Prostate Cancer Research Review

Making Education Easy Issue 82 - 2024

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Abbreviations used in this issue:

¹⁷⁷Lu = lutetium-177; ADT = androgen deprivation therapy; $\begin{aligned} \textbf{ARPI} &= \text{androgen receptor pathway inhibitor; } \textbf{BMI} &= \text{body mass index;} \\ \textbf{CI} &= \text{confidence interval; } \text{$^{16}\textbf{FDG}$} = \text{$^{16}\textbf{F}$} \text{-fluorodeoxyglucose; } \textbf{Gy} &= \text{Gray;} \end{aligned}$ HR = hazard ratio; HRQoL = health-related quality of life; mCRPC = metastatic castration-resistant prostate cancer;

$$\label{eq:mhspc} \begin{split} & \text{mHSPC} = \text{metastatic hormone-sensitive prostate cancer}; \\ & \text{MRI} = \text{magnetic resonance imaging; NS} = \text{non-significant; OS} = \text{overall survival;} \end{split}$$

PET = positron emission tomography; PFS = progression-free survival; PLND = pelvic lymph node dissection; PSA = prostate-specific antigen;

PSMA = prostate-specific membrane antigen; RALP = robot-assisted laparoscopic radical prostatectomy;

rPFS = radiographic progression-free survival; RTOG = Radiation Therapy Oncology Group; SBRT = stereotactic body radiotherapy;

TRAE = treatment-related adverse event



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Welcome to Issue 82 of Prostate Cancer Research Review.

In the PACE-B trial, 5-fraction SBRT was non-inferior to control radiotherapy with respect to biochemical or clinical failure in men with low-to-intermediate-risk localised prostate cancer. In a study from the US, men with prostate cancer whose surgical planning of RALP involved 3D digital models had better oncologic and functional outcomes than those whose planning was based on 2D scans. We conclude this issue with a post hoc analysis of the phase III VISION study, which found that although rPFS correlated well with OS in men with PSMA-positive mCRPC, the correlation with symptomatic deterioration and HRQoL was much weaker.

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,

Professor Niall Corcoran

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Phase 3 trial of stereotactic body radiotherapy in localized prostate cancer

Authors: van As N et al.

Summary: This multinational, open-label, randomised, controlled phase III trial examined whether SBRT (36.25 Gy in 5 fractions over 1 or 2 weeks) was non-inferior to conventionally or moderately hypofractionated radiotherapy regimens (78 Gy in 39 fractions over 7.5 weeks or 62 Gy in 20 fractions over 4 weeks) in 874 patients with localised T1 or T2 prostate cancer (median age 69.8 years; median PSA 8 ng/mL). After a median 74.0 months follow-up, 5-year incidence of freedom from biochemical (PSA) or clinical failure was 95.8% (95% CI 93.3-97.4) with SBRT versus 94.6% (95% CI 91.9-96.4) with conventional radiotherapy (HR 0.73; 90% Cl 0.48-1.12; p = 0.004 for non-inferiority). The 5-year cumulative incidence of late RTOG grade ≥2 genitourinary toxic effects was 26.9% (95% Cl 22.8-31.5) with SBRT versus 18.3% (95% Cl 14.8-22.5) with conventional radiotherapy (p < 0.001), and that of late RTOG grade ≥2 gastrointestinal toxic effects was 10.7% (95% CI 8.1-14.2) versus 10.2% (95% CI 7.7-13.5; NS).

Comment: The march to true radiosurgery (ablative radiotherapy in a single fraction) continues apace. This large study from the UK, Canada and Ireland (PACE-B) randomised men with predominantly unfavourable intermediate-risk localised prostate cancer to SBRT to the primary (36.25 Gy in 5 fractions) or conventional/moderate hypofractionated dosing (78 Gy in 39 fractions/62 Gy in 20 fractions), without concomitant ADT. SBRT was found to be non-inferior to the control regimens using PSA and clinical failure as a composite endpoint. Toxicity overall was low, although an increase in late genitourinary toxicity was noted in the SBRT arm. Early adoption would certainly be more convenient for patients, and cheaper as well!

Reference: N Engl J Med. 2024;391(15):1413-1425

Abstract

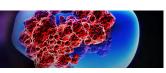


Independent commentary by Professor Niall Corcoran.

