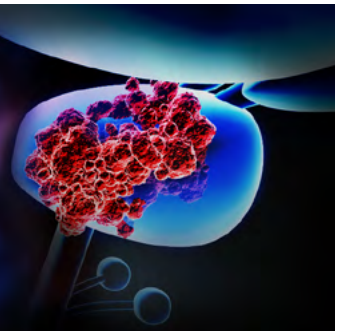
Prostate Cancer Research Review™



Making Education Easy

Issue 70 - 2023

In this issue:

- Biochemical recurrence and mortality after radiotherapy or radical prostatectomy
- Retzius-sparing vs standard RARP
- PSMA PET local recurrence concordance with radical prostatectomy histopathology
- Predictors of PSMA PET positivity
- MRI-based machine learning for Ki67 and Gleason grade group prediction
- Niraparib + abiraterone acetate in mCRPC with HRR gene alteration
- Cytoreductive radical prostatectomy for bone-metastatic prostate cancer
- ^{18}F-rhPSMA-7.3 imaging in prostate cancer
- PSA-based screening and prostate cancer morbidity and mortality
- Free PSA and clinically significant and fatal prostate cancer

Abbreviations used in this issue:

AUC = area under the curve; **BCR** = biochemical recurrence; **CI** = confidence interval; **GG** = grade group; **HR** = hazard ratio; **HRR** = homologous recombination repair; **ISUP** = International Society of Urological Pathology; **mCRPC** = metastatic castration-resistant prostate cancer; **MRI** = magnetic resonance imaging; **OS** = overall survival; **PARP** = poly-adenosine diphosphate-ribose polymerase; **PCSM** = prostate cancer-specific mortality; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RARP** = robot-assisted radical prostatectomy.

Kindly supported by

Australian Prostate Centre apc

Welcome to Issue 70 of Prostate Cancer Research Review.

First up, a Swedish population-based cohort study highlights the differences in clinical significance between surgical and radiation definitions of recurrence in patients with prostate cancer. Following on, in an Italian study a significant improvement in immediate urinary continence, but not in early potency recovery, was observed with a Retzius-sparing compared to the standard approach for RARP in men with clinically localised prostate cancer. Other topics covered in this issue include PSMA PET local recurrence concordance with radical prostatectomy histopathology, predictors of PSMA PET positivity, MRI-based machine learning for Ki67 and Gleason grade group prediction, niraparib plus abiraterone acetate in mCRPC with HRR gene alteration, PSA-based screening and prostate cancer morbidity and mortality, and free PSA and clinically significant and fatal 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

Biochemical recurrence and risk of mortality following radiotherapy or radical prostatectomy

Authors: Falagario UG et al.

Summary: This Swedish population-based cohort study (n = 16,311) examined the relationship of biochemical recurrence (BCR) after radical prostatectomy (n = 10,364; median age 64 years) or radiotherapy (n = 5947; median age 69 years) and risk stratification using European Association of Urology (EAU) criteria of low- or high-risk of prostate cancer-specific mortality (PCSM). Over a median follow-up for survivors of 88 months (radical prostatectomy cohort) and 89 months (radiotherapy cohort), the 15-year BCR cumulative incidence after radical prostatectomy was 16% (95% CI 15-18) in the D'Amico low-risk group, 30% (95% CI 27-32) in the intermediate-risk group, and 46% (95% CI 42-51) in the high-risk group; following radiotherapy, 15-year BCR cumulative incidences were 18% (95% CI 15-21), 24% (95% CI 21-26), and 36% (95% CI 33-39), respectively. The 10-year PCSM cumulative incidences after radical prostatectomy were 4% (95% CI 2-6) for low-risk and 9% (95% CI 5-13) for high-risk EAU-BCR; after radiotherapy, the 10-year PCSM cumulative incidences were 24% (95% CI 19-29) and 46% (95% CI 40-51).

Comment: Although BCR is frequently reported as an endpoint for trials in early prostate cancer, it correlates poorly with disease-specific and OS and is no longer recommended as an intermediate endpoint. Recent data suggest that the mortality risk of BCR, however, is influenced by primary tumour grade (ISUP GG <3 vs >4) and PSA doubling time (<12 vs >12 months post-prostatectomy; <18 vs >18 months post-radiation), suggesting patients with BCR can be risk stratified as low- or high-risk. This population-based cohort study from Sweden is interesting in that it again highlights the differences in clinical significance between surgical and radiation definitions of recurrence, patients with high-risk BCR following surgery had a 9% incidence of PCSM at 10 years, whereas the incidence following radiation was a whopping 24% for low-risk and 46% for high-risk BCR. Apples and oranges.

