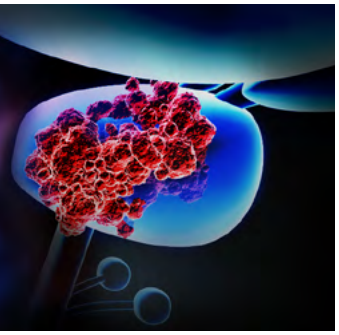
Prostate Cancer Research Review™



Making Education Easy

Issue 79 - 2024

In this issue:

Abbreviations used in this issue:

^{177}Lu = Lutetium-177; **^{68}Ga** = Gallium-68; **ADT** = androgen-deprivation therapy; **CI** = confidence interval; **CT** = computed tomography; **GI** = gastrointestinal; **GU** = genitourinary; **HR** = hazard ratio; **ISUP** = International Society for Urological Pathology; **mCRPC** = metastatic castration-resistant prostate cancer; **mCSPC** = metastatic castration-sensitive prostate cancer; **MFS** = metastasis-free survival; **OS** = overall survival; **PCSM** = prostate cancer-specific mortality; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RCT** = randomised controlled trial; **RR** = rate ratio; **RT** = radiotherapy; **SBRT** = stereotactic body radiation therapy.

Follow us at:

Welcome to Issue 79 of Prostate Cancer Research Review.

Findings from the RADICALS-HD randomised controlled trial published in The Lancet report that adding 6 months of ADT to postoperative bed radiotherapy after prostatectomy for biochemically recurrent prostate cancer does not improve metastasis-free survival compared with no ADT. In another analysis of that study, also published in The Lancet, compared with adding 6 months of ADT, adding 24 months of ADT improved metastasis-free survival in these men. We conclude this issue with an interesting longitudinal US study showing that higher intake of plant foods after prostate cancer diagnosis was associated with a lower risk of cancer progression.

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
niall.corcoran@researchreview.com.au

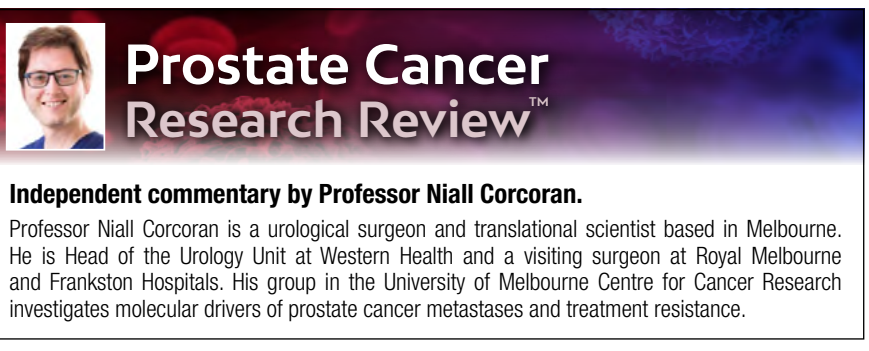
Covalent targeted radioligands potentiate radionuclide therapy

Authors: Cui X-Y et al.

Summary: This experimental study assessed the use of a sulphur (VI) fluoride exchange (SuFEx) chemistry-based linker on radiopharmaceuticals for targeted radionuclide therapy to prevent rapid tumour clearance. After binding to a tumour-specific protein, a binding-to-ligation transition leads to conjugation with tyrosine residues through a 'click' SuFEx reaction. In a fibroblast activation protein inhibitor (FAPI) model this process achieved >80% covalent binding to the protein and almost no dissociation over 6 days. In a mouse model, SuFEx-engineered FAPI had a 2.57-fold greater tumour uptake than standard FAPI and increased tumour retention 13-fold. In healthy tissues FAPI was rapidly cleared. In an imaging study, more tumour lesions were identified in cancer patients than with other methods. SuFEx-engineered FAPI in mice achieved targeted β- and α-radionuclide therapy, causing nearly complete tumour regression. A SuFEx-engineered radioligand targeting PSMA also had enhanced therapeutic efficacy.

