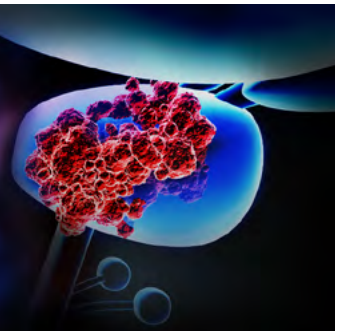
Prostate Cancer Research Review™



Making Education Easy

Issue 66 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **BMI** = body mass index; **CI** = confidence interval; **Gy** = Gray; **HR** = hazard ratio; **ISUP** = International Society of Urological Pathology; **LHRH** = luteinising hormone-releasing hormone; **mCRPC** = metastatic castration-resistant prostate cancer; **MRI** = magnetic resonance imaging; **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; **RCT** = randomised controlled trial; **TRUS** = transrectal ultrasound scan.

Welcome to Issue 66 of Prostate Cancer Research Review.

In a UK study comparing 15-year outcomes of active monitoring, prostatectomy, or radiotherapy in men with prostate cancer, prostate cancer-specific mortality was low regardless of the treatment assigned. Analysis of a large international database found that among men with pT2-4N0 or NXM0 prostate cancer, initiating salvage radiation therapy above a PSA of 0.25 ng/mL was associated with increased all-cause mortality risk. Meanwhile, preoperative endogenous total testosterone level has been identified as a predictor of prostate cancer progression.

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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Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer

Authors: Hamdy FC et al.

Summary: This randomised controlled trial (RCT) compared outcomes in 1643 men assigned to active monitoring (n = 545), prostatectomy (n = 553), or radiotherapy (n = 545) after a median follow-up of 15 years in 98% of participants. Prostate cancer-related death occurred in 45 (2.7%) patients, including 17 (3.1%) active-monitoring, 12 (2.2%) prostatectomy, and 16 (2.9%) radiotherapy recipients. Metastases developed in 51 (9.4%) active monitoring recipients, 26 (4.7%) prostatectomy recipients, and 27 (5.0%) radiotherapy recipients. Long-term ADT was used in 69 (12.7%), 40 (7.2%), and 42 (7.7%), while 141 (25.9%), 58 (10.5%), and 60 (11.0%), respectively, experienced clinical progression. At the end of follow-up, 133 (24.4%) men receiving active monitoring remained alive with no prostate cancer treatment. There was no difference in cancer-specific mortality associated with baseline PSA level, tumour stage or grade, or risk-stratification score. There were no treatment complications identified over a 10-year analysis.

Comment: This updated ProtecT publication reports on the 15-year outcomes in men aged between 50 and 69 diagnosed with clinically localised disease based on an elevated PSA, randomised to surgery, radiation, or active monitoring. Similar to the 10-year data, active monitoring was associated with an increased risk of metastatic events, but this did not translate into a difference in overall survival (OS). The event rate in the cohort overall was very low (6.3% for metastasis and 2.7% for prostate cancer-related deaths), which is likely due to the preponderance of lower risk cases included in the study, which may limit the power to detect differences in patients with higher-risk disease. That said, 20-30% of patients had intermediate-/high-risk disease at diagnosis, and there was likely significant under-grading of tumours at diagnosis based upon limited core TRUS biopsies without MRI. It is also important to note that the control arm was not 'no treatment', as 60% of men progressed to active radical treatment at some stage, although often many years down the track.

Reference: N Engl J Med. 2023;388(17):1547-1558
Abstract

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Targeting androgen receptor and the variants by an orally bioavailable Proteolysis Targeting Chimeras compound in castration resistant prostate cancer

Authors: Hung C-L et al.

Summary: This study assessed the use of Proteolysis Targeting Chimeras (PROTAC) to induce degradation of both full-length androgen receptor (AR) and ligand-binding domain truncated AR variants. *In vitro*, PROTAC degraded both proteins via the ubiquitin-proteasome system, causing impaired AR transactivation on target gene expression, and reduced cell proliferation along with apoptosis activation. PROTAC also inhibited enzalutamide-resistant growth of castration-resistant prostate cancer cells. In a castration-, enzalutamide-resistant xenograft model, one PROTAC compound had good oral bioavailability and strong antitumor efficacy.

