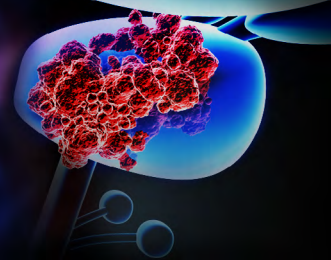


Prostate Cancer Research Review™



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Issue 83 - 2024

In this issue:

- > Circulating tumour cell count and OS in mHSPC
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Abbreviations used in this issue:

ADT = androgen deprivation therapy; ARPI = androgen receptor pathway inhibitor; AUC = area under the curve; BCR = biochemical recurrence; CI = confidence interval; HR = hazard ratio; HRQoL = health-related quality of life; ISUP = International Society of Urological Pathology; mHSPC = metastatic hormone-sensitive prostate cancer; MRI = magnetic resonance imaging; OR = odds ratio; OS = overall survival; PET = positron emission tomography; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RARP = robot-assisted radical prostatectomy; TRUS = transrectal ultrasound.



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Welcome to Issue 83 of Prostate Cancer Research Review.

According to the findings of a prospective US study, circulating tumour cell count is a prognostic biomarker that has potential as a non-invasive tool to identify men with prostate cancer who may have poor survival. In a multicentre study, postprostatectomy radiotherapy was found to be negatively associated with long-term HRQoL across all domains in men with prostate cancer. We conclude this issue with a study from China, which shows that a large prostate within a narrow and deep pelvis may be associated with increased surgical difficulty during robot-assisted radical prostatectomy.

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

niall.corcoran@researchreview.com.au

Circulating tumor cell count and overall survival in patients with metastatic hormone-sensitive prostate cancer

Authors: Goldkorn A et al.

Summary: This analysis of blood samples from the prospective, randomised phase III S1216 clinical trial assessed the prognostic value of circulating tumour cell (CTC) count in men with metastatic hormone-sensitive prostate cancer (mHSPC). Median OS for 60 men with >5 CTCs per 7.5 mL was 27.9 months (95% CI 24.1-31.2) versus 56.2 months (95% CI 45.7-69.8) for 107 men with 1-4 CTCs per 7.5 mL and not reached by 78.0 months in 336 men with 0 CTCs per 7.5 mL. After adjustment for baseline clinical covariates, >5 CTCs per 7.5 mL at baseline gave a greater risk of death (HR 3.22; 95% CI 2.22-4.68) and disease progression (HR 2.46; 95% CI 1.76-3.43) and a lower likelihood of PSA complete response (OR 0.26; 95% CI 0.12-0.54) versus 0 CTCs per 7.5 mL. Adding baseline CTC count to other prognostic factors (AUC 0.73; 95% CI 0.67-0.79) improved prognostic value for 3-year survival (AUC 0.79; 95% CI 0.73-0.84).

Comment: As the role of combination ADT plus ARPI crystallises as standard therapy for men presenting with mHSPC, those who may benefit from further treatment intensification remains an open question. One potential biomarker for selection is CTCs, cancer cells which are shed into the blood stream and reflect both tumour burden and aggressiveness. This *post hoc* analysis of a subset of patients enrolled in a phase III ADT plus ARPI trial enumerated CTCs at both baseline and the onset of castration resistance, finding that higher baseline CTC counts were associated with shortened progression-free and overall survival even when adjusted for other prognostic variables (including extent of metastatic disease). Indeed, CTC count had the greatest HR of any of the variables included in the model! Similar associations were observed following the onset of castration resistance. Certainly merits further study.

Reference: *JAMA Netw Open* 2024;7(10):e2437871

[Abstract](#)



Prostate Cancer Research Review™

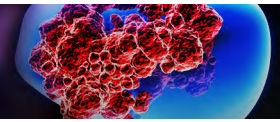
Independent commentary by Professor Niall Corcoran.

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.

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Postprostatectomy radiotherapy timing and long-term health-related quality of life

Authors: Patel SA et al.