Reference: JAMA Netw Open 2023;6(9):e2332900
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.

Retzius-sparing vs. standard robot-assisted radical prostatectomy for clinically localised prostate cancer: A comparative study

Authors: Ficarra V et al.

Summary: This single-surgeon cohort study examined outcomes in 207 patients with clinically localised prostate cancer undergoing Retzius-sparing (n = 102) versus standard robot-assisted radical prostatectomy (RARP) controls (n = 105). Retzius-sparing RARP recipients had higher urinary continence recovery rates at 1 week (91.2% vs 54.3%; $p < 0.001$), 1 month (92.2% vs 66.7%; $p < 0.001$), 2 months (95.1% vs 74.3%; $p < 0.001$), 3 months (96.1% vs 83.8%; $p = 0.01$), but not 6 months (97% vs 90.5%) after catheter removal. Potency recovery rates were also higher with Retzius-sparing RARP (68.2% vs 51.6%; $p = 0.03$) 6 months after catheter removal. Multivariate analyses suggested that Retzius-sparing RARP independently predicted 1-week urinary continence recovery, but not 6-month potency recovery. There were no differences in perioperative complication rate (9.8% vs 14.3%) nor positive surgical margin rate (9.8% vs 8.6%).

Comment: This single-surgeon series reports on just over 200 consecutive patients undergoing RARP, the first 105 by the conventional anterior approach and the remainder using a Retzius-sparing, posterior approach. Certainly, early urinary incontinence was improved with the Retzius-sparing approach (91% with 0-1 pads 1 week post-catheter removal!), but overall rates of continence were similar by 6 months. Interestingly there was no reported difference in positive margin rates for either pT2 or pT3 disease, which were impressive overall. Within the limitations of this type of study it certainly suggests the technique has benefits in expert hands, but for lesser mortals the jury is still out.

Reference: Prostate Cancer Prostatic Dis. 2023;26(3):568-574
Abstract

Re-defining ^{18}F-DCFPyl prostate-specific membrane antigen positron emission tomography detected local recurrence from radical prostatectomy histopathology

Authors: Tissot S et al.

Summary: This prospective non-randomised study assessed the topographic concordance of histopathological features of radical prostatectomy specimens and the location of the PSMA PET local recurrences in 24 men (median age 71 years, median PSA 0.37 ng/mL, time between prostatectomy and PSMA PET 2.6 years) receiving an ^{18}F-DCFPyL PET scan. Overall, 15 patients had recurrences within the vesicourethral anastomotic region and 9 within the lateral surgical margins, with 100% concordance in the left-right plane between tumour location and local recurrence, and 79% were concordant in 3 dimensions (3D). 10 of 16 (63%) patients with extraprostatic extension and 5 of 9 patients with positive margins had 3D concordance between pathology and local recurrence. Quantitatively, 17 patients had local recurrences correlating with the original tumour location in the craniocaudal plane.

Comment: With better imaging improving anatomical localisation of recurrent disease post-radical prostatectomy, there is increasing interest in the use of more targeted radiation to achieve the same oncological outcomes, but less morbidity compared with the traditional whole-prostate-bed salvage radiation field. In this context, this study from St Vincent's hospital in Melbourne investigated the correlation between the anatomical position of the tumour within the prostate as well as other pathological features with the site of local recurrence as detected by postoperative PSMA-PET imaging. Overall, there was a high correlation between tumour location in 3D space within the prostate and site of recurrence, with weaker correlations with sites of extra-prostatic extension and positive surgical margins. Small numbers in the study, but certainly an interesting observation that could be explored in a larger cohort.

Reference: BJU Int. 2023;132(4):411-419
Abstract

Predictors of PSMA PET positivity: Analysis in a selected cohort of biochemical recurrence prostate cancer patients after radical prostatectomy

Authors: Mapelli P et al.

Summary: This study examined potential clinical and pathological predictors of PSMA PET positivity with validation by clinical and instrumental follow-up or histopathology in a selected cohort of BCR patients after radical prostatectomy with no other prostate cancer-related therapy. Multivariate analysis suggested that pathological staging after radical prostatectomy ≥pT3a and higher PSA levels were correlated with PSMA PET positivity.

