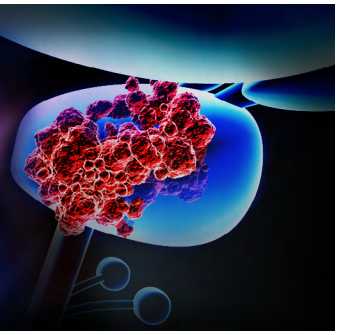
Prostate Cancer Research Review™



Making Education Easy

Issue 73 - 2024

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **ARBs** = androgen receptor blockers; **AUC** = area under the receiver operating characteristic curve; **CI** = confidence interval; **CRPC** = castration-resistant prostate cancer; **ED** = erectile dysfunction; **ePLND** = extended pelvic lymph-node dissection; **G-CSF** = granulocyte colony stimulating factor; **HR** = hazard ratio; **ISUP** = International Society of Urological Pathology; **mCRPC** = metastatic castration-resistant prostate cancer; **MRI** = magnetic resonance imaging; **OR** = odds ratio; **PET** = positron emission tomography; **PLN** = pelvic lymph node; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RARP** = robot-assisted radical prostatectomy; **SBRT** = stereotactic body radiation therapy.

Welcome to Issue 73 of Prostate Cancer Research Review.

A recent study published in Nature provides evidence that senescence-associated myeloid inflammation can fuel metastatic CRPC progression and resistance to androgen receptor blockade. In a phase II trial, a clinical advantage for SBRT in addition to first-line abiraterone acetate and prednisone in patients with metastatic castration-resistant prostate cancer is suggested. We wrap up this issue with a study investigating cabazitaxel dosing frequency and the risk of Grade 3 or greater neutropenia and/or neutropenic complications in older patients with mCRPC.

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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Targeting myeloid chemotaxis to reverse prostate cancer therapy resistance

Authors: Guo C et al.

Summary: This laboratory and clinical trial examined whether myeloid inflammation drives progression of prostate cancer. Results indicate that the inhibition of myeloid chemotaxis reduced tumour-elicited myeloid inflammation and reversed resistance in patients with mCRPC. Higher blood neutrophil-to-lymphocyte ratios were found to reflect tumour myeloid infiltration and the expression in the tumour of senescence-associated mRNA, including myeloid-chemoattracting CXCR2 ligands. An investigator-initiated, proof-of-concept, dose finding phase I clinical trial assessed whether myeloid cells sustain resistance to androgen receptor signalling inhibitors (ARSIs) using a CXCR2 inhibitor plus enzalutamide in 23 patients with metastatic CRPC resistant to ARSIs. Combination therapy was well tolerated and did not exhibit dose-limiting toxicities, while decreasing circulating neutrophil levels, intra-tumoural CD11b^{+}HLA-DRloCD15^{+}CD14^{-} myeloid cell infiltration and providing a durable clinical benefit (biochemical and radiological responses) in a subgroup with metastatic CRPC.

Comment: Inflammation is increasingly recognised as a hallmark of cancer, with 'myeloid-cell inflammation' (as reflected in elevated neutrophil-to-lymphocyte ratio in the blood) known to be a poor prognostic feature in many tumour types. Prostate cancer in particular, is characterised by tumour infiltration by tumour-associated neutrophils, which have been shown in pre-clinical models to promote tumour progression. This interesting study shows that blocking inflammatory cell recruitment (with an inhibitor to the chemoattractant cytokine CXCR2) in association with enzalutamide, slowed tumour growth in a subset of heavily pre-treated patients with known ARSI resistance. This is exciting, as targeting non-tumour cells who have less capacity to develop resistance mechanisms for therapeutic gain may have long-term traction, although who is most likely to benefit is not clear.

Reference: Nature 2023;623(7989):1053-1061
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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Stereotactic body radiation therapy and abiraterone acetate for patients affected by oligometastatic castrate-resistant prostate cancer: A randomized phase II trial (ARTO)

Authors: Francolini G et al.

Summary: The multicentre, randomised, phase II clinical trial assessed the addition of SBRT to abiraterone acetate plus prednisone in 157 patients with oligometastatic CRPC. A biochemical response occurred in 92% of SRBT and 68.3% of control patients (OR 5.34; 95% CI 2.05-13.88; p = 0.001); a complete biochemical response occurred in 56% versus 23.2% (OR 4.22; 95% CI 2.12-8.38; p < 0.001). SBRT also improved progression-free survival (HR 0.35; 95% CI 0.21-0.57; p < 0.001).