Comment: AR signalling is important in driving prostate cancer progression, and therapies that target this by suppressing androgen synthesis (e.g., LHRH agonists/antagonists, abiraterone) or receptor binding/nuclear translocation/DNA binding (e.g., enzalutamide, darolutamide etc.) are the backbone of treatment of advanced disease. Overexpression of AR or a number of constitutively active splice variants have been associated with resistance to AR targeting agents, prompting investigators to develop novel therapeutic strategies to combat this. This interesting study describes a novel proteolysis targeting chimera that uses the N-terminal domain to AR as a bait for the native receptor and a ubiquitin ligase-binding moiety to target it for degradation. The authors demonstrate activity with oral dosing in an animal model of castration- and enzalutamide-resistance, however, demonstrating target protein specificity will be key to clinical translation.

Reference: EBioMedicine 2023;90:104500
Abstract

Development and validation of a multi-institutional nomogram of outcomes for PSMA-PET-based salvage radiotherapy for recurrent prostate cancer

Authors: Zamboglou C et al.

Summary: This retrospective cohort study sought to develop and validate a nomogram for prediction of freedom from biochemical failure after PSMA-PET-targeted salvage radiotherapy based on 1029 patients with prostate cancer divided into a training dataset (n = 708), an internal validation dataset (n = 271), and external outlier validation dataset (n = 50). Over a median follow-up of 32 months, 437 (42.5%) patients had local recurrences and 313 (30.4%) patients had nodal recurrences. Multivariate analysis suggested that freedom from biochemical failure was associated with baseline PSA level (HR 1.80; 95% CI 1.41-2.31), surgery specimen ISUP grade 5 versus grade 1/2 (HR 2.39; 95% CI 1.63-3.50), pT3b/pT4 stage versus pT2 stage (HR 1.91; 95% CI 1.39-2.67), R0 versus R1/R2/Rx surgical margins (HR 0.60; 95% CI 0.48-0.78), ADT (HR 0.49; 95% CI 0.37-0.65), salvage radiotherapy dose >70 versus ≤66 Gy (HR 0.44; 95% CI 0.29-0.67), and nodal recurrence observed with PSMA-PET (HR 1.42; 95% CI 1.09-1.85). Mean nomogram concordance index for freedom from biochemical failure was 0.72 in the internal validation dataset and 0.67 with the external outlier validation dataset.

Comment: PSMA-PET is now the go-to investigation in patients with biochemically recurrent disease post prostatectomy considering salvage pelvic radiation. However, how the results impact on rates of success of salvage therapy in patients with a negative scan or pelvic only recurrence is unclear. This large retrospective multicentre study investigated factors associated with freedom from biochemical recurrence in patients undergoing salvage radiotherapy in whom distant disease was excluded by PSMA-PET. Interestingly, although the presence of lymph node disease was independently associated with a higher risk of failure, it was not the strongest factor in the model, with pre-radiotherapy PSA levels, tumour grade and stage dominating. That said, salvage treatment may have been influenced by the PET findings (ADT use, pelvic side wall radiation etc.), so the real value may be underestimated.

Reference: JAMA Netw Open 2023;6(5):e2314748
Abstract

Abiraterone acetate plus prednisolone with or without enzalutamide for patients with metastatic prostate cancer starting androgen deprivation therapy: Final results from two randomised phase 3 trials of the STAMPEDE platform protocol

Authors: Attard G et al.

Summary: This pooled analysis of two multinational, randomised, controlled, open-label, phase III STAMPEDE platform protocol trials examined long-term outcomes and the effect of combining enzalutamide with abiraterone and ADT on survival in 1003 patients with metastatic prostate cancer receiving standard of care (SOC; n = 502) or SOC plus abiraterone (n = 501) in an abiraterone trial and 916 patients receiving SOC (n = 454) or SOC plus abiraterone and enzalutamide (n = 462) in an abiraterone plus enzalutamide trial. Over a median follow-up of 96 months in the abiraterone trial and 72 months in the abiraterone plus enzalutamide trial, median OS was 76.6 months (95% CI 67.8-86.9) in abiraterone versus 45.7 months (95% CI 41.6-52.0) in SOC recipients (HR 0.62; 95% CI 0.53-0.73; p < 0.0001), and 73.1 months (95% CI 61.9-81.3) in abiraterone plus enzalutamide versus 51.8 months (95% CI 45.3-59.0) in SOC recipients (HR 0.65; 95% CI 0.55-0.77; p < 0.0001). There was no difference in treatment effect between the trials (interaction HR 1.05; 95% CI 0.83-1.32) or between-trial heterogeneity. Over the initial 5 years of treatment, grade 3-5 toxic effects were greater with abiraterone plus SOC versus SOC (54% vs 38%) and abiraterone plus enzalutamide plus SOC versus SOC (68% vs 45%). The most common cause of death due to adverse events was cardiac related.

