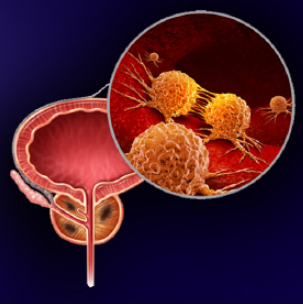
Prostate Cancer Practice Review™



Making Education Easy

Issue 16 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen-deprivation therapy
CT = computed tomography
GI = gastrointestinal
GU = genitourinary
HSPC = hormone-sensitive prostate cancer
ISUP = International Society of Urological Pathologists
LND = lymph node dissection
MRg = magnetic resonance-guided
OS = overall survival
PFS = progression-free survival
PSA = prostate-specific antigen
PSMA = prostate-specific membrane antigen
SBRT = stereotactic body radiotherapy

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Welcome to the 16th issue of Prostate Cancer Practice Review.

This Review covers news and issues relevant to clinical practice in prostate cancer. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our COVID-19 resources, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

Dr Janette Tenne
Editor
janette.tenne@researchreview.com.au

Clinical Practice

Acute toxicity comparison of magnetic resonance-guided adaptive versus fiducial or computed tomography-guided non-adaptive prostate stereotactic body radiotherapy

A systematic review and meta-analysis suggests that magnetic resonance-guided (MRg) radiotherapy coupled with daily adaptive planning to optimise precision of dose delivery and accuracy of radiation beam to the prostate while avoiding nearby organs may reduce acute toxicity compared to fiducial or computed tomography (CT)-guided non-adaptive prostate stereotactic body radiotherapy (SBRT). A search of online databases yielded 29 prospective trials conducted between 2018 and 2022 including over 2,500 men with prostate cancer that reported acute toxicity rates for a fractionated prostate SBRT regimen (total dose of 35-45 Gy) utilising photon radiation. Random effects and fixed effects models estimated significantly lower pooled grade 2 or worse genitourinary (GU) toxicity and gastrointestinal (GI) toxicity in the first three months with MRg daily adaptive SBRT versus CT-guided non-adaptive SBRT (16% vs 28% and 4% vs 9%, respectively). The likelihood of short-term urinary side effects was reduced by 44% and the odds of bowel toxicity improved by 60% with MRg daily adaptive SBRT on meta-regression analyses (odds ratios, 0.56 and 0.40). The use of fiducial markers in CT-SBRT had no impact on toxicity. Severe adverse events were rare and comparable between methodologies (grade ≥ 3 GU and GI adverse events, 0% vs 1%). The study was not able to discern what aspect of MRg adapted SBRT facilitated the improved tolerability, whether the benefit derived from the minimisation of dosing to the bladder, urethra and rectum due to daily adaptive planning, imaging-based monitoring or due to the imaging modality itself. Further research will be needed to explicate late toxicity, as well as disease control outcomes and to disentangle whether the benefits outweigh the inherent higher costs and resource requirements of MRg adapted SBRT.

Cancer. 2023;129(19):3044-52

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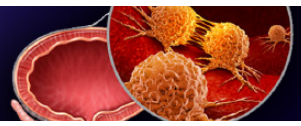

Race and treatment outcomes in patients with metastatic castration-sensitive prostate cancer: A secondary analysis of the SWOG 1216 phase 3 trial

Previously published results from the US multicentre phase 3 Southwest Oncology Group (SWOG) 1216 trial demonstrated a doubling in the duration of radiographic progression-free survival (PFS) and improved complete prostate-specific antigen (PSA) response rate with addition of orteronel, versus bicalutamide, to continuous androgen-deprivation therapy (ADT) in men with newly diagnosed metastatic hormone-sensitive prostate cancer (HSPC). Although an absolute almost 11-month difference in overall survival (OS) in favour of orteronel was also found, the magnitude of risk reduction did not meet prespecified targets to meet the trials primary efficacy outcome measure and Takeda has subsequently terminated their orteronel development program in prostate cancer.