Comment: Ablative radiotherapy is very effective for lesion control, with very low rates of in-field recurrence reported. This phase II study investigated the additional benefit of SBRT to all visible lesions (detected by conventional or PET imaging) in patients with oligometastatic mCRPC (≤3 bony and/or lymph node metastases) treated systemically with abiraterone in the first-line setting. Biochemical response rates were higher in patients receiving combination therapy, as was progression-free survival, which perhaps may have been more favourable if only patients with lesions detected by PSMA-PET were included. Exciting data, and makes sense given the high rates of metastasis-to-metastasis spread observed in mCRPC.

Reference: J Clin Oncol. 2023;41(36):5561-5568
Abstract

Development and external validation of a novel nomogram to predict the probability of pelvic lymph-node metastases in prostate cancer patients using magnetic resonance imaging and molecular imaging with prostate-specific membrane antigen positron emission tomography

Authors: Vis AN et al.

Summary: The modelling study sought to develop a prognostic nomogram for predicting pathological lymph-node (pN) status using data from 700 patients with primary diagnosed localised prostate cancer who underwent RARP and ePLND and an external validation cohort of 305 surgically treated patients. The nomogram (Amsterdam-Brisbane-Sydney nomogram) included initial PSA, MRI T stage, highest biopsy grade group (GG), biopsy technique, percentage of cores with clinically significant prostate cancer (GG ≥2), and PSMA-PET lymph-node. The area under the receiver operating characteristic curve (AUC) pN status was 0.81 (95% CI 0.78-0.85). External validation cohort results (AUC 0.75; 95% CI 0.69-0.81), suggested a superior discrimination to the Briganti-2017 (AUC 0.67; 95% CI 0.61-0.74; p < 0.05) and Memorial Sloan Kettering Cancer Center (MSKCC) nomograms (AUC 0.65; 95% CI 0.58-0.72; p < 0.05), and similar discrimination to the Briganti-2019 nomogram (AUC 0.78; 95% CI 0.71-0.86; vs AUC 0.80; 95% CI 0.73-0.86).

Comment: Do we really need another nomogram to predict pN1 disease when many surgeons have abandoned PLND due to its lack of oncological benefit? Apparently, we do. This international multicentre study (including groups from Queensland and New South Wales) developed a new prognostic model (the Amsterdam-Brisbane-Sydney nomogram) based on standard clinic-pathological variables but also including findings from MRI and PSMA-PET imaging. The strongest predictor in the model by far was PSMA-PET detectable lymph nodes pre-operatively. Although the model performs better than both the Briganti 2019 and MSKCC nomograms, given that proPSMA reports sensitivity for pelvic nodal disease >80% with a specificity >90%, it would be interesting to compare its performance against PSMA-PET alone.

Reference: Eur Urol Oncol. 2023;6(6):553-563
Abstract

Digital rectal examination is not a useful screening test for prostate cancer

Authors: Krilaviciute A et al.

Summary: This analysis, conducted within the multicentre, randomised PROBASE trial, in >46,000 men at age 45, assessed the use of an annual digital rectal examination (DRE; n = 6537) as a one-time, stand-alone screening test for prostate cancer. In a prospective analysis of 57 men with suspicious DRE at age 45, there were three prostate cancers detected, with a detection rate of 0.05% versus a four-fold higher rate identified by PSA screening (48 of 23,301; 0.21%). The true-positive DRE detection rate relative to PSA screening was 0.22 (95% CI 0.07-0.72) and the false-positive detection rate was 2.2 (95% CI 1.50-3.17). Among PSA-screen-detected cases, 86% had unsuspicious DRE (sensitivity 14% relative to PSA), with most tumours (86%) located in potentially accessible prostate zones as identified by MRI.

Comment: Palpation of the prostate gland to diagnose and stage prostate cancer continues to fall out of favour, largely replaced by reflex PSA testing and MRI. This is further supported by this German study which evaluated the diagnostic yield of DRE in an RCT of early versus deferred PSA screening in men aged 45. Standalone DRE had poor sensitivity for prostate cancer detection compared to PSA measurement, with all cases detected purely by palpable abnormality being low grade. Additionally, most patients diagnosed with prostate cancer at PSA-indicated biopsy had no palpable abnormality, although the rate of abnormal DRE was higher in patients with higher ISUP GG disease. As the focus of the report is on population-based screening, it is difficult to say whether DRE can be safely omitted during case finding or in the clinical assessment of LUTS, although personally I stick with the old adage – "put your finger in it or put your foot in it". I think most patients would prefer the finger.

