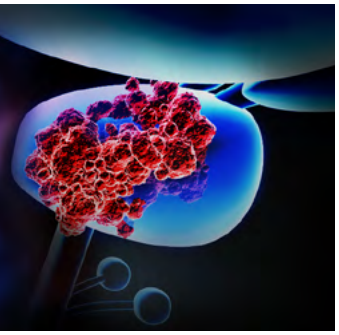
Prostate Cancer Research Review™



Making Education Easy

Issue 68 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **AUC** = area under the curve; **BMI** = body mass index; **CI** = confidence interval; **HR** = hazard ratio; **mCRPC** = metastatic castration-resistant prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer; **MRI** = magnetic resonance imaging; **OR** = odds ratio; **OS** = overall survival; **PSA** = prostate-specific antigen; **TRUS** = transrectal ultrasonography.

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Welcome to Issue 68 of Prostate Cancer Research Review.

First up, a study of European men highlights the potential utility of incorporating genetically-adjusted PSA levels for prostate cancer screening. Following on, the REASSURE study gives insight into radium-223 use in global real-world clinical practice. Other topics covered in this issue include response to new hormonal agents in metastatic hormone-sensitive prostate cancer, darolutamide plus androgen deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer by disease volume and risk, post-diagnostic health behaviour and prostate cancer progression and mortality, standardised prostate cancer incidence and mortality rates after initial non-malignant biopsy, and second-line therapies for metastatic neuroendocrine prostate cancer.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Associate Professor Niall Corcoran
niall.corcoran@researchreview.com.au

Genetically adjusted PSA levels for prostate cancer screening

Authors: Kachuri L et al.

Summary: This study examined constitutive, non-cancer-related genetic PSA variations using 128 genome-wide associations (GWAS) in a multi-ancestry meta-analysis of 95,768 men and developed a PSA polygenic score that explains 9.61% of constitutive PSA variation. Among European men, a polygenic score-adjusted PSA would avoid up to 31% of negative prostate biopsies and result in 12% fewer biopsies in prostate cancer patients, mostly with Gleason score <7 tumours. Genetics-adjusted PSA was more predictive of aggressive prostate cancer (OR 3.44, $p = 6.2 \times 10^{-14}$; AUC 0.755) than unadjusted PSA (OR 3.31; $p = 1.1 \times 10^{-12}$; AUC 0.738). Compared to prostate cancer polygenic score alone (AUC 0.712), inclusion of a genetically adjusted PSA improved aggressive disease detection (AUC = 0.786, $p = 7.2 \times 10^{-4}$).

Comment: PSA is an imperfect tumour marker and elevated levels may reflect conditions other than prostate cancer. This is well appreciated for benign conditions affecting the prostate such as benign prostate enlargement and prostatitis, but there is also a constitutive element in that some men just have higher levels of PSA expression than others. Using a GWAS meta-analysis approach across a number of previously genotyped cohorts, the authors identified 128 variants that could explain up to 10% of the constitutive variability in men of European ancestry. They then generated a polygenic risk score which they used to 'adjust' PSA levels to improve test specificity, which was more predictive of aggressive disease. Interesting data, but at the moment it is unclear how to translate it into something clinically actionable within the gallery of 'reflex' tests already available for elevated PSA.

Reference: Nature Med. 2023;29(6):1412-1423

Abstract

Clinical outcomes and treatment patterns in REASSURE: Planned interim analysis of a real-world observational study of radium-223 in metastatic castration-resistant prostate cancer

Authors: Higano CS et al.

Summary: The multinational, prospective, observational REASSURE study was conducted to examine long-term safety and treatment patterns with radium-223 used to treat bone-dominant mCRPC in 1465 men in real-world clinical practice. Over a median follow-up of 11.5 months, second primary malignancies occurred in 21 (1%; 23 events) of 1470 evaluable patients. During therapy, 311 (21%) patients experienced treatment-emergent serious adverse events, and 510 (35%) experienced drug-related adverse events. During the 6 months after therapy, 214 (15%) patients experienced grade 3/4 haematological toxicities; 80 (5%) patients had post-treatment drug-related serious adverse events. Median OS was 15.6 months (95% CI 14.6-16.5); 70 (5%) patients suffered fractures.

