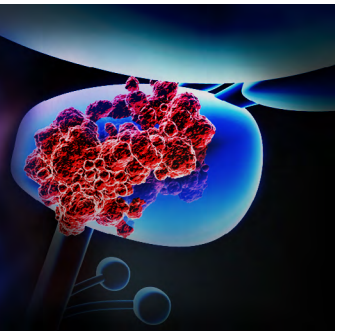
Prostate Cancer Research Review™



Making Education Easy

Issue 67 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **aHR** = adjusted hazard ratio; **aRR** = adjusted risk ratio; **AS** = active surveillance; **CI** = confidence interval; **Gy** = Grey; **HR** = hazard ratio; **HRQoL** = health-related quality of life; **ISUP** = International Society of Urological Pathology; **LHRH** = luteinising hormone-releasing hormone; **LUTS** = lower urinary tract symptoms; **mCRPC** = metastatic castration-resistant prostate cancer; **MDT** = multidisciplinary team; **mHSPC** = metastatic hormone-sensitive prostate cancer; **OS** = overall survival; **PARP** = poly ADP-ribose polymerase; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RCT** = randomised controlled trial; **rPFS** = radiographic progression-free survival; **RT** = radiotherapy; **TRAEs** = treatment-related adverse events.

Welcome to Issue 67 of Prostate Cancer Research Review.

Findings from the VISION trial demonstrate that despite a higher observed frequency of haematological adverse events in patients with metastatic castration-resistant prostate cancer receiving 177Lu-PSMA-617, such treatment when added to standard of care delayed worsening of health-related quality of life and disease-related pain. Meanwhile, in the EXTEND trial we discover that the addition of metastasis-directed therapy to intermittent androgen deprivation therapy in men with oligometastatic prostate cancer improves progression-free survival and eugonadal progression-free survival versus androgen deprivation therapy alone. Other topics covered in this issue include 5α-reductase inhibitors and prostate cancer mortality, niraparib plus abiraterone acetate for metastatic castration-resistant prostate cancer, salvage stereotactic reirradiation for local recurrence after prostatectomy, and confocal laser microscopy for surgical margin assessment.

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,

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Health-related quality of life and pain outcomes with [^{177}Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): A multicentre, open-label, randomised, phase 3 trial

Authors: Fizazi K et al.

Summary: This analysis reports health-related quality of life (HRQoL), pain, and symptomatic skeletal event results from the multicentre, open-label, randomised, controlled, phase III VISION trial of the PSMA-targeted radioligand therapy lutetium-177 (^{177}Lu-PSMA-617; vipivotide tetraxetan) plus standard of care in 385 patients and 196 controls (standard of care) with mCRPC. Median time to first symptomatic skeletal event or death was 11.5 months (95% CI 10.3-13.2) versus 6.8 months (HR 0.50; 95% CI 0.40-0.62). Time to worsening was delayed for Functional Assessment of Cancer Therapy-Prostate (FACT-P) score (HR 0.54; 95% CI 0.45-0.66), the Brief Pain Inventory-Short Form (BPI-SF) pain intensity score (HR 0.52; 95% CI 0.42-0.63), and the EuroQol 5-dimensional 5-level questionnaire (EQ-5D-5L) utility score (HR 0.65; 95% CI 0.54-0.78) in ^{177}Lu-PSMA-617 plus standard of care recipients versus controls. Haematological adverse events of grade 3/4 included decreased haemoglobin (15% vs 6%), lymphocyte concentrations (51% vs 19%), and platelet counts (9% vs 2%). TRAEs leading to death occurred in 1% of ^{177}Lu-PSMA-617 recipients (pancytopenia, bone marrow failure, subdural haematoma, and intracranial haemorrhage) versus no control patients.

Comment: The VISION RCT demonstrated that ^{177}Lu-PSMA-617 improved rPFS and OS in men with mCRPC progressing after at least one novel androgen receptor signalling inhibitor and a taxane chemotherapy, establishing it as a standard of care in the third-line setting. This follow-up study reports on HRQoL, demonstrating that despite a higher observed frequency of haematological adverse events in patients receiving ^{177}Lu-PSMA-617, treatment delayed worsening of HRQoL and disease-related pain. Important information to consider as the list of potentially life-extending treatment options continue to expand, although patient selection could possibly be improved using dual PET imaging as in the local TheraP trial.