Now, in an effort to elucidate the role that race plays in the well-documented disparity in prostate cancer survival between black and white patients, researchers conducted a secondary analysis of patient-level data from SWOG 1216. Briefly, enrolled patients (n=1,313) were allocated to receive continuous ADT (luteinizing hormone-releasing hormone agonist) plus either orteronel (300 mg twice daily) or bicalutamide (50 mg once daily). Analysis of outcomes according to race included 1,212 men who self-identified as White or Black (11%) with a median follow-up of almost five years. Black men treated in the trial achieved similar survival outcomes as white men, with comparable PFS, PSA response and OS, in spite of more aggressive disease at presentation (higher baseline PSA level and significantly younger age). No impact of race on treatment efficacy could be found and the finding of comparable outcomes between races remained after adjustment for treatment group, disease extent, age and baseline PSA. The study authors noted that the finding of no worse outcomes in Black men with prostate cancer under equalised care access conditions are congruent with population-based research and concluded that equitable health care resource access may alleviate the racial survival disparities in prostate cancer.

JAMA Netw Open. 2023;6(8): e2326546

Is radiotherapy after radical prostatectomy associated with higher other-cause mortality?

This retrospective single-centre study from a Dutch cancer centre evaluated the impact of post-prostatectomy salvage radiotherapy on life expectancy due to mortality from non-prostate cancer-related causes. A cohort of 439 1:1 matched patient sets, treated in the approximately 14-year period between 2005 and 2019 with radical prostatectomy ± radiotherapy at recurrence, were identified. Patients were matched for age, initial PSA, pathological (p)T/N stages and International Society of Urological Pathologists (ISUP) score. Analysis revealed a three-fold higher other-cause mortality rate at five years in patients who did not receive rescue radiotherapy (1.2% vs 4.4%; $p<0.001$), which translated into a 72% reduced risk of non-prostate cancer-related death with post-prostatectomy radiotherapy in Cox regression modelling. The prostate cancer-specific mortality rate was comparable between cohorts. While pT/N stages and ISUP score both had a positive association with prostate-specific mortality, they did not associate with other-cause mortality. The study authors speculated that factors such as performance status may have influenced patient selection for post-prostatectomy salvage radiotherapy, skewing the findings.

Cancer Causes Control. 2023; Jul 31. Online ahead of print

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Long-term complications and health-related quality of life outcomes after radical prostatectomy with or without subsequent radiation treatment for prostate cancer

This analysis of six years of data from a large US multi-institutional registry database finds a heightened risk of urinary tract infections and general deterioration in health after receipt of postoperative radiotherapy in men with prostate cancer. Data derived from the observational CaPSURE™ (UCSF Cancer of the Prostate Strategic Urologic Research Endeavor) registry and included more than six thousand men with any-stage prostate cancer who underwent a curative-intent radical prostatectomy ± subsequent EBRT between 1995 and 2020. The median post-surgical follow-up was seven years, with a maximum of 13 years. Just under 10% of the study cohort received post-surgical EBRT within five years. Overall, 9.3% of men experienced a post-surgical complication, most commonly urinary stricture (4.9%) or cystitis (2.3%). Cox proportional hazard modelling revealed a more than five-fold elevated risk of cystitis in recipients of adjuvant radiotherapy compared to men treated surgically without radiotherapy. No increased risk of GI toxicity, incontinence requiring surgical intervention, ureteral injury or urinary stricture was found. Regardless of the presence of post- prostatectomy complications, worse long-term general health was associated with radiotherapy in repeated measure models, although it was noted that radiotherapy did not adversely impact urinary, bowel or sexual function. The authors cautioned that although there are oncological control benefits conferred by post-operative radiotherapy, patients should be aware of the risks.