Professor Niall Corcoran is a urological surgeon and translational scientist based in Melbourne. He is Head of the Urology Unit at Western Health and a visiting surgeon at Royal Melbourne and Frankston Hospitals. His group in the University of Melbourne Centre for Cancer Research investigates molecular drivers of prostate cancer metastases and treatment resistance.

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Prostate Cancer Research Review



Lu-177 PSMA vs comparator treatments and survival in metastatic castration-resistant prostate cancer

Authors: Soon YY et al.

Summary: This comparative effectiveness study of the effect of ¹⁷⁷Lu vipivotide tetraxetan PSMA on OS in patients with mCRPC used individual participant data (n = 1031) from the TheraP and VISION randomised clinical trials. In TheraP, better OS (HR 0.53; 95% CI 0.39-0.71) was observed with the comparator (cabazitaxel) versus the VISION trial comparator (physicians' choice of treatments including hormonal treatments [e.g., abiraterone and enzalutamide], bisphosphonates, radiotherapy, denosumab, or glucocorticoids, but not cabazitaxel), whereas ¹⁷⁷Lu-PSMA in both trials had similar OS (HR 0.92; 95% CI, 0.70-1.19). In TheraP, 20% of cabazitaxel recipients crossed over to ¹⁷⁷Lu-PSMA, while 32% of ¹⁷⁷Lu-PSMA recipients crossed over to cabazitaxel; there were no differences in OS after controlling for crossover to either ¹⁷⁷Lu-PSMA or cabazitaxel, suggesting that the choice of comparator treatments may explain differences in the effect of ¹⁷⁷Lu-PSMA.

Comment: ¹⁷⁷Lu-PSMA has demonstrated efficacy in patients with mCRPC after taxane chemotherapy in both the Australian phase II TheraP and the international phase III VISION trials, with both showing improvements in PSA response and rPFS compared to their respective control arms. However, VISION also observed an improvement in OS, not seen in TheraP. This Australian-led secondary analysis of patient-level data from both trials (inferred for the VISION study) shows that this difference is attributable to the use of an 'active' cabazitaxel control arm in the TheraP study, which was excluded from the control arm in VISION. Instead, VISION used an array of 'protocol-permitted treatments', mainly supportive therapies (glucocorticoids, bisphosphonates) or likely inactive agents given cross resistance (ARPIs). Good reminder to carefully consider the comparator arm when evaluating 'headline' efficacy claims.

Reference: JAMA Netw Open 2024;7(9):e2433863

<u>Abstract</u>

Trifecta outcomes after use of 3-dimensional digital models for planning of robotic prostatectomy: A secondary analysis of a randomized clinical trial

Authors: Shirk JD et al.

Summary: This secondary analysis of a multicentre, single-blind, randomised clinical trial (n = 92) examined surgical outcomes after RALP using 3-D digital models during operative planning. After 18 months, rates of biochemical recurrence (PSA level >0.1 ng/mL) were lower (0% vs 17.9%; difference 17.9%; 95% CI 1.8-31.8; p = 0.01) and patients were less likely to undergo adjuvant or salvage radiotherapy (3.1% vs 31.6%; difference 28.5%; 95% CI 10.1-46.7; p = 0.002) if planning had included the 3-D model. Sexual function was better in the intervention group (mean Sexual Health Inventory for Men [SHIM] score 16.8 vs 9.8; difference 7.0; 95% CI 2.6-11.4; p = 0.002) and urinary function was unchanged (continence 78.6% vs 80.6%; difference 2.0%; 95% CI -17.9 to 21.9). Trifecta outcomes (undetectable PSA without radiotherapy or ADT, SHIM score unchanged or improved vs preoperative, complete continence) were more common after use of the 3-D model (48.0% vs 10.0%; difference 38.0%; 95% CI 14.4-61.6; p = 0.002).

Comment: Whether more granular and easily transferable information about tumour location within the prostate can improve surgical outcomes was investigated in this small US study. Patients undergoing RALP randomised to the intervention arm had bespoke 3-D models generated from their pre-operative MRI, depicting tumour location(s) within the prostate and their relationship to key structures (prostate capsule, urethra, neuro-vascular bundles etc.). Models were available to review pre-operatively, and in real time during surgery using the picture-in-picture function on the robotic console screen. In comparison to surgical planning based on 2-D MRI pictures and biopsy data, inclusion of the 3-D model resulted in significantly lower risk of biochemical recurrence, need for postoperative radiation and better erectile function. Certainly merits broader study.

