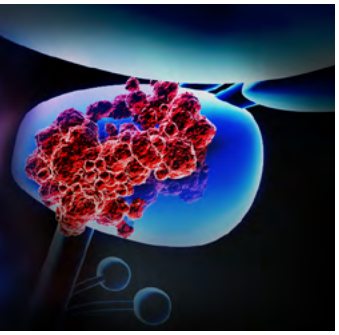
Prostate Cancer Research Review™



Making Education Easy

Issue 77 - 2024

In this issue:

Abbreviations used in this issue:

ADT = androgen-deprivation therapy; **BMI** = body mass index; **CRPC** = castration resistant prostate cancer; **CSPC** = castration-sensitive prostate cancer; **DRE** = digital rectal exam; **EBRT** = external beam radiotherapy; **GG** = grade group; **IL** = interleukin; **ISUP** = International Society of Urological Pathology; **mCRPC** = metastatic castration-resistant prostate cancer; **MRI** = magnetic resonance imaging; **OR** = odds ratio; **OS** = overall survival; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSMA** = prostate-specific membrane antigen; **RR** = relative risk.

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Welcome to Issue 77 of Prostate Cancer Research Review.

In a phase 2/3 imaging trial, ^{68}Ga-RM2 PET–MRI showed better diagnostic performance than MRI alone in patients with biochemical recurrence of prostate cancer. In the PRESTO study, intensified androgen receptor blockade with apalutamide prolonged progression-free survival without impacting testosterone recovery in men with biochemically recurrent prostate cancer. We conclude this issue with a first-in-human study of acapatamab, a half-life extended, PSMA-targeting bispecific T-cell engager for metastatic castration-resistant 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,

Professor Niall Corcoran
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^{68}Ga-RM2 PET-MRI versus MRI alone for evaluation of patients with biochemical recurrence of prostate cancer: A single-centre, single-arm, phase II/III imaging trial

Authors: Duan H et al.

Summary: This single-centre, single-arm, phase II/III trial assessed the diagnostic performance of a gastrin-releasing peptide receptors (GRPR)-targeting tracer ^{68}Ga-RM2 in PET-MRI in 100 men with prostate cancer biochemical recurrence. Over a median follow-up of 49.3 months, ^{68}Ga-RM2 PET-MRI was positive in 69% of patients versus 20% positive by MRI alone ($p < 0.0001$). In per-lesion analysis ^{68}Ga-RM2 PET-MRI had higher detection rates than MRI alone (143 vs 96 lesions; $p < 0.0001$).

Comment: Up to 10% of prostate tumours do not express PSMA, so there is increasing interest in identifying other potential markers that may be targeted for imaging or therapy. One of these is GRPR, which is aberrantly overexpressed on the cell surface of prostate cancer. This single-arm study compared the rates of disease detection by PET-MRI using a radiolabelled GRPR ligand compared to MRI alone in patients with biochemical recurrence post-surgery or radiation and negative conventional imaging. Compared with whole body MRI with contrast enhanced delayed imaging of the pelvis, ^{68}Ga-RM2 PET-MRI was more sensitive for disease detection, largely driven by better detection of local recurrence and lymph node metastases. Interesting findings, but we really need a head-to-head comparison with PSMA targeted imaging to clarify incremental benefit.

Reference: Lancet Oncol. 2024;25(4):501-508
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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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.

PRESTO: A phase III, open-label study of intensification of androgen blockade in patients with high-risk biochemically relapsed castration-sensitive prostate cancer (AFT-19)

Authors: Aggarwal R et al.