Comment: Radioligand therapies, such as ^{177}Lu-PSMA, rely on selective binding and retention of the payload specifically within tumour cells. Cell killing activity can be undermined by the reversible nature of these ligand-receptor interactions leading to rapid clearance, which also increases the risk of off target effects. Using some neat chemistry, this Chinese group have developed a radiolabelled ligand that covalently bind to the receptor, dramatically increasing intra-tumour retention, which they demonstrate improved the detection of metastatic disease in patients with medullary thyroid cancer using ^{68}Ga-labelled FAPI. They also show increased activity of a covalently targeted ^{177}Lu-PSMA construct in prostate cancer xenografts, although no corresponding patient data is presented. An intriguing approach, but one must be concerned about the potential for increased adverse events such as dry mouth.

Reference: Nature 2024;630(8015):206-213
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.

Adding 6 months of androgen deprivation therapy to postoperative radiotherapy for prostate cancer: A comparison of short-course versus no androgen deprivation therapy in the RADICALS-HD randomised controlled trial

Authors: Parker CC et al.

Summary: The multinational randomised controlled RADICALS-HD trial assessed the use of ADT in combination with postoperative radiotherapy (RT) for prostate cancer in 1480 patients (median age 66 years) receiving no ADT (n = 737) or short-course ADT (n = 743) in addition to RT. Over a median follow-up of 9.0 years, metastasis-free survival (MFS) events occurred in 142 no ADT and 126 short-course ADT recipients (HR 0.886; 95% CI 0.688-1.140). Ten-year metastasis-free survival was 79.2% (95% CI 75.4-82.5) with no ADT and 80.4% (95% CI 76.6-83.6) with short-course ADT. Toxicity of grade ≥3 was reported in 17% of no ADT and 14% of short-course ADT recipients; there were no treatment-related deaths.

Comment: The suite of RADICALS trials has dramatically changed our approach to the use of radiation post-prostatectomy, most notably the shift away from adjuvant to early salvage therapy based on RADICALS-RT. Given that concomitant ADT improves MFS and OS in patients undergoing primary radiotherapy for higher risk, clinically localised disease, it is an open question whether a similar benefit is observed in the salvage setting. RADICALS-HD assessed the role of concomitant ADT on metastasis-free survival in patients with prostate cancer undergoing adjuvant or salvage RT following prostatectomy. In this first report, the investigators analysed MFS in patients randomised to either no ADT or 6 months of concomitant ADT in those treated with postoperative prostate bed RT (~29% adjuvant, ~71% early salvage). Although short-course ADT improved PFS (like RTOG 0534), MFS was not different between the groups. Given the low rates of true high-risk patients enrolled, as well as the inclusion of patients treated in the adjuvant setting, a role in the salvage setting (particularly when combined with pelvic nodal irradiation) cannot be ruled out.

Reference: Lancet 2024;403(10442):2405-2415
Abstract

Duration of androgen deprivation therapy with postoperative radiotherapy for prostate cancer: A comparison of long-course versus short-course androgen deprivation therapy in the RADICALS-HD randomised trial

Authors: Parker CC et al.

Summary: This analysis of RADICALS-HD assessed the use of short-course (6 months; n = 761) versus long-course (24 months; n = 762) ADT with postoperative RT after radical prostatectomy. Over a median follow-up of 8.9 years, 174 MFS events were reported in the short-course ADT cohort and 139 in the long-course ADT cohort (HR 0.773; 95% CI 0.612-0.975). The 10-year MFS rate was 71.9% (95% CI 67.6-75.7) with short-course ADT and 78.1% (95% CI 74.2-81.5) with long-course ADT. Toxicity of grade ≥3 occurred in 14% of short-course ADT and 19% of long-course ADT recipients; no treatment-related deaths were reported.

Comment: Following on from the previous report, this second analysis reports MFS in patients randomised to 24 months compared to 6 months of ADT. In contrast to the first study, patients in this cohort had higher-risk disease, with 29% and 30% having >ISUP 4 and > pT3b disease respectively, and the use of RT in the adjuvant setting (43%) was also higher. The metastasis rate was subsequently higher (including in the short-course group in comparison to the first trial). Treatment with long-course ADT improved both PFS and MFS, which for the latter translated into an absolute benefit at 10 years of 6%, although this may be more for higher-risk patients. However, there was no significant difference in OS at 10 years with an around 1% risk of prostate cancer death for the cohort, so potential benefits must be weighed against the well-known harms of prolonged ADT in individual patients.

Reference: Lancet 2024;403(10442):2416-2425
Abstract

Prostate-specific antigen screening and 15-year prostate cancer mortality: A secondary analysis of the CAP randomized clinical trial

Authors: Martin RM et al.