Reference: JAMA Netw Open 2024;7(9):e2434143

Abstract

Sequential [177Lu]Lu-PSMA-617 and docetaxel versus docetaxel in patients with metastatic hormone-sensitive prostate cancer (UpFrontPSMA): A multicentre, open-label, randomised, phase 2 study

Authors: Azad AA et al.

Summary: The Australian UpFrontPSMA investigator-initiated, multicentre, open-label, randomised phase II trial assessed 177 Lu-PSMA-617 before docetaxel treatment in 130 patients with de-novo high-volume mHSPC. At 48 weeks, 25 of 61 (41%; 95% Cl 30-54) evaluable 177 Lu-PSMA-617 plus docetaxel recipients had undetectable PSA (<0.2 ng/mL) versus 10 of 61 (16%; 95% Cl 9-28) docetaxel alone recipients (0R 3.88; 95% Cl 1.61-9.38; p = 0.0020). The most common grade 3/4 TRAEs were febrile neutropenia (11% vs 10%) and diarrhoea (6% vs 0%); serious adverse events occurred in 25% vs 25%.

Comment: This was an Australian study investigating the potential benefit of two cycles of PSMA radioligand therapy prior to 6 cycles of docetaxel in patients with high-volume PMSA/¹8FDG PET concordant mHSPC commencing ADT compared to 6 cycles of docetaxel alone. Sequential therapy significantly improved the proportion of patients with a PSA <0.2 ng/mL at 48 weeks (primary endpoint), as well as at any time. Secondary endpoints (PSA-PFS and castration resistance-free survival) also favoured sequential therapy, without a noticeable increase in toxicity. How these results will impact current practice is unclear, as combination ADT plus ARPI has become the standard doublet treatment even in patients with high volume disease. As the authors point out this may be resolved when the PSMAddition trial (ADT + ARPI +/ PSMA radioligand) is reported.

Reference: Lancet Oncol. 2024;25(10):1267-1276

Abstract

Circulating tumor DNA assessment for treatment monitoring adds value to PSA in metastatic castration-resistant prostate cancer

Authors: Sweeney CJ et al.

Summary: This analysis of data from the phase III IMbassador250 trial of enzalutamide with or without atezolizumab after abiraterone examined the value of changes in circulating tumour DNA (ctDNA) tumour fraction (TF) from 494 evaluable patients with mCRPC to predict survival benefit from enzalutamide. Overall, ctDNA TF detection at baseline and/or at cycle 3 day 1 was associated with shorter rPFS and OS. ctDNA TF observed at cycle 3 day 1, with or without detection at cycle 1 day 1, was associated with worse rPFS and median OS than no detection. Discordant ctDNA TF and PSA responses at cycle 3 day 1 predicted more favourable outcomes when ctDNA TF was undetected but PSA not reduced than when ctDNA TF was detected but PSA reduced (median OS 22.1 vs 16 months; p < 0.001).

Comment: ctDNA is shed by degenerating tumour cells and reflects both tumour volume as well as the rapidity of cell turnover. As such, measured ctDNA levels have shown prognostic utility across numerous cancer types. This translational study (led by Chris Sweeney from Adelaide) measured ctDNA levels in samples from patients with mCRPC enrolled in the IMbassador250 trial. Detection of ctDNA at baseline and/or after 2 cycles of treatment was associated with shorter rPFS and OS. In addition, ctDNA response to treatment had additional prognostic significance compared to PSA response alone. Encouraging results, particularly given the relative insensitivity of the assay (FoundationOne Monitor) compared to a custom assay.

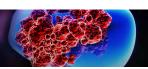
Reference: Clin Cancer Res. 2024;30(18):4115-4122 Abstract

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Abbreviations: ADT: androgen deprivation therapy; HR: hazard ratio; mHSPC: metastatic hormone-sensitive prostate cancer; OS: overall survival; PBS: Pharmaceutical Benefits Scheme. References: 1. PBS Schedule of Pharmaceutical Benefits. 2023. Available at: https://www.pbs.gov.au/pbs/home 2. Chi KN et al. N Engl J Med 2019;381:13—24. 3. Chi K et al. J Clin Oncol 2021;39:2294—2303. Further information is available on request from Janssen-Cilag Pty Ltd, ABN 47 000 129 975, 1-5 Khartoum Road, Macquarie Park NSW 2113. Ph: 1800 226 334. ERLYAND® is a registered trademark of Janssen-Cilag Pty Ltd. CP-387406 EMVERL0367 Date of preparation: October 2024

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Pathologic and short-term oncologic outcomes of prostate cancer patients following transvesical robot-assisted radical prostatectomy

Authors: Benidir T et al.

