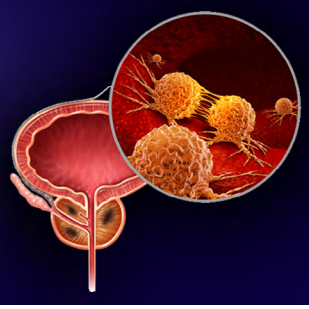
Prostate Cancer Practice Review™



Making Education Easy

Issue 24 - 2024

In this issue:

Abbreviations used in this issue:

AI = artificial intelligence; **AR** = androgen receptor;
BCRP = breast cancer resistance protein; **BRCA 1/2** = breast cancer gene 1/2;
COPD = chronic obstructive pulmonary disease;
COSA = Clinical Oncology Society of Australia;
CPD = continuing professional development; **DDIs** = drug-drug interactions;
HRR = homologous recombination repair;
ISUP = International Society of Urological Pathology;
JAK/STAT = Janus kinase/signal transducers and activators of transcription;
mCRPC = metastatic castration-resistant prostate cancer;
mGSTP1 = methylated glutathione S-transferase 1;
MOGA = Medical Oncology Group of Australia; **MRI** = magnetic resonance imaging;
mTOR = mechanistic Target of Rapamycin;
nmCRPC = non-metastatic castration-resistant prostate cancer;
OATPs = organic anion transporting polypeptides;
PBS = Pharmaceutical Benefits Scheme; **PET** = positron emission tomography;
PFMT = pelvic floor muscle training; **PI3K** = phosphoinositide 3-kinase;
PPI = post-prostatectomy urinary incontinence; **PSA** = prostate-specific antigen;
SGARIs = second-generation androgen receptor inhibitors;
TGA = Therapeutic Goods Administration;
USANZ = Urological Society of Australia and New Zealand.

Welcome to the 24th 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

Prostate Cancer Awareness Month: Family History Guidelines for PSA Testing

September marks Prostate Cancer Awareness Month. There are over 25,000 new cases of prostate cancer diagnosed annually in Australia.

Genetic predisposition plays a crucial role in risk stratification. Men with a first-degree relative diagnosed with prostate cancer face a two-fold increased risk, while those with two or more affected close male relatives have a five-fold higher lifetime risk. Additionally, a strong family history of breast or ovarian cancer, particularly involving *BRCA1* or *BRCA2* mutations, elevates prostate cancer risk.

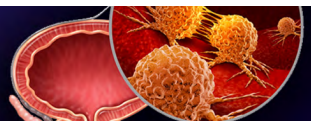
Current National Health and Medical Research Council guidelines recommend prostate-specific antigen (PSA) testing for men with a family history starting at age 40. For the general male population, screening can commence at age 50. The recommended screening interval is biennial until the age of 69 years.

Clinicians should be aware that early-stage prostate cancer often presents asymptomatically. Therefore, adherence to screening guidelines and risk-based patient counselling is essential for the timely detection and management of this prevalent malignancy.

https://tinyurl.com/2mjychzy

Earn CPD

Nursing and Midwifery Board of Australia (NMBA) Journal reading and watching videos (including Research Reviews') may be considered a self-directed activity set out in the NMBA Registration Standard: Continuing Professional Development. One hour of active learning will equal one hour of CPD. Details at NMBA CPD page.



Active surveillance and watchful waiting in the management of prostate cancer

A recent article provides an updated overview of conservative management strategies, specifically active surveillance and watchful waiting, for prostate cancer.

Active surveillance is a structured approach with curative intent, recommended for men with low-risk disease (PSA <10 ng/mL, ISUP 1, Clinical stage T1–T2a). It involves regular monitoring through PSA tests, digital rectal exams, MRI, and interval biopsies. Long-term studies have shown high disease-specific survival rates for patients managed conservatively. The strategy aims to minimise overtreatment while maintaining the option for curative intervention if disease progression is detected.

