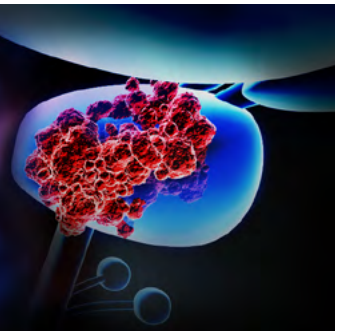
Prostate Cancer Research Review™



Making Education Easy

Issue 69 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen-deprivation therapy; **CI** = confidence interval; **ctDNA** = circulating tumour DNA; **EBRT** = external beam radiotherapy; **GI** = gastrointestinal; **GU** = genitourinary; **Gy** = Gray; **HR** = hazard ratio; **IPSS** = International Prostate Symptom Score; **ISUP** = International Society of Urological Pathology; **mCRPC** = metastatic castration-resistant prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer; **mpMRI** = multiparametric magnetic resonance imaging; **MRI** = magnetic resonance imaging; **OR** = odds ratio; **OS** = overall survival; **RCT** = randomised controlled trial; **PET/CT** = positron emission tomography/computed tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **PTEN** = phosphatase and tensin homolog; **SBRT** = stereotactic body radiotherapy.

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Welcome to Issue 69 of Prostate Cancer Research Review.

According to the findings of a phase III international trial, talazoparib plus enzalutamide results in clinically meaningful and statistically significant improvement in radiographic progression-free survival compared with enzalutamide alone as first-line treatment for patients with metastatic castration-resistant prostate cancer. In a US study, the addition of external beam radiation therapy to brachytherapy in men with intermediate-risk prostate cancer did not provide additional benefits over brachytherapy alone. Other topics covered in this issue include hypofractionation adoption in prostate cancer radiotherapy, transcriptomic signatures associated with recurrent prostate cancer outcomes, early on-treatment changes in circulating tumour DNA fraction in metastatic castration-resistant prostate cancer, prostatectomy bed image-guided dose-escalated salvage radiotherapy, and long-term risks of depression and suicide among men with 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,

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Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): A randomised, placebo-controlled, phase 3 trial

Authors: Agarwal N et al.

Summary: The randomised, double-blind, phase III trial TALAPRO-2 compared the poly (ADP-ribose) polymerase (PARP) inhibitor talazoparib plus enzalutamide versus placebo plus enzalutamide in 805 patients with mCRPC. Over a median follow-up of 24.9 months in talazoparib recipients and 24.6 months in placebo recipients, median radiographic progression-free survival (rPFS) was not reached (NR; 95% CI 27.5-NR) with talazoparib versus 21.9 months (95% CI 16.6-25.1) with placebo (HR 0.63; 95% CI 0.51-0.78; p < 0.0001). The most common treatment-emergent adverse events (TEAEs) with talazoparib were anaemia, neutropenia, and fatigue and the most common grade 3-4 event was anaemia (46%), which was improved by dose reduction; 8% of talazoparib recipients discontinued treatment because of anaemia. Treatment-related deaths did not occur in the talazoparib group and occurred in 2 (<1%) placebo recipients.

Comment: Preclinical studies and the PROpel trial suggest that treatment with novel androgen receptor signalling inhibitors can induce a 'DNA damage repair-like' defect in prostate cancer cells, resulting in synthetic lethality in response to PARP inhibition even in the absence of known defects such as *BRCA1/2* mutation. This concept is further supported by the results of the TALAPRO-2 study, where patients with mCRPC randomised to enzalutamide and the PAPR inhibitor talazoparib in the first-line setting experienced significantly longer rPFS compared to patients treated with enzalutamide and placebo. Again, although the magnitude of response was greater in patients with known defects in homologous recombination, a significant improvement was also observed in non-deficient patients. Would be interesting to evaluate in the hormone-sensitive space.

Reference: Lancet 2023;402(10398):291-303
Abstract

Race and treatment outcomes in patients with metastatic castration-sensitive prostate cancer – A secondary analysis of the SWOG 1216 phase 3 trial

Authors: Sayegh N et al.

