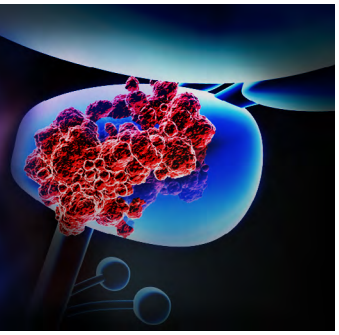
Prostate Cancer Research Review™



Making Education Easy

Issue 80 - 2024

In this issue:

Abbreviations used in this issue:

ADT = androgen-deprivation therapy;
bpMRI = biparametric magnetic resonance imaging; **CI** = confidence interval;
CT = computed tomography;
CTCAE = Common Terminology Criteria for Adverse Events Grade;
HR = hazard ratio; **mCRPC** = metastatic castration-resistant prostate cancer;
mHSPC = metastatic hormone-sensitive prostate cancer;
mpMRI = multiparametric magnetic resonance imaging;
MRI = magnetic resonance imaging; **OR** = odds ratio; **OS** = overall 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;
RARP = robot-assisted radical prostatectomy; **RCT** = randomised controlled trial;
RR = risk ratio; **SBRT** = stereotactic body radiation therapy.

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Welcome to Issue 80 of Prostate Cancer Research Review.

In a post hoc analysis of the SWOG-1216 trial of orteronel versus bicalutamide for metastatic hormone-sensitive prostate cancer, men with bone pain at diagnosis were found to have worse survival outcomes than those without bone pain. A meta-analysis suggests that patients with advanced prostate cancer receiving androgen receptor signaling inhibitors alongside conventional hormonal therapy should be counselled and monitored for an increased risk of cardiovascular events. We conclude this issue with a study showing that larger prostate size may offer protection against higher-stage disease and positive surgical margins in patients with localised 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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Bone pain and survival among patients with metastatic, hormone-sensitive prostate cancer: A secondary analysis of the SWOG-1216 trial

Authors: Gebrael G et al.

Summary: These authors undertook a post hoc secondary analysis of the SWOG-1216 trial, which compared ADT plus orteronel 300 mg twice daily and ADT plus bicalutamide 50 mg daily until disease progression, unacceptable toxic effects, or patient withdrawal in men (n = 1279) with metastatic hormone-sensitive prostate cancer (mHSPC), to compare survival outcomes by presence or absence of baseline bone pain at diagnosis. Data on bone pain was available for 1197 men (median age 67.6 years), 301 (23.5%) of whom had baseline bone pain at mHSPC diagnosis and 896 (70.1%) who did not. Men with bone pain were significantly ($p = 0.02$) younger than men without bone pain at baseline (median age 66 vs 68.2 years), and exhibited a significantly ($p < 0.001$) higher incidence of high-volume disease (70.4% vs 41.6%). At a median follow-up of 4.0 years, men with baseline bone pain had a median OS (primary endpoint) of 3.9 years (95% CI 1.1-1.7 years) versus not reached (95% CI 6.6 years to not reached); adjusted HR 1.66 (95% CI 1.34-2.05), $p < 0.001$. At a median 4-years follow-up, PFS (secondary endpoint) in men with, versus without baseline bone pain was 1.3 years (95% CI 1.1-1.7 years) versus 3.7 years (95% CI 3.3-4.2 years); adjusted HR 1.46 (95% CI 1.22-1.74, $p < 0.001$).

Comment: Presenting with symptoms is usually a bad prognostic sign in any advanced cancer. This secondary analysis of the previously published negative phase III study of orteronel (a non-steroidal CYP17A1 inhibitor that interferes with androgen synthesis) finds that patients with newly diagnosed mHSPC presenting with bone pain have worse PFS and OS than those who don't, even after adjustment for volume of disease. However, timing of presentation (de novo versus metachronous disease) is not controlled for, and with approximately 25% of the entire cohort having a prior radical prostatectomy, introduces the possibility of a lead time bias in the analysis. Needs to be repeated taking this into account.

