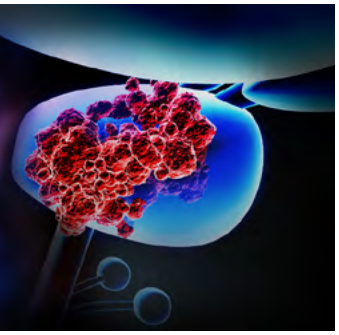
Prostate Cancer Research Review™



Making Education Easy

Issue 64 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **AS** = active surveillance; **BMI** = body mass index; **CI** = confidence interval; **CT** = computed tomography; **ECOG** = Eastern Cooperative Oncology Group; **HR** = hazard ratio; **IHC** = Immunohistochemical; **ISUP** = International Society of Urological Pathology; **LDL-C** = low-density lipoprotein cholesterol; **mCRPC** = metastatic castration-resistant prostate cancer; **MRI** = magnetic resonance imaging; **OS** = overall survival; **PARP** = poly-ADP ribose polymerase; **PBS** = Pharmaceutical Benefits Scheme; **PET** = positron emission tomography; **PFS** = progression-free survival; **PLND** = pelvic lymph node dissection; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RCT** = randomised controlled trial; **SRT** = salvage radiation therapy; **TRUS** = transrectal ultrasound scan; **TURP** = transurethral resection of the prostate.

Welcome to Issue 64 of Prostate Cancer Research Review.

First up we take a look at a study investigating rucaparib in patients with metastatic castration-resistant prostate cancer and discover that rucaparib significantly improves the duration of imaging-based progression-free survival versus physician's choice of treatment in those with *BRAC* alterations. Following on, we learn that geminin or Ki67, and *PTEN*, predicted response to radiotherapy independently of established prognostic factors in patients with prostate cancer. Other topics covered in this issue include chemohormonal therapy versus extended pelvic lymph-node dissection, uncontrolled cardiovascular risk factors with prostate cancer, healthy lifestyle in men at increased genetic risk for prostate cancer, darolutamide effects on local urinary and bowel symptoms, and nadir PSA as an independent predictor of survival outcomes.

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
niall.corcoran@researchreview.com.au

Rucaparib or physician's choice in metastatic prostate cancer

Authors: Fizazi K et al.

Summary: This randomised controlled phase III trial assessed the use of rucaparib in 405 patients with metastatic castration-resistant prostate cancer (mCRPC) with a *BRCA1*, *BRCA2*, or *ATM* mutation who had progressed after a second-generation androgen-receptor pathway inhibitor (ARPI). A *BRCA* alteration was observed in 201 rucaparib and 101 control recipients. After 62 months, the duration of imaging-based progression-free survival (PFS) was longer in rucaparib than control recipients overall (median 10.2 vs 6.4 months; HR 0.61; 95% CI 0.47-0.80; $p < 0.001$) and in the *BRCA* subgroup (median 11.2 vs 6.4 months; HR 0.50; 95% CI 0.36-0.69; $p < 0.001$). An exploratory analysis in the ATM subgroup suggested that the median duration of imaging-based PFS did not differ between treatment groups (median 8.1 vs 6.8 months; HR 0.95; 95% CI 0.59-1.52). The most frequent rucaparib adverse events were fatigue and nausea.

Comment: Further data supporting the efficacy of PARP inhibitors in patients with mCRPC harbouring genomic alterations in DNA damage repair genes. In this phase III RCT, patients with germline or somatic alterations in *BRCA1*, *BRCA2* or *ATM* who progressed following treatment with second-generation ARPIs were randomised to either the PARP inhibitor rucaparib or physician's choice control. Overall patients treated with rucaparib had a 40% increase in time to radiographic progression, but the effect was more pronounced in patients with *BRCA* alterations compared to those with changes in *ATM*. One thing to note is the number of patients needed to be screened (almost 5000) to identify 405 patients with deleterious mutations. In addition, 45% of patients in the control arm received an alternative ARPI, which has previously been shown to have limited activity in this space and so may artificially inflate the efficacy of the PARP inhibitor.

Reference: N Engl J Med. 2023;388(8):719-732
Abstract

Multi-candidate immunohistochemical markers to assess radiation response and prognosis in prostate cancer: Results from the CHHiP trial of radiotherapy fractionation

Authors: Wilkins A et al.