Summary: This secondary analysis of patient-level data of a US prospective phase III trial examined differences in survival outcomes of patients with mHSPC by race in a trial (n = 1313) with 10% Black patients. Black patients were younger (median age 65.8 vs 68.4 years; p = 0.001) and had a higher median baseline PSA response rate than White patients (54.7 vs 26.7 ng/mL; p < 0.001). After a median 4.9-year follow-up, median PFS did not differ between Black (2.3 years; 95% CI 1.8-1.4 years) and White (2.9 years; 95% CI 2.5-3.3 years) patients, nor did overall survival (OS 5.5 years; 95% CI 4.8-NR vs 6.3 years; 95% CI 5.7-NR).

Comment: At least in the US, Black race is associated with more aggressive disease and poorer cancer outcomes. Whether this is due to racial differences in disease biology or inequity in access to health care resources is unclear. In this interesting study, the authors retrospectively analysed patient-level data from a phase III study that investigated the effectiveness of orteronel, a nonsteroidal CYP17A1 inhibitor in patients with mHSPC, in which over 10% of patients recruited were Black. Compared to White patients, there was no difference in PFS or OS observed in Black patients, suggesting that at least in this setting, with equal access to treatment through trial participation, race-related differences in disease trajectory are not obvious. Food for thought.

Reference: JAMA Netw Open 2023;6(8):e2326546
Abstract

Effect of brachytherapy with external beam radiation therapy versus brachytherapy alone for intermediate-risk prostate cancer: NRG oncology RTOG 0232 randomized clinical trial

Authors: Michalski JM et al.

Summary: This randomised clinical trial examined the addition of external beam radiation therapy (EBRT) to brachytherapy versus brachytherapy alone to improve 5-year freedom from progression in 579 intermediate-risk prostate cancer patients (median age 67 years; 89.1% PSA <10 ng/mL, 89.1% had Gleason Score 7, and 66.7% had T1 disease). The 5-year freedom from progression did not differ, when based on PSA failure by the American Society for Therapeutic Radiology and Oncology (ASTRO) definition, between combination therapy and brachytherapy alone (85.6%; 95% CI 81.4-89.7; vs 82.7%; 95% CI 78.3-87.1; OR 0.80; 95% CI 0.51-1.26) or based on the Phoenix definition (88.0%; 95% CI 84.2-91.9; vs 85.5%; 95% CI 81.3-89.6; OR 0.80; 95% CI 0.49-1.30). There were no differences in acute genitourinary (GU) or gastrointestinal (GI) toxicities; however, 5-year cumulative incidence of GU/GI grade ≥2 was worse with combination therapy 42.8% (95% CI 37.0-48.6) versus 25.8% (95% CI 20.9-31.0; p < 0.0001), as was late GU/GI grade ≥3 toxicity 8.2% (95% CI 5.4-11.8) versus 3.8% (95% CI 2.0-6.5; p = 0.006).

Comment: Low-dose brachytherapy was once considered under treatment for potentially lethal prostate cancer, leading to a school of thought that it should be combined with other modalities to improve its therapeutic effect. This co-operative group trial examined the impact of combination brachytherapy and external beam radiation (EBRT to prostate and seminal vesicles to 45 Gy) followed by a brachytherapy boost to the prostate alone (up to 110 Gy) versus brachytherapy alone (up to 145 Gy to the prostate alone) in men with predominantly ISUP 2 disease. There was no difference in the primary endpoint, freedom from progression (a composite endpoint of biochemical recurrence, local or distant failure, or death) between the two approaches, although addition of EBRT increased the rate of late GI and GU toxicity. However, long-term data reporting metastasis-free survival is required for reassurance that this approach is safe in this population.

Reference: J Clin Oncol. 2023;41(24):4035-4044
Abstract

Hypofractionation adoption in prostate cancer radiotherapy: Results of an international survey

Authors: Sabbagh A et al.

Summary: This analysis of data from the European Society of Radiation Oncology's (ESTRO) Global Impact of Radiotherapy in Oncology (GIRO) initiative survey (1157 physician responses; 60% from high-income countries [HICs]) on hypofractionation, examined rates of hypofractionation adoption in prostate cancer, facilitating factors, and barriers across World Bank income groups. Hypofractionation with curative intent was most often preferred for low- (52% of respondents reporting hypofractionation use in ≥50% of patients) and intermediate- (47%) risk prostate cancers. These rates were 35% in high-risk prostate cancer and 20% where pelvic irradiation was indicated. In the palliative setting, most (89%) respondents preferred hypofractionation. Overall, upper-middle-income and lower-middle- and low-income countries were less likely to prefer hypofractionation than HICs (p < 0.001). The most frequent justifications or barriers to hypofractionation adoption were availability of published evidence and fear of worse late toxicity.