Reference: Eur Urol Oncol. 2023;6(6):566-573
Abstract

Head-to-head comparison of ^{18}F-PSMA-1007 positron emission tomography/computed tomography and multiparametric magnetic resonance imaging with whole-mount histopathology as reference in localisation and staging of primary prostate cancer

Authors: Exterkate L et al.

Summary: This study assessed the diagnostic performance of ^{18}F-PSMA-1007 PET/CT versus multiparametric MRI (mpMRI) for prostate tumour localisation and detection of extraprostatic extension (EPE) and seminal vesicle invasion (SVI) in 105 men undergoing RARP. Across 80 histopathological whole-mount prostate specimens there were 129 lesions, with 96 being clinically significant. Per-lesion localisation sensitivity of overall prostate cancer was 85% (95% CI 77-90) with PSMA PET/CT versus 62% (95% CI 53-70; p < 0.001) with mpMRI; per-lesion sensitivity was 95% (95% CI 88-98) versus 73% (95% CI 63-81; p < 0.001). Diagnostic accuracy for detection of EPE per lesion did not differ and the sensitivity and specificity for detection of SVI also did not differ between PSMA PET/CT and mpMRI.

Comment: Whether PSMA-PET has similar or complementary ability to detect localised prostate cancer compared with mpMRI is the research focus of numerous groups, particularly in Australia. The obvious advantage of using PSMA-PET as a standalone test is the potential to obtain staging information as well as tumour localisation for biopsy (as well as potentially prognostic information) in a single scan. This small Dutch study compared the accuracy of both PSMA-PET and mpMRI in detecting clinically significant prostate cancer using prostatectomy whole-mount histopathology as the ground state truth. PSMA-PET outperformed mpMRI for the intraprostatic localisation of clinically significant tumours, with similar diagnostic accuracy for EPE and SVI. All patients undergoing PSMA-PET had already biopsy proven intermediate/high risk disease, which somewhat limits generalisability to the pre-diagnosis population.

Reference: Eur Urol Oncol. 2023;6(6):574-581
Abstract

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References: 1. ZYTIGA® Approved Product Information, available at http://www.janssen.com.au/Zytiga_PI. 2. Thiery-Vuillemin A, *et al. Eur Urol* 2020;77:380-387 (including supplementary appendix). 3. Thiery-Vuillemin A, *et al. ESMO Open* 2018;3:e000397. doi:10.1136/esmoopen-2018-000397. 4. Gotto G, *et al. Can Urol Assoc J* 2020;14:E616-20.

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Predictors of recurrence after metastasis-directed therapy in oligorecurrent prostate cancer following radical prostatectomy

Authors: Milenkovic U et al.

Summary: This two-centre, retrospective (2006-20) study assessed predictors of therapeutic response of metastasis-directed therapy (MDT; SBRT n = 48; salvage lymph node dissection [sLND] n = 119; whole-pelvis/retroperitoneal radiation therapy [WP[R]RT] n = 31; sLND + SBRT n = 2; sLND + WPRT n = 1), or metastasectomy (n = 11) for oligorecurrent prostate cancer after radical prostatectomy (n = 211). Overall, 122 (58%) patients had a secondary recurrence. Over a median follow-up of 100 months after prostatectomy and 42 months after MDT; the 5-year radiographic progression-free survival was 23%, metastasis-free survival (MFS) was 68%, androgen deprivation treatment-free survival was 58%, castration-resistant prostate cancer-free survival was 82%, cancer-specific survival (CSS) was 93% and overall survival (OS) was 87%. There was a significant difference between cN1 (n = 114) and cM+ (n = 97) for 5-year MFS (83% vs 51%; p < 0.001), palliative ADT (pADT)-free survival (70% vs 49%; p = 0.014), and CSS (100% vs 86%; p = 0.019). Significant risk factors for MFS in cN1 disease were higher PSA at primary MDT (HR 2.38; 95% CI 1.07-5.24; p = 0.032), and number of positive nodes on imaging (HR 1.65; 95% CI 1.14-2.40; p < 0.01). Risk factors for MFS in cM+ disease were cM1b/cM1c (HR 2.62; 95% CI 1.58-4.34; p < 0.001).

Comment: The optimal group of patients who benefit from MDT has yet to be defined. This large series reports on recurrence rates in men treated with either surgery (salvage PLND or metastasectomy) or radiation (SBRT or salvage WPRT) for oligorecurrent disease post prostatectomy. Metastases were detected per-MDT by PET/CET, predominantly using a PSMA ligand. 23% of patients had a durable response as measured by progression-free survival at 5 years. Unsurprisingly, outcomes were worse in patients with M1 compared to N1 recurrence. Risk factors for recurrence post MDT were as expected, although given the heterogeneity of the cohort and small number of events it is hard to draw any firm conclusions. So, it clearly works in some patients, although in whom is only clear in retrospect!