Recent evidence suggests active surveillance may also be appropriate for select patients with favourable intermediate-risk disease, particularly those with low-volume ISUP 2. However, this approach requires more stringent monitoring and is not yet routinely recommended in Australia, despite being included in European and American guidelines.

Watchful waiting, on the other hand, is a palliative strategy typically employed for patients with a life expectancy of less than 10 years. This approach involves less intensive monitoring, with treatment initiated only when symptoms develop or there are signs of rapid disease progression. The goal is to minimise treatment-related morbidity in patients unlikely to benefit from radical intervention.

The article emphasises the importance of effective communication and shared decision-making in implementing these strategies. Patients need to understand that active surveillance is a safe and effective management option that can help maintain quality of life by avoiding potential side effects associated with radical treatments.

The decision between active surveillance and watchful waiting should be based on life expectancy, disease biology, and patient preference. Both approaches have demonstrated similar long-term oncological outcomes to radical treatment while reducing harm from overtreatment.

As survivorship populations increase, primary care will play a growing role in the shared conservative management of prostate cancer. The article provides a practical algorithm to guide clinicians in understanding and implementing these conservative strategies.

https://tinyurl.com/2ydkpd2y

Prostate cancer trials in Australia

The Australian and New Zealand Urogenital and Prostate cancer trials group has listed ongoing prostate cancer trials in Australia on its website. The following clinical trials are currently enrolling patients:

- **ANZadapt** aims to find out if a strategy to pause hormone treatment if the cancer is controlled and restart treatment if the cancer starts to grow again is better than taking hormone tablets every day continuously.
- **GUIDE** aims to investigate whether a prostate cancer marker in the blood (mGSTP1) can be used to guide chemotherapy treatment.
- **WOMBAT** aims to test if bipolar androgen therapy can prolong the time it takes for non-metastatic castration-resistant prostate cancer (nmCRPC) to become detectable in other areas of the body.
- **NINJA** aims to compare two emerging schedules of radiotherapy in the treatment of intermediate or high-risk prostate cancer.

https://tinyurl.com/mtky28y7

Managing non-metastatic castration-resistant prostate cancer

A recent publication provides a comprehensive overview of the management of nmCRPC, focusing on using second-generation androgen receptor inhibitors (SGARIs) and addressing unmet needs in patient care.

The treatment landscape for nmCRPC has evolved significantly with the approval of three SGARIs: enzalutamide, apalutamide, and darolutamide. Clinical trials have demonstrated that these drugs improve metastasis-free survival and overall survival compared with placebo in patients with high-risk nmCRPC. While the efficacy of these agents is generally comparable, important distinctions exist in their safety profiles and potential for drug-drug interactions (DDIs).

The review highlights the importance of individualised treatment selection, considering factors such as comorbidities, concomitant medications, and potential DDIs. Enzalutamide and apalutamide are potent inducers of several cytochrome P450 enzymes, potentially affecting the metabolism of many commonly prescribed medications. In contrast, darolutamide has a more favourable DDI profile, primarily inhibiting BCRP and OATP transporters.

Patient monitoring strategies are evolving, with evidence suggesting that PSA levels alone may not be sufficient to detect disease progression in patients treated with SGARIs. The authors emphasise the need for regular radiographic imaging, including the potential role of prostate-specific membrane antigen PET imaging for earlier detection of metastases.

The article also discusses challenges in clinical decision-making, including the underuse of novel therapies and the need for further research on treatment sequencing and patient selection. Real-world studies have shown variations in SGARI uptake and effectiveness, highlighting the importance of ongoing research to optimise patient outcomes.

Cost considerations and access to treatment are addressed, with budget impact models suggesting potential long-term cost savings with certain SGARIs due to reduced adverse events and hospitalisations.