Summary: This randomised, open-label, phase III trial evaluated whether ADT intensification improved outcomes in 503 patients with biochemically recurrent prostate cancer (BRPC) after radical prostatectomy comparing ADT control, ADT plus apalutamide, or ADT plus apalutamide plus abiraterone acetate plus prednisone (AAP). At a first interim analysis, compared with controls, PSA progression-free survival (PSA-PFS; serum PSA >0.2 ng/mL) was prolonged in ADT plus apalutamide recipients (median 24.9 vs 20.3 months; HR 0.52; 95% CI 0.35-0.77; p = 0.00047) and ADT plus apalutamide plus AAP recipients (median 26.0 vs 20.0 months; HR 0.48; 95% CI 0.32-0.71; p = 0.00008). Median time to testosterone recovery did not differ between treatments. Hypertension was the most common grade ≥3 adverse event in ADT, ADT plus apalutamide, and ADT plus apalutamide plus AAP recipients (7.5% vs 7.4% vs 18%).

Comment: The EMBARK study previously showed that treatment intensification of men with high-risk biochemical recurrence (PSA doubling time <9 months) with a combination of ADT pus enzalutamide following radical prostatectomy +/- salvage radiation improved metastasis-free survival (MFS) compared to ADT alone. This similar study reports on the impact of 52 weeks of ADT plus apalutamide or ADT plus apalutamide plus abiraterone on PSA-PFS compared to ADT alone in essentially the same clinical population. Treatment intensification delayed time to PSA progression (the primary study endpoint) in both groups compared to ADT, which is not unexpected considering the previous findings. However, the additional benefit of using two novel hormonal agents was incremental and offset somewhat by an increased grade 3/4 toxicity. Data on more impactful outcomes such as MFS are awaited.

Reference: J Clin Oncol. 2024;42(10):1114-1123
Abstract

Pelvic irradiation for node-positive prostate cancer after prostatectomy: Long-term results of the prospective PLATIN-4 and PLATIN-5 trials

Authors: Fink CA et al.

Summary: These two small phase II trials assessed the use of salvage radiation therapy (RT) to the pelvic lymph nodes in 78 patients with node-positive prostate cancer after radical prostatectomy (PLATIN-4 trial) or after radical prostatectomy and prostate bed radiation therapy (PLATIN-5 trial), who received salvage pelvic lymph node RT with boost to involved nodes as field abutment (PLATIN-5) or boost to the prostate bed (PLATIN-4). ADT was commenced 2 months before radiation and continued for 24 months. Median OS was not reached in PLATIN-4 and 117 months in PLATIN-5, and median PFS was 66 months and 39 months. Late grade >3 genitourinary and gastrointestinal toxicities occurred in 4% of patients at 24 months.

Comment: There is a paucity of long-term prospective data on the utility of pelvic side wall irradiation in patients with residual/recurrent nodal disease following radical prostatectomy with a lymph node dissection. This German report synthesises data from two prospective phase II studies which investigated the efficacy of pelvic nodal basin irradiation (including a boost to positive nodes on conventional imaging or PSMA-PET) in combination with 2 years of ADT for lymph node recurrence after prostatectomy, with or without previous adjuvant/salvage prostate bed irradiation. Although the populations of both trials differed in terms of their risk of undetected systemic disease, a significant proportion remained disease free after irradiation in both cohorts suggesting it can produce long-term disease control in selected patients. The strongest predictor of failure in both groups was involvement of common iliac nodes.

Reference: Int J Radiat Oncol Biol Phys. 2024;118(4):1011-1017
Abstract

The association of body mass index with tumor aggression among men undergoing radical prostatectomy

Authors: Gregg JR et al.

Summary: This study examined the association of preoperative BMI with adverse pathology in peripheral and transition zone tumours in 923 patients undergoing prostatectomy for localised prostate cancer. Overall, 15% of patients had "normal" BMI (18.5-24.9 kg/m^2), 45% were "overweight" (25-29.9 kg/m^2), and 40% were "obese" (>29.9 kg/m^2) while 51% of patients had aggressive peripheral zone tumours and 11% had aggressive transition zone tumours. An "obese" BMI was not associated with aggressive transition zone tumours compared to a “normal” weight; however, increasing BMI was associated with an increased risk of aggressive peripheral zone tumours (HR 1.56; 95% CI 1.04-2.34; p = 0.03). In patients with grade group (GG) 1 or GG2 tumours, increasing BMI was associated with pT3a or greater transition zone tumours (p = 0.03).