Reference: Eur Urol Oncol. 2023;6(6):582-589
Abstract

Patient-reported outcome measures compared to clinician reported outcomes regarding incontinence and erectile dysfunction in localized prostate carcinoma after robot assisted radical prostatectomy: Impact on management

Authors: Tillier CN et al.

Summary: This study examined the discrepancy between patient-reported outcome measures (PROMs) and clinician report outcomes (CROs) and the impact of any difference on the management of urine incontinence (UI) and erectile dysfunction (ED) up to 1 year after RARP in 312 men with localised and locally advanced prostate cancer. International Consultation Incontinence Questionnaire Short-Form (ICIQ-SF) PRO score matched with CRO scores in all sum score categories except ICIQ sum score 6-12, where UI was underreported in 58% and 59% of patients at 8 and 12 months (p < 0.001); CROs also underreported UI in 29% and 23% of patients with ICIQ scores of 13-18 (p < 0.001). Clinicians also over-reported recovery of ED (p < 0.001), especially in men with IIEF-EF sum scores 6-16. Discrepancies between PROs and CROs did not affect management and counselling offered for UI and ED.

Comment: Patients frequently underreport treatment-related morbidity when questioned by their treating surgeon, who in turn often make a rosier interpretation of the side effects that are reported, which in general makes CROs unreliable. This is underlined by this Dutch cohort study which compared prospectively collected PROMs and CROs in men with localised prostate cancer treated with RARP and followed for 12 months. Although there was good agreement between CROs and PROMs at either end of the symptom severity scale (completely dry and completely wet; normal erections and no erections), clinicians consistently under-reported intermediate grade morbidity, although this did not affect the treatments offered. This supports the need for PROMs in research involving treatment of localised disease, as CROs can't be trusted.

Reference: Urol Oncol. 2023;41(11):454.e1-454.e8
Abstract

The role of multiparametric MRI and MRI-targeted biopsy in the diagnosis of radiorecurrent prostate cancer: An analysis from the FORECAST trial

Authors: Light A et al.

Summary: The FOcal RECurrent Assessment and Salvage Treatment (FORECAST) prospective cohort diagnostic study (n = 144) examined MRI and MRI-targeted biopsies for the detection of intraprostatic cancer recurrence and for planning salvage focal ablation. In total, 111 (77%) patients had cancer detected on transperineal template mapping biopsies. MRI sensitivity was 0.95 (95% CI 0.92-0.99) and specificity was 0.21 (95% CI 0.07-0.35). At the prostate quadrant level, 45% quadrants had cancer on biopsy with sensitivity of 0.66 (95% CI 0.59-0.73) and specificity of 0.54 (95% CI 0.46-0.62). At the quadrant level, MRI-detected tumours had longer maximum cancer core length than MRI-undetected tumours (median difference 3 mm; 95% CI 1-4; p < 0.001) and a higher grade group (p = 0.002). Of those undergoing an MRI-targeted biopsy (n = 84), 73 (87%) had recurrent cancer. An MRI-targeted biopsy alone missed cancer in 7% of patients (95% CI 3-15); with additional systematic sampling of other ipsilateral and contralateral posterior quadrants, 3% (95% CI 0-10) would have had cancer missed (difference 4%; 95% CI -3 to 11). An MRI-targeted biopsy alone 43/73 would have allowed undetected additional tumours in unsampled quadrants in 59% (95% CI 47-69) of patients. This reduced to 10% (95% CI 4-19) with systematic sampling of ipsilateral and contralateral posterior quadrants (difference 49%; 95% CI 36-62; p < 0.0001). Among 73 patients, 43 (59%; 95% CI 47-69) had localised radiorecurrent cancer suitable for focal ablation.

Comment: MRI is very sensitive for detecting clinically significant prostate cancer in the pre-diagnostic setting, but its role in assessing intraprostatic recurrence after definitive radiotherapy is less clear. This analysis from the FORECAST study demonstrates similar accuracy (sensitivity 95%), with an MRI-targeted biopsy in the majority of patients. However, many patients also had disease in the systematic cores (although usually lower grade and lower volume), indicating that targeted and perilesional cores alone are insufficient in patients being considered for salvage focal therapy.

