a subsequent increase in late presentation; however, only now is the potential scale of the problem becoming evident. This prospective cohort study used NHS-England data to estimate the number of prostate cancer cases missed, reporting a greater than 30% reduction in diagnoses compared to preceding years. This equates to more than 20,000 missed diagnoses of prostate cancer, who based on current figures are still yet to enter the healthcare system. How this will impact patient outcomes is unclear, but if even a fraction of the patients progress to requiring long-term systemic therapy it will likely prove costly from a healthcare payers' perspective.

Reference: BJU Int. 2024;133(5):587-595
Abstract

Clinical characterization of patients diagnosed with prostate cancer and undergoing conservative management: A PIONEER analysis based on big data

Authors: Gandaglia G et al.

Summary: The PIONEER analysis used data from 8 databases to describe clinical characteristics and long-term outcomes of 12,146 newly diagnosed prostate cancer patients receiving conservative management (did not receive curative or palliative treatment for ≥6 months after diagnosis). The most common comorbidities in these patients were hypertension (35-73%), obesity (9.2-54%), and type 2 diabetes (11-28%). The rate of prostate cancer-related symptomatic progression ranged from 2.6% to 6.2%. During the 1st year of follow-up, hospitalisation (12-25%) and emergency department visits (10-14%) were common, while the probability of being free from both palliative and curative treatments decreased during follow-up.

Comment: PIONEER, part of the European Innovative Medicine Initiative's (IMI's) "Big Data for Better Outcomes" program aims to improve care through the application of big data analysis. This initial report looked at data from 8 European and US electronic health-related registries (medical records, claims data) to identify men treated with observation for at least the first 6 months following diagnosis. They report common co-morbidities within the cohort as well as rates of symptomatic progression and intervention with curative or palliative intent. However, key data are missing, such as clinical and pathological characteristics as well as more importantly the 'intent' of observation (AS vs watchful waiting), which makes it very difficult to discern any meaningful insights from the data.

Reference: Eur Urol. 2024;85(5):457-465
Abstract

Clinical validation of circulating GDF15/MIC-1 as a marker of response to docetaxel and survival in men with metastatic castration-resistant prostate cancer

Authors: Mahon KL et al.

Summary: This study assessed level 2 evidence of cytokine biomarker utility associated with resistance to docetaxel in patients with mCRPC. In 120 patients, higher growth differentiation factor (GDF15/MIC-1) levels at baseline ($p = 0.03$) and day 21 ($p = 0.004$) of docetaxel treatment were associated with shorter OS, but IL-4 and IL-6 levels were not associated with outcomes. In another cohort of 430 patients, higher GDF15 levels at baseline ($p < 0.0001$) and day 42 ($p < 0.0001$) predicted shorter OS. Plasma samples from men with high GDF15 levels caused an increase in monocyte CD86 expression ($p = 0.03$), but this effect was not observed with recombinant GDF15.

Comment: Previous work has identified that an anti-inflammatory response mediated by tumour associated macrophages contributes to docetaxel resistance in CRPC. This study from Kate Mahon in Sydney investigated the association between specific cytokines measured at baseline and end of cycle 1 or 2 with OS in men with mCRPC treated with docetaxel. Only elevated levels of GDF15, previously known as macrophage inhibitory cytokine-1, were associated with a shorter OS independent of other established prognostic markers. Interestingly, plasma from patients with high GDF15 was shown to activate monocytes *in vitro*, whereas recombinant GDF15 did not, suggesting GDF15 is a marker rather than a mediator of the response.

Reference: Prostate 2024;84(8):747-755
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.

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The Transatlantic Recommendations for Prostate Gland Evaluation with Magnetic Resonance Imaging After Focal Therapy (TARGET): A systematic review and international consensus recommendations

Authors: Light A et al.

Summary: This systematic review aimed to develop consensus statements on MRI acquisition, interpretation, and reporting after focal therapy for prostate cancer based on 73 studies. In 20 studies reporting suspicious imaging features, all cited focal contrast enhancement as suspicious for cancer recurrence, while among 31 studies reporting MRI assessment criteria, the PI-RADS score was used most often (20 studies; 65%), followed by 5-point Likert scores (6 studies; 19%). Key recommendations include performing routine MRI at 12 months using an mpMRI compliant with PI-RADS version 2.1 standards. PI-RADS scores for assessing recurrence within ablation zones should be avoided. An alternative 5-point scoring system using a major dynamic contrast enhancement (DCE) sequence and minor diffusion-weighted and T2-weighted sequences was proposed. In the DCE sequence, focal nodular strong early enhancement was considered the most suspicious finding.

Comment: How do you know if focal therapy has worked? This international group performed a systematic literature review of the role of MRI in detecting recurrent disease after focal ablation to develop some management guidelines. The main recommendations were to perform annual MRIs for surveillance, regardless of negative finding on interval biopsy (if done), and to use DCE sequences as the dominant sequence to detect recurrence in the ablation zone findings reported on a 5-pont Likert scale rather than using the PI-RADS system. For lesions outside the ablation zone, both the PI-RADS and the 5-point score should be reported. Good to get some practical recommendations, but I'm still not sure how to tell if focal therapy has worked; as it turns out, neither do the people who do it.

Reference: Eur Urol. 2024;85(5):466-482
Abstract

The impact of genomic biomarkers on a clinical risk prediction model for upgrading/upstaging among men with favorable-risk prostate cancer

Authors: Braun AE et al.

Summary: This study sought to assess the impact of genomic classifiers on upgrading or upstaging risk prediction in a clinicopathologic model to distinguishing indolent from aggressive prostate cancer using data from 864 men for the prediction model (cohort 1) and validated in 2267 participants (cohort 2). The prediction model included biopsy Gleason grade group 1 versus Gleason grade group 2 (OR 5.83; 95% CI 3.73-9.10), PSA (OR 1.10; 95% CI 1.01-1.20; per 1 ng/mL), percent positive biopsy cores (OR 1.01 per 1%; 95% CI 1.01-1.02), prostate volume (OR 0.98 per mL; 95% CI 0.97-0.99), and age (OR 1. 05 per year; 95% CI 1.02-1.07), and had an AUC of 0.70 (cohort 1) and AUC of 0.69 (cohort 2). Oncotype Dx Genomic Prostate Score was associated with upgrading or upstaging (OR 1.03; 95% CI 1.01-1.06; $p < 0.01$) and an AUC of 0.72, indicating a similar performance to the prediction model.

Comment: Clinical outcomes for men with favourable intermediate-risk disease are quite heterogenous. The vast majority follow an indolent course; however, a small group of men have more aggressive disease with the potential to metastasise in the absence of, or despite, early radical treatment. This prospective cohort study measured the utility of two transcription-based tumour assays (Oncotype Dx or Prolaris) measured in diagnostic biopsies to improve on a clinical risk predictor of subsequent tumour upgrading and/or upstaging (in those who underwent surgery) in men with low-risk or low-volume favourable intermediate-risk prostate cancer undergoing prostatectomy. Overall, the transcriptional assays added little to the clinical model in terms of predicting more adverse pathology, an inaccurate surrogate endpoint of disease 'lethality'. The appropriate measure should have been development of metastases in patients treated conservatively.

Reference: Cancer 2024;130(10):1766-1772
Abstract