Summary: An analysis of prospective, multicentre, longitudinal data from the PROST-QA (2003-06) and RP2 consortia (2010-13) examined the association between radiotherapy (RT) timing after radical prostatectomy (prostatectomy only $n = 1082$; early RT $n = 57$; late RT $n = 64$) and long-term patient-reported health-related quality of life (HRQoL). Over a median follow-up of 85.6 months, men receiving post-prostatectomy RT had greater decreases in sexual, incontinence, and urinary irritation HRQoL than those men receiving prostatectomy alone. However, postprostatectomy RT timing was not associated with a long-term decrease in any HRQoL domain. Improved recovery of sexual, continence, and urinary irritation scores were observed in men receiving early versus late RT after prostatectomy. Before post-prostatectomy RT, 39.3% of early and 73.4% of late RT recipients were incontinence pad-free. By the sixth visit post-RT, 67.4% of early and 47.6% of late RT recipients were pad-free.

Comment: Many urologists are reluctant to send patients for early salvage RT (SRT) for post prostatectomy recurrence due to the belief that subsequent long-term morbidity is worse, particularly for urinary incontinence. This prospective cohort study finds that although all patients receiving SRT experienced decreases in sexual and urinary incontinence function domains as measured by EPIC-26 compared to patients receiving prostatectomy alone, there was no difference in long-term outcomes based on timing (early [<12 months] vs late [≥ 12 months]). However, the numbers of men receiving SRT were relatively small and how generalisable the results are to earlier timepoints (say 3-6 months post surgery) is less clear.

Reference: *JAMA Netw Open* 2024;7(10):e2440747

[Abstract](#)

Comparison of infection risk between enzalutamide and abiraterone in patients with prostate cancer

Authors: Lee YHA et al.

Summary: This Hong Kong retrospective cohort compared the risk of infection in 1582 patients with prostate cancer receiving enzalutamide or abiraterone in combination with ADT. Over a median follow-up of 10.6 months, enzalutamide recipients had lower cumulative incidences of sepsis (adjusted sub-HR [aSHR] 0.70; 95% CI 0.53-0.93; $p = 0.014$), pneumonia (aSHR 0.76; 95% CI 0.59-0.99; $p = 0.040$), and cellulitis or skin abscess (aSHR 0.55; 95% CI 0.39-0.79; $p = 0.001$), but not urinary tract infection (aSHR 0.91; 95% CI 0.62-1.35) than abiraterone recipients.

Comment: Given the general similarity in efficacy of ARPIs in metastatic prostate cancer, patient factors largely determine choice of agent now that a number are reimbursed. Abiraterone requires co-administration with a corticosteroid, which along with an increase in hypertension, glucose intolerance and truncal obesity, may increase the risk of infection due to its immunomodulatory effects. This retrospective cohort study from Hong Kong suggest that this may be the case, reporting a higher risk of pneumonia, sepsis and skin infections in patients receiving abiraterone plus prednisolone compared to enzalutamide. Significance was retained after adjustment for multiple treatment-related factors and co-morbidities, with a clear dose effect observed (rate of infection was higher in those receiving abiraterone plus 10 mg vs 5 mg prednisolone), suggesting the observation is real.

Reference: *Cancer* 2024;130(22):3826-3835

[Abstract](#)

Evaluation of margins during radical prostatectomy: Confocal microscopy vs frozen section analysis

Authors: Musi G et al.

Summary: This study examined *ex vivo* fluorescence confocal microscopy (FCM) versus intra-operative frozen section (IFS) analysis to evaluate surgical margins during RARP based on 54 margins examined in 45 patients. *Ex vivo* FCM had an inter-observer agreement between two experienced (10 years) and highly experienced (>30 years) pathologists that ranged from moderate (Cohen's $\kappa = 0.74$) to almost perfect ($\kappa = 0.90$), according to the four categories of results. The highly experienced pathologist had the best balance between sensitivity (70.5%), specificity (91.8%), positive predictive value (PPV; 80.0%) and negative predictive value (NPV; 87.1%). Conversely, in IFS analysis, sensitivity, specificity, PPV and NPV were 88.2%, 100%, 100%, and 94.8%. Agreement between the *ex vivo* FCM and IFS analyses ranged from moderate ($\kappa = 0.62$) to strong ($\kappa = 0.86$).