Comment: PSMA PET is the investigation of choice for deciding subsequent management in patients with disease recurrence following either surgery or radiation. In this relatively small Italian study, the authors investigated the impact of various clinical and pathological variables on a positive scan in patients with BCR post-surgery. They find that the presence of pT3 disease and the PSA level at the time of scanning were both positively associated with the finding of disease recurrence on imaging, essentially confirming previous findings. However, sensitivity remains an issue, particularly at PSA levels <0.5 ng/mL when salvage radiation is more likely to be beneficial.

Reference: Cancers (Basel) 2023;15(18):4589
Abstract

MRI radiomics-based machine learning models for Ki67 expression and Gleason grade group prediction in prostate cancer

Authors: Qiao X et al.

Summary: This retrospective study (n = 122) assessed the use of biparametric MRI (bpMRI) radiomics using feature-based machine learning models in the prediction of the Ki67, or mitotic, index and Gleason grade group of prostate cancer. A machine learning model based on logistic regression and apparent diffusion coefficient plus T2 (receiver operating characteristic AUC 0.8882) was the best model for predicting Ki67 expression. Another machine learning model using diffusion-weighted imaging plus T2 (AUC 0.9248) performed best in predicting Gleason grade group. The Ki67 and Gleason grade group measures had a weak positive correlation ($r = 0.382$; $p < 0.001$), and a logistic regression model using apparent diffusion coefficient plus T2 had the highest diagnostic accuracy in predicting both Ki67 and Gleason grade group (AUC 0.6230).

Comment: There is significant ongoing interest in investigating if various imaging parameters from both MRI sequences as well as PET imaging can be used to predict future tumour behaviour. This has a number of potential advantages, including the possibility of making a diagnosis, performing risk stratification and proceeding to treatment without the need for a tissue biopsy (as was reported last year in a small German study), as well as limiting the effect of 'sampling error' associated with biopsy of heterogenous primary tumours. This small study uses a number of machine learning approaches to investigate the association between various MRI sequence features and Gleason grade group and a marker of cell proliferation demonstrating reasonable performance. Useful as a proof-of-concept, although it would be more informative to assess patients who are treated conservatively, using progression to metastases as the endpoint.

Reference: Cancers (Basel) 2023;15(18):4536
Abstract

Extra

Zoladex®
goserelin

We're doing more for men's business*

*At AstraZeneca, we're investing in advancements in the diagnosis and treatment of prostate cancer and we're offering Z-Extra - a comprehensive program supporting patients receiving ***Zoladex.***

Zoladex is indicated for:[1,2] Palliative treatment of metastatic (M+) or locally advanced prostate cancer where suitable for hormonal manipulation. Adjuvant and neoadjuvant therapy in combination with radiotherapy for the management of locally advanced prostate cancer in men suitable for hormonal manipulation.

PBS Information: Zoladex 10.8mg. Restricted benefit for locally advanced (equivalent to stage C) or metastatic (equivalent to stage D) carcinoma of the prostate.

PLEASE CLICK HERE TO REVIEW FULL PRODUCT INFORMATION BEFORE PRESCRIBING.
FURTHER INFORMATION AVAILABLE ON REQUEST FROM ASTRAZENECA.

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

Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: Second interim analysis of the randomized phase III MAGNITUDE trial

Authors: Chi KN et al.

Summary: This report provides longer follow-up data from the second prespecified interim analysis of the randomised, placebo controlled, phase III MAGNITUDE trial in 212 patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair gene alterations (HRR; *BRCA1/2* n = 113) receiving niraparib plus abiraterone acetate with prednisone (AAP). After a median 24.8 months of follow-up in *BRCA1/2* patients, niraparib plus AAP prolonged median radiographic PFS (19.5 vs 10.9 months; HR 0.55; 95% CI 0.39-0.78; p = 0.0007). Radiographic PFS was also prolonged in the total HRR positive population (HR 0.76; 95% CI 0.60-0.97; p = 0.0280). Time to symptomatic progression and time to initiation of cytotoxic chemotherapy were also improved with niraparib plus AAP. In *BRCA1/2* patients, OS with niraparib plus AAP did not differ from placebo (HR 0.88; 95% CI 0.58-1.34); however, a prespecified inverse probability analysis, accounting for imbalances in subsequent use of PARP inhibitors and other life-prolonging therapies, suggested an improved OS (HR 0.54; 95% CI 0.33-0.90; p = 0.0181)

Comment: Up to 30% of patients with mCRPC harbour defects in DNA damage repair genes (germline and somatic), predominantly *BRCA2* and *BRCA1*, and may benefit from treatment with a PARP inhibitor. This updated interim analysis from the MAGNITUDE trial confirms that the combination of niraparib and abiraterone improves radiographic PFS in the first line setting in patients harbouring *BRCA1/2*, in addition to delays in time to symptomatic progression and time to initiation of cytotoxic chemotherapy. Consistent responses were also observed in patients harbouring defects in HRR genes other than *BRCA1/2* (including *PALB2*, *CHEK2*, *FANCA*) although the magnitude of effect was less. Important to consider tissue and/or germline testing in all men presenting with metastatic disease.