Comment: There is a well-recognised lag time between the generation of new evidence and widespread implementation in routine clinical practice. Between 2016-18 several published RCTs reported the non-inferiority of hypofractionation for the treatment localised low- and intermediate-risk prostate cancer, but with considerable cost savings and decreased treatment burden for patients. This international survey conducted the following year found significant heterogeneity in evidence adoption, which varied by both treatment indication (highest for low/intermediate- vs high-risk disease) and country income level (highest for high income vs low/middle income), which is interesting given that lower-income level countries with fewer resources may have the most to gain by shorter treatment times. A knowledge gap of current evidence (or lack of confidence in the results) and lack of advanced targeting technologies were identified as potential barriers to adoption.

Reference: JCO Glob Oncol. 2023;9:e2300046
Abstract

Transcriptomic signatures associated with outcomes in recurrent prostate cancer treated with salvage radiation, androgen-deprivation therapy, and enzalutamide: Correlative analysis of the STREAM Trial

Authors: Bitting RL et al.

Summary: This retrospective analysis of the prospective, multicentre, phase II STREAM trial of enzalutamide, ADT, and salvage radiotherapy in men with rising PSA after radical prostatectomy (n = 31), assessed the use of tissue-based transcriptomic signatures to identify patients who might benefit from a more aggressive systemic approach. Luminal differentiated subtype tumours had the longest 3-year PFS compared to the luminal proliferating subtype (89% vs 19%). PFS was worse in men with signatures of PTEN loss (HR 1.32; 95% CI 1.07-1.64; p = 0.01) or homologous recombination deficiency (HR 1.21; 95% CI 1.05-1.39; p = 0.009), while a higher ADT response signature score was associated with improved PFS (HR 0.75; 95% CI 0.61-0.94; p = 0.01). In a large cohort (n = 5,330) of radical prostatectomy samples from patients with biochemical recurrence, these transcriptomic signatures provided complementary information on salvage radiation outcomes.

Comment: Gene transcriptional signatures such as Decipher, Prolaris and Oncotype Dx are predictive of adverse pathology or recurrence in a number of different clinical settings, but their adoption in Australia has been limited both by their high cost and unclear clinical utility. However, evidence is accumulating that they may be useful predictive markers for guiding treatment escalation/de-escalation in early disease. This interesting study examined the correlation of various molecular signatures identified using the Decipher assay with response to ADT plus enzalutamide in the salvage radiation setting. Despite aggressive treatment, nearly 50% of patients relapsed within 3 years, but this varied significantly, with patients expressing signatures characteristic of luminal proliferating subtype, PTEN loss and homologous recombination deficiency observed to have significantly worse recurrence rates. It is likely that such molecular testing will be routinely incorporated into treatment decision-making in the not too distant future.

Reference: JCO Precis Oncol. 2023;7:e2300214
Abstract

Early on-treatment changes in circulating tumor DNA fraction and response to enzalutamide or abiraterone in metastatic castration-resistant prostate cancer

Authors: Tolmeijer SH et al.

Summary: This *post hoc* analysis of plasma cell-free DNA samples from two prospective multicentre observational studies assessed whether changes in ctDNA fraction during androgen receptor pathway inhibitor treatment were linked with mCRPC clinical outcomes in 81 patients. ctDNA was detected in 59% of baseline and 36% of 4-week samples; median ctDNA fraction for samples with detectable ctDNA was lower at 4 weeks than at baseline (5.0% vs 14.5%; p = 0.017). Independent of clinical prognostic factors, patients with persistent ctDNA at 4 weeks had the shortest PFS (HR 4.79; 95% CI 2.62-8.77) and OS (HR 5.49; 95% CI 2.76-10.91). For patients with a change from detected to undetected ctDNA by 4 weeks, there was no PFS difference compared with those with undetected ctDNA at baseline. The ctDNA change provided a positive predictive value of 88% and a negative predictive value of 92% for the identification of nondurable responses.

