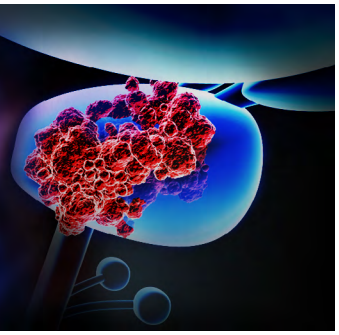
Prostate Cancer Research Review™



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Issue 72 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **AS** = active surveillance; **CI** = confidence interval; **mCRPC** = metastatic castration-resistant prostate cancer; **MRI** = magnetic resonance imaging; **NCCN** = National Comprehensive Cancer Network; **OS** = overall survival; **PET** = positron emission tomography; **PI-RADS** = Prostate Imaging-Reporting and Data System; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RECIST** = Response Evaluation Criteria in Solid Tumours; **TRAE** = treatment-related adverse event; **TRUS** = transrectal ultrasound; **UCSF** = University of California San Francisco.

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Welcome to Issue 72 of Prostate Cancer Research Review.

According to the findings of a phase III trial, in patients with prostate cancer with high-risk biochemical recurrence, the combination of enzalutamide plus leuprolide is superior to leuprolide monotherapy in terms of metastasis-free survival, and enzalutamide monotherapy is superior to leuprolide alone. In a single-centre retrospective review, testosterone replacement therapy was not associated with conversion to treatment among patients with localised prostate cancer on active surveillance. We wrap up this issue with a follow-up study of a multicentre, prospective, phase III imaging trial which found that presurgical PSMA-PET was a strong prognostic biomarker improving biochemical recurrence-free survival risk assessment.

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,

Associate Professor Niall Corcoran
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Improved outcomes with enzalutamide in biochemically recurrent prostate cancer

Authors: Freedland SJ et al.

Summary: This randomised controlled, phase III trial examined enzalutamide plus ADT with leuprolide and enzalutamide monotherapy versus leuprolide ADT alone in 1068 patients with prostate cancer who had high-risk biochemical recurrence with a PSA doubling time of ≤9 months. Over a median follow-up of 60.7 months, metastasis-free survival was 87.3% (95% CI 83.0-90.6) with combination therapy, 71.4% (95% CI 65.7-76.3) with leuprolide alone, and 80.0% (95% CI 75.0-84.1) with enzalutamide monotherapy; enzalutamide plus leuprolide was superior to leuprolide alone (HR 0.42; 95% CI 0.30-0.61; p <0.001) and enzalutamide monotherapy was superior to leuprolide alone (HR 0.63; 95% CI 0.46-0.87; p = 0.005).

Comment: There are a couple of key take-aways from this study of enzalutamide +/- ADT in patients with high-risk biochemical recurrence following prostatectomy. The first is that the combination of enzalutamide plus ADT significantly delayed the development of radiologically apparent metastasis, which is perhaps not surprising as most of these patients have 'very low volume' metastatic hormone-sensitive prostate cancer, and so is consistent with previous studies showing clinical benefit regardless of disease volume. The second is that enzalutamide monotherapy also showed superior metastasis-free survival compared to leuprolide (although to a lesser extent than the combination), with less hot flashes, which might be advantageous in some patients. Given cross resistance between androgen receptor targeting agents, response to subsequent lines of therapy and overall survival will be important in determining if this treatment strategy is worth the additional treatment burden relatively early in the disease.

Reference: N Engl J Med. 2023;389(16):1453-1465
Abstract

Prostate Cancer Research Review™

Independent commentary by Associate Professor Niall Corcoran.

Associate Professor Niall Corcoran is a urological surgeon at the Royal Melbourne and Frankston Hospitals, and a principal research fellow in the Department of Surgery, University of Melbourne. He is also the Research and Education Lead for GU oncology for the Victorian Comprehensive Cancer Centre.

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Single-dose ^{177}Lu-PSMA-617 followed by maintenance pembrolizumab in patients with metastatic castration-resistant prostate cancer: An open-label, dose-expansion, phase 1 trial

Authors: Aggarwal R et al.

Summary: This US open-label, dose-expansion, phase I study assessed a single-dose of lutetium-177 [^{177}Lu]-prostate-specific membrane antigen (PSMA)-617 (^{177}Lu-PSMA-617) followed by maintenance pembrolizumab in 43 patients with mCRPC. A recommended phase II dosage of ^{177}Lu-PSMA-617 7.4 gigabecquerel (GBq) intravenously (IV) 28 days before maintenance intravenous pembrolizumab (200 mg every 3 weeks) was selected based on safety and feasibility of administration in 18 patients. In a follow-up series in 25 patients, 14 (56%; 95% CI 35-76) had a confirmed objective response. Overall, 2 (5%) patients experienced a TRAE of grade ≥3 (arthritis, pneumonitis); there was 1 serious adverse event (death due to aspiration pneumonia) and no treatment-related deaths.