Reference: JAMA Netw Open 2024;7(7):e2419966
Abstract

Prostate Cancer Research Review™

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.

Lifetime health and economic outcomes of biparametric magnetic resonance imaging as first-line screening for prostate cancer: A decision model analysis

Authors: Gulati R et al.

Summary: This study used a microsimulation model using data from the Surveillance, Epidemiology, and End Results (SEER) database and randomised trials to evaluate the comparative effectiveness and cost-effectiveness from the perspective of the US health care system over a lifetime of biennial screening to age 69 years using PSA-based prostate cancer screening (threshold 4 µg/L), with or without second-line mpMRI, versus first-line bpMRI (PI-RADS 3-5 or 4-5), followed by biopsy guided by MRI or MRI plus transrectal ultrasonography. Using a model of 1000 men, first-line bpMRI prevented 2-3 prostate cancer deaths and added 10-30 life-years (4-11 days per person) versus first-line PSA testing, but increased biopsy number by 1506-4174 and number of overdiagnoses by 38-124. Using conventional cost-effectiveness thresholds, first-line PSA testing with second-line mpMRI followed by biopsy for PI-RADS 4-5 gave the greatest net monetary benefits. First-line PSA testing was more cost-effective even if bpMRI was free, all low-risk prostate cancer underwent surveillance, or screening was quadrennial.

Comment: There are several studies in progress investigating the potential of MRI as an initial screening test for prostate cancer, rather than PSA. This health economic analysis used SEER and RCT data to estimate the costs of two alternative biennial screening models from age 55-69. The first approach used a PSA threshold of 4 µg/L followed by mpMRI if indicated; the second approach used bpMRI as the first-line screening test. Biopsy was recommended if PIRADS 3-5 lesions were identified. In the simulation, a bpMRI screening model was found to lead to a greater number of biopsies performed and a higher diagnosis of clinically insignificant cancer, and in all permutations tested was less cost-effective than PSA followed by a reflex mpMRI, even if the bpMRI was free!

Reference: Ann Intern Med. 2024;177(7):871-881
Abstract

Cardiovascular events and androgen receptor signaling inhibitors in advanced prostate cancer: A systematic review and meta-analysis

Authors: El-Taji O et al.

Summary: This systematic review and meta-analysis assessed the incidence of cardiovascular events with addition of androgen receptor signalling inhibitors (ARSI) to standard of care in locally advanced (M0) and metastatic (M1) prostate cancer based on 24 studies including 22,166 patients (median age 63-77 years; median follow-up time 3.9-96 months). ARSI therapy increased the risk of all-grade cardiovascular events (RR 1.75; 95% CI 1.50-2.04; $p < 0.001$) and grade ≥3 events (RR 2.10; 95% 1.72-2.55; $p < 0.001$). ARSI therapy also increased risk for grade ≥3 events for hypertension (RR 2.25; 95% CI 1.74-2.90; $p < 0.001$), acute coronary syndrome (RR 1.93; 95% CI 1.43-1.60; $p < 0.01$), cardiac dysrhythmia (RR 1.64; 95% CI 1.23-2.17; $p < 0.001$), cerebrovascular events (RR 1.86; 95% CI 1.34-2.59; $p < 0.001$) and cardiovascular-related death (RR 2.02; 95% CI 1.32-3.10; $p = 0.001$). Subgroup analysis suggested increased risk of all cardiovascular events across the prostate cancer spectrum.

Comment: As ARSI use is brought earlier in the prostate cancer treatment paradigm, consideration of their potential long-term side effects becomes more important. This analysis reports on patients from 24 RCTs spanning the disease spectrum from non-mHSPC to metastatic castration-resistant disease. Across the studies there was a consistent two-fold increase in the risk of adverse cardiovascular events associated with ARSI usage, including hypertension, acute coronary syndrome, dysrhythmia and sudden cardiac death. This risk increased to four-fold when two ARSIs were used in combination. Perhaps worth thinking about a cardiac assessment and optimisation of modifiable risk factors before pulling out the script pad.