Summary: This retrospective (2015-22) single-surgeon review assessed prospectively collected data from 169 patients with low- and intermediaterisk prostate cancer undergoing single-port transvesical (n = 85) or multiport transperitoneal (n = 84) radical prostatectomy. The 2 groups had similar final Gleason Grades, T stage, rates of adverse pathological features and positive surgical margins. Despite a lower median number of nodes in the single-port cohort (2; 95% Cl 0-5) versus the multi-port cohort (6; 95% Cl 4-9; p \leq 0.001), there was no difference in rates of lymph node invasion. After a median follow-up of 12 months, there were no differences in biochemical recurrence-free survival rates. Surgical approach was not an independent predictor of biochemical recurrence (HR 0.53; 95% Cl 0.13-2.23).

Comment: Transvesical single-port prostatectomy has been promoted as a potential alternative to transperitoneal Retzius-sparing surgery in patients with a hostile abdomen or pelvis who prioritise continence preservation. This small retrospective series from the US shows that at least in expert hands, similar oncological outcomes (positive surgical margins, biochemical recurrence at 1 year) can be achieved in selected patients with low- or intermediate-risk disease. A disadvantage was limited access to the pelvic side wall, which significantly reduced the number of resected nodes in patients undergoing a PLND (important if you believe in these things). Functional outcomes aren't reported, nor are complication rates, a significant limitation given that they are likely to require an indwelling catheter for longer with the vesicostomy. Seems like a lot of effort though.

Reference: Urol Oncol. 2024;42(11):370.e15-370.e21

<u>Abstract</u>

Healthy lifestyle and prostate cancer risk in the Million Veteran Program

Authors: Pagadala MS et al.

Summary: This analysis of data from the Million Veteran Program examined the impact of a healthy lifestyle on prostate cancer risk. After adjustment for ancestry, family history, and genetic risk, an increased risk of metastatic (HR 1.83; 95% Cl 1.64-2.02; p < 10^{-16}) and fatal (HR 2.73; 95% Cl 2.36-3.25; p < 10^{-16}) prostate cancer was associated with smoking. A reduced risk of fatal prostate cancer was associated with exercise (HR 0.86; 95% Cl 0.76-0.98; p = 0.03). A higher BMI was associated with a reduced risk of fatal prostate cancer, but diet was not associated with any endpoint. The association with exercise was strongest among those with nonmetastatic prostate cancer at enrolment. Absolute reductions in risk of fatal prostate cancer for smoking were higher in men of African ancestry (6.1% vs 1.7%) or those at higher genetic risk (4.3% vs 1.4%).

Comment: Men are always keen to know if there are any steps they can take to reduce their risk of lethal prostate cancer. This large prospective cohort study of self-reported lifestyle factors at baseline suggests that once heritable risk is controlled for, smoking is associated with an increased risk of metastatic and lethal prostate cancer, whereas exercise is protective. The absolute risk reduction is highest in those with a higher a priori risk (African ancestry, high polygenic risk scores), suggesting any intervention could be targeted to these groups. However, the associations are unlikely to be casual (for instance there is no increase in smoking-related DNA mutational signatures in lethal prostate cancer genomes), but more likely reflect overall approach to health care. So, if you exercise more, you are more likely to be interested in other ways of maintaining health in the long term, and so may be more likely to have a PSA screening test. Smokers, not so much.

Reference: Cancer 2024;130(20):3496-3505

<u>Abstract</u>

Performance of 4Kscore as a reflex test to prostate-specific antigen in the GÖTEBORG-2 Prostate Cancer Screening Trial

Authors: Josefsson A et al.