Reference: Lancet Oncol. 2023;24(6):597-610
Abstract

Addition of metastasis-directed therapy to intermittent hormone therapy for oligometastatic prostate cancer: The EXTEND phase 2 randomized clinical trial

Authors: Tang C et al.

Summary: The basket randomised phase II External Beam Radiation to Eliminate Nominal Metastatic Disease (EXTEND) clinical trial examined whether metastasis-directed therapy added to intermittent ADT affected oncologic outcomes and preserved time with eugonadal testosterone versus intermittent ADT alone in 87 men (median age 67 years) with oligometastatic prostate cancer. Over a median follow-up of 22.0 months, median PFS was improved in the combined therapy arm versus ADT only arm (median not reached vs 15.8 months; 95% CI 13.6-21.2; HR 0.25; 95% CI 0.12-0.55; p < 0.001). Eugonadal PFS was also improved (median not reached vs 6.1 months; 95% CI 3.7 to not estimable; HR 0.32; 95% CI 0.11-0.91; p = 0.03). Markers of T-cell activation, proliferation, and clonal expansion improved only in the combined therapy arm.

Comment: Despite some evidence of efficacy, the role of metastasis-directed therapy in the management of oligometastatic disease remains to be clarified. This interesting study examined the impact of combining metastasis-directed therapy with intermittent ADT in patients with prostate cancer enrolled in the broader EXTEND study, with the hypothesis that stereotactic radiotherapy would synergise with the therapeutic action of 6 months of androgen suppression. Compared to the control arm, patients randomised to ablation of all visible metastasis with short-term ADT had prolonged PFS (composite of radiographic, clinical and biochemical endpoints) compared to short-term ADT alone. Time to eugonadal PFS and new lesion failure were also improved, with combination patients showing evidence of a stimulated immune response as a possible mechanism. Interesting data, and although the use of intermittent hormonal therapy with single-agent LHRH agonists/antagonist is no longer standard of care in mHSPC, at some stage consideration will need to be given to possible treatment de-escalation in select patients.

Reference: JAMA Oncol. 2023;9(6):825-834
Abstract

Association between 5α-reductase inhibitors and prostate cancer mortality: A systematic review and meta-analysis

Authors: Baboudjian M et al.

Summary: This systematic review and meta-analysis assessed evidence of the effect of 5α-reductase inhibitor (5-ARI) use and prostate cancer mortality based on 11 studies including 3,243,575 patients (138,477 5-ARI recipients). There was no association between 5-ARI use and prostate cancer mortality (aHR 1.04; 95% CI 0.80-1.35) overall, nor when analysis was restricted to studies excluding prostate cancer at baseline (aHR 1.00; 95% CI 0.60-1.67) or PSA-adjusted studies (aHR 0.76; 95% CI 0.57-1.03).

Comment: Nearly two decades after the publication of the Prostate Cancer Prevention Trial, the debate continues to smoulder as to whether 5-ARIs increase the risk of potentially lethal prostate cancer, or, by shrinking the prostate, just make them easier to detect on prostate biopsy. This large systematic review and meta-analysis of over three million patients finds that use of 5-ARIs is not associated with an increased risk of prostate cancer mortality (although they probably did improve bothersome LUTS in men who had them!). Hopefully this is the last word in this distracting saga.

Reference: JAMA Oncol. 2023;9(6):847-850
Abstract

Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer

Authors: Chi KN et al.