Comment: The ALSYMPCA study showed that radium-223 prolongs OS in men with bone-predominant mCRPC, although widespread uptake in Australia has been limited with the more recent availability of novel androgen signalling inhibitors. This phase IV study reports on close to 1500 patients treated with radium-223 with a median follow-up of almost 1 year. 59% of patients completed all planned 6 cycles, with 19% and 10% terminating early due to disease progression or adverse events, respectively. A second primary malignancy occurred in 1% of patients (most commonly lung), although 1 (monocytic leukaemia) was judged to be related to the radium. The most common drug-related serious adverse events were related to bone marrow suppression and the median OS was 15.6 months. Post-treatment haematological toxicity occurred in a higher proportion of patients who received chemotherapy before, compared with after, radium-223, suggesting treatment sequencing requires some consideration.

Reference: EClinicalMedicine 2023;60:101993
Abstract

Visceral metastasis predicts response to new hormonal agents in metastatic castration-sensitive prostate cancer

Authors: Yekedüz E et al.

Summary: This pooled analysis of six phase III randomised controlled trials (RCTs) assessed the use of abiraterone acetate plus prednisone versus second-generation non-steroidal anti-androgens (NSAAs) in 6485 patients with metastatic hormone-sensitive prostate cancer (mHSPC; 15.2% with visceral metastasis). Abiraterone acetate plus prednisone improved OS among patients with visceral metastasis (HR 0.58; 95% CI 0.40-0.84; p = 0.004) but second-generation NSAAs did not (HR 0.89; 95% CI 0.72-1.11). In patients without visceral metastasis, OS was improved with both second-generation NSAAs (HR 0.63; 95% CI 0.57-0.70; p < 0.001) and abiraterone acetate plus prednisone (HR 0.68; 95% CI 0.57-0.81; p < 0.001).

Comment: Visceral metastases are considered to be a uniformly poor prognostic indicator in metastatic prostate cancer, although there appears to be some organ hierarchy, with for instance patients with lung metastases having a better prognosis than those with spread to the liver. This pooled analysis of phase III trial data assessing the efficacy of novel hormonal agents in patients with mHSPC suggest that the presence of visceral metastases may also be predictive of differential response to therapy. They found that although both second-generation NSAAs and abiraterone improved OS in patients without visceral metastases, only abiraterone improved OS in patients with visceral metastases. There are a number of problems with the analysis, but interesting hypothesis-generating data, particularly as a greater proportion of patients in the abiraterone group had liver metastases.

Reference: Oncologist 2023;28(7):596-603
Abstract

Darolutamide plus androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer by disease volume and risk subgroups in the phase III ARASENS trial

Authors: Hussain M et al.

Summary: This *post-hoc* analysis of data from the randomised, placebo controlled, ARASENS trial assessed the efficacy and safety of darolutamide plus ADT and docetaxel in 1305 patients with mHSPC across subgroups delineated by disease volume and risk (high-volume disease n = 1,005; high-risk disease n = 912). Compared with placebo, darolutamide increased OS in high-volume (HR 0.69; 95% CI 0.57-0.82), high-risk (HR 0.71; 95% CI 0.58-0.86), and low-risk disease (HR 0.62; 95% CI 0.42-0.90), while in a smaller low-volume subgroup, the results suggested a possible survival benefit (HR 0.68; 95% CI 0.41-1.13). Darolutamide improved time to castration-resistant prostate cancer and subsequent antineoplastic therapy in all disease volume and risk subgroups. Adverse events were similar across subgroups, with grade 3-4 adverse events occurring in 64.9% of darolutamide versus 64.2% of placebo recipients with high-volume disease and 70.1% versus 61.1% with low-volume disease. Many common adverse events were known toxicities related to docetaxel.