Comment: Triplet therapy, combining ADT plus chemotherapy plus a novel androgen receptor signalling inhibitor upfront in patients with metastatic hormone-sensitive prostate cancer is currently flavour of the month, although the additional benefit is still being debated. So, what about combining two novel androgen signalling inhibitors with proposed independent mechanisms of action with ADT with or without docetaxel? This timely report analysed data from two RCTs from within the STAMPEDE arm, which investigated the benefit of SOC versus SOC plus abiraterone, as well as SOC versus SOC plus abiraterone and enzalutamide. Consistent with previous reports, adding abiraterone to SOC improved OS, however the addition of enzalutamide did not appear to result in any additional therapeutic benefit (with all the caveats of inter-trial comparisons!). Toxic effects were higher for SOC plus abiraterone, and higher still for the abiraterone plus enzalutamide combination.

Reference: Lancet Oncol. 2023;24(5):443-456
Abstract

First-in-patient study of OTL78 for intraoperative fluorescence imaging of prostate-specific membrane antigen-positive prostate cancer: A single-arm, phase 2a, feasibility trial

Authors: Stibbe JA et al.

Summary: This Dutch single-arm, phase IIa feasibility trial examined targeted real-time imaging during robot-assisted radical prostatectomy (RARP) using the PSMA-targeted fluorescent tracer OTL78 in 18 patients (median age 69 years, median PSA 15 ng/mL) with prostate cancer. In 16 (89%) patients, RARP was accompanied by extended pelvic lymph node dissection. There were three serious adverse events in one (6%) patient considered unrelated to OTL78 or intraoperative fluorescence imaging; infected lymphocele, urosepsis, and intraperitoneal haemorrhage. Dose-normalised maximum serum concentration (C_{max}/dose) was 84.1 ng/mL/mg using a 0.03 mg/kg dose and 79.6 ng/mL/mg using a 0.06 mg/kg dose, half-lives were 5.1 hours and 4.7 hours, while volumes of distribution were 22.9 L and 19.5 L, and clearances were 3.1 L/h and 3.0 L/h.

Comment: Being able to visualise cancer directly during radical prostatectomy would be expected to improve neurovascular bundle preservation and urethral length, while at the same time maximising surgical clearance with negative margins. This first-in-man study from the Netherlands examined the efficacy of three different dosing regimens of a novel fluorescent agent consisting of a high affinity PSMA-targeting ligand conjugated to a near-infrared dye, with fluorescence detected intraoperatively with Visionsense near-infrared imaging system (Medtronic) and visualised with the TilePro function of the Da Vinci Surgical System. Sensitivity for the visual detection of tumour intra-operatively was pretty good compared with *ex-vivo* back-table imaging (up to 65%) and microscopic assessment (up to 89%), although it did vary with tumour grade, volume and PSMA staining intensity. We now need demonstration that its use can impact oncological and functional outcomes.

Reference: Lancet Oncol. 2023;24(5):457-467
Abstract

Prostate-specific antigen level at the time of salvage therapy after radical prostatectomy for prostate cancer and the risk of death

Authors: Tilki D et al.

Summary: This analysis of a multinational database of 25,551 patients with pT2-4N0 or NXM0 prostate cancer, examined whether there is a PSA level after PSA failure above which initiating salvage radiotherapy is associated with increased all-cause mortality. Over a median follow-up of 6.0 years, salvage radiotherapy at a PSA level >0.25 ng/mL had a higher all-cause mortality risk (adjusted HR 1.49; 95% CI 1.11-2.00; p = 0.008) versus PSA ≤0.25 mg/mL. This elevated risk was observed at all PSA thresholds in 0.05 ng/mL increments up to 0.50 ng/mL, but not at PSA levels below 0.25 ng/mL.