Summary: The GÖTEBORG-2 prostate cancer screening trial examined whether adding the 4Kscore (total PSA, free PSA, intact PSA, and human kallikrein-2 enzyme) as a reflex test to PSA screening in 571 men with PSA \geq 3.0 ng/mL would improve rates of prostate cancer detection at MRI. The 4Kscore area under the curve that identified intermediate-and high-risk prostate cancer was 0.84 (95% CI 0.79-0.89), with a positive predictive value of 15% (95% CI 0.12-0.20), and a negative predictive value of 99% (95% CI 97-100). Among 54 men with intermediate- or high-grade prostate cancer, 2 had a 4Kscore cut-off below 7.5%, both of whom had organ-confined intermediate-risk prostate cancer. Per 1000 elevated PSA screening results, the 4Kscore would have avoided MRI in 408 men (41%), biopsies in 95 men (28% reduction), and low-grade cancer detection in 23 men (23% reduction), while delaying diagnosis in 4 men (4%) with intermediate-grade cancer.

Comment: In Australia, before an MRI is subsidised for evaluation of an elevated PSA, a repeat PSA plus a free/total (F/T) PSA ratio is used as a reflex test to improve specificity in a decision that was based on expert opinion. This is validated by this study nested within the GOTEBORG-2 screening study (evaluating screening PSA followed by MRI in those ≥3 ng/mL and cognitive targeting of positive lesions), which investigated the impact of a reflex 4K score (total PSA, free PSA, intact PSA, and human kallikrein-2 enzyme) on rates of progression to MRI/biopsy in men with an elevated PSA. Incorporation of a 4K threshold reduced the number of men requiring an MRI by over 40%, as well as those progressing to a biopsy by 28%, with significant potential savings to the healthcare system. Reflex PSA with free/total PSA ratio within 1-3 months is likely to have a similar impact.

Reference: Eur Urol. 2024;86(3):223-229

Abstract

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Authors: Tobing E et al.

Summary: This meta-analysis examined the prognostic impact of the Prognostic Nutritional Index (PNI) on survival outcomes in 2229 patients diagnosed with prostate cancer across 13 studies. Pooled data analysis suggested that low PNI was associated with shorter OS (adjusted HR [aHR] 1.99; 95% CI 1.45-2.72; p < 0.0001], and PFS (aHR 1.97; 95% CI 1.55-2.51; p < 0.00001). Sub-group analysis suggested the ability of PNI to predict poor outcomes was clearer for patients with mCRPC and those receiving ARPIs.

Comment: The PNI, based on measurement of serum albumin and total lymphocyte count, was developed over 40 years ago to predict the risk of complications in patients undergoing gastrointestinal surgery. Since then, it has been shown to have some prognostic utility in a diverse array of tumour types, which is perhaps intuitive, given its an overall indicator of nutritional status and systemic immune competence. This metaanalysis of retrospective studies in which PNI was linked to outcomes in various clinical scenarios (localised disease to mCRPC) suggests lower PNI is associated with shortened PFS and OS. Likely true, particularly in advanced disease, but the robustness of the findings is tempered by the relatively low quality of studies included in the analysis.

Reference: Clin Genitourin Cancer 2024;22(5):102142

Abstract

Correlation analyses of radiographic progression-free survival with clinical and health-related quality of life outcomes in metastatic castration-resistant prostate cancer: Analysis of the phase 3 VISION trial

Authors: Morris MJ et al.

Summary: This *post hoc* analysis of the VISION study (N = 831) examined correlations between OS and rPFS and between rPFS or OS and time to symptomatic skeletal events (SSE) and health-related quality of life (HRQoL; Functional Assessment of Cancer Therapy-Prostate [FACT-P] and 5-level EQ-5D [EQ-5D-5L]) in men with PSMA-positive mCRPC. Overall, rPFS was strongly correlated with OS (p \geq 0.7), whereas correlations between rPFS or OS and time to SSE without death were weak or mild. Time to worsening overall FACT-P total score and emotional and physical well-being domains were mildly or moderately correlated with rPFS and moderately correlated with OS. Correlations with time-to-worsening EQ-5D-5L scores were mild to moderate for rPFS and OS.

Comment: The primary endpoint in cancer trials would ideally be a good surrogate for the 'total disease impost' experienced by the patient. OS is often thought of as the gold standard; however, this may be misleading, particularly if life-extending interventions prolong the pre-terminal, symptomatic phase of disease, when many patients may be happy to trade overall time gained for maintaining a better HRQoL as long as possible. This *post hoc* analysis of the VISION study showed that although rPFS correlated well with OS, the correlation with symptomatic deterioration and HRQoL was much weaker. Is it time to develop more patient-centred primary endpoints for trials?

Reference: Cancer 2024;130(20):3426-3435

Abstract







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