Comment: The ARASENS trial demonstrated that the addition of darolutamide to ADT plus docetaxel improves OS in men with mHSPC over placebo. This *post-hoc* analysis examined efficacy by disease volume (with high volume defined using the CHAARTED criteria; Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) and risk (high risk having ≥2 risk factors: Gleason score ≥8, ≥3 bone lesions, visceral metastases) subgroups. The beneficial effect of darolutamide was consistent across subgroups, although didn't reach significance to date for patients with low-volume disease with relatively late separation of the survival curves. There were also consistent effects across subgroups for other secondary endpoints including time to castration resistance and time to subsequent anti-neoplastic therapy. The vast majority of patients included in the study presented with *de novo* metastases, so too few cases to address the synchronous versus metachronous debate, but certainly worth considering triplet therapy for all patients presenting for the first time with metastases.

Reference: J Clin Oncol. 2023;41(20):3595-3607
Abstract

Darolutamide maintenance in patients with metastatic castration-resistant prostate cancer with nonprogressive disease after taxane treatment (SAKK 08/16)

Authors: Gillessen S et al.

Summary: The multicentre, randomised, placebo controlled, phase II Swiss Group for Clinical Cancer Research (SAKK) 08/16 study examined the use of darolutamide maintenance after successful taxane chemotherapy (docetaxel in 93% and cabazitaxel in 7%) and prior androgen-receptor pathway inhibitors (ARPIs; abiraterone in 60%, enzalutamide in 31%, both in 9%) in 92 patients with metastatic castration-resistant prostate cancer (mCRPC). Radiographic progression-free survival (rPFS) at 12 weeks was 64.7% with darolutamide versus 52.2% with placebo; median rPFS was 5.5 versus 4.5 months (HR 0.54; 95% CI 0.320.91; p = 0.017), and median event-free survival was 5.4 versus 2.9 months (HR 0.46; 95% CI 0.29-0.73; p = 0.001). PSA 50% response rate was also higher with darolutamide (22% vs 4%; p = 0.014), but median OS did not differ between treatment groups (24 vs 21.3 months; HR 0.62; 95% CI 0.3-1.26). Treatment-related adverse event rates did not differ between treatments.

Comment: Switch maintenance treatment, where a second anti-neoplastic agent is added as an adjuvant therapy after a good initial response to the first list treatment, is now standard of care in many tumour types (for instance avelumab maintenance therapy in patients with non-progressive disease after first-line chemotherapy in advanced urothelial cancer). This small phase II study investigated this approach using darolutamide in patients with mCRPC previously treated with a novel hormonal agent with non-progressive disease following taxane chemotherapy, demonstrating a statistically significant but clinically modest improvement in the primary endpoint of rPFS at 12 months. Given cross-resistance between novel hormonal agents, this approach may be more effective in patients receiving taxane chemotherapy in the first-line setting, mimicked to a certain extent by triplet therapy.

Reference: J Clin Oncol. 2023;41(20):3608-3615
Abstract

Post-diagnostic health behaviour scores and risk of prostate cancer progression and mortality

Authors: Langlais CS et al.

Summary: This analysis of data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE; n = 2156) cohort examined the association between six *a priori* health behaviour scores (2 scores based on survivorship literature '2021 Score [+ Diet]'; a score based on pre-diagnostic literature '2015 Score' and 3 scores based on US cancer prevention recommendations 'WCRF/AICR Score' and survival 'ACS Score [+ Alcohol]') and risk of prostate cancer progression and mortality. Over a median of 6.4 years, there were 192 progression and 73 prostate cancer mortality events. Progression risk was inversely associated with higher '2021 score + Diet' (HR 0.76; 95% CI 0.63-0.90) and 'WCRF/AICR Score' (HR 0.83; 95% CI 0.67-1.02), as was mortality (HR 0.65; 95% CI 0.45-0.93; HR 0.71; 95% CI 0.57-0.89). 'ACS Score + Alcohol' was associated only with progression (HR 0.89; 95% CI 0.81-0.98) and the '2021 Score' was only associated with prostate cancer mortality (HR 0.62; 95% CI 0.45-0.85). The '2015 Score' was not associated with prostate cancer progression or mortality.