Comment: The optimal PSA threshold at which to initiate salvage therapy for biochemically recurrent prostate cancer is unknown. Given that PSMA-PET imaging is more likely to be positive at higher PSA levels, the authors suggest there is a concern that patients' salvage treatment may be delayed in some men as the PSA rises to a point at which imaging is more likely to be informative, which may adversely affect treatment outcomes. In this context the authors performed a retrospective review of the impact of incremental increases in PSA level at which salvage radiation was instituted on all-cause mortality, finding that salvage radiotherapy started at a PSA level >0.25 ng/ml was associated with worse outcomes compared to when it was commenced below this threshold. Interesting data but needs to be interpreted with caution given the number of potential confounders (performance status, co-morbidities etc.) that may impact OS as well as the PSA threshold at which salvage radiotherapy is instituted.

Reference: J Clin Oncol. 2023;41(13):2428-2435
Abstract

Clinical performance of magnetic resonance imaging and biomarkers for prostate cancer diagnosis in men at high genetic risk

Authors: Cussenot O et al.

Summary: This study examined different scenarios for the management of early diagnosis in 322 men at high genetic risk for prostate cancer, using blood and urinary molecular biomarkers with multiparametric MRI (mpMRI). An mpMRI PI-RADS score ≥3 had higher sensitivity than a PI-RADS score ≥4 for detection of prostate cancer (82% vs 61%) and for the detection of ISUP grade >1 lesions (96% vs 80%). An mpMRI PI-RADS score ≥3 was also better than a PSA level of ≥3 ng/mL for both sensitivity (96% vs 91%) and specificity (53% vs 8%) of detecting clinically significant prostate cancer. With negative mpMRI results, the most useful indicators of decision to biopsy were urinary markers and PSA density ≥0.10 ng/mL/mL.

Comment: What is the optimal test to screen for early prostate cancer in patients at high genetic risk of the disease? This study compared the sensitivity and specificity of a number of different tests (PSA level, PSA density, prostate health index, urine Prostate Cancer antigen 3 score, urine levels of the gene fusion of androgen-regulated transmembrane serine protease [TMPRSS2] and the erythroblast transformation specific [ETS] transcription factor [T2:ERG] score, and prostate MRI) for the detection of clinically significant prostate cancer in men with a significant family history of prostate cancer or carriers of a known predisposing germline variant undergoing a 12-core TRUS biopsy. Overall MRI (PIRADS >3) was the best performing test on which to decide to biopsy regardless of PSA level, although performance improved when PSA and PSA density were also included. Important information, and certainly justifies the lower PSA threshold for accessing Medicare Benefits Schedule rebatable MRIs in patients with a family history.

Reference: BJU Int. 2023;131(6):745-754
Abstract

Effect of prior local therapy on response to first-line androgen receptor axis targeted therapy in metastatic castrate-resistant prostate cancer: A secondary analysis of the COU-AA-302 trial

Authors: Roy S et al.

Summary: This exploratory analysis of the multicentre double-blinded, randomised controlled, phase III COU-AA-302 trial of abiraterone plus prednisone or placebo plus prednisone in 1053 docetaxel-naive mCRPC patients with no to mild symptoms assessed whether prior prostate-directed local therapy (n = 669; 64%) altered response to first-line systemic therapy and survival. There was no heterogeneity of time-dependent treatment effects of abiraterone on radiographic progression-free survival with prior local therapy (HR 0.36; 95% CI 0.27-0.49) at ≤6 months or > 6 months (HR 0.64; 95% CI 0.49-0.83) or without prior local therapy (HR 0.37; 95% CI 0.26-0.55 at ≤6 months; HR 0.72; 95% CI 0.50-1.03 at >6 months). There was also no heterogeneity of abiraterone effects on OS with prior local therapy (HR 0.88; 95% CI 0.71-1.10) at ≤36 months or at >36 months (HR 0.76; 95% CI 0.52-1.11) or without prior local therapy (HR 0.78; 95% CI 0.60-1.01 at ≤36 months; HR 0.55; 95% CI 0.30-0.99 at >36 months). Overall, prior local therapy was associated with an improvement in OS (average HR 0.72; 95% CI 0.59-0.89).