Reference: Ann Oncol. 2023;34(9):772-782
Abstract

The role of cytoreductive radical prostatectomy and lymph node dissection in bone-metastatic prostate cancer: A population-based study

Authors: Zhai T et al.

Summary: This population-based study used US Surveillance, Epidemiology and End Results (SEER) Medicare data to examine whether cytoreductive radical prostatectomy and lymph node dissection could benefit 317 patients with bone-metastatic prostate cancer. Cytoreductive radical prostatectomy was increasingly performed for bone-metastatic prostate cancer from 2010 (2.2%) to 2019 (3.0%; p < 0.05). Multivariate analyses suggested that cytoreductive radical prostatectomy led to better OS or cancer-specific survival rates in patients aged <75 years, those with PSA <98 ng/mL, those with bone-only metastatic sites or those not receiving chemotherapy (all p < 0.05). Among patients undergoing cytoreductive radical prostatectomy, lymph node dissection, especially extended lymph node dissection, was associated with a better OS and cancer-specific survival rates (both p < 0.05).

Comment: STAMPEDE has established radiation therapy to the primary as a standard of care in patients with low-volume metastatic disease. Although it is assumed that radical prostatectomy offers a similar benefit, this has yet to be established in a prospective setting. This retrospective analysis of the SEER database describes the role of cytoreductive prostatectomy in the US over the last decade and attempts to offer some insights into its potential benefit. Cytoreductive prostatectomy with or without a pelvic lymph node dissection was performed in only a very small percentage of men with established bony metastatic disease, and although the authors suggest improvements in OS in some patients, there are far too many unaccounted-for confounders to meaningfully interpret the results. So not a particularly helpful study.

Reference: Cancer Med. 2023;12(16):16697-16706
Abstract

Diagnostic performance and safety of positron emission tomography with ^{18}F-rhPSMA-7.3 in patients with newly diagnosed unfavourable intermediate- to very-high-risk prostate cancer: Results from a phase 3, prospective, multicentre study (LIGHTHOUSE)

Authors: Surasi DS et al.

Summary: The prospective, multicentre phase III LIGHTHOUSE study assessed the diagnostic performance and safety of ^{18}F-rhPSMA-7.3 for the detection of pelvic lymph node metastases in 352 newly diagnosed prostate cancer patients. In total, 296 patients (99 with unfavourable intermediate-risk and 197 with high- or very-high-risk prostate cancer) underwent surgery. Blinded independent reads suggested that 7.8% to 13% of patients had ^{18}F-rhPSMA-7.3-positive pelvic lymph node metastases.; with 24% patients having ≥1 positive pelvic lymph nodes on histopathology. Sensitivity for pelvic lymph node detection was 30% (95% CI 19.6-42.1) for reader 1, 27% (95% CI 17.2-39.1) for reader 2, and 23% (95% CI 13.7-34.4) for reader 3, which did not meet prespecified thresholds for sensitivity (lower bounds of 95% CI 22.5%). Specificity among the 3 readers were 93% (95% CI 88.8-95.9), 94% (95% CI 89.8-96.6), and 97% (95% CI 93.7-98.7), exceeding the prespecified threshold (82.5%). Specificity was ≥92% across risk stratifications, with higher sensitivity in high-risk/very-high risk prostate cancer (24-33%) versus unfavourable intermediate-risk cancer (16-21%). Extra-pelvic lesions were reported in 16-28% of patients who underwent ^{18}F-rhPSMA-7.3-PET/CT irrespective of surgery. Verification of these lesions, mostly by conventional imaging, suggested a verified detection rate of 9.9-14% (positive predictive value 51-63%).