Comment: How does an individual patient's behaviour after a diagnosis of prostate cancer impact upon their future risk of progression? This interesting study examined the impact of various measures of lifestyle behaviours including smoking, physical activity, BMI, and diet (intake of saturated fat, whole milk, processed meat and wine) on measures of disease progression in men diagnosed with localised prostate cancer within the CaPSURE longitudinal cohort study in the US. In general, measures of healthier lifestyle were associated with a reduced risk of both disease progression and prostate cancer-specific mortality; useful data when counselling patients looking to optimise oncological outcomes after treatment.

Reference: Br J Cancer 2023;129(2):346-355
Abstract

Standardized prostate cancer incidence and mortality rates following initial non-malignant biopsy result

Authors: Stromberg HV et al.

Summary: This Danish population-based analysis used data from the NORDCAN 9.1 database to compare the incidence of subsequent prostate cancer diagnosis and death in men with an initial non-malignant TRUS biopsy matched to age and calendar year controls between 1995 and 2016 (n = 37,231). Median time to censoring was 11 years with 4434 men followed for more than 15 years. The age- and calendar year-corrected standardised prostate cancer incidence (SIR) was 5.2 (95% CI 5.1-5.4) and the corrected prostate cancer-specific mortality ratio (SMR) was 0.74 (95% CI 0.67-0.81). SIR and SMR estimates were higher among younger men ($p < 0.001$ for both).

Comment: What is the risk of dying of prostate cancer if an initial biopsy is negative? This comprehensive registry-based study investigated the subsequent risk of diagnosis with and death from prostate cancer in all Danish men who underwent a for-cause TRUS biopsy over a 12-year period in whom no cancer was identified. The cumulative 15-year incidence of prostate cancer diagnosis after an initial negative biopsy was 21.5%, with the 15-year risk of subsequent diagnosis being highest in men aged 60-69 at 23.8%. The 15-year risk of death from prostate cancer death was low, being highest for men having their initial negative biopsy over the age of 80 years at 2.7%. Interestingly, it was observed that after an initial non-malignant TRUS biopsy, prostate cancer incidence was higher but prostate cancer mortality was lower compared to the background population. Certainly, raises questions about the potential 'lethality' of cancers identified only on targeted biopsies, regardless of tumour grade.

Reference: BJU Int. 2023;132(2):181-187
Abstract

Androgen deprivation and radiotherapy with or without docetaxel for localized high-risk prostate cancer: Long-term follow-up from the randomized NRG oncology RTOG 0521 trial

Authors: Sartor O et al.

Summary: This was an analysis of long-term follow-up data from the randomised phase III RTOG 0521 trial comparing ADT plus external beam radiation therapy (EBRT) plus docetaxel with ADT plus EBRT. After a median 10.4-year follow-up among survivors, the OS HR was 0.89 (90% CI 0.70-1.14; p = 0.22) and the survival rate at 10 years was 64% for ADT plus EBRT and 69% for ADT plus EBRT plus docetaxel. The restricted mean survival time at 12 years did not differ between treatments (0.45 years) and there were no differences in the incidence of disease-free survival (DFS; HR 0.92; 95% CI 0.73-1.14), distant metastasis (HR 0.84; 95% CI 0.73-1.14), or PSA recurrence risk (HR 0.97; 95% CI 0.74-1.29). Two patients experienced grade 5 toxicity with chemotherapy versus none in the control arm.