Summary: This secondary analysis of the UK-based Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) clinical trial assessed the benefit of an invitation for PSA screening versus no invitation for screening on prostate cancer-specific mortality in 415,357 eligible men. At 15-year follow-up, 12,013 men in the intervention and 12,958 in the control group had a prostate cancer diagnosis; cumulative risk was 7.08% (95% CI 6.95-7.21) versus 6.94% (95% CI 6.82-7.06). At a median 15-year follow-up, 0.69% of the intervention group (95% CI 0.65-0.73) and 0.78% of the control group (95% CI 0.73-0.82) died of prostate cancer (RR 0.92; 95% CI 0.85-0.99; p = 0.03). PSA screening increased the detection of low-grade (Gleason score [GS] ≤6: 2.2% vs 1.6%; p < 0.001) and localised (T1/T2: 3.6% vs 3.1%; p < 0.001) tumours but not other tumour grades. There were 45,084 all-cause deaths in intervention recipients (23.2%; 95% CI 23.0-23.4) and 50,336 deaths in control recipients (23.3%; 95% CI 23.1-23.5; RR 0.97; 95% CI 0.94-1.01). Eight (0.7%) prostate cancer deaths in the intervention group and 7 (0.5%) in the control group were related to diagnostic biopsy or treatment.

Comment: Another day, another population-based screening trial showing PSA testing reduces prostate cancer mortality, but at a cost. This was an updated analysis of the UK CAP trial, a primary care-based cluster randomised trial that tested the effects of a single invitation for a PSA test (subsequent invitation for further investigation of PSA >3.0 ng/mL) compared with usual care in men aged 50-69 years. The primary outcome of OS at 10 years was previously reported, with no difference observed between the groups. This secondary analysis, with follow-up out to 15 years, does show a small but significant reduction in prostate cancer mortality, but no impact upon OS. Interestingly, the cumulative incidence of prostate cancer diagnosis was similar at 15 years, although diagnosis in the intervention group was heavily skewed towards the first 18 months as expected.

Reference: JAMA 2024;331(17):1460-1470
Abstract

Prognostic impact of prostate-specific antigen at 6 months after radiotherapy in localized prostate cancer: An individual patient data analysis of randomized trials

Authors: Kwak L et al.

Summary: This pooled analysis of patient data from 16 randomised trials evaluated the prognostic impact of PSA at 6 months after RT in patients treated with RT alone (n = 2376), RT plus short-term ADT (3-6 months; n = 5658), and RT plus long-term ADT (24-36 months; n = 1626). PSA was ≥0.1 ng/mL within 6 months after completing RT in 98% of patients on RT alone, 84% of those allocated to RT plus short-term ADT, and 77% of those on RT plus long-term ADT. Among recipients of RT with or without ADT, a PSA ≥0.1 ng/mL was associated with lower MFS (HR 2.24; 95% CI 1.21-4.16) and OS (HR 1.72; 95% CI 0.97-3.05) and higher prostate cancer-specific mortality (PCSM; HR 1.82; 95% CI 0.51-6.49), as was the case in RT short-term ADT recipients (MFS HR 1.27; 95% 1.12-1.44; OS HR 1.26; 95% CI 1.11-1.44; PCSM HR 2.10; 95% CI 1.52-2.92) and RT plus long-term ADT recipients (MFS HR 1.58; 95% CI 1.27-1.96; OS HR 1.59; 95% CI 1.27-1.99; PCSM HR 1.97; 95% CI 1.11-3.49). In patients sub-grouped by PSA < or ≥0.1 ng/mL, 5-year MFS rates were 91% versus 79%, 83% versus 76%, and 87% versus 74% in RT with or without ADT, RT short-term ADT and RT plus long-term ADT recipients, respectively.

Comment: PSA levels can be hard to interpret after primary RT, but in general the lower the nadir the better the expected outcomes. This is emphasised by this analysis from Chris Sweeney, which analysed individual patient level data from multiple RCTs, dichotomising outcomes based on achieving a nadir PSA <0.1 ng/mL after radiation alone or in combination with short- or long-course ADT within the first 6 months of treatment. Patients who achieved an 'undetectable' PSA had better MFS, prostate cancer-specific survival and OS compared to those who failed to achieve this benchmark. This observation was consistent regardless of ADT strategy but was achieved much more frequently in patients receiving some form of adjuvant ADT.

Reference: J Clin Oncol. 2024;42(18):2132-2138
Abstract

Multivitamin use after diagnosis and prostate cancer survival among men with nonmetastatic prostate cancer

Authors: Zhang Y et al.

