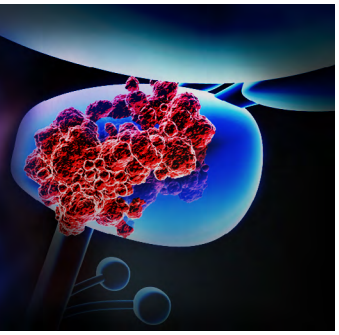
Prostate Cancer Research Review™



Making Education Easy

Issue 71 - 2023

In this issue:

Abbreviations used in this issue:

ANZUP = Australian and New Zealand Urogenital and Prostate Cancer Trials Group; **AS** = active surveillance; **CI** = confidence interval; **HR** = hazard ratio; **IGF-1** = insulin-like growth factor 1; **mCRPC** = metastatic castration-resistant prostate cancer; **MRI** = magnetic resonance imaging; **NCCN** = National Comprehensive Cancer Network; **OR** = odds ratio; **OS** = overall survival; **PARP** = poly (ADP-ribose) polymerase; **PCSM** = prostate cancer-specific mortality; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **TEAE** = treatment-emergent.

Welcome to Issue 71 of Prostate Cancer Research Review.

A large Australian-led study has emphasised that the *BRCA* genes are key prognostic biomarkers in metastatic castration-resistant prostate cancer, with patients with alterations in *BRAC2* having significantly reduced progression-free and overall survival compared to *BRCA2* intact patients. In a study from the US, we learn that the financial burden of care in patients with metastatic castration-resistant prostate cancer has increased substantially, emphasising that treatments that delay metastatic spread (such as surgery or radiation for localised disease) are the most beneficial in terms of societal costs. We wrap up this issue with a Mexican study revealing that pubertal characteristics might be helpful in identifying risk groups for high-grade 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,

Associate Professor Niall Corcoran
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BRCA-deficient metastatic prostate cancer has an adverse prognosis and distinct genomic phenotype

Authors: Fettke H et al.

Summary: This study examined changes in DNA damage response (DDR) genes in 375 patients with mCRPC. Overall, 34.5% of patients had ≥1 DDR alterations (including monoallelic alterations) with the most frequently affected genes being *BRCA2* (19%), *ATM* (13%), *FANCA* (5%), *CHEK2* (5%) and *BRCA1* (3%). *BRCA* alterations, and particularly *BRCA2*, led to poorer PFS (HR 3.3; 95% CI 1.9-6.0; p < 0.001), OS (HR 2.2; 95% CI 1.1-4.5; p = 0.02) and PSA response rates to androgen receptor (AR) inhibitors (32% vs 60%; p = 0.02). *BRCA*-deficient tumours also had alterations in genes including the AR and phosphoinositide 3-kinase (PI3K) pathways. Monoallelic and biallelic *BRCA2* alterations did not differentially affect clinical outcomes (median PFS 3.9 vs 3.4 months vs copy neutral 9.8 months).

Comment: Genomic alterations in DDR genes are present in 20-30% of patients with mCRPC, and at least for *BRCA*, confer sensitivity to PARP inhibitors. This large Australian-led study examined the impact of DDR gene alterations detected by circulating tumour DNA (ctDNA) analysis in patients with mCRPC, predominantly undergoing first-line non-PARP inhibitor treatment, had on patient outcomes. Patients with alterations in *BRAC2* were found to have significantly reduced PFS and OS compared to *BRCA2* intact patients, consistent with previous reports, and any abnormality in DDR genes predicted a worse response to AR signalling inhibitors. The authors also found that detection of an alteration in a single allele of *BRAC2* had the same prognostic/predictive impact as biallelic variation. However, given most aberrations identified were copy number loss events, which are easier to detect in patients with higher ctDNA levels (also a known poor prognostic indicator), it is a little hard to interpret. Would be interesting to go back to the primary tumours to confirm (as proposed early truncal events).

Reference: EBioMedicine 2023:95:104738
Abstract

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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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Healthcare costs in men with metastatic castration-resistant prostate cancer: An analysis of US Medicare Fee-For-Service claims

Authors: Freedland SJ et al.

Summary: This analysis of data from the US fee-for-service Medicare population was conducted to estimate healthcare resource utilisation (HRU) and healthcare costs in 14,780 men with mCRPC. Overall, 11,528 men initiated first-line mCRPC therapy, 6275 initiated second-line therapy, and 2945 initiated third-line therapy. All-cause medical HRU (days per patient per year [PPPY]) increased after diagnosis and from first-line through third-line therapy, particularly outpatient care and physician/other visits. Mean all-cause healthcare costs PPPY were $27,468 before diagnosis and increased over 4-fold after mCRPC diagnosis ($124,379) and continued to rise during first- ($148,325), second- ($160,118) and third-line ($165,186) therapy.