Comment: ^{18}F-rhPSMA-7.3 is a novel PSMA targeting PET tracer which is reported to have lower urinary excretion than both ^{18}F-DCFPyL and ^{68}Ga-PSMA-11, and so may facilitate better pelvic imaging. This study reports the diagnostic performance of ^{18}F-rhPSMA-7.3 in a large cohort of men with unfavourable intermediate risk to very-high risk prostate cancer undergoing radical prostatectomy and pelvic lymph node dissection. Similar to the other trials in this area, sensitivity for pelvic lymph node metastases was low compared to histopathological assessment, but specificity was high, with a similar negative predictive value as other agents. A notable exception to this is the proPSMA study which reported a sensitivity rate for pelvic nodal metastases of greater than 80%, which may reflect differences in either the tracer used, or the extent of pelvic lymph node dissection performed in imaging-negative patients to establish the ground truth state. Low sensitivity is likely a function of tumour deposit size (the limit for detection by PSMA-PET appears to be about 4 mm).

Reference: Eur Urol. 2023;84(4):361-370
Abstract

A detailed evaluation of the effect of prostate-specific antigen-based screening on morbidity and mortality of prostate cancer: 21-year follow-up results of the Rotterdam section of the European Randomised Study of Screening for Prostate Cancer

Authors: de Vos Il et al.

Summary: This study updated PSA-based screening results in the Dutch arm of the European Randomised Study of Screening for Prostate Cancer (ERSPC; n = 42,376) in terms of PCSM, metastatic disease, and overdiagnosis. Over a median follow-up of 21 years, the rate ratio (RR) of PCSM was 0.73 (95% CI 0.61-0.88), favouring screening. The number needed to invite (NNI) was 246 and number needed to diagnose (NND) was 14 to prevent one prostate cancer death. For metastatic prostate cancer, the RR was 0.67 (95% CI 0.58-0.78), also favouring screening. The NNI to prevent one metastasis was 121 and the NND was 7. No difference in PCSM (RR 1.18; 95% CI 0.87-1.62) occurred in men aged ≥70 years at randomisation.

Comment: The ERSPC study continues to inform the value of early prostate cancer detection based on PSA testing. This latest report from the Rotterdam section demonstrates that population-based testing in asymptomatic men between the ages of 55 and 69 years decreases PCSM by 27% and the development of metastases by 33% relative to no screening at 21 years post-randomisation. Interestingly, over half of patients who developed metastases in the screening arm were diagnosed with prostate cancer in the first screening round (PSA screening was performed every 4 years with a prostate biopsy recommended for patients with a PSA level >3 ng/mL), suggesting the benefit may be greater if screening is commenced at an earlier age. There was no benefit to starting screening after the age of 70 years.

Reference: Eur Urol. 2023;84(4):426-434
Abstract

Free PSA and clinically significant and fatal prostate cancer in the PLCO screening trial

Authors: Yim K et al.

Summary: This analysis of data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO; n = 6,727) assessed whether adding percent free PSA to total PSA improved the prediction of clinically significant and fatal prostate cancer. Over a median follow-up of 19.7 years, 475 patients had clinically significant prostate cancer and 98 had fatal prostate cancer; median baseline PSA was 1.19 ng/mL, median percent free PSA was 18%. The cumulative incidence of fatal prostate cancer in patients with a baseline PSA ≥2 ng/mL and percent free PSA ≤10 was 3.2% at 15 years and 6.1% at 25 years, compared to 0.03% and 1.1% in patients with a percent free PSA >25%. In younger (55-64 years) patients with baseline PSA 2-10 ng/mL, the addition of percent free PSA improved Harrell's C index (evaluating predictive ability) from 0.56 to 0.60 for clinically significant prostate cancer and from 0.53 to 0.64 for fatal prostate cancer. Among older (65-74 years) patients, the C index for clinically significant prostate cancer was improved from 0.60 to 0.66, with no change in fatal prostate cancer. After adjustment for age, digital rectal exam, family history of prostate cancer, and total PSA, every 1% decrease in percent free PSA was associated with clinically significant prostate cancer (HR 1.05; p < 0.001).

Comment: Over the years a number of different biomarkers have been developed to improve the specificity of PSA for prostate cancer screening, particularly in the analytical grey zone of 4-10 ng/mL. This report from the intervention arm of the PLCO study investigated the incremental utility of including free PSA measurement to further stratify risk. Overall, decreasing free PSA levels was associated with an increased cumulative incidence of both clinically significant and lethal prostate cancer over 20 years of follow-up, although the impact was marginal. Interesting data, although the contemporary relevance is unclear given the push for replacement of PSA-based case finding completely with MRI screening.

Reference: J Urol. 2023;210(4):630-638
Abstract

Claim CPD/CME points Click here for more info.

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

Research Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au.
Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists. **Privacy Policy:** Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. **Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.
Research Review publications are intended for Australian health professionals.

RESEARCH REVIEW™ Australia's Leader in Specialist Publications