Summary: The randomised, double-blinded, phase III MAGNITUDE study examined the use of niraparib and abiraterone acetate plus prednisone (niraparib + AAP) in mCRPC patients with homologous recombination repair positive (HRR+; n = 423) or negative (HRR-; n = 247) gene alterations. Median rPFS in a *BRCA1/2* subgroup was longer with niraparib + AAP versus placebo + AAP (16.6 vs 10.9 months; HR 0.53; 95% CI 0.36-0.79; p = 0.001). In the full HRR+ group, rPFS was also longer with niraparib + AAP (16.5 vs 13.7 months; HR 0.73; 95% CI 0.56-0.96; p = 0.022). Secondary endpoints were also improved including time to symptomatic progression and time to initiation of cytotoxic chemotherapy. Based on prespecified criteria, futility was declared in HRR- patients. The most reported grade ≥3 adverse events with niraparib + AAP were anaemia and hypertension.

Comment: PARP inhibitors have demonstrated consistent efficacy in patients with mCRPC harbouring homologous recombination repair defects (HRR, *BRAC1/2* etc.). However, results from the recent PROpel study suggest benefit in combination with abiraterone even in patients without these genomic alterations, raising the possibility that abiraterone can induce an 'HRR defect-like state' in tumour cells. However, this premise is not supported by this study, which demonstrates prolonged rPFS in patients receiving a PARP inhibitor (niraparib) and abiraterone combination over abiraterone alone in HRR+ patients, but not in HRR- patients. Why this is the case is unclear but may relate to differences in prior exposure to androgen receptor signalling inhibitors.

Reference: J Clin Oncol. 2023;41(18):3339-3351
Abstract

Dose-escalated radiotherapy alone or in combination with short-term androgen deprivation for intermediate-risk prostate cancer: Results of a phase III multi-institutional trial

Authors: Krauss DJ et al.

Summary: The randomised, controlled, phase II NRG Oncology/Radiation Therapy Oncology Group 0815 study assessed dose-escalated radiotherapy (RT; external-beam RT alone to 79.2 Gy or external beam [45 Gy] with brachytherapy boost) alone or with short-term ADT in 1492 patients with intermediate-risk prostate cancer (stage T2b-T2c, Gleason score 7, or PSA >10 and ≤20 ng/mL). Over a median follow-up of 6.3 years, 219 deaths occurred (119 with RT alone and 100 with RT and ADT); 5-year OS estimates did not differ between groups (90% vs 91%; HR 0.85; 95% CI 0.65-1.11). Short-term ADT reduced PSA failure (HR 0.52; p < 0.001), distant metastases (HR 0.25; p < 0.001), prostate cancer-specific mortality (HR 0.10; p = 0.007), and salvage therapy (HR 0.62; p = 0.025). Acute grade ≥3 adverse events occurred in 2% versus 12% of patients (p < 0.001) and the cumulative incidence of late grade ≥3 adverse events was 14% versus 15%.

Comment: Short-term ADT improves disease control and survival outcomes in historical trials of patients with intermediate-risk prostate cancer treated with what are now considered suboptimal doses of external beam RT. Given similar outcomes with contemporary dose escalated monotherapy, routine use of ADT has fallen out of favour, despite the potential for therapeutic synergy. This large RCT found that the addition of 6 months of ADT beginning 8 weeks before definitive RT improved prostate cancer disease control, as measured by significant increases in biochemical failure-free, metastasis-free, and prostate cancer-specific mortality-free survival, but had no effect on OS, which was the primary endpoint of the study. The reason for this discordance is unclear, although an OS benefit may yet emerge with further follow-up.

Reference: J Clin Oncol. 2023;41(17):3203-3216
Abstract

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References: 1. Zoladex 10.8mg Approved Product Information. **2.** Zoladex 3.6mg Approved Product Information.

Analysis of a biopsy-based genomic classifier in high-risk prostate cancer: Meta-analysis of the NRG Oncology/Radiation Therapy Oncology Group 9202, 9413, and 9902 phase 3 randomized trials

Authors: Nguyen PL et al.