Urol Oncol. 2023; Jul 3. Online ahead of print

First-in-human evaluation of a prostate-specific membrane antigen-targeted near-infrared fluorescent small molecule for fluorescence-based identification of prostate cancer in patients with high-risk prostate cancer undergoing robotic-assisted prostatectomy

Following positive pre-clinical results of IS-002, a novel near-infrared fluorescently labelled prostate-specific membrane antigen (PSMA)-targeting fluorescence imaging agent, a first-in-human dose-escalation study was conducted to evaluate its utility intraoperatively in men with high-risk prostate cancer undergoing robotic-assisted prostatectomy. IS-002 is a urea-based PSMA-binding peptide tagged with a near-infrared polymethine cyanine dye with excitation/emission wavelengths of 774/793 nm, respectively. A total of 24 men with histology-confirmed prostate adenocarcinoma, considered high-risk based on cancer of the prostate risk assessment (CAPRA) score ≥6, T3a or b disease on imaging, or with regional lymphadenopathy suspicious for nodal metastases were enrolled and received a single infusion of IS-002 at a dose of between 25-150 µg/kg 24 hours prior to undergoing radical prostatectomy with extended pelvic lymph node dissection (LND) with the da Vinci surgical system equipped with Firefly fluorescence imaging. The agent was safe and tolerable with adverse events exclusively mild, and predominantly comprised of urine discolouration. Pharmacokinetic evaluation showed a positive dose-C_{max} relationship and rapid biphasic plasma concentration decline, regardless of kidney function (half-life, 5-7.6 hours). IS-002 demonstrated potential efficacy in intra-operative identification of locoregional metastasis in an exploratory analysis, enabling visualisation of occult disease in the resection bed in 29% of patients that would have been missed by conventional white light imaging. Nodal positive disease was also detected in five patients, although all were located within the boundaries of the dissection area. A promising diagnostic accuracy was reported at the 25 µg/kg dosing level with negative predictive values exceeding 97% in both lymph nodes and in the resection bed and a positive predictive value of 80% for locoregional/residual disease using pathology as the gold standard.

Intra-operative use of IS-002 during prostatectomy may facilitate real-time recognition of residual and metastatic disease, improve the precision of surgery and reduce the incidence of positive margins and, potentially reduce disease recurrence in patients with locally advanced malignancy. Recruitment for a phase 2 sham comparator trial of IS-002 has commenced in the US and will provide further data on efficacy for detection of micrometastatic nodal and locoregional disease as well as diagnostic performance (NCT05946603).

Eur Urol Oncol. 2023; Jul 27. Online ahead of print

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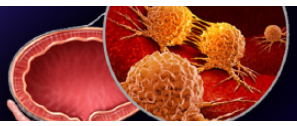


Safety and efficiency of repeat salvage lymph node dissection for recurrence of prostate cancer using PSMA-radioguided surgery (RGS) after prior salvage lymph node dissection with or without initial RGS support

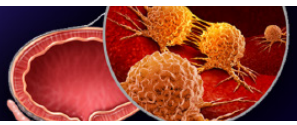
Retrospective evaluation of data from two German tertiary referral centres concludes that a second metastasis-directed surgery after initial salvage LND may be a reasonable option for men with recurrent, isolated lymph node prostate cancer metastases. A total of 37 men who underwent a repeat LND in the eight-year period between 2014 and 2021 subsequent to initial radical prostatectomy ± pelvic radiotherapy and rescue LND were identified from institution patient records. In 43% of cases, primary LND was performed with PSMA-radioguidance, while the remainder of patients received standard salvage LND without radioguided support. Almost two-thirds of evaluable patients (n=20/32; 62.5%) had a complete biochemical response to repeat LND with reduction in PSA level to less than 0.2 ng/mL, which were durable (mean biochemical recurrence-free survival, 10.8 months; range, 5.3-22 months). Elevated pre-operative PSA levels were associated with earlier biochemical recurrence on multivariable regression analysis, but did not reach statistical significance for predictive utility. Most patients (89%) did not receive further treatment in the year after repeat LND. The procedure was reported to be safe with low rates of serious complications (Clavien–Dindo grade >3a complications; 8%). It was concluded that in appropriately selected patients a repeat salvage LND surgery with PSMA-radioguided support for prostate cancer recurrence following first rescue LND elicits good oncological control with a clinically meaningful benefit and is safe.