Comment: Early treatment intensification for patients with high-risk disease is currently in vogue, but which patients, when, and how intense remains to be clarified. In this context it is useful to reflect on previous experience, such as this RCT in which randomised men with clinically localised, high-risk disease to ADT plus EBRT with or without six cycles of docetaxel. With a median follow-up of over 10 years, the addition of docetaxel did not result in an improvement in OS, DFS or biochemical recurrence-free survival, but was associated with two treatment-related deaths. Clearly, we need better markers to indicate at least the who and the when.

Reference: Eur Urol. 2023;84(2):156-163
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.

Stability of prognostic estimation using the CAPRA score incorporating imaging-based vs physical exam-based staging

Authors: Chang K et al.

Summary: This retrospective (2000-19) analysis of data from 2222 men with stage ≤cT3a prostate cancer, assessed the incorporation of TRUS and MRI imaging findings into T-staging on performance of the CAPRA (Cancer of the Prostate Risk Assessment) prognostic instrument. Overall, 377 (17%) patients had their CAPRA score increased by inclusion of imaging-based staging ($p < 0.01$). Digital rectal examination-based CAPRA scores (HR 1.54; 95% CI 1.48-1.61) and imaging-based CAPRA scores (HR 1.52; 95% CI 1.46-1.58) were similarly accurate for predicting recurrence. Multivariate analysis suggested that biochemical recurrence was independently associated with a positive digital rectal examination (HR 1.29; 95% CI 1.09-1.53) and imaging-based clinical T3/4 disease (HR 1.72; 95% CI 1.43-2.07).

Comment: With the widespread use of MRI prior to prostate biopsy, digital rectal examination is becoming less frequently performed, and certainly from local experience, the findings less clearly documented. While this may be clinically appropriate, it is not clear how substituting clinical stage determined radiologically for that determined by examination impacts prognostication. This neat study from University of California, San Francisco investigated the impact of substituting imaging derived clinical stage (predominantly from TRUS) with clinical stage on the performance of the CAPRA score to predict biochemical recurrence post prostatectomy. Although there was a dramatic upstaging with imaging versus clinical findings in the cohort, this had little effect on the accuracy of the CAPRA score, likely due to the low relative weighting of T-stage compared to other variables (particularly Gleason score and PSA) in the original model.

Reference: J Urol. 2023;210(2):281-289
Abstract

Outcomes of second-line therapies in patients with metastatic de novo and treatment-emergent neuroendocrine prostate cancer: A multi-institutional study

Authors: Eule CJ et al.

Summary: This multicentre retrospective analysis of 58 patients (median age 65.0 years; median PSA 3.0 ng/dL) with *de novo* neuroendocrine prostate cancer (NEPC) and treatment-emergent neuroendocrine prostate cancer (T-NEPC) sought to determine optimal second-line therapy (36.2% platinum, 17.2% taxane, 19.0% immunotherapy, 17.2% other chemotherapy, and 16.2% other systemic therapy) after first-line platinum therapy. Among 41 evaluable patients, objective response rate (ORR) was 23.5% and the median OS after second-line therapy was 7.4 months (95% CI 6.1-11.9).

Comment: Platinum-based chemotherapy is generally considered first-line therapy for patients with metastatic NEPC; however, there is no consensus on second-line treatments. This North American multicentre retrospective series reports on experience with second therapies in patients failing first-line platinum chemotherapy (given concomitantly with ADT in 75%) in 58 patients, presenting predominantly with *de novo* disease. A wide range of different treatments were used, including further platinum chemotherapy plus etoposide, taxane monotherapy as well as immunotherapy, but the objective response rate was low (24%) and OS was poor (7.4 months). Platinum rechallenge had the highest objective response rates, but better therapies directly targeting key molecular drivers (*MYCN* for instance) are clearly needed.

Reference: Clin Genitourin Cancer 2023;21(4):483-490
Abstract

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