Summary: This study assessed the validity of the Decipher genomic classifier in pre-treatment biopsy samples (265 microarray quality-controlled samples) across three randomised phase III high-risk definitive RT trials. Over a median follow-up of 11 years, the genomic classifier was a prognostic factor for distant metastases (HR 1.29; 95% CI 1.18-1.41; $p < 0.001$), prostate cancer-specific mortality (HR 1.28; 95% CI 1.16-1.41; $p < 0.001$), and OS (HR 1.16; 95% CI 1.08-1.22; $p < 0.001$). Multivariate analyses after adjusting for age, PSA, Gleason score, cT stage, trial, and randomised treatment arm suggested that the genomic classifier was independently associated with distant metastases (HR 1.22; 95% CI 1.09-1.36), prostate cancer-specific mortality (HR 1.23; 95% CI 1.09-1.39), and OS (HR 1.12; 95% CI 1.05-1.20).

Comment: Accumulating evidence suggests that treatment intensification earlier in the disease course is beneficial in patients with potentially lethal prostate cancer. However, rates of progression to metastasis and death are often low, even in patients considered high risk using conventional clinical and pathological variables, so better markers are needed to select those patients most likely to benefit and avoid unnecessary toxicity in those less likely to. This study examined the association of the Decipher genome classifier score (a transcription-based assay) performed on pre-treatment diagnostic cores from men enrolled in three RCTs of definitive RT for high-risk disease. Higher genome classifier scores were associated with an increased risk of distant metastases, prostate cancer-specific survival as well as OS, even after adjusting for other variables. Should really be incorporated as a standard in any protocol investigating treatment intensification in early-stage disease.

Reference: Int J Radiat Oncol Biol Phys. 2023;116(3):521-529
Abstract

Salvage stereotactic reirradiation for local recurrence in the prostatic bed after prostatectomy: A retrospective multicenter study

Authors: Archer P et al.

Summary: This multinational, retrospective, case series included 117 patients treated with salvage stereotactic body RT (SBRT; median dose 35 Gy) for local recurrence in the prostatic bed after radical prostatectomy and RT. Over a median follow-up of 19.5 months, median PFS was 23.5 months (95% CI 17.6-33.2). Multivariate analysis suggested that the volume of the recurrence (HR per 10 cm^3 1.46; 95% CI 1.08-1.96; $p = 0.01$) and its contact with the urethrovesical anastomosis (HR 3.35; 95% CI 1.38-8.16; $p = 0.008$) were associated with PFS. Three-year cumulative incidence of grade ≥2 late genitourinary or gastrointestinal toxicity was 18% (95% CI 10-26). Late toxicities of any grade were associated with recurrence in contact with the urethrovesical anastomosis (HR 3.65; 95% CI 1.61-8.24; $p = 0.002$) and minimum dose to 2% of the volume of the bladder (HR 10 Gy 1.88; 95% CI 1.12-3.16; $p = 0.02$).

Comment: An increasingly common problem in an age of widespread availability of advanced imaging is what to do with a macroscopic recurrence in an already irradiated prostate bed post prostatectomy. This retrospective multicentre study examined the safety and efficacy of SBRT to a median dose of 35 Gy to image detected local recurrence post salvage RT, with or without ADT. Almost half the patients recurred within 20 months, of whom almost half were metastatic. In-field recurrence was also quite common, suggesting that normal tissue constraints limited effective dosing in some cases. Larger recurrences and contact with the anastomosis were associated with poorer PFS. Grade 3 toxicity occurred in 6% of patients, most commonly urinary. Certainly not for everyone, but perhaps in select cases.

Reference: Eur Urol Oncol. 2023;6(3):303-310
Abstract

Confocal laser microscopy for assessment of surgical margins during radical prostatectomy

Authors: Baas DJH et al.

Summary: This study assessed the use of confocal laser microscopy (CLM) compared to neurovascular structure-adjacent frozen-section examination (NeuroSAFE) for intraoperative margin assessment during 50 robot-assisted radical prostatectomy (RARP) procedures. Based on 96 posterolateral sections, CLM identified 15 (16%) positive surgical margins and NeuroSAFE identified 14 (15%) positive surgical margins. CLM sensitivity was 86%, specificity was 96%, positive predictive value was 80% and negative predictive value was 98% for detection of positive surgical margins compared to definite pathology. After secondary resection, residual tumour was found in 6/13 cases (46%), all of which were identified by both techniques. Median CLM procedure time was shorter than NeuroSAFE (8 vs 50 min; $p < 0.001$).