World J Urol. 2023;41(9):2343-50

Relative burden of cancer and noncancer mortality among long-term survivors of breast, prostate, and colorectal cancer in the US

Madhav et al. analysed data on long-term cancer survivors from the Surveillance, Epidemiology, and End Results cancer registry data to estimate the relative risks of mortality from index cancer versus nononcologic-specific causes of death. Analysis included over 627 thousand adults diagnosed with stage 1-3 localised breast, prostate, colon or rectal cancer in a 12-year period up to 2014 who underwent definitive treatment and survived at least five years, with follow-up until 2019 (maximum follow-up, 17 years). The median age of the study cohort was 61.1 years, and patients with prostate cancer comprised 19% (n=118,839). Factors associated with cancer-related and non-cancer-related death were identified via the least absolute shrinkage and selection operator method. Mortality and survival time ratio rates were evaluated by oncologic risk groups employing accelerated failure time models to create cumulative incidence function curves. Results showed that across the four malignancies the most common cause of death was unrelated to cancer, with only approximately one-third of long-term breast cancer survivors and just over one-fifth of long-term prostate cancer survivors succumbing to their primary cancer. The principal causes of death in the other 66% and 77.9% of long-term breast and prostate cancer survivors, respectively, were heart disease, Alzheimer's disease, chronic obstructive pulmonary disease and cerebrovascular disease. With respect to cancer-specific mortality in men with prostate cancer, the two factors found to negatively influence survival were high PSA level and a Gleason score of ≥ 8. Analysis of mortality at 10 years after cancer diagnosis according to risk groups with established adverse prognostic characteristics revealed wide variations in cancer-specific mortality. Patients with low oncologic risk prostate cancer were almost nine-times more likely to die from non-prostate cancer-specific causes (14.2% vs 1.7%; cumulative mortality ratio, 8.6). While an almost doubled cumulative incidence of cancer-specific death was found in men with high-risk prostate cancer versus those with low-risk disease, unlike the other malignancies analysed, the cumulative incidence of cancer-specific death never exceeded non-cancer-related mortality (6% vs 3.4%). These data are a step towards elimination of unnecessary prolonged oncologic follow-up by allocating long-term care to primary care physicians or other specialty care, if appropriate.

JAMA Netw Open. 2023;6(7): e2323115



Yonsa MPRED
(abiraterone acetate + methylprednisolone)

SUN PHARMA

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Yonsa MPRED is the first abiraterone + steroid combination pack that can be taken with or without food*

*TGA-approved fine particle abiraterone acetate + methylprednisolone combi pack indicated for naïve, high-risk mHSPC & mCRPC (after ADT or taxane). Yonsa MPRED can be taken with or without food.[2]

PBS Information: Authority required.
Refer to PBS Schedule for full authority information.

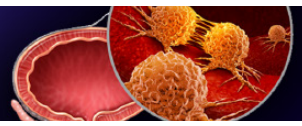
Please review Product Information before prescribing available from www.ebs.tga.gov.au or Sun Pharma by calling 1800 726 229