Comment: Small Italian study comparing the accuracy of *ex-vivo* FCM with IFS analysis to evaluate surgical margin status at the time of prostatectomy. Although the confocal microscopy technique performed pretty well, it was not quite as good as frozen section analysis when using final pathology as the reference standard. Additionally, the technique did not offer much in the way of a time advantage (15-18 minutes vs 18-22 minutes) as it still required transport to a pathology laboratory for processing. Certainly not as promising as some of the other real-time intraoperative margin assessment techniques recently described for clinical translation.

Reference: *BJU Int.* 2024;134(5):773-780

[Abstract](#)

Randomised trial of no, short-term, or long-term androgen deprivation therapy with postoperative radiotherapy after radical prostatectomy: Results from the three-way comparison of RADICALS-HD (NCT00541047)

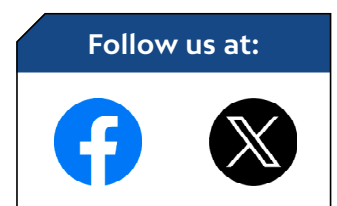
Authors: Parker CC et al.

Summary: This secondary analysis of the randomised controlled RADICALS-HD trial compared no ADT ($n = 166$), short-term (6 months; $n = 164$), or long-term (24 months; $n = 162$) ADT with postoperative RT after radical prostatectomy. Over a median follow-up of 9.0 years, metastasis-free survival (MFS) events were reported in 32 no ADT, 31 short-term, and 26 long-term ADT recipients, with no difference overall in MFS. After 10 years, 80% of no ADT, 77% of short-term, and 81% of long-term ADT recipients were alive without metastatic disease.

Comment: Secondary analysis of RADICALS-HD trial, this time focussing on the outcomes of men randomised to none, 6 or 24 months of concomitant ADT in patients receiving post-prostatectomy radiation (~40% adjuvant ~60% salvage). The headline finding is that there was no difference in MFS (the primary outcome) between the three arms, nor any effect on freedom from distant metastases or OS. ADT use was associated with a longer time to the initiation of salvage ADT, but given this is presumably due to a rising PSA in the absence of detectable metastasis, its clinical relevance is unclear. One significant limitation is the low-risk nature of the cohort (although PSA doubling time is not reported for the salvage cases, greater than 80% of patients have grade group ≤ 3 disease, suggesting that many would be low-risk biochemical recurrence [BCR] using the European Association of Urology definition), so is significantly underpowered to detect a difference in higher risk cases where the findings are more relevant.

Reference: *Eur Urol.* 2024;86(5):422-430

[Abstract](#)





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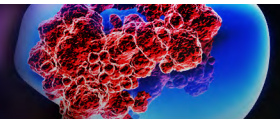
References: 1. XTANDI (enzalutamide) Approved Product Information. 2. Armstrong AJ et al. *J Clin Oncol* 2022;40(15):1616-1622. 3. Armstrong AJ et al. *J Clin Oncol* 2019;37(32):2974-2986. 4. Davis ID, et al. *N Engl J Med* 2019;381:121-131. 5. Sweeney CJ et al. *Lancet Oncol* 2023;24:323-34. 6. Data on file, MAT-ABC-XTD-2023-00061.

ADT=androgen deprivation therapy; **mHSPC**=metastatic hormone-sensitive prostate cancer.

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Bimodal imaging: Detection rate of clinically significant prostate cancer is higher in MRI lesions visible to transrectal ultrasound

Authors: Falkenbach F et al.

Summary: This retrospective analysis examined detection rates of clinically significant prostate cancer (csPCa; ISUP ≥ 2) in 277 patients with a single MRI lesion (PI-RADS score ≥ 3) visible (53%) or invisible on TRUS during biopsy. csPCa was detected in 45% of patients without and 69% of patients with a corresponding TRUS lesion. In multivariate analysis independent predictors of csPCa were TRUS-visibility (OR 2.13; 95% CI 1.14-4.03; $p = 0.02$) and PI-RADS score (PI-RADS 4: OR 7.28; 95% CI 3.33-17.19, PI-RADS 5: OR 13.39; 95% CI 5.27-36.83; $p < 0.001$).