Comment: ctDNA levels appear to be a reasonably good quantitative marker of overall tumour burden. Further evidence of its potential use as an early biomarker of treatment response comes from this analysis from Alex Wyatt's group, who measured ctDNA levels in patients with mCRPC undergoing first-line treatment with enzalutamide or abiraterone. Patients who had detectable ctDNA at baseline that then became undetectable at 4 weeks (indicating responsive disease) had a PFS similar to patients who had undetectable levels at baseline. In contrast, patients with detectable ctDNA levels at baseline that persisted at 4 weeks (treatment unresponsive) had a shorter PFS and OS independent of other clinical prognostic factors. This suggests changes in ctDNA levels may be an early marker of treatment resistance and potentially guide an early switch in therapy.

Reference: Clin Cancer Res. 2023;29(15):2835-2844
Abstract

Prostatectomy bed image-guided dose-escalated salvage radiotherapy (SPIDER): An international multicenter retrospective study

Authors: Benziane-Ouaritini N et al.

Summary: This European, multinational, retrospective (2000-19) study examined the use of functional image-guided (mpMRI, PET/CT choline, PSMA PET/CT) salvage radiotherapy (SRT) in 335 patients with macroscopic local recurrence in the prostate bed after radical prostatectomy (310 patients received ≥1 dose escalation [>66 Gy]; 25 patients did not; median PSA level before SRT 0.63 ng/mL). Over a median follow-up of 54 months, 5-year PFS was 70% (95% CI 64-75) and metastasis-free survival was 84% (95% CI 78-88). Grade ≥2 GU and GI late toxicities occurred in 12% and 3% of patients. When prescribed dose on the macroscopic local recurrence lesion was ≥72 Gy, 5-year PFS improved for patients receiving ≥1 dose escalation (73%; 95% CI 65-79; vs 60%; 95% CI 48-70; p = 0.03).

Comment: An ongoing debate in the SRT setting is whether you should give the same dose to the entire treatment volume, or whether the dose should be modified based on imaging findings. This retrospective, multicentre study reports on the results of dose escalation to an image detected macroscopic local recurrence, either in addition to standard salvage dosing (60-66 Gy) of the whole prostate bed (the majority) or dose escalated to the whole planned treatment volume. Patients with dose escalation to the target lesion experienced better PFS independent of Gleason sum and PSA at start of treatment, with reasonable tolerability. It is interesting to ponder if imaging can also inform dose de-escalation, for instance to the anastomosis if a pedicle recurrence is seen on imaging.

Reference: Eur Urol Oncol. 2023;6(4):390-398
Abstract

The safety and efficacy of salvage stereotactic radiation therapy in patients with intraprostatic tumor recurrence after previous external radiation therapy: Phase 1 results from the GETUG-AFU 31 study

Authors: Pasquier D et al.

Summary: The multicentre, open-label, phase I GETUG-AFU 31 study sought to determine the optimal dose regimen for salvage SBRT (5 or 6 fractions of 6 Gy) in 21 patients (median age 76.8 years) with prostate cancer recurrence (histologically proven biochemical recurrence, clinical stage T1-T2 upon relapse, mpMRI data, PSA level ≤10 ng/mL, PSA doubling time >10 months, IPSS ≤12) after primary EBRT. No dose-limiting toxicity (grade ≥3 GI or GU tract toxicity, nor any grade 4 toxicity [National Cancer Institute Common Terminology Criteria for Adverse Events v 4.03]) was observed; acute grade 2 GU tract toxicity rate was 19%. Over a median follow-up of 12.3 months, the estimated cumulative incidence of late grade 2 GU toxicity was 41.2% (95% CI 18.1-63.1) and no grade >2 GU or GI toxicity was reported.

Comment: Salvage options for patients with intraprostatic recurrence following definitive radiotherapy are frequently associated with either suboptimal oncological outcomes and/or unpalatable morbidity. This prospective, multicentre phase I study reports on the feasibility and safety of salvage SBRT to MRI detectable lesions plus a margin in men with histological proven disease recurrence following definitive radiotherapy for low- or intermediate-risk disease at initial diagnosis. Although disease control appears good and rates of severe toxicity low, as acknowledged by the authors the follow-up is short. Looks promising, and it is moving forward to a phase II study, but it does not address what to do with high-risk patients who are more likely to develop a recurrence and potentially have the most to gain!