In conclusion, the authors stress the importance of multidisciplinary approaches to ensure optimal and individualised disease management for patients with nmCRPC. They call for continued research to address unmet needs and further refine treatment strategies in this evolving field of prostate cancer care.

https://tinyurl.com/tdm4vhpu

Recent advances in diagnosing and treating post-prostatectomy urinary incontinence

A recent article examines advances in diagnosing and treating post-prostatectomy urinary incontinence (PPI), a common complication following radical prostatectomy for prostate cancer. The incidence of PPI varies widely from 1–87%, depending on the definition used and assessment methods. Stricter definitions of continence (e.g. "no pads") generally correlate with better patient outcomes.

Key risk factors for PPI include older age, obesity, comorbidities, and anatomical features like shorter membranous urethral length. Tumour characteristics and surgical factors such as nerve-sparing techniques also influence PPI risk. The pathophysiology is complex, involving sphincter deficiency and bladder dysfunction.

Diagnosis relies on patient history, physical examination, pad tests, questionnaires, and urodynamic studies. The 24-hour pad test is considered more objective for quantifying urine leakage. Cystoscopy may be necessary before surgical intervention.

Conservative management, including lifestyle modifications and pelvic floor muscle training (PFMT), is the first-line treatment. Evidence suggests PFMT benefits early recovery but may not impact long-term continence. Pharmacological options like duloxetine show some promise but require further study.

When conservative measures fail, surgical interventions are considered. The artificial urinary sphincter remains the gold standard for moderate to severe PPI, with success rates of 61–100%. However, it carries risks of infection and mechanical failure. Male slings are an alternative for mild to moderate PPI, with fixed slings showing fewer adverse events than artificial urinary sphincters in some studies. Newer options like adjustable slings and periurethral balloons require more long-term data.

The review emphasises the importance of individualised treatment approaches based on PPI severity and patient factors. It highlights the need for standardised definitions and assessment methods to improve comparability across studies. Future research should focus on refining surgical techniques, exploring novel interventions, and identifying predictive factors for treatment success to optimise patient outcomes.

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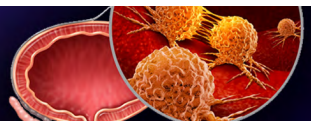

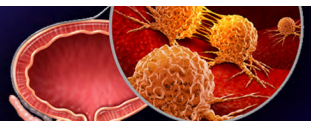

Therapy resistance in prostate cancer: Mechanism, signalling and reversal strategies

A recent comprehensive review examined the complex mechanisms of therapy resistance in prostate cancer, focusing on the tumour microenvironment and key signalling pathways. Despite advances in treatment, resistance to therapies remains a significant challenge in managing prostate cancer, particularly as it progresses to castration-resistant prostate cancer.

The tumour microenvironment promotes resistance through various mechanisms, including epithelial-mesenchymal transition, anoikis suppression, and angiogenesis stimulation. Cancer-associated fibroblasts and hypoxic conditions within the tumour contribute to treatment resistance and disease progression.

Several signalling pathways are implicated in therapy resistance. The androgen receptor (AR) pathway, a primary target for PC treatment, can be activated through AR amplification, mutations, and splice variants like AR-V7. The mTOR/PI3K/AKT pathway influences tumour growth and interacts with other oncogenic pathways, contributing to resistance. DNA damage repair pathways, when dysregulated, can affect tumour cell response to genotoxic therapies. The JAK/STAT pathway activation promotes stem cell plasticity and cancer stem cell phenotypes, contributing to treatment resistance.

The review discusses resistance mechanisms to specific therapies. Docetaxel resistance involves altered expression of survival genes, cytokine production, and β-tubulin isoforms. Resistance to AR-targeted therapies like abiraterone and enzalutamide can occur through AR pathway reactivation, alternative androgen synthesis, and activation of bypass signalling pathways.

Cross-resistance between different therapies is a growing concern, with patients showing decreased response to subsequent treatments after failing initial therapies. This highlights the need for strategic sequencing and a combination of treatments.

The emergence of neuroendocrine prostate cancer, either de novo or treatment-induced, presents additional challenges due to its lack of AR expression and activation of alternative growth pathways.