Comment: It is a clinical adage that if a lesion is visible on two different imaging modalities it is more likely to be real. This is again borne out by this retrospective series from the Martini-Klinik, which finds that for patients with a PI-RADS ≥ 3 lesion on MRI in whom a corresponding lesion could also be identified on TRUS, the risk of clinically significant prostate cancer was significantly increased. Interestingly, the number of positive cores was higher in both the target and the systematic biopsies in the TRUS positive cohort, likely reflecting the lower overall risk profile of the TRUS negative group (higher rates of previous negative prostate biopsy and lower risk distribution of PI-RADS scores). Potentially useful in deciding which PI-RADS 3 lesions require biopsy, as the pick-up rate of significant cancer in the absence of a corresponding TRUS lesion is quite low.

Reference: *Prostate* 2024;84(16):1448-1455

[Abstract](#)

Prior local therapy and first-line apalutamide in patients with nonmetastatic castration-resistant prostate cancer: A secondary analysis of the SPARTAN randomized clinical trial

Authors: Roy S et al.

Summary: This *post hoc* secondary analysis of the double-blinded, placebo-controlled randomised phase III SPARTAN (Study of Apalutamide [ARN-509] in Men With Non-Metastatic Castration-Resistant Prostate Cancer) trial examined whether exposure to prior prostate-directed local therapy (LT; radical prostatectomy [RP], RT, or both) modified the effect of subsequent systemic therapy with apalutamide on metastasis-free survival (MFS) or OS in 1179 patients with nonmetastatic castrate-resistant prostate cancer (nmCRPC). Over a median follow-up of 52.0 months, a differential treatment effect of apalutamide on MFS was observed with and without prior LT ($p = 0.009$), with greater benefits for prior LT (aHR 0.22; 95% CI 0.17-0.27) compared with no prior LT (aHR 0.35; 95% CI 0.25-0.51). However, there was no evidence of a differential treatment effect on OS, with improved OS with prior LT (aHR 0.72; 95% CI 0.57-0.92) but not without prior LT (aHR 0.92; 95% CI 0.64-1.31).

Comment: An *in situ* untreated primary prostate cancer is increasingly recognised as a source of ongoing metastatic dissemination as well as a possible site of emergence of treatment resistance in men undergoing systemic management. This is further highlighted in this secondary analysis of the SPARTAN trial (RCT of apalutamide vs placebo in men with nmCRPC and a PSA doubling time ≤ 10 months). Men receiving prior local therapy had improved MFS on ADT plus apalutamide compared to those that didn't, which was numerically similar for both radical prostatectomy and RT. There was no significant impact on OS, which may reflect treatment crossover on disease progression. Interesting data as the role of local definitive therapy in metastatic disease continues to evolve.

Reference: *JAMA Netw Open* 2024;7(10):e2439434

[Abstract](#)

Long-term outcomes of prostate-specific membrane antigen-PET imaging of recurrent prostate cancer

Authors: Kunst N et al.

Summary: This decision analytic modelling study sought to estimate the long-term outcomes of integrating PSMA-PET into the staging pathway for patients with BCR prostate cancer following initial definitive local therapy. Per 1000 simulated BCR patients, PSMA-PET alone was expected to diagnose 611 patients (95% uncertainty interval [UI] 565-656) with metastasis versus 630 patients (95% UI 586-675) diagnosed using CT and bone scan (CTBS) followed by PSMA-PET and 297 (95% UI 202-410) patients diagnosed with CTBS alone. Estimated number of prostate cancer deaths was 512 (95% UI 472-552) using PSMA-PET alone, 520 deaths (95% UI 480-559) using CTBS followed by PSMA-PET, and 587 deaths (95% UI 538-632) with CTBS alone. PSMA-PET gave the highest number of quality-adjusted life-years (QALYs) gained, 824 QALYs (95% UI 698-885) higher than CTBS. The highest number of incremental life-years and QALYs and lowest number of deaths from prostate cancer was found in patients with PSA levels of ≥ 5.0 ng/mL. Estimates were sensitive to the expected benefit of initiating therapy earlier in the disease course.