Summary: This translational case control sub-study within the CHHiP trial of radiotherapy fractionation assessed whether protein markers of cellular proliferation, hypoxia, apoptosis, cell cycle checkpoints, growth factor signalling, and inflammation could improve prediction of prognosis and assist treatment stratification following either conventional or hypofractionated radiotherapy in patients with prostate cancer. After adjustment for multiple comparisons, immunohistochemical (IHC) analysis of 336 tumours suggested that *PTEN*, geminin, mean Ki67 and max Ki67 were prognostic. In a multivariate model (n = 212, 106 matched pairs), *PTEN* and geminin predicted prognosis, although no marker predicted biochemical recurrence dependent on fractionation.

Comment: Although genomic and transcriptomic analyses have come to dominate the prognostic biomarker space in localised prostate cancer, the biological processes underlying these biomarkers can be integrated into single or limited numbers of protein biomarkers that can be easily measured by IHC (for example Ki67, a protein proliferation marker, as a surrogate of the Prolaris Cell Cycle Progression Score). This is significantly easier and cheaper than 'genomic' analyses, although without specialised techniques to accurately quantify differential staining, some of the dynamic range is lost. This biomarker study examined the prognostic potential of selected IHC markers in patients enrolled within the CHHiP study, a large RCT comparing conventional versus moderately hypofractionated radiotherapy in patients with localised prostate cancer. In this case-control translational sub-study, *PTEN* loss and IHC markers of cell proliferation (Ki67, geminin) predicted prognosis independently of other variables. Would be interesting to apply to active surveillance cohorts.

Reference: EBioMedicine. 2023;88:104436
Abstract

Comparison of neoadjuvant chemohormonal therapy vs. extended pelvic lymph-node dissection in high-risk prostate cancer treated with robot-assisted radical prostatectomy

Authors: Oishi T et al.

Summary: This retrospective study compared postoperative complications and prognosis after robot-assisted radical prostatectomy (RARP) plus extended pelvic lymph-node dissection (ePLND) versus RARP plus neoadjuvant chemohormonal therapy without ePLND in 452 patients with high-risk prostate cancer (PSA ≥20 ng/mL, Gleason score 8-10, or cT2c-3). Post-operative complications were more common in ePLND versus non-ePLND patients ($p < 0.001$). Inverse probability weighting-adjusted biochemical recurrence-free survival (HR 0.29; $p < 0.001$) and castration-resistant prostate cancer (CRPC)-free survival (HR 0.29, $p = 0.010$) were better in non-ePLND recipients.

Comment: Neoadjuvant chemohormonal therapy and ePLND are both trying to achieve the same thing, namely the eradication of micrometastatic disease in the hope this translates in better disease control. *A priori* it might be assumed that systemic therapy would be superior, given it is able to target lymph node disease outside of the surgical template, as well as at distant sites, however, this has not been tested. This interesting Japanese retrospective cohort study compared biochemical recurrence-free survival in patients with high-risk disease treated either with neoadjuvant chemohormonal therapy (ADT plus estramustine phosphate for 6-9 months) or concomitant ePLND. Postoperative complications were higher in those patients who underwent a lymph node dissection, whereas time to biochemical recurrence as well as time to castration resistance was higher (and substantially!) in patients treated systemically. Hypothesis generating rather than definitive, but likely another nail in the coffin of ePLND.

Reference: Sci Rep. 2023;13(1):3436
Abstract

The burden of uncontrolled cardiovascular risk factors in men with prostate cancer: A RADICAL-PC analysis

Authors: Klimis H et al.

Summary: This multinational prospective study examined the rate and correlates of poor cardiovascular risk factor control among 2811 men with prostate cancer (mean age 68 years; 9% metastatic disease; 23% pre-existing cardiovascular disease [CVD]). Overall, 99% of participants had ≥1 uncontrolled cardiovascular risk factor, and 51% had poor overall risk factor control (defined as ≥3 elements including elevated LDL-C, current smoker, physical inactivity, elevated blood pressure [BP], and waist/hip ratio >0.9). After adjustment for education, cancer characteristics, ADT, depression, and ECOG functional status, poor overall risk factor control was associated with not taking a statin (OR 2.55; 95% CI 2.00-3.26), physical frailty (OR 2.37; 95% CI 1.51-3.71), a requirement for BP control drugs (OR 2.36; 95% CI 1.84-3.03), and age (OR per 10-years 1.34; 95% CI 1.14-1.59).