Comment: Turning immunologically cold tumours hot to take advantage of the powerful and sustained cancer control potential of immune checkpoint inhibitors is a very active area of research globally. In this small phase I study, the authors primed patients with mCRPC who had progressed on at least one androgen receptor signalling inhibitor (ARSI) with a single dose of ^{177}Lu-PSMA followed by maintenance therapy with pembrolizumab. Just over half of patients had a confirmed objective response by RECIST criteria. The median progression-free survival was 6.9 months, with a small number of patients showing more durable responses. Responders had evidence of immune cell activation suggesting successful priming by ^{177}Lu-PSMA. Interesting data, but still a lot of work to do before it's ready for clinical implementation.

Reference: Lancet Oncol. 2023;24(11):1266-1276
Abstract

The oncologic risk of magnetic resonance imaging-targeted and systematic cores in patients treated with radical prostatectomy

Authors: Gaffney CD et al.

Summary: This US, single-centre, retrospective (2014-22) analysis of 991 patients (359 with adverse pathology) who had both an MRI-targeted prostate biopsy and a systematic biopsy compared the relative oncologic risk of Grade Group (GG) prostate cancers diagnosed by both techniques. MRI-guided biopsy GG influenced oncologic risk versus systematic biopsy GG alone ($p < 0.001$); however, for discordant grades between biopsies, the risk was intermediate between grades (e.g., average risk of advanced pathology for GG2 and GG3 on systematic biopsy was 19% and 66%, but average risk was 47% for GG2 on systematic biopsy and GG3 on MRI-guided biopsy). The equivalent 12-month biochemical recurrence estimates were 5.8%, 15%, and 10%.

Comment: Traditional biopsy techniques are subject to significant sampling error, but because cores were taken over a template it did include implicit information about the volume of the cancer present, which has prognostic implications. Now that image guided biopsies are the routine, this information is lost to some degree, so it is now not clear that grade for grade, cancers detected by contemporary techniques carry the same clinical risk as those detected by untargeted cores. This is important, as almost all of the information we have about subsequent risk of metastases and death (as well as the potential benefits of treatment) is based on untargeted tumour biopsies. This downward risk migration is demonstrated in this study from Memorial Sloan Kettering, which shows that patients with higher-grade disease detected only on MRI-targeted biopsies have a lower risk of adverse features/biochemical recurrence than patients with the same disease detected by a systematic biopsy. Important information to consider.

Reference: Cancer 2023;129(23):3790-3796
Abstract

Genomic profiling of metastatic castration-resistant prostate cancer samples resistant to androgen receptor pathway inhibitors

Authors: Menssouri N et al.

Summary: This was an analysis of samples collected during the prospective MATCH-R trial in patients with mCRPC who underwent whole-exome sequencing (WES; n= 59) and/or RNA sequencing (RNA-seq) before androgen receptor inhibition and 18 patients with biopsies taken at the time of development of resistance, to identify genomic alterations associated with resistance to androgen receptor inhibition. WES suggested no single-gene genomic alterations strongly associated with primary resistance, while RNA-seq indicated that androgen receptor (AR) gene alterations and expression levels did not differ between responders and non-responders. RNA-based pathway analysis suggested primary resistance was associated with a higher Hedgehog pathway score, lower AR pathway score and lower NOTCH pathway score. Sub-clonal evolution and AR-related gene alterations or neuroendocrine differentiation were associated with acquired resistance, but androgen receptor inhibition did not induce tumour transcriptome changes in most patients; however, cell proliferation programs were enriched in resistant samples.

Comment: Upregulation of AR signalling, most commonly by amplification of the AR gene, drives resistance to conventional ADT and spurred the development of novel hormonal agents such as enzalutamide. But how does prostate cancer become resistant to these new treatments? This interesting study, leveraging access to paired samples from the same patients pre- and post-treatment, attempts to address this question. However, the answer is not clear, with no single-gene alterations associated with acquired resistance at least as revealed by whole exome and transcriptome sequencing. The usual suspects were identified though, acquisition of additional known drivers, neuro-endocrine differentiation etc., most of which have been identified in conventional ADT resistance studies. Perhaps not surprising, as the treatment target is still the same.

Reference: Clin Cancer Res. 2023;29(21):4504-4517
Abstract

Impact of genomic testing on urologists' treatment preference in favorable risk prostate cancer: A randomized trial

Authors: Carbunaru S et al.