MINIMUM PRODUCT INFORMATION YONSA MPRED 125 mg abiraterone acetate tablets and 4 mg methylprednisolone tablets bottles composite pack. **Indications:** newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT), or patients with metastatic advanced prostate cancer (castration resistant prostate cancer, mCRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) or patients with mCRPC who have received prior chemotherapy containing a taxane. **Contraindications:** Abiraterone acetate: women who are or may potentially be pregnant, patients with severe hepatic impairment [Child Pugh Class C], in combination with XOFIGO, known hypersensitivity to abiraterone acetate or any excipient in the formulation; Methylprednisolone: known hypersensitivity to methylprednisolone or any excipient in the formulation. **Precautions:** Abiraterone Acetate: Hypertension, hypokalaemia and fluid retention due to mineralocorticoid excess, Hepatotoxicity, Use with chemotherapy, Use in combination with radium 223 dichloride; Methylprednisolone: Corticosteroid withdrawal and coverage of stress situations, hyperglycaemia, immune system effects, cardiac effects, vascular effects, endocrine effects, hepatobiliary effects, ocular effects, psychiatric effects, gastrointestinal effects, nervous system effects, use with NSAIDs. *Paediatric Use:* Abiraterone acetate: not for use in children; Methylprednisolone: No data available. Please refer full PI. **Interactions:** Abiraterone: dextromethorphan, strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital), pioglitazone, theophylline, spironolactone; Methylprednisolone: CYP3A4 Inhibitors, CYP3A4 Inducers, CYP3A4 Substrates. Please refer full PI. Pregnancy: Category D. **Adverse effects:** Abiraterone acetate: peripheral oedema, hypokalaemia, hypertension, urinary tract infection, and alanine aminotransferase increased, and/or aspartate aminotransferase increased, allergic alveolitis, rhabdomyolysis, myopathy, diarrhoea, hepatitis fulminant, hepatic failure, QT prolongation and Torsades de Pointes, anaphylactic reaction; Methylprednisolone: adverse effects typical for all systemic corticosteroids. Please refer full PI. **Dosage and administration:** The recommended dose of YONSA abiraterone acetate tablets is 500 mg (four 125 mg tablets) administered orally once daily in combination with methylprednisolone. The recommended dose of methylprednisolone for metastatic hormone sensitive prostate cancer is 4 mg administered once daily. To avoid medication errors and overdose, be aware that YONSA tablets may have different dosing and food effects than other abiraterone acetate products. YONSA tablets can be taken with or without food. The tablets should be swallowed whole with water. Do not crush or chew tablets. Please refer full PI. **Storage:** Store at or below 25°C. **Date of preparation:** May 2023.

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

References: 1. PBS Handbook 1 May 2023, **2.** Yonsa MPRED Approved Product Information.

Sun Pharma ANZ Pty Ltd ABN 17 110 871 826, Macquarie Park NSW 2113 Ph: 1800 726 229. Fax: +61 2 8008 1613. Med Info: 1800 726 229 Adverse events may be reported to Sun Pharma by either email: adverse.events.aus@sunpharma.com or phone: 1800 726 229. Date of preparation: May 2023. YON2023/05ADVRR.



News in Brief

Robot partial prostatectomy for anterior cancer

Long-term functional and oncological outcomes at seven years after a robotic partial prostatectomy for anteriorly located prostate tumours at least partially within the anterior fibromuscular stroma are reported in this case series of 28 men. Median PSA was reduced significantly from 9.6 ng/mL prior to surgery to a post-operative nadir of 0.36 ng/mL. Cancer recurrence at resection margins in the setting of rising PSA was reported in 28.6% of men and treated with salvage radical prostatectomy at a median time of 3.5 years after first surgery. There were no deaths within the follow-up period and no cases of metastasis. Most (92%) men experienced no adverse impact on continence and 69% maintained erectile function without drug assistance. Partial prostatectomy may be a feasible option for localised low- to intermediate-risk prostate cancer, especially in patients with a tumour volume of <3 cc.

Eur Urol Open Sci. 2023; 55:11-14

Effects of supervised exercise and self-managed psychosexual therapy on sexual health in men with prostate cancer: A randomized clinical trial

Results from an Australian trial presented at the 2023 ASCO Breakthrough meeting in August suggest that exercise may improve sexual health in men with prostate cancer. The trial evaluated a six-month resistance and aerobic exercise program ± psychosexual therapy versus usual care. Results showed a significant and clinically relevant improvement in erectile function and intercourse satisfaction in the exercise cohort versus usual care, regardless of psychosexual therapy.