Comment: It is a truism that the biggest cause of death at all stages of prostate cancer (except for mCRPC) is cardiovascular disease, not prostate cancer. There is probably an element of selection bias in this, as advancing age is a significant risk for both. This informative report from a prospective cohort study documents the rate of modifiable risk factors for cardiovascular events in patients with newly diagnosed prostate cancer or commencing on ADT across multiple jurisdictions (including Australia). Almost every patient had one or more uncontrolled modifiable risk factor, most commonly obesity and uncontrolled hypertension, with over half having poor overall risk factor control. Useful information, for nearly every newly diagnosed patient asks what lifestyle modifications they can make to decrease the risk of disease progression, if they look after their heart they probably live longer!

Reference: JACC CardioOncol. 2023;5(1):70-81
Abstract

A healthy lifestyle in men at increased genetic risk for prostate cancer

Authors: Plym A et al.

Summary: This analysis assessed whether 12,411 genotyped men from the prospective Health Professionals Follow-up Study (1993-2019) and the Physicians' Health Study (1983-2010) who were at an increased genetic risk of prostate cancer could reduce their risk with a healthy lifestyle (healthy weight, healthy diet, vigorous physical activity, not smoking). Over a 27-year follow-up, 3005 prostate cancer and 435 lethal prostate cancer events occurred with a 4-fold difference between the highest and lowest quartiles (HR 4.32; 95% CI 3.16-5.89). In the highest quartile, a healthy lifestyle was associated with a decreased rate of lethal prostate cancer (HR 0.55; 95% CI 0.36-0.86) versus an unhealthy lifestyle, with a lifetime risk of 1.6% (95% CI 0.8-3.1) with a healthy and a 5.3% (95% CI 3.6-7.8) with an unhealthy lifestyle. A healthy lifestyle did not affect the risk of overall prostate cancer.

Comment: Complementing this report is this study on the impact of lifestyle factors on overall and lethal prostate cancer events in men enrolled in the Health Professionals Follow-up Study and the Physicians' Health Study stratified by genetic risk as measured using a polygenic risk score (269 germline polymorphisms associated with prostate cancer in genome wide association studies). In patients within the highest quartile of genetic risk, a healthy lifestyle (4 of 6 of: BMI <30 kg/m^2, high vigorous physical activity, smoking status, high intake of tomato-based products, high intake of fatty fish, low intake of processed meat) was associated with an almost 50% reduction in the risk of lethal prostate cancer, although prostate cancer incidence overall was unaffected. Something to consider when reaching for the second salami sandwich!

Reference: Eur Urol. 2023;83(4):343-351
Abstract

Phase II randomized study of salvage radiation therapy plus enzalutamide or placebo for high-risk prostate-specific antigen recurrent prostate cancer after radical prostatectomy: The SALV-ENZA trial

Authors: Tran PT et al.

Summary: The multicentre, randomised, double-blind, placebo-controlled, phase II SALV-ENZA trial assessed whether enzalutamide, without concurrent ADT increases freedom from PSA progression when combined with SRT in 86 men with recurrent prostate cancer after radical prostatectomy. Over a median follow-up of 34 months PSA progression rate was lower in enzalutamide versus placebo recipients (HR 0.42; 95% CI 0.19-0.92; p = 0.031), and 2-year freedom from progression rate was 84% versus 66%. Subgroup analyses suggested a differential benefit of enzalutamide in men with pT3 (HR 0.22; 95% CI 0.07-0.69) versus pT2 disease (HR 1.54; 95% CI 0.43-5.47; p = 0.019) and R1 (HR 0.14; 95% CI 0.03-0.64) versus R0 disease (HR 1.00; 95% CI 0.36-2.76; p = 0.023). The most common adverse events in enzalutamide and placebo recipients were grade 1-2 fatigue (65% vs 53%) and urinary frequency (40% vs 49%).