Reference: JAMA Oncol. 2024;10(7):874-884
Abstract

Evaluating immune checkpoint blockade in metastatic castration-resistant prostate cancers with deleterious *CDK12* alterations in the phase 2 IMPACT trial

Authors: Nguyen CB et al.

Summary: This phase II trial assessed the use of immune checkpoint inhibitor (ICI) therapy in patients with *CDK12*-altered mCRPC treated with ipilimumab (1 mg/kg) with nivolumab (3 mg/kg) every 3 weeks for ≤4 cycles, followed by nivolumab 480 mg every 4 weeks (n = 23) or nivolumab alone 480 mg every 4 weeks (n = 14). A 50% reduction in PSA (PSA50) rate was observed in 9% (95% CI 1-28) of ipilimumab plus nivolumab and no PSA50 responses in nivolumab alone recipients. Median PSA PFS was 7.0 (95% CI 3.6-11.4) versus 4.5 months (95% CI 3.4-13.8) and median OS was 9.0 (95% CI, 6.2-12.3) versus 13.8 (95% CI 3.6-not reached) months.

Comment: CDK12 is a cyclin-dependent kinase involved in regulating gene transcription. Loss of function of *CDK12* leads to a specific reduction in the expression of a number of homologous recombination repair genes resulting in a '*BRCA*-like' state, with a potential for increased accumulation of mutations, neo-antigen formation and potentially increased responses to immunotherapy. This small phase II study investigated the activity of nivolumab +/- ipilimumab in patients with heavily pre-treated mCRPC harbouring a defect in *CDK12*. Responses, however, were poor and not predicted by microsatellite instability or tumour mutational burden, reflecting again that defects in only some components of homologous recombination repair lead to increased ICI sensitivity.

Reference: Clin Cancer Res. 2024;30(15):3200-3210
Abstract

A phase 1 trial of salvage stereotactic body radiation therapy for radiorecurrent prostate cancer after brachytherapy

Authors: Patel KR et al.

Summary: This phase I trial sought to identify the maximum tolerated dose (MTD; 40 Gy, 42.5 Gy, and 45 Gy in 5 fractions) of SBRT in nine patients with local prostate cancer recurrence after brachytherapy. Over a median of 22 months, no grade 3-5 adverse events related to study treatment occurred. Dose escalation was halted because of excellent biochemical control at 40 Gy and 42.5 Gy. The most frequent clinically significant late grade 2 adverse event was genitourinary toxicity. The 1-year biochemical PFS rate was 100% and the 2-year PFS rate was 86%.

Comment: Given the increased morbidity of salvage prostatectomy in localised radio-recurrent disease, there is ongoing interest in investigating alternative approaches. This small, phase I study aimed to determine the maximum tolerated dose of SBRT delivered to recurrent local disease following brachytherapy, with gross tumour volume defined by MRI and PSMA-PET. After nearly 2 years of follow-up, no dose-limiting toxicity was observed even with the highest dose tested. Only 1/9 patients experienced biochemical failure in the observation period, suggesting this may be a viable alternative to salvage surgery and worthy of further investigation. The downside was a high incidence of clinically significant late grade 2 genitourinary toxicity.

Reference: Int J Radiat Oncol Biol Phys. 2024;119(5):1471-1480
Abstract

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Outcomes of cytoreductive radical prostatectomy for oligometastatic prostate cancer on prostate-specific membrane antigen positron emission tomography: Results of a multicenter European study

Authors: Rajwa P et al.