Summary: This randomised controlled trial assessed the impact of the Oncotype Dx Genomic Prostate Score (GPS) on 10 urologists' preference for active surveillance versus active treatment (i.e., prostatectomy/radiation) in 200 men with favourable-risk prostate cancer. The urologists' preference for prostatectomy/radiation was almost double in the GPS versus the control arm (29.3% vs 14.1%; $p = 0.01$). Multivariate analysis suggested that predictors of urologists' preference for active treatment were GPS, intermediate NCCN risk level, and lower patient health literacy.

Comment: Clinicians will increasingly be asked to incorporate the results of molecular biomarker testing into treatment decision-making in early prostate cancer. This study randomised men with low and favourable intermediate-risk prostate cancer to either standard of care or further risk stratification using the GPS assay (a transcriptional assay of 17 genes). Randomisation to the GPS group increased the likelihood of a recommendation of active treatment in this relatively low-risk setting. Given the higher risk of under sampling in the study cohort (no pre-biopsy MRI, 10-12 core TRUS biopsy) this is perhaps understandable, given anxiety around missing a more aggressive tumour. I wonder if a similar study in the Australian setting might reduce recommendations for radical treatment.

Reference: Cancer Med. 2023;12(19):19690-19700
Abstract

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Does testosterone replacement therapy increase the risk of conversion to treatment in patients with prostate cancer on active surveillance?

Authors: Daza J et al.

Summary: This single-centre retrospective review assessed testosterone replacement therapy (TRT) in 96 patients with localised prostate cancer on active surveillance. Over a median follow-up of 5.82 years there were no differences in conversion to treatment (24% vs 21%) nor in treatment-free survival. PSA density was the only variable associated with treatment-free survival (HR 1.08; 95% CI 1.03-1.13; p = 0.001).

Comment: Given the association of androgen signalling with prostate cancer progression, there has been some long-held uncertainty regarding the safety of TRT in men with prostate cancer, particularly when the tumour is still *in situ*. This retrospective study compared rates of progression to active management in a small cohort of men treated with TRT compared to a propensity matched control group. After almost 6 years of follow-up, TRT was not associated with an increased risk of conversion to treatment, although longer follow-up is still required to allay lingering doubts. From a clinical perspective it makes little sense to deny symptomatic hypogonadal men TRT back to normal physiological levels, as there is plenty of data to suggest tumours arising in a low androgen receptor signalling environment are more aggressive from the get go.

Reference: Urol Oncol. 2023;41(10):429.e1-429.e7
Abstract

Long-term complications and health-related quality of life outcomes after radical prostatectomy with or without subsequent radiation treatment for prostate cancer

Authors: Baskin A et al.

Summary: This analysis of data from the UCSF Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE™) registry assessed long-term complications and health-related quality of life (HRQoL) after radical prostatectomy with and without radiation therapy in 6258 men with prostate cancer. At 5 years, cumulative incidence of external beam radiation therapy (EBRT) was 9.1%. Those receiving postoperative radiation had a greater risk of onset of cystitis (HR 5.60; 95% CI 3.40-9.22; p < 0.01). Radiation therapy had no association with other complications. Post-operative radiation therapy was associated with worse general health scores.

Comment: Urologists are often reluctant to refer patients with biochemical recurrence post-prostatectomy for salvage radiation (SRT) due to concerns about additional toxicity, particularly worsening urinary incontinence. This retrospective analysis of the CaPSURE registry at UCSF investigated the rate of complications and quality of life in men receiving SRT (9% of the cohort) versus those who did not. The only 'coded' complication that was higher in the SRT group was cystitis, although the absolute incidence was low. SRT however was associated with a decrease in health-related quality of life outcomes across all domains (urinary, bowel and sexual function), as well as overall HRQoL which was significant even after adjustment for other variables. The models don't appear to be adjusted for disease recurrence though, which would also be expected to be a bit of a downer.

Reference: Urol Oncol. 2023;41(10):429.e9-429.e14
Abstract

Is prostatic adenocarcinoma with cribriform architecture more difficult to detect on prostate MRI?

Authors: Belue MJ et al.

Summary: This retrospective study assessed whether the cribriform (CBFM) pattern on prostate biopsy was associated with false-negative MRI and the association between MRI and histopathological disease burden in 131 patients. Among those with confirmed CBFM pathology, targeted biopsy alone identified CBFM in 76.3% of patients and detected prostate cancer in 97.7% of patients. Systematic biopsy alone detected CBFM in 61.1% of patients and prostate cancer in 90.8% of patients. In prostate cancer patients with no CBFM pattern, and those with a CBFM pattern there was a correlation between maximum MRI lesion dimension and cancer core length (CCL). There was a difference in CCL between CBFM and non-CBFM lesions for T2-weighted scores of 3 and 5 and PI-RADS 5 lesions, with CBFM lesions having larger CCL, despite no difference in dimension of MRI lesions.