Summary: This analysis of data from the Health Professionals Follow-up Study (1986-2016) prospectively assessed post-diagnostic multivitamin use and prostate cancer survival among 4756 men with nonmetastatic prostate cancer. Over median follow-up of 11 years, there were 438 lethal prostate cancer diagnoses and 2609 deaths. After adjustment for potential confounders, post-diagnostic multivitamin use was not associated with risk of lethal prostate cancer (HR 0.98; 95% CI 0.74-1.30) or all-cause mortality (HR 1.00; 95% CI 0.88-1.12). Men who used multivitamins regularly (6-9 tablets/week) after cancer diagnosis had similar risk of lethal prostate cancer (HR 0.96; 95% CI 0.72-1.28]) and all-cause mortality (HR 0.99; 95% CI 0.88-1.12).

Comment: For many years it was promulgated that multivitamins, full of antioxidants, co-enzymes and hormonal regulators, were the key to a long and healthy life. This changed almost 15 years ago, as a number of RCTs (notably Physicians Health Study II) demonstrated modest if any benefits in well-nourished participants across a wide range of clinical outcomes. This retrospective analysis of data from the well-known Health Professionals Follow-up Study finds that in men diagnosed with non-metastatic prostate cancer, subsequent use of multivitamins had no impact on subsequent risk of cancer death or OS. Useful for counselling patients, if only to save them a little money.

Reference: Br J Cancer 2024;130(10):1709-1715
Abstract

Psoas mass index at the level of the third lumbar vertebra on computed tomography is a prognostic predictor for metastatic castration-sensitive prostate cancer

Authors: Owa S et al.

Summary: This retrospective study (2005-21) examined the association between mCRPC and psoas muscle parameters determined at the level of the third lumbar vertebra by non-contrast CT in 121 patients with N1 and/or M1 mCRPC who underwent primary ADT. Over a median follow-up of 56.9 months, 67.7% of patients progressed to castration-resistant prostate cancer and 43.8% patients died. Multivariate analysis suggested that castration-resistant prostate cancer-free survival and OS differed by Gleason score, clinical N-stage, and psoas muscle index (median cut off 3.044 cm^2/m^2).

Comment: Sarcopenia is an important contributor to patient frailty and is associated with poorer outcomes across a wide range of cancer types, including prostate cancer. Most of the studies in prostate cancer are in mCRPC, where both tumour factors and prolonged ADT can contribute to muscle atrophy. This small retrospective study attempts to deconvolve this by measuring psoas muscle mass in patients with regional or metastatic disease prior to commencing hormonal therapy, finding significant negative associations between psoas muscle bulk and castration resistance progression-free and OS. Would have been interesting to know if there was any correlation with burden of metastatic disease at diagnosis.

Reference: Int J Clin Oncol. 2024;29;840-846
Abstract

Prostate-specific antigen response to androgen deprivation therapy in the neoadjuvant setting for high-risk prostate adenocarcinoma (PIRANHA): Pooled analysis of two randomized clinical trials

Authors: Nikitas J et al.

Summary: This *post hoc* pooled analysis of the multicentre Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) and Prostate Cancer Study (PCS) IV randomised clinical trials assessed the prognostic impact of poor PSA response to neoadjuvant ADT in 930 men with high-risk prostate cancer. At a median of 3 months of neoadjuvant ADT, median PSA was 0.60 ng/mL, with 535 men (57%) having a PSA >0.5 ng/mL. Poor PSA response was associated with worse MFS (HR 3.93; p = 0.02), biochemical recurrence (HR 2.39; p = 0.003), PCSM (HR 1.50; p = 0.005), and OS (HR 4.51; p = 0.05).

Comment: Modern RT for high-risk prostate cancer has two components: ADT to downsize tumour volume, sensitise tumour cells to ionising radiation, and potentially eliminate regional micro-metastatic disease; and the radiation itself. But what if ADT doesn't work that well? This pooled analysis of two RCTs demonstrates that poor response to neoadjuvant ADT as measured by a PSA >0.5 ng/mL after 3 months of treatment was associated with significantly worse oncological outcomes, including OS. The authors suggest that this should be an indication for treatment intensification (adding an androgen receptor signalling inhibitor for instance), but given the MFS curves only begin to separate after 72 months, changing tack and taking the prostate out might also be appropriate.