Summary: This European multinational retrospective study examined outcomes of 116 patients treated with cytoreductive radical prostatectomy for *de novo* oligometastatic prostate cancer on PSMA-PET. Overall, 82% of patients had miM1b, 16% had miM1a, and 2.6% had miM1c oligometastatic prostate cancer; median pre-biopsy PSA was 14 ng/mL, and 88% of men had biopsy grade group ≥3 prostate cancer. On PSMA-PET, median number of metastases was two; with 33% of patients having one distant positive lesion, 25% having two lesions, and 42% having ≥3 distant positive lesions. Neoadjuvant systemic therapy was used in 60% of patients, and 32% underwent metastasis-directed therapy. Any complications occurred in 31% of men and Clavien-Dindo grade ≥3 complications in 5% of patients. After a median follow-up of 27 months, 16% of patients developed CRPC and 7% of patients died. The 1-year urinary continence rate was 82%, while the 2-year CRPC-free survival rate was 85.8% (95% CI 78.5-93.7) and OS was 98.9% (95% CI 96.8-100).

Comment: STAMPEDE Arm H found that radiotherapy of the primary tumour improves OS in patients with low metastatic volume by conventional imaging. But does prostatectomy offer a similar benefit? This multicentre study reports on a retrospective cohort of patients with oligometastatic disease on PSMA-PET, of whom 59% were also M1 on conventional imaging. The main finding was that cytoreductive prostatectomy was possible and safe in this cohort of men, although the rates of post-operative complications and urinary incontinence were higher than observed in large series of localised disease. However, progression rates were high even with the short period of follow-up, particularly in patients who did not receive neoadjuvant therapy, reinforcing that in this cohort of patients, surgery is only one part of a multimodal approach.

Reference: Eur Urol Oncol. 2024;7(4):721-734
Abstract

Outcomes of biopsy grade group 1 prostate cancer diagnosis in the Danish population

Authors: Stroomberg HV et al.

Summary: This population-based observational study used data on 12,621 men with grade group 1 prostate cancer from the Danish Prostate Registry to describe outcomes with a particular focus on conservative treatment. Cumulative incidence of endocrine therapy at 10 years was 5.3% (95% CI 4.3-6.3) for men receiving initial active surveillance and 21% (95% CI 19-23) for those undergoing watchful waiting. The prostate cancer-specific mortality rate at 15 years was 14% (95 CI% 11-16) for watchful waiting, 10% (95 CI% 6.7-14) for PSA <10 ng/mL on watchful waiting, and 16% (95 CI% 13-19) for those who did not receive curative-intent treatment or histological assessment.

Comment: With widespread recognition of the very low (if any) metastatic potential of grade group 1 disease, there has been some discussion in the literature as whether it should be termed cancer at all in an effort to reduce patient anxiety. This retrospective analysis of a national cancer registry finds that in patients initially diagnosed with clinically localised grade group 1 disease, the rate of progression to either requiring hormonal treatment or resulting in prostate cancer death were non-trivial, at up to 21% and 14% respectively. The main issue with these results is the historical nature of the cohort (2006 onwards), in which there have been significant advances in improving sampling accuracy at diagnosis as well as significant changes to tumour grading (particularly the reclassification of cribriform growth patterns). The relevance to contemporary debate is therefore dubious.

Reference: Eur Urol Oncol. 2024;7(4):770-777
Abstract

Targeted microwave ablation for prostate cancer (FOSTINE1b): A prospective 'ablate-and-resect' study

Authors: Peltier A et al.

Summary: This French, prospective, single-centre, phase IIa study used an 'ablate-and-resect' design to examine histopathological outcomes, feasibility and safety of targeted microwave ablation (TMA) using the Trinity® system in 11 patients with localised prostate cancer. MRI was undertaken at 7 days and RARP (n = 9) at 1 month after TMA; two patients chose active surveillance after confirmation of low-risk prostate cancer. There were no severe adverse events (CTCAE grade ≥3) at 7 days or 1 month, and no changes occurred in urinary, sexual and ejaculation functional outcomes. T1-weighted MRI showed clear and well-defined ablation zones and RARP was conducted with no difficulties, particularly during dissection of the posterior plane. Histopathological assessment confirmed the absence of viable cells and ablation zone volumetry identified no distinctions between the 3D segmentation of the virtual ablation zone at TMA (median volume 2 mL) and MRI (median volume 1.923 mL); however, there was a reduction in the surgical specimen (median volume 0.221 mL) removed at RARP.