Comment: Patients with metastatic prostate cancer tend to survive a long time compared to other tumour types, and with the increased development of life prolonging therapies, the financial burden of care in this phase of the disease is exploding. This is confirmed by this Medicare claims-based analysis of US patient data, which shows the cost of care increasing over 4-fold in the first year after diagnosis of mCRPC, with increases for each subsequent line of therapy. This supports Australian analyses that show that, at least from a healthcare payer's perspective, treatments that delay metastatic spread (such as surgery or radiation for localised disease) are the most beneficial in terms of societal cost, even if this results in significant overtreatment.

Reference: Adv Ther. 2023;40(10):4480-4492
Abstract

Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): Final prespecified overall survival results of a randomised, double-blind, phase 3 trial

Authors: Saad F et al.

Summary: This analysis provided the final prespecified OS results from the randomised, double-blind, phase III PROpel trial of olaparib plus abiraterone (n = 399) versus placebo plus abiraterone (n = 397) in men with mCRPC. Over a median follow-up of 36.6 months for olaparib plus abiraterone and 36.5 months for placebo plus abiraterone, median OS was marginal (42.1 months; 95% CI 38.4-not reached vs 34.7 months; 95% CI 31.0-39.3; HR 0.81; 95% CI 0.67-1.00; p = 0.054). Grade 3-4 adverse events included anaemia in 16% of olaparib plus abiraterone and 3% of placebo plus abiraterone recipients; serious adverse events occurred (40% vs 32%). One death (interstitial lung disease) in the placebo plus abiraterone group was considered treatment related.

Comment: Pre-clinical data suggests that AR signalling is important for efficient homologous recombination repair, and that interfering with this (such as with enzalutamide) could replicate a '*BRCA*-deficient state', rendering them susceptible to PARP inhibition, even in patients with normal *BRCA* genes. This was supported by the initial report of the PROpel study, which demonstrated that the combination of abiraterone with olaparib improved PFS in patients with mCRPC treated in the first-line setting unselected for *BRCA* status. However, in this final report, OS was not significantly different between the treatment arms and so at least in unselected patients, it is unclear if the small incremental benefit is worth the additional toxicity.

Reference: Lancet Oncol. 2023;24(10):1094-1108
Abstract

Efficacy and safety outcomes of darolutamide in patients with non-metastatic castration-resistant prostate cancer with comorbidities and concomitant medications from the randomised phase 3 ARAMIS trial

Authors: Fizazi K et al.

Summary: This *post hoc* analysis of the Androgen Receptor Antagonizing Agent for Metastasis-free Survival (ARAMIS) trial assessed the use of darolutamide in patients with non-mCRPC stratified by number of comorbidities and concomitant medications. Darolutamide increased OS versus placebo among patients with ≤6 (HR 0.65) and >6 (HR 0.73) comorbidities, and this was consistent for cardiovascular, metabolic, and other comorbidities (HR 0.39-0.88). Increased OS was also observed among patients receiving ≤10 (HR 0.76) and >10 (HR 0.66) concomitant medications and was observed across all medication classes (HR 0.45-0.80). TEAEs and TEAEs leading to treatment discontinuation did not differ from placebo across subgroups.

Comment: The ARAMIS trial demonstrated that treatment of non-mCRPC patients with darolutamide improved metastasis-free survival and OS compared with placebo, with a favourable safety and tolerability profile. Given that many prostate cancer patients with advanced disease are older, with multiple co-morbidities requiring numerous medications, this *post-hoc* analysis investigated the impact of the number of co-morbidities and concomitant medications on treatment efficacy. The investigators report no difference in efficacy based on either concomitant medication use or co-morbidities, suggesting this approach is safe even in frailer patients. Useful information, although the prevalence of non-mCRPC in Australian practice appears to be very low.

Reference: Eur J Cancer 2023:192:113258
Abstract

Neoadjuvant cabazitaxel plus abiraterone/leuprolide acetate in patients with high-risk prostate cancer: ACDC-RP phase II trial

Authors: Fleshner NE et al.

Summary: This open-label, multicentre, phase II trial compared early treatment intensification with neoadjuvant abiraterone acetate plus leuprolide acetate, with or without cabazitaxel, before radical prostatectomy in 70 patients (median age 63.5 years; PSA 21.9 ng/mL) with high-risk, localised prostate cancer. Pathologic complete response (pCR) or minimal residual disease (MRD) rates did not differ between treatments (43.2% vs 45.5%); pCR (5.4% vs 9.1%). Patients with ≤25% positive total biopsy cores had greater odds of pCR/MRD (p = 0.04). Those who achieved pCR/MRD had better 12-month biochemical relapse-free survival rates (96.0% vs 62.0%; p = 0.03). Grade ≥3 adverse events occurred in 42.5% and 23.7% of patients.