Reference: Int J Radiat Oncol Biol Phys. 2024;119(3):826-831
Abstract

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.

Kindly Supported by

Australian Prostate Centre apc

ANZUP Cancer Trials Group Limited

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.

PEACE V—Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM): Acute toxicity of a randomized phase 2 trial

Authors: Ost P et al.

Summary: The multinational, open-label, randomised, phase II, PEACE V-Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases (STORM) trial compared acute toxicity and quality of life (QoL; European Organisation for Research and Treatment of Cancer QLQ C30 and PR25 questionnaires) between metastasis-directed therapy (MDT) with or without elective nodal pelvic radiotherapy (ENRT) in 196 patients, with 97 MDT and 93 ENRT patients receiving per-protocol treatment. Worst acute GI toxicity included grade ≥2 events in 3 (3%) MDT versus 4 (4%) ENRT recipients, while worst acute GU toxicity included grade ≥2 events in 8 (8%) MDT versus 12 (13%) ENRT recipients. There were no differences in the proportion of patients with a clinically significant QoL reduction for any subdomain score area.

Comment: The STORM study is an international multicentre salvage study, which includes sites in Melbourne led by Shankar Siva. This phase II randomised study aims to determine if in patients with oligo-recurrent pelvic nodal disease (5 or fewer nodal metastases detected by PET imaging) who have previously undergone treatment of the primary (RT or radical prostatectomy), 6 months of ADT plus metastasis directed therapy (SBRT or salvage PLND) is superior to ADT plus ENRT (plus a boost to imaged nodal metastasis) as measured by MFS. To date, the data is immature for the primary endpoint, and this initial report focusses on acute toxicity and patient QoL 3 months post-treatment, which was broadly similar between the two groups. The MFS data are keenly awaited, but one can't help feeling that whole pelvis radiation will win out.

Reference: Eur Urol Oncol. 2024;7(3):462-468
Abstract

Plant-based diets and disease progression in men with prostate cancer

Authors: Liu VN et al.

Summary: This longitudinal study, using data from men with biopsy-proven non-metastatic prostate cancer (stage ≤T3a) enrolled in the diet and lifestyle sub-study within the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), investigated whether post-diagnostic plant-based dietary patterns are associated with risk of prostate cancer progression and prostate cancer-specific mortality. CaPSURE enrolled men from 43 urology practices across the US from 1999 to 2018 and a total of 2062 men (median age 65 years; 95% White; 3% African American; <1% American Indian or Alaska Native; <1% Asian or Pacific Islander; 1% Latino) were included in this analysis. Participants completed a comprehensive diet and lifestyle questionnaire (including a validated food frequency questionnaire [FFQ]) between 2004 and 2016. From the FFQ, overall Plant-based Diet Index (PDI) and Healthful Plant-Based Diet Index (hPDI) scores were calculated. The median time from prostate cancer diagnosis to FFQ was 31.3 months. A total of 190 prostate cancer progression (recurrence, secondary treatment, bone metastases, or prostate cancer-specific mortality) events occurred during a median follow-up of 6.5 years. A 47% lower risk of prostate cancer progression was observed for men scoring in the highest versus lowest quintile of PDI (HR 0.53; 95% CI 0.37-0.74; p for trend 0.003). While there was no association observed between hPDI and risk of progression overall, among 680 individuals with Gleason grade ≥7 at diagnosis, the highest hPDI quintile was associated with a 55% lower risk of progression compared with the lowest hPDI quintile (HR 0.45; 95% CI 0.25-0.81; p for trend 0.01); there was no association for those with Gleason grade <7.

Comment: The old saying about vegetarianism is that while it might not make you live forever, it can certainly make you feel like you are! This longitudinal cohort study embedded within CaPSURE in the US assessed the association between a post diagnosis plant-based diet using a patient-reported food-frequency questionnaire and prostate cancer progression in patients with non-metastatic prostate cancer. Patients in the cohort had almost exclusively low- or intermediate- risk disease, with two-thirds undergoing prostatectomy, and most of the remainder some form of radiation. The authors report an association between increasing plant-based dietary intake and prostate cancer progression (a composite of biochemical recurrence, secondary treatment, metastases and death), which persisted even after adjustment for other known clinical and pathological prognostic variables. There was no significant association with prostate cancer mortality however, and there was no clear dose-response, which makes it harder to instruct patients to eat their greens.

Reference: JAMA Netw Open 2024;7(5):e249053
Abstract

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.