JCO Global Oncology 2023;9 (suppl 1; abstr 71)

Prostate cancer screening and management: Caution against over-interpreting the results of the latest study, ProtecT

Caution against over-interpreting the results of the ProtecT study has been advised in an editorial by Dr Isaac Kim, a urologic oncologist and surgeon and Yale Urology Chair. The ProtecT trial, discussed in the May issue of *Prostate Cancer Practice Review* and published in the *New England Journal of Medicine*, found low rates of cancer-specific mortality in men with localised disease at 15-year follow-up whether they were treated surgically or with radiotherapy, or underwent active surveillance. Dr Kim disagrees with the study's conclusion that delaying treatment does not adversely impact survival in this population for a multitude of reasons and suggests that the favourable survival rates actually demonstrate the efficacy of definite treatments. Treatment options tailored to oncologic risk may be a more suitable strategy, with definitive options used in patients with intermediate-risk or high-risk disease.

Investig Clin Urol. 2023;64(4):310-11

VAPOR 2 trial of water vapor ablation in localised prostate cancer launches

The US multicentre VAPOR 2 trial (NCT05683691) has commenced evaluation of the Vanquish minimally invasive water vapor ablation device in men with intermediate-risk (Gleason Grade Group 2), localised prostate cancer and has been granted US Food and Drug- Administration Breakthrough Device Designation to facilitate rapid commercialisation options and possible Medicare reimbursement. The trial has an estimated enrolment of 400 men and primary data is expected in 2027.

More information can be found here and here

COVID-19 Resources

Cancer Australia
The Royal Australian and New Zealand College of Radiologists
Royal Australasian College of Surgeons
European Urology Journal
British Association of Urological Surgeons
European Society of Medical Oncology
American Society of Clinical Oncology

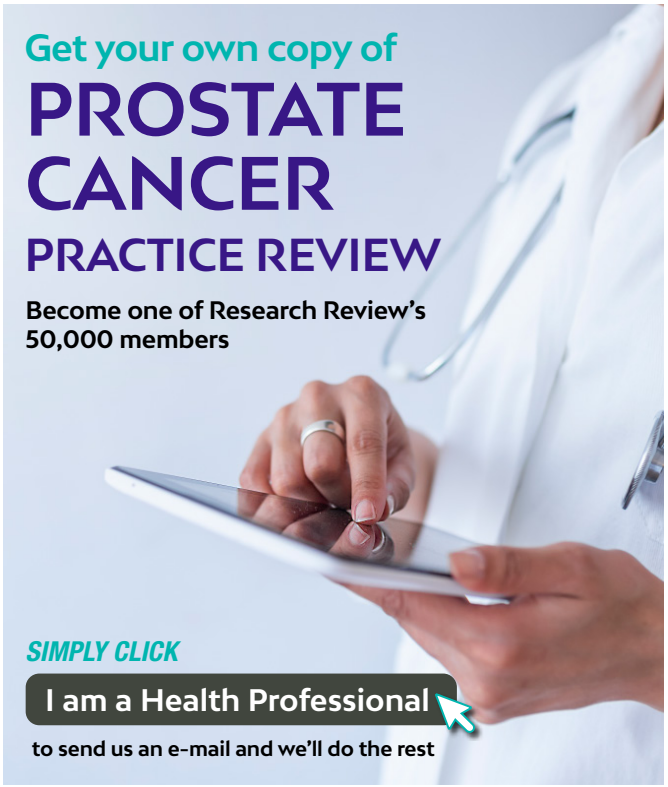
Conferences, Workshops, and CPD

Please click on the links below for upcoming local and international prostate cancer meetings, workshops and CPD.

COSA – Events
MOGA – Events
USANZ – Events
COMS – Conferences and Meetings on Urology

Research Review Publications

Prostate Cancer Research Review with Associate Professor Niall Corcoran and Professor Nathan Lawrentschuk
Urology Research Review with Professor Eric Chung



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