Comment: Neoadjuvant 'window-of-opportunity' studies are useful to test the potential activity of novel combinations as well as gain insights into molecular mechanisms of response/resistance. There is also increasing evidence that patients who achieve excellent pathological responses have significantly lower rates of recurrence and progression, a hypothesis currently being tested in the recently fully recruited PROTEUS study. This phase II study shows that adding in cabazitaxel to combination abiraterone and leuprolide did not improve pathological response, only increased toxicity. However, they did observe a similar trend towards better clinical outcomes in men achieving complete pCR/MRD.

Reference: Clin Cancer Res. 2023;29(19):3867-3874
Abstract

Genomic classifier performance in intermediate-risk prostate cancer: Results from NRG Oncology/RTOG 0126 randomized phase 3 trial

Authors: Spratt DE et al.

Summary: This retrospective analysis of data from the NRG Oncology/RTOG 0126 randomised phase III trial assessed the performance of the 22-gene Decipher genomic classifier (GC) in 215 samples from men with intermediate-risk disease. Over a median follow-up of 12.8 years, multivariate analysis suggested that the 22-gene GC (per 0.1 unit) was prognostic for prostate cancer-specific mortality (PCSM; HR 1.45; 95% CI 1.20-1.76; $p < 0.001$), distant metastasis (HR 1.28; 95% CI 1.06-1.55; $p = 0.01$), biochemical failure (HR 1.22; 95% CI 1.10-1.37; $p < 0.001$), and disease progression (HR 1.12; 95% CI; 1.00-1.26; $p = 0.04$). The ten-year distant metastasis rate was 45 versus 16 in GC low-risk versus high-risk patients. In those with lower GC scores, the 10-year difference in metastasis-free survival rate was -7% versus 21% for higher GC scores ($p = 0.04$).

Comment: Acknowledging that many patients currently classified as intermediate-risk disease have a relatively indolent clinical trajectory, there is increasing interest in applying molecular testing in this cohort to improve risk stratification. In this retrospective study the authors analysed the GC score (an RNA-based gene expression signature) in biopsy samples from patients enrolled in a randomised controlled trial investigating the benefit of dose-escalated radiation in men with localised intermediate-risk prostate cancer. Higher GC scores were associated with increased rates of disease progression, development of metastases as well as PCSM independent of other variables. So, it looks useful, and good to the know that the Decipher GC will be one of three molecular stratification tools used in the soon to commence ANZUP sponsored GenI-AIRSPACE study.

Reference: Int J Radiat Oncol Biol Phys. 2023;117(2):370-377
Abstract

Efficacy of National Comprehensive Cancer Network guidelines in identifying pathogenic germline variants among unselected patients with prostate cancer: The PROCLAIM trial

Authors: Shore N et al.

Summary: This US, prospective, multicentre study sought to determine the prevalence of actionable pathogenic germline variants (PGVs) among unselected 958 prostate cancer patients (median age at diagnosis 65 years; 65% low- or intermediate-risk disease), stratified by NCCN guideline eligibility. In total, 77 PGVs from 17 genes were found in 74 (7.7%) patients (95% CI 6.2-9.6). There were no differences in the prevalence of PGVs among patients who did (8.8%; 95% CI 6.6-12) or did not (6.6%; 95% CI 4.6-9.2) meet 2019 NCCN prostate criteria (OR 1.38; 95% CI 0.85-2.23), suggesting that these criteria would miss 42% (95% CI 31-53) of patients with PGVs. Most PGVs (81%) were clinically actionable.

Comment: Who to test for germline variants (such as *BRCA2*), and when, is an area of significant controversy, with the Americans pushing a 'test all and test early' approach. Australian practice appears much more conservative (probably related to funding restrictions for testing), with referral favoured for men with a strong family history, or with mCRPC who may be candidates for treatment with a PARP inhibitor. This study finds that even men who do not meet the very generous NCCN criteria for germline variants have similar rates of pathogenic variants compared to those meeting criteria. Although this brings into question the relevance of these variants to prostate cancer progression, it is important to note that the results are largely driven by higher prevalence variants of 'unclear importance' (*CHECK2*) rather than bona fide pathogenic variants (*BRCA2*, *HOXB13*) genes, which were enriched in the 'in criteria' cohort.

Reference: Eur Urol Oncol. 2023;6(5):477-483
Abstract

Is active surveillance an option for the management of men with low-grade prostate cancer and a positive family history? Results from a large, single-institution series

Authors: Leni R et al.