Comment: The NeuroSAFE technique evolved as a way of maximising preservation of the bundles without increasing positive margin rates, but is both labour intensive and time consuming. In this prospective cohort study, the authors compared a more rapid margin assessment using ex-vivo fluorescent CLM with the Histolog scanner against the standard NeuroSAFE procedure in the same specimens. Although concordance with definitive pathology for the presence of residual tissue was marginally higher with NeuroSAFE, CLM was about five times faster, making it readily incorporated into routine clinical practice. Where both techniques will sit with emergence of a number of *in vivo* real-time tumour visualisation procedures remains to be determined.

Reference: BJU Int. 2023;132(1):40-46
Abstract

Prostate Cancer Research Review™

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.

Identifying men who can remain on active surveillance despite biopsy reclassification to Grade Group 2 prostate cancer

Authors: Baraban E et al.

Summary: This study assessed subgroups of men who can remain on active surveillance despite preoperative reclassification to ISUP Grade Group 2 prostate cancer who underwent radical prostatectomy. Multivariate analysis identified PSA density and perineural invasion as stratification variables that predict radical prostatectomy adverse pathology risk among active surveillance patients. Overall, 57% (39/68) of Grade Group 1 patients reclassified to Grade Group 2 had favourable radical prostatectomy pathology. Those without biopsy perineural invasion and with low PSA density more often had favourable radical prostatectomy pathology.

Comment: Upgrading from ISUP Grade Group 1 to 2 during interval biopsies has traditionally been considered a trigger for definitive management in men undergoing active surveillance. This recommendation persists despite the very low rates of metastases and prostate cancer-specific death in conservatively treated men with favourable intermediate-risk disease. This small study from Johns Hopkins found that men reclassified from Grade Group 1 to 2 during surveillance had similar rates of adverse pathology at prostatectomy as men with Grade Group 1 disease, with a higher PSA density and the presence of perineural invasion on biopsy being associated with a higher risk of adverse pathology. Although using pathological findings at prostatectomy as a surrogate for long-term clinical outcomes in localised prostate cancer is highly dubious, it does add further weight to the argument to routinely extend active surveillance to patients with intermediate-risk disease.

Reference: J Urol. 2023;210(1):99-107
Abstract

Comparison of the treatment of men with prostate cancer between the US and England: An international population-based study

Authors: Parry MG et al.

Summary: This analysis of the US Surveillance, Epidemiology, and End Results (SEER; n = 109,697) database and the English National Prostate Cancer Audit (NPCA; n = 74,393) database identified men newly diagnosed with prostate cancer (2014-16) and characterised the differences in initial treatment between US and English prostate cancer patients. US patients were more likely than English patients to receive radical local treatment across all prognostic groups; Cambridge Prognostic Group 1 (CPG1; 38.1% vs 14.3%; aRR 2.57; 95% CI 2.47-2.68), CPG2 (68.6% vs 52.6%; aRR 1.27; 95% CI 1.25-1.29), CPG3 (76.7% vs 67.1%; aRR 1.12; 95% CI 1.10-1.13), CPG4 (82.6% vs 72.4%; aRR 1.09; 95% CI 1.08-1.10) and CPG5 (78.2% vs 71.7%; aRR 1.06; 95% CI 1.04-1.07).

Comment: Despite little evidence of clinical benefit for the radical treatment of the majority of men with clinically localised prostate cancer, whether you are a hawk or a dove in Australia frequently comes down to where you did your fellowship training. This difference in clinical practice is highlighted in this study which compared treatment rates within the SEER database in the US and the NPCA database in England. Using the CPG 5-tiered prognostic grouping, all prognostic group patients in the US were more likely to receive radical treatment, with the difference being greatest in the lowest risk prognostic group. Interestingly the most common treatment modality for higher-risk disease in England was RT, whereas in the US it was surgery, which may reflect the lack of mandatory MDT discussion/management of cancer cases. However, the data are a little out of date.

Reference: Prostate Cancer Prostatic Dis. 2023;26(2):287-292
Abstract

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