Strategies to overcome resistance are being explored, including targeting multiple pathways simultaneously, developing new AR antagonists, and using nanoparticle drug delivery systems. The review emphasises the importance of understanding resistance mechanisms to develop more effective treatment strategies and improve patient outcomes.

https://tinyurl.com/4jcu4ejn

Earn CPD

Royal Australasian College of Physicians (RACP) MyCPD participants can claim the time spent reading and evaluating research reviews as CPD in the online MyCPD program. Please contact MyCPD@racp.edu.au for any assistance.

Royal Australian & New Zealand College of Radiologists (RANZCR) members can claim reading related to their practice as a CPD activity under the category 'journal reading and web based no certificate *reflection required'. More info.

Meeting your professional obligations when using AI in healthcare

Since artificial intelligence (AI) is becoming increasingly integrated into healthcare, the Australian Health Practitioner Regulation Agency (AHPRA) has published guidance on how clinicians can use AI tools responsibly while adhering to professional obligations. In healthcare, AI encompasses various technologies, from diagnostic tools to generative AI for administrative tasks. While some AI tools are regulated by the Therapeutic Goods Administration (TGA) as medical devices, many general-purpose tools used in clinical practice are not.

The potential benefits of AI in healthcare include improved health outcomes, enhanced diagnostics, and reduced administrative burdens. However, clinicians must be aware of the challenges and ethical considerations associated with AI use. Regardless of the technology employed, practitioners remain accountable for delivering safe, quality care and meeting professional standards outlined in their Code of Conduct.

When using AI, clinicians should understand the tool's intended use, limitations, and potential risks. This includes reviewing product information, training data, and clinical contexts where the tool may not be appropriate. Transparency with patients about AI use is crucial, particularly when it involves personal data input or recording consultations.

Informed consent is essential when using AI tools that require patient data input or for recommended diagnostic devices. Clinicians should document patient consent, especially when using AI scribing tools that employ generative AI.

Other important considerations include ensuring patient privacy and confidentiality, being aware of potential biases in AI algorithms, complying with relevant legislation and regulatory requirements, and understanding the governance arrangements established by employers or practices for AI implementation.

AHPRA will update the guidance regularly to reflect new developments in AI and share updates from other regulators.

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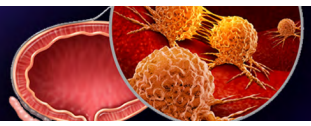

Regulatory News

TGA approves the first targeted nuclear medicine for men with prostate cancer

The TGA has approved lutetium Lu 177 vipivotide tetraxetan (Pluvicto®) as the first targeted radioligand therapy for eligible Australian men with metastatic castration-resistant prostate cancer (mCRPC). This precision medicine identifies and targets cancerous cells while minimising its effects on healthy tissue. The approval is based on the Phase III VISION study, which demonstrated improved overall survival and quality of life in suitable patients with advanced prostate cancer.

Lutetium Lu 177 vipivotide tetraxetan works by binding to prostate-specific membrane antigen on cancer cells and delivering targeted radiation therapy. This approach offers a new treatment option for patients with mCRPC who have limited alternatives and face a poor prognosis, with only a 30% five-year survival rate.

While the TGA registration is a crucial step, stakeholders are now focused on ensuring widespread availability and access to lutetium Lu 177 vipivotide tetraxetan across Australia. The therapy is not currently listed on the Pharmaceutical Benefits Scheme (PBS), and efforts are underway to navigate regulations and procedures for this new technology to enable consistent and equitable access for eligible patients.

https://tinyurl.com/3wfdfsdf

Release of Stage 3 for 60-day prescriptions

The final phase of the 60-day prescription implementation commenced on September 1, 2024, marking a significant expansion in medication access for patients with stable chronic conditions. This third stage encompasses 264 medicines, representing 766 PBS items when accounting for various strengths and formulations. The expanded list now includes treatments for asthma, COPD, anxiety disorders, Parkinson's disease, and other chronic conditions.