Comment: The addition of a second-generation androgen-signalling inhibitor to standard therapy has improved oncological outcomes in almost every phase of the disease (with the exception of the misguided attempt to introduce enzalutamide into active surveillance!). Further evidence of this comes from this small phase II RCT of SRT for patients with biochemical recurrence post-prostatectomy, in which patients randomised to 6 months of neoadjuvant/adjuvant enzalutamide had longer freedom from PSA progression compared to those assigned to placebo. This is perhaps not surprising given that the endpoint is directly affected by the intervention in a way that may be independent of any anti-cancer activity, so reporting of any effect on metastasis-free survival is awaited.

Reference: J Clin Oncol. 2023;41(6):1307-1317
Abstract

Multicenter external validation of a nomogram for predicting positive prostate-specific membrane antigen/positron emission tomography scan in patients with prostate cancer recurrence

Authors: Bianchi L et al.

Summary: This multicentre retrospective study conducted an external validation of a nomogram developed to predict ^{68}Ga-labeled PSMA-11 PET/CT results in a new cohort of 1639 recurrent prostate cancer patients with first-time biochemical recurrence (Group 1; n = 774); PSA relapse after salvage therapy (Group 2; n = 499); biochemical persistence after radical prostatectomy (Group 3; n = 210); and advanced-stage prostate cancer before second-line systemic therapies (Group 4; n = 124). Overall detection rate was 53.8% in the new cohort versus 51.2% in the original population. Multivariate analysis suggested that ISUP grade group, PSA, PSA doubling time, and clinical setting independently predicted a positive scan (all p ≤ 0.02). The predictive accuracy of the nomogram with the new cohort was identical to that with the original cohort (82.0%) and the model had an optimal calibration curve. The best nomogram cut-off was 55%. Decision curve analysis identified a clinical net benefit when the threshold nomogram probabilities were ≥20%.

Comment: One of the vagaries of PBS approval for PSMA-PET scanning in Australia is that patients are only entitled to two reimbursable scans to restage following biochemical recurrence after definitive treatment. There is therefore considerable interest is determining the PSA sweet spot at which a PSMA-PET scan will be most informative at a level that is still salvageable. In this multi-institutional study, the authors validated the performance of a previously developed nomogram to predict scan positivity. The PSA doubling time was by far the strongest predictor of a positive scan, followed by PSA level at the time of scanning, clinical stage (persistence vs recurrence; post-salvage radiation vs recurrence) followed by tumour grade. The nomogram performed well, with a net clinical benefit observed when the predicted positive rate was >20%.

Reference: Eur Urol Oncol. 2023;6(1):41-48
Abstract

Impact of darolutamide on local symptoms: Pre-planned and post hoc analyses of the ARAMIS trial

Authors: Shore ND et al.

Summary: This analysis of data from the randomised, placebo-controlled, phase III ARAMIS trial assessed the effect of the androgen receptor inhibitor darolutamide on urinary and bowel symptoms in patients with non-mCRPC treated with darolutamide (n = 955) or placebo (n = 554). Fewer darolutamide (4.7%) than placebo (9.6%) recipients underwent invasive procedures, with a longer time to first procedure (HR 0.42; 95% CI 0.28-0.62). Darolutamide delayed worsening of quality of life for total urinary and bowel symptoms versus placebo (p < 0.01), mostly due to symptoms of urinary frequency, pain, and interference with daily activities. Adverse events of urinary retention and dysuria were less common with darolutamide, and greater PSA responses in darolutamide recipients were associated with lower incidences of urinary retention and dysuria.

Comment: ADT and other systemic therapies usually have more of an effect on the growth of extra-prostatic deposits than they do on the primary tumour. In this context this analysis of deterioration in urinary symptoms or invasive intervention (such as catheter or TURP) in patients enrolled in the ARAMIS study (darolutamide vs placebo in men with non-mCRPC) is interesting. Equal proportions of patients had either prior prostatectomy (~25%) or radiation (~17%) in both arms, with the majority having an untreated primary *in situ*. Patients treated with darolutamide had less deterioration in urinary symptoms, and half the rate of invasive intervention. That said rate of invasive intervention in the placebo group was low, with only 3% requiring a TURP and <1% upper tract drainage.