Comment: An older medical oncology colleague used to say that patients with metastatic disease were easier to manage when the prostate was out, presumably due to the reduction in complications related to local progression. Another suggested advantage is that local therapy may remove a major potential source of treatment resistant cell populations, and thereby prolong the efficacy of systemic treatments. This analysis from the COU-AA-302 trial, which demonstrated an improvement in OS in men with chemotherapy-naive mCRPC randomised to receive abiraterone plus prednisone or placebo plus prednisone, shows that although prior local therapy (radical prostatectomy, radiotherapy, or radical prostatectomy plus radiotherapy) did not affect the efficacy of abiraterone, it was associated with an observed increase in OS. Would assume this reflects the different disease trajectories of synchronous versus metachronous disease, rather than a true treatment benefit.

Reference: Eur Urol. 2023;83(6):571-579
Abstract

Impact of concurrent tumour events on the prostate cancer outcomes of germline *BRCA2* mutation carriers

Authors: Lozano R et al.

Summary: This study examined the role of somatic genomic alterations and histology subtypes in 73 germline *BRCA2* mutation carriers and non-carriers. Somatic *BRCA2-RB1* co-deletion (41% vs 12%; $p < 0.001$) and *MYC* amplification (53.4% vs 18.8%; $p < 0.001$) were enriched in patients with germline *BRCA2* compared to sporadic tumours. Median cause-specific survival from diagnosis of cancer was 9.1 in germline *BRCA2* carriers versus 17.6 years in non-carriers (HR 2.12; $p = 0.002$), median cause-specific survival in germline *BRCA2* carriers was 11.3 in the absence of *BRCA2-RB1* deletion and 13.4 years without *MYC* amplification, while the median cause-specific survival of non-carriers was 8 years with *BRCA2-RB1* deletion and 2.6 years with *MYC* amplification.

Comment: It is clear from the IMPACT study that patients with germline mutations in *BRACA2* have a higher incidence of prostate cancer diagnosis, younger age of diagnosis as well as more adverse pathological features compared to non-carriers. Multiple studies also show that germline mutations in *BRCA2* are associated with reduced metastasis free- and castration resistance free-survival, as well as increased cancer-specific mortality. This retrospective case control study investigated the impact of germline mutations on the acquisition of high-risk somatic alterations in the tumour and subsequent outcomes. They find that patients with germline *BRCA2* mutations more commonly had intra-tumoural *RB1* co-deletion and *MYC* amplification, which were associated with further significant reductions in survival outcomes. This compounding effect of high-risk genomic features is increasingly recognised in early prostate cancer and may be important in clinical risk stratification in the near future.

Reference: Eur J Cancer 2023;185:105-118
Abstract

Preoperative endogenous total testosterone predicts prostate cancer progression: Results in 580 consecutive patients treated with robot assisted radical prostatectomy for clinically localized disease

Authors: Porcaro AB et al.

Summary: This study examined the role of endogenous total testosterone (ETT) level (≤350 vs >350 ng/dL) as a predictor of prostate cancer progression in 580 patients treated with RARP for clinically localised disease. Preoperative ETT ≤350 ng/dL was observed in 173 (29.8%) patients and disease progression occurred in 101 (17.1%) patients. Patients who progressed were more likely to have PSA >10 ng/mL, along with unfavourable tumour grade (ISUP 4-5) and stage pT3b at final pathology, but were less likely to have ETT ≤350 ng/mL. Multivariate analysis suggested that ETT ≤350 ng/mL had a protective effect on tumour progression (HR 0.57; $p = 0.013$). Patients with ETT levels ≤350 ng/mL were less likely to have ISUP 4-5 tumours at either biopsy (OR 0.46; $p = 0.028$) or final pathology (OR 0.45; $p = 0.032$).

Comment: The relationship between circulating androgen levels and prostate cancer incidence and prognosis is complex, but there is certainly evidence that tumours that develop in a low androgen signalling environment (for instance a bulky primary with a low PSA) are associated with adverse pathological features and poorer outcomes. Adding to the complexity is this Italian series, which finds that high levels of total testosterone prior to RARP were associated with higher tumour grade, whereas a low pre-operative total testosterone was an independent protective factor against tumour progression. Patients with low testosterone were more likely to be overweight/obese, so may well be just a surrogate of the established impact of BMI on prostate cancer outcomes.

Reference: Int Urol Nephrol. 2023;55(5):1139-1148
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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