Comment: PSMA-PET is more sensitive at detecting prostate cancer recurrence after attempted curative therapy than conventional imaging. Although more cost effective in the short term, how this translates into improved patient outcomes and overall health care costs remains to be determined. This decision analysis study suggests that early diagnosis of recurrent disease with PSMA-PET is associated with fewer deaths and a greater gain in QALYs than more delayed diagnosis with conventional imaging. Interestingly in the model, the greatest gain was seen in those with higher PSA, presumably from the earlier institution of systemic therapy for which there is clear evidence of improvement in OS.

Reference: *JAMA Netw Open* 2024;7(10):e2440591

[Abstract](#)

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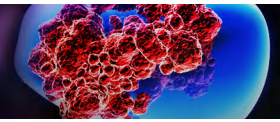
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Stockholm3 in a multiethnic cohort for prostate cancer detection (SEPTA): A prospective multicentered trial

Authors: Vigneswaran HT et al.

Summary: The SEPTA study used an observational prospective multicentre clinical trial (2019-23), supplemented by prospectively recruited participants (2008-20) from a urology clinic examined whether the Stockholm3 risk score could improve prostate cancer detection in a diverse cohort (n = 2119) of Asian (16%), Black or African American (24%), Hispanic or Latino and White (14%), and non-Hispanic or non-Latino and White (46%) men with suspicion of prostate cancer undergoing prostate biopsy. Overall, Stockholm3 risk score had noninferior sensitivity compared with PSA ≥ 4 ng/mL (relative sensitivity 0.95; 95% CI 0.92-0.99) and 3-fold higher specificity (relative specificity 2.91; 95% CI 2.63-3.22), with consistent results across racial and ethnic subgroups showing noninferior sensitivity (0.91-0.98) and superior specificity (2.51-4.70). Stockholm3 risk scoring could reduce benign and ISUP 1 biopsies overall by 45% and by 42- 52% across racial and ethnic subgroups.

Comment: There is still much interest in non-imaging based reflex tests for men with a suspicion of prostate cancer, either due to lack of access or cost considerations. This prospective cohort study investigated the performance of the Stockholm3 test (an algorithmic combination of clinical variables, various serum protein levels including total and free PSA, and a germline polygenic risk score) compared to PSA in ethnically diverse men undergoing prostate biopsy. Overall Stockholm3 had the same sensitivity as PSA but a 3-fold higher specificity for clinically significant prostate cancer. Similar performance to MRI, but without the added value of a lesion to target.

Reference: *J Clin Oncol.* 2024;42(32):3806-3816

[Abstract](#)

Effects of bony pelvic and prostate dimensions on surgical difficulty of robot-assisted radical prostatectomy: An original study and meta-analysis

Authors: Lu H et al.

Summary: This study and meta-analysis study examined the effect of bony pelvic and prostate dimensions in robot-assisted radical prostatectomy (RARP) procedures in 219 patients undergoing multiport RARP between 2021 and 2022. Longer operative time (OT), was associated ($p < 0.05$) with prostate volume (PV) and prostate volume-to-pelvic cavity index (PCI) ratio (PV-to-PCI ratio). In restricted cubic spline (RCS) models, U-shaped associations between prostate anteroposterior diameter (PAD) and OT, and between the prostate height (PH) and estimated blood loss (EBL) were observed, and there was an L-shaped association between anteroposterior diameter of the pelvic inlet (API) and EBL. Meta-analysis suggested that greater PV was associated with longer OT (β 0.20; 95% CI 0.12-0.27; OR 1.05; 95% CI 1.00-1.11), and smaller PV increased the risk of positive surgical margin (OR 0.82; 95% CI 0.77-0.88).

Comment: Operating down a deep narrow pelvis is not much fun whatever your approach, particularly when the prostate is taking up most of the space! This interesting study from China tries to predict surgical difficulty using various measurements of the bony pelvis and prostate volume derived from pre-treatment MRI. They find that larger prostates, particularly within a smaller pelvis take longer to excise, although there was no significant impact on blood loss or positive margin rate. Makes sense, although it is not clear that the endpoints chosen (operative time, estimated blood loss and positive margin rate) are the best outcome measures of surgical difficulty. May be useful for screening training appropriate cases.

Reference: *Ann Surg Oncol.* 2024;31(12):8405-8420

[Abstract](#)

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