Summary: This single-centre study examined the association between family history and reclassification of active surveillance candidates and defined predictors of adverse outcomes in men receiving delayed radical prostatectomy (n = 197) or external-beam radiation therapy (n = 64). In total, 119 (18%) men had a family history of prostate cancer; over a median follow-up of 54 months, 264 patients were reclassified. The 5-year reclassification-free survival rate in those with a family history was 39% versus 57% without ($p = 0.006$), and a family history was associated with reclassification to grade group ≥2 (HR 1.60; 95% CI 1.19-2.15; $p = 0.002$). In those with a family history, the highest predictors of reclassification were PSA density (HR 2.87), high-volume GG 1 (≥33% of cores or ≥50% of any core; HR = 3.04), and suspicious MRI (HR 3.87; all $p < 0.05$). There was no association between family history, adverse pathologic features, and biochemical recurrence.

Comment: A positive family history of prostate cancer, particularly one of metastatic or lethal disease is often seen as a soft contra-indication to active surveillance in otherwise suitable patients. This Italian, single-centre study investigated the impact of a positive family history (first- or second-degree relative, maternal or paternal) on subsequent grade classification in patients initially diagnosed with low-grade prostate cancer and placed on active surveillance. Overall, a positive family history increased the risk of re-classification 1.6-fold, independent of other variables, but did not translate into an increased risk of adverse pathology at prostatectomy or higher rates of biochemical recurrence in those proceeding to definitive treatment. So, from these data it would appear active surveillance is safe, but the lack of clinical data about disease trajectory in the affected relative means important questions remain unaddressed.

Reference: Eur Urol Oncol. 2023;6(5):493-500
Abstract

Relationship between baseline prostate-specific antigen on cancer detection and prostate cancer death: Long-term follow-up from the European Randomized Study of Screening for Prostate Cancer

Authors: Remmers S et al.

Summary: This analysis of data from the European Randomized Study of Screening for Prostate Cancer (ERSSPC) assessed impact of first PSA level on prostate cancer detection and PCSM in a population-based screening trial (repeated every 2-4 years) in 25,589 men aged 55-59 years, 16,898 men aged 60-64 years, and 12,936 men aged 65-69 years. Overall actuarial probability at 16 years ranged from 12-16% for any prostate cancer and from 3.7-5.7% for clinically significant prostate cancer across the age groups ranging from 1.2-1.5% for a PSA <1.0 ng/mL to 13.3-13.8% for a PSA ≥3.0 ng/mL. In men aged 60-61 years 92% of lethal prostate cancer cases occurred in those with a PSA level above the median (1.21 ng/mL). In men initially screened at 60-61 years of age with baseline PSA <2 ng/mL, further screening is unlikely to be beneficial after 68-70 years of age if PSA remains <2 ng/mL, as no PCSM emerged in the subsequent 8 years.

Comment: It is clear that baseline PSA at the first screening visit significantly impacts the risk of the development of lethal prostate cancer in the future and can be used to risk stratify patients for ongoing case-finding surveillance. This is further reinforced by this report from the ERSSPC trial which found that the actuarial probability of clinically significant prostate cancer at 16 years is approximately 10-fold higher in men presenting with a PSA >3.0 ng/mL compared to those with a PSA of <1.0 ng/mL, regardless of age. The authors suggest PSA of <1.0 ng/mL for men aged 55-69 years is a strong indicator to delay or stop further screening, which could result in significant cost savings from a health care payer's perspective.

Reference: Eur Urol. 2023;84(5):503-509
Abstract

Late puberty onset and lack of acne during adolescence reduce high-grade prostate cancer at adulthood

Authors: Hernández-Pérez JG et al.

Summary: This Mexican case-control study examined pubertal events patterns (PEP), prostate cancer and prostate cancer histological differentiation in 371 incident prostate cancer cases and 775 age-matched controls. Late PEP (age at maximum height attainment ≈23 years; no history of acne), was inversely associated with incident prostate cancer (OR 0.27; 95% CI 0.15-0.48; p < 0.01) and high-grade prostate cancer (OR 0.24; 95% CI 0.09-0.59; p < 0.01). Similar associations were obtained after adjusting by IGF-1 (OR 0.19; 95% CI 0.06-0.58) and androgens excretion (OR 0.21; 95% CI 0.06-0.66); after adjustment for these biomarkers, the association between the absence of acne and prostate cancer was still significant.

Comment: The relationship between androgen levels and prostate cancer development is complex. This interesting Mexican study investigated the association between timing in onset of puberty in boys using various clinical measures and future development of high-grade prostate cancer. They find that late-onset puberty significantly mitigates the risk of future development of both incident and high-grade prostate cancer. Reassuring that there is an evolutionary benefit for never making the rugby firsts in high school!

Reference: Prostate 2023;83(14):1342-1350
Abstract