Reference: Eur Urol. 2024;85(1):35-46
Abstract

Local treatment and treatment-related adverse effects among patients with advanced prostate cancer

Authors: Khan S et al.

Summary: This cohort study assessed the association of local treatment (radical prostatectomy or radiation; n = 1705) on treatment-related adverse effects among 5502 men (mean age 68.7 years) with advanced (T4, N1, and/or M1) prostate cancer and treated at Veterans Health Administration medical centres. A high prevalence of adverse events was observed in men receiving both local and nonlocal treatment, and such events persisted for >2 to ≤5 years after initial treatment; 75.2% vs 67.1%, respectively, experienced ≥1 adverse event during this time period. During the first year of treatment, local treatment (vs nonlocal) was associated with adverse gastrointestinal (multivariable-adjusted odds ratio [aOR] 4.08; 95% CI 3.06-5.45), pain (aOR 1.57; 95% CI 1.35-1.83), sexual (aOR, 2.96; 95% CI 2.42-3.62), and urinary (aOR, 2.25; 95% CI 1.90-2.66) conditions. At >2 to ≤5 years after initial treatment, local treatment (without secondary treatment) remained significantly associated with adverse gastrointestinal (aOR 2.39; 95% CI 1.52-3.77), sexual (aOR 3.36; 95% CI 2.56-4.41), and urinary (aOR 1.39; 95% CI 1.09-1.78) conditions.

Comment: Accumulating evidence indicates that treatment of the primary in patients with advanced prostate cancer, either with radiation or surgery, improves long-term survival outcomes. However, as maintaining quality of life is a key goal for many men as they age, balancing the morbidity of treatment against the potential survival gains is important for patient counselling. This timely report describes treatment-related adverse effects of men with advanced disease (T4 and/or N1 and/or M1) receiving local treatment versus those receiving ADT alone over a 15-year period up to 2013. Unsurprisingly, local treatment was associated with a 2-4-fold higher rate of urinary, sexual and gastrointestinal toxicity that persisted out to 5 years. A bit to ponder, although more contemporary treatment techniques hopefully result in less morbidity.

Reference: JAMA Netw Open 2023;6(12):e2348057
Abstract

Biweekly vs triweekly cabazitaxel in older patients with metastatic castration-resistant prostate cancer: The CABASTY phase 3 randomized clinical trial

Authors: Oudard S et al.

Summary: This prospective phase 3 randomised clinical trial undertaken in France and Germany involving 196 patients ≥65 years (median age 74.6 years) with progressive mCRPC, aimed to determine whether daily prednisolone plus biweekly cabazitaxel 16 mg/m^2 (CBZ16) and prophylactic granulocyte colony-stimulating factor (G-CSF) at each cycle reduces the risk of Grade 3 or greater neutropenia and/or neutropenic complications (e.g., febrile neutropenia, neutropenic infection, or sepsis) compared with prednisolone plus triweekly cabazitaxel 25 mg/m^2 (triweekly CBZ25) and G-CSF. Patients had also received docetaxel and ≥1 novel androgen receptor-targeted agent and 92.3% had an Eastern Cooperative Oncology Group performance status of 0 or 1. During a median follow-up of 31.3 months, the rate of Grade 3 or higher neutropenia and/or neutropenic complications was significantly higher in triweekly CBZ25 recipients than biweekly CBZ16 recipients (62.5% vs 5 5.1%; OR 0.03 [95% CI 0.01-0.08]; p < .001), as was the rate of Grade 3 or higher adverse events (72.9% vs 56.1%). There was one death reported due to neutropenic complication, in a patient receiving triweekly CBZ25.

Comment: Many elderly patients with mCRPC are considered unsuitable for taxane-based chemotherapy due to concerns about potential toxicity. For cabizitaxel (usually the second-line choice in Australia after docetaxel) the main side effect of concern is neutropenia, which can lead to fatal overwhelming infection. This small study investigated the impact of giving reduced doses of cabazitaxel at day 1 and day 8 of a 4-week cycle compared to a standard dose at day 1 of a 3-week cycle (in addition to G-CSF and prednisolone in both groups) on Grade 3 neutropenia in patients previously treated with docetaxel. Grade 3 neutropenia was substantially less in patients treated with the biweekly schedule, which resulted in significantly fewer complications such as febrile neutropenia. There were also fewer dose delays and reductions in the biweekly group, with no observed differences in tumour response, with the caveat that the study was not powered for these endpoints.

Reference: JAMA Oncol. 2023;9(12):1629-1638
Abstract

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