Reference: BJU Int. 2023;131(4):452-460
Abstract

Long-term outcomes following active surveillance of low-grade prostate cancer: A population-based study using a landmark approach

Authors: Timilshina N et al.

Summary: This Canadian retrospective, population-based study sought to determine long-term population-level oncological outcomes in 21,282 low-grade prostate cancer patients on active surveillance and the active surveillance discontinuation rate. Over a median follow-up of 9.8 years, the 10-year follow-up survival rate for remaining on active surveillance was 39%, the metastasis-free survival rate was 94.2%, the OS rate was 88.7%, and the cancer-specific survival rate was 98.1%. In an adjusted analysis, active surveillance was associated with a higher risk of metastasis (HR 1.34, 95% CI 1.15-1.57), overall mortality (HR 1.12, 95% CI 1.01-1.24), and prostate cancer-specific mortality (HR 1.66, 95% CI 1.15-2.39) than initial treatment. Survival analysis based on 7525 propensity-matched pairs was consistent with the results for metastasis-free survival, OS and cancer-specific survival.

Comment: Active surveillance for low grade prostate cancer has been around for some time, but its impact on oncological outcomes in the real-world setting has yet to be fully defined. This large, retrospective, population-based study investigated the effect of an initial period of active surveillance on metastasis-free and prostate cancer-specific mortality-free survival in patients with newly diagnosed low-grade cancer in Ontario, comparing outcomes to those electing upfront treatment. Over 60% of patients treated with active surveillance converted to radical therapy with time, and although patients treated upfront had higher volume disease, initial active surveillance was associated with a reduction in both metastasis-free and prostate-cancer-specific-mortality-free survival independent of other tumour factors. The absolute incidence of both of these outcomes were low in both groups, however, even out to 15 years, with patient selection based on 8-12 core TRUS biopsy without pre-biopsy MRI likely leading to significant misclassification in both groups.

Reference: J Urol. 2023;209(3):540-548
Abstract

Nadir prostate-specific antigen as an independent predictor of survival outcomes: A post hoc analysis of the PROSPER randomized clinical trial

Authors: Hussain M et al.

Summary: This *post hoc* analysis of the multinational, randomised, double-blind, placebo-controlled, phase III PROSPER trial evaluated the relationship between depth of PSA decline and clinical outcomes in enzalutamide-treated men with non-mCRPC. Enzalutamide-treated men with PSA declines of <50%, 50-90%, 90% with nadir ≥0.2 ng/mL, and ≥90% with nadir <0.2 ng/mL were associated with median metastasis-free survival of 22.1 months (95% CI 14.8-not reached), 34.2 months (95% CI 29.4-not reached), 36.6 months (95% CI 33.4-not reached), and not reached, and OS of 40.8 months (95% CI 31.7-44.9), 54.4 months (95% CI 49.0-67.0), 64.3 months (95% CI 63.4-not reached), and not reached.

Comment: The efficacy of ADT and similar androgen receptor signalling inhibitors in individual patients is quite variable and can be hard to predict. However, nadir PSA (the lowest absolute level of PSA after treatment), has consistently been shown to be associated with longer disease response in a number of different clinical settings. Adding to this evidence base is this report from the PROSPER study, which demonstrated significantly improved metastasis-free and OS in patients treated with combination ADT plus enzalutamide versus ADT plus placebo in patients with non-mCRPC. Both the magnitude percentage decline in PSA as well as the PSA nadir were positively associated with significant improvements in both metastasis-free survival and OS. As expected, meaningful PSA responses were not observed in the placebo group.

Reference: J Urol. 2023;209(3):532-539
Abstract

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.

RACGP Accredited GP education webinar on Testicular Cancer

Date: Wednesday 3 May 2023.

Time: 7.00-8.15pm.

Where: Online via Zoom.

Topics and Speakers:

Testicular cancer & other benign & malignant scrotal conditions, Dr Pras Sivam, Urological Surgeon and Uro-Oncologist.

Exercise physiology & cancer, Molly Lowther, Accredited Exercise Physiologist.

Moderator, Dr Jane Crowe, General Practitioner.

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