Comment: Different MRI sequences detect differences in the molecular composition of the imaged tissues, for instance T2-weighted imaging detects local water content, whereas diffusion weighted imaging (DWI) measures local water molecule mobility. Although there is a clear association between tumour grade and image characteristics (for instance in higher grade tumours, cells are more tightly packed which restricts free water movement, appearing as bright on DWI with a corresponding low signal on the apparent diffusion coefficient [ADC] map), how histological patterns affect these characteristics are not clear. This small study suggests that cribriform architecture (a growth pattern of high-grade disease) may be more difficult to detect on MRI, but given it is based on biopsy findings without a ground state truth it is difficult to interpret. A more appropriate methodology would be to compare tumours maps from prostatectomy specimens to MRI findings in patients with or without variant growth patterns.

Reference: Prostate 2023;83(16):1519-1528
Abstract

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Survival of veterans treated with enzalutamide and abiraterone for metastatic castrate resistant prostate cancer based on comorbid diseases

Authors: Schoen MW et al.

Summary: This was a US retrospective observational study of 5822 veterans initiating mCRPC treatment with abiraterone (57% of patients) or enzalutamide (43%). Enzalutamide recipients were older (mean 75.8 vs 75.0 years) with higher mean Charlson comorbidity index (4.4 vs 4.1), and greater rates of cardiovascular disease or diabetes (74.2% vs 70.6%). Enzalutamide recipients had longer median OS compared to abiraterone (24.2 vs 22.1 months; $p = 0.001$). Patients with cardiovascular disease or diabetes had a longer median treatment duration with enzalutamide (11.4 vs 8.6 months; $p < 0.001$) and a longer median OS (23.2 vs. 20.5 months; $p < 0.001$) than with abiraterone. Propensity score-matched analysis suggested that enzalutamide was associated with decreased mortality compared to abiraterone (HR 0.90; 95% CI 0.84-0.96).

Comment: With broadly equal efficacy across the novel hormonal agents, the choice of medication usually comes down to access/funding and patient co-morbidities. In this context, this retrospective cohort study reports on men with mCRPC in the Veterans Administration system treated in the first-line setting either with abiraterone or enzalutamide. Despite being a little older and more comorbid compared to patients treated with abiraterone, those treated with enzalutamide had a small but significant increase in overall survival. Useful data, particularly for patients with diabetes and/or significant cardiovascular disease.

Reference: Prostate Cancer Prostatic Dis. 2023;26(4):743-750
Abstract

Presurgical ^{68}Ga-PSMA-11 positron emission tomography for biochemical recurrence risk assessment: A follow-up analysis of a multicenter prospective phase 3 imaging trial

Authors: Djaïleb L et al.

Summary: This follow-up study of a multicentre, prospective, phase III imaging trial examined the added prognostic value of presurgical PSMA-PET on biochemical recurrence-free survival versus presurgical Cancer of the Prostate Risk Assessment (CAPRA) and postsurgical CAPRA-Surgery (CAPRA-S) scores in 277 patients with intermediate- to high-risk prostate cancer receiving radical prostatectomy and pelvic lymph node dissection. In 240 (87%) patients with clinical follow-up over a median follow-up of 32.4 months, 91 (38%) biochemical recurrence events were observed. PSMA-PET N1/M1 occurred in 17% of patients. Univariate predictors of biochemical recurrence were PSMA-PET prostate uptake, PSMA-PET N1/M1, and CAPRA and CAPRA-S scores. Addition of PSMA-PET N1/M1 status to presurgical CAPRA score improved the risk assessment (c-statistic 0.70 vs 0.63; $p < 0.001$). The postsurgical CAPRA-S score alone did not differ from a model combining the presurgical CAPRA score and PSMA-PET N1/M1 status.

Comment: With the Australian PRIMARY study suggesting that the pattern and intensity of PSMA-PET avidity in the prostate can be predictive of tumour aggressiveness, there is increasing interest in using various radiomic measures as biomarkers to predict future tumour behaviour. This US study investigated the impact of high prostate uptake (PROMISE score >2) as well as the detection of extra-prostatic disease on the risk of biochemical recurrence in post-prostatectomy patients enrolled in a multicentre prospective phase III imaging trial. As a single variable, high prostate PSMA avidity was associated with a shorter biochemical recurrence free survival, but this lost significance in multivariable models containing standard clinical and pathological variables reflected in the CAPRA score. However, there appears to be enough of a signal to continue this line of inquiry.

Reference: Eur Urol. 2023;84(6):588-596
Abstract

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