Comment: Another day, another focal therapy treatment promulgated for localised prostate cancer, in this case TMA, which is well established for kidney and liver lesions causing high temperature coagulative necrosis less affected by heat sinks. This interesting phase IIa study investigated the tumour ablative capacity of the Trinity® system in the outpatient setting, demonstrating complete necrosis in targeted tumours in eight of nine patients undergoing subsequent prostatectomy. Like all focal therapies, efficacy depends on the accuracy of pre-treatment MRI-based planning and the ability to completely cover the planned treatment volume without excessive toxicity. Certainly, looks like it has the grunt to kill the tumour though.

Reference: BJU Int. 2024 Aug;134(2):258-267
Abstract

Impact of prostate-specific membrane antigen positron emission tomography/computed tomography on prostate cancer salvage radiotherapy management: Results from a prospective multicenter randomized phase 3 Trial (PSMA-SRT NCT03582774)

Authors: Armstrong WR et al.

Summary: This prospective, multicentre, randomised, controlled, phase III clinical trial examined the impact of PSMA-PET on salvage radiotherapy (SRT) planning (secondary endpoint) on biochemical recurrence-free survival rate in 103 patients with biochemical recurrence of prostate cancer after radical prostatectomy comparing SRT (control; n = 90) or PSMA-PET CT prior to SRT planning (n = 103). PSMA-PET localised recurrences occurred in 37% of patients. There was a 23% difference (95% CI 9-35; p = 0.002) in the frequency of major changes between the control arm (22%) and the PSMA-PET intervention arm (45%); of the major changes, 72% were related to PSMA-PET. There was a 17.6% difference (95% CI 5.4-28.5; p = 0.005) in treatment escalation frequency between the control (12%) and intervention arms (29%). Treatment de-escalation occurred in 10.5% of control and 11.8% of intervention arm patients, and mixed changes in 0% and 3.9% of patients.

Comment: PSMA-PET has become the imaging modality of choice in patients with biochemical recurrence post-prostatectomy, although it has yet to be demonstrated that treatment based on the additional information provided is better than previous clinical/pathological risk-based decision-making. To address this, this phase III study has randomised patients with biochemical recurrence selected for SRT and volume planning based on conventional imaging (standard of care, including choline-PET) or PSMA-PET. The primary endpoint is biochemical recurrence-free survival at 5 years, which is due to readout in 2025. This interim analysis focuses on the impact of PSMA-PET scanning to treatment planning, with 23% more patients experiencing a change to treatment plan (most commonly dose escalation and the addition of extra fields). Whether this improves patient's outcomes will become clear in time.

Reference: Eur Urol. 2024 Jul;86(1):52-60
Abstract

Does larger prostate size provide protection for cancer specific outcomes in localized prostate cancer

Authors: Abedali Z et al.

Summary: This retrospective single-centre study assessed the effect of prostate volume as a continuous variable on cancer-specific outcomes in 3425 patients with localised prostate cancer who underwent robotic prostatectomy. Overall, 37.4% of patients had a final pathologic stage of ≥T3, 21.2% had positive surgical margins, and over a median follow-up of 52 months, 24.7% experienced biochemical recurrence with prostate size predictive of all three outcomes. Increasing prostate size was protective against higher pathologic stage (OR 0.989; p < 0.001) and positive surgical margins (OR 0.990; p < 0.001), and there was a modest increase in risk of biochemical recurrence with increasing size (HR 1.006; p < 0.001).

Comment: A larger prostate size has consistently been shown to be associated with more favourable cancer outcomes, likely due to the diagnostic bias driven by benign prostate enlargement-associated PSA elevation. This is largely re-enforced by this large retrospective study, which found increasing prostate size was associated with greater rates of both organ and specimen-confined disease. Interestingly, the authors also suggest that a larger prostate size increases the risk of biochemical recurrence, although including PSA density and prostate volume in the same model is likely leading to instability due to collinearity. Suffice to say I'd rather have a larger prostate than a small one!

Reference: Prostate 2024;84(12):1098-1103
Abstract

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