Reference: Eur Urol Oncol. 2023;6(4):399-405
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.

Optimal PSA density threshold and predictive factors for the detection of clinically significant prostate cancer in patient with a PI-RADS 3 lesion on MRI

Authors: Nguyen T-A et al.

Summary: This single-centre, retrospective, analysis of a prospectively maintained database sought to determine the optimal PSA density threshold and predictive factors of clinically significant prostate cancer in 158 patients with a Prostate Imaging Reporting and Data System (PI-RADS) grade 3 lesion on MRI. Overall, the detection rate of clinically significant prostate cancer was 22.2%. For a PSA density ≤0.15 ng/mL/cm^3, prostate biopsy would be omitted in 71.5% of men at the cost of missing 15.0% of clinically significant prostate cancer cases. Using a PSA density threshold of 0.15 ng/mL/cm^3, sensitivity was 0.51 and specificity was 0.78, positive predictive value was 0.40 and negative predictive value was 0.85. Multivariate analysis suggested that age (OR 1.10; 95% CI 1.03-1.19; p = 0.007), and PSA density threshold of ≥0.15 ng/mL/cm^3 (OR 3.59; 95% CI 1.41-9.47; p = 0.008) were independent predictive factors of clinically significant prostate cancer. Previous negative biopsy was negatively associated with clinically significant prostate cancer (OR 0.24; 95% CI 0.07-0.66; p = 0.01).

Comment: Up to 30% of patients with a PIRADS 3 lesion on MRI will have a clinically significant prostate cancer on subsequent biopsy, but whether all patients require immediate assessment in the absence of other red flags is contentious. This retrospective review found that patients with a PSAD >0.15 ng/mL/cm^3 were more likely to harbour ISUP grade group 2 cancer at biopsy, whereas lower levels and a previous negative biopsy were protective. Whether all grade 2 cancers are clinically significant is a matter of debate and given the increasingly recognised harms associated with a diagnosis of prostate cancer (see below), any strategy that reduces the risk of a prostate biopsy in the first place is to be encouraged!

Reference: Urol Oncol. 2023;41(8):354.e11-354.e18
Abstract

Long-term risks of depression and suicide among men with prostate cancer: A national cohort study

Authors: Crump C et al.

Summary: This retrospective (1998-2017) Swedish national cohort study of 180,189 men with prostate cancer and 1,801,890 age-matched, population-based, controls sought to determine the long-term risks of major depression and death by suicide. After adjustment for sociodemographic factors and comorbidities, men with high-risk prostate cancer had elevated risks for major depression (adjusted HR [aHR] 1.82; 95% CI 1.75-1.89) and death by suicide (aHR 2.43; 95% CI 2.01-2.95), and these associations persisted for ≥10 year after diagnosis. The increase in major depression was lower in patients treated with radiation (aHR 1.44; 95% CI 1.31-1.57) or surgery (aHR 1.60; 95% CI 1.31-1.95) compared with ADT alone (aHR 2.02; 95% CI 1.89-2.16), but the rate of suicide was higher only among those treated solely with ADT (aHR 2.83; 95% CI 1.80-4.43). Men with low- or intermediate-risk prostate cancer had a small increase in risk of major depression (aHR 1.19; 95% CI 1.16-1.23) and suicide death at 3-12 months after diagnosis (aHR 1.88; 95% CI 1.11-3.18), but not for the entire follow-up period (aHR 1.02; 95% CI 0.84-1.25).

Comment: This national cohort from Sweden examined the impact of a diagnosis with prostate cancer as well as subsequent treatment on the rates of major depression and suicide over a 20-year period. Compared to an age- and sex-matched population, patients with high-risk disease (clinically localised, regional or distant metastasis) had higher rates of both major depressive illness and suicide which persisted for more than 10 years regardless of disease extent at diagnosis. Use of ADT appears to be a major contributor to both of these observations, although higher rates of depression were also observed in men treated with surgery or radiation alone. A more important observation was the more modest but still significant increase in both depression and suicide in men with low- or intermediate-risk disease in the first year after diagnosis. Instructive.

Reference: Eur Urol. 2023;84(3):263-272
Abstract