Clinicians retain complete discretion over prescribing quantities, allowing for tailored patient care. While this change offers potential cost savings and convenience for patients, it necessitates vigilance in medication management. Healthcare providers should implement robust recall and review systems to ensure regular patient assessments, particularly for conditions like asthma, where ongoing monitoring is crucial.

The reform has been widely adopted, with over 10 million 60-day scripts dispensed in its first year. This change not only alleviates the financial burden for patients but also potentially reduces unnecessary GP visits for prescription renewals. As the program reaches full implementation, clinicians should familiarise themselves with the comprehensive list of eligible medications and consider updating their prescribing practices accordingly.

https://tinyurl.com/mttzwkce

591-day delay for new medicines

The Australian Patient Access Gap Report has revealed significant delays in accessing new medicines for life-threatening illnesses in Australia. On average, patients wait 591 days between TGA approval and PBS listing, with some life-saving drugs taking up to three years to become available. This delay, known as the 'patient access gap', is particularly concerning for conditions like prostate cancer, where ten men die daily.

The report analysed all TGA-approved medicines from January 2021 to April 2024. Applications based on cost-effectiveness often required multiple attempts for listing, taking an average of 638 days, compared to 488 days for cost-minimization applications. Alarmingly, over 40 new medicines recommended by the Pharmaceutical Benefits Advisory Committee remained unfunded after 1,000 days.

Prostate Cancer Foundation of Australia has called for urgent reform, highlighting that Australia lags behind other countries in approving new medicines and therapies. The current system's high discount rates and lack of international harmonisation make it challenging for pharmaceutical companies to operate in Australia despite their investments in clinical trials and patient access schemes.

The impact on patients is significant, with many unable to afford crucial medications without PBS listing. For instance, some prostate cancer drugs cost over $35,000 per year without subsidisation. The foundation argues that without rapid modernisation of the PBS, Australians' life expectancy may become limited by their financial means.

This situation underscores the need for a more efficient and responsive approval process to ensure timely access to life-saving medications for Australians with serious illnesses.

https://tinyurl.com/5n6d8vn8

Bacterial infections

Amoxicillin + clavulanic acid (CLAVULIN- I 25F®; 125 mg/5ml + 31.25 mg/5 ml powder for oral liquid, 100 ml) is now listed on the PBS for the current supply shortage under Section 19A. It is listed as a restricted benefit.

https://tinyurl.com/4xra66ch

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News in Brief

BINS 4 Blokes 2024

The Continence Foundation of Australia's BINS4Blokes campaign advocates for installing incontinence product disposal bins in male public toilets. This initiative addresses a significant health concern, as over 1.34 million Australian men and boys live with incontinence. The lack of proper disposal facilities in public restrooms often leads to social isolation, with up to 50% of affected males avoiding situations where hygienic disposal is uncertain. By promoting the widespread availability of these bins, the campaign aims to improve the quality of life and social participation of men and boys managing incontinence. The National Public Toilet Map is a valuable resource, helping individuals locate nearby facilities with appropriate disposal bins.

https://tinyurl.com/4udv9v3m

Olaparib may be effective without hormone therapy for HRR-positive patients

A phase 2 trial assessed olaparib monotherapy in 51 patients with high-risk biochemically recurrent prostate cancer post-prostatectomy. A ≥50% PSA decline was observed in 26% of patients, primarily in those with BRCA2 alterations, where all 11 participants responded. Efficacy was limited to HRR-positive patients, and the safety profile was consistent with prior studies. These results indicate that olaparib may be effective for select patients with biochemically recurrent prostate cancer, especially those with HRR alterations, and support further investigation as a treatment option in this population.

https://tinyurl.com/ypha4yf3

COVID-19 Resources

Royal Australasian College of Surgeons
European Urology Journal
British Association of Urological Surgeons
American Urological Association
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 Professor Niall Corcoran and Professor Nathan Lawrentschuk

Urology Research Review with Professor Eric Chung

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