Comment: The association of increased BMI with more aggressive prostate cancer is well documented, attributed both to underestimation of disease risk in obese men (low relative PSA levels due to haemodilution; DRE less sensitive) as well as an increase in molecular drivers of progression (for instance, IL-6). This observation is further supported by this case series from MD Anderson, where increasing BMI category was associated with an increased risk of aggressive disease, defined as either ISUP GG >3 or pT >3a. The more interesting observation is the distribution of BMIs in patients undergoing RARP at this centre – only 15% were normal weight, and 40% were obese or higher. Testing times in Texas.

Reference: Urol Oncol. 2024;42(4):116.e1-116.e7
Abstract

Focal therapy with high-intensity focused ultrasound for prostate cancer: 3-year outcomes from a prospective trial

Authors: Kaufmann B et al.

Summary: This 3-year, multicentre, prospective study used periodic post-ablation saturation biopsies to assess outcomes of focal high-intensity focused ultrasound (HIFU) in 91 patients with localised prostate cancer (6 with GG1 and 85 GG ≥2). Overall, 83 (91%) patients received at least one follow-up biopsy, with biopsy attendance rates at 6, 12, and 36 months of 84%, 67%, and 51%. Failure-free survival (FFS) rates at 6, 12, and 36 months for any GG ≥2 prostate cancer were 79% (95% CI 80-88), 57% (95% CI 48-69) and 44% (95% CI 34-56%). Using a second definition of FFS (GG ≥3 or core involvement of ≥6 mm) rates were 88% (95% CI 81-95), 70% (95% CI 61-81) and 65% (95% CI 55-77); 3-year cancer-specific survival was 100%, and freedom from metastasis was 99%. MRI and relative decrease of PSA values were poor at detecting residual disease. Overall, 17 (21%) patients reported worsening erectile function.

Comment: A consistent criticism of data in support of focal therapy is that most of the outcomes reported are based on short-term follow-up in patients with reasonably indolent disease. Addressing, at least in part, the latter, the authors report on 3-year outcomes for patients with low/intermediate risk disease (67% ISUP GG2; 24% ISUP GG3) treated with HIFU (up to 2 lesions) in a multicentre prospective study. As expected, reported functional outcomes were excellent, with little change to baseline urinary or sexual function. However less than half of patients remained free of ISUP GG2 disease at 3 years, with almost 20% progressing to whole gland or systemic therapy. An additional concern is that MRI post HIFU has poor test performance for detecting recurrent disease. Caveat emptor.

Reference: BJU Int. 2024;133(4):413-424
Abstract

Effects of androgen deprivation therapy on prostate cancer outcomes according to competing event risk: Secondary analysis of a phase 3 randomised trial

Authors: Mell LK et al.

Summary: This ancillary analysis of a phase III trial in 1945 prostate cancer patients assessed whether a quantitative stratification method using risk for competing events (omega score) could identify subgroups that benefit from ADT. Relative risk (RR) for cancer-related versus competing mortality events (a higher omega score) was increased by T category (T2b), higher Gleason score, and higher PSA and decreased by increased age and comorbidity. Among 996 patients with low-risk/favourable intermediate-risk disease, 28.7% had a high omega score (≥0.314), while among 768 patients with unfavourable intermediate-risk disease 22.8% had a low omega score. Overall risk classification discordance was 26.1%. There were significant interactions for the effect of ADT on cancer-related events and late mortality across low- versus high-risk subgroups. Within the low-/favourable risk subgroup, a higher omega score identified patients where ADT reduced cancer events and improved event-free survival.

Comment: ADT improves the efficacy of external beam radiotherapy but comes at a cost of physiological changes that may increase the risk of death from other causes. This competing risk analysis examined data from a large, randomised control trial which showed that short course ADT improved oncological outcomes in men with low/intermediate risk disease treated with EBRT, to identify factors that select patients most likely to benefit (cancer benefits > deleterious effect on non-cancer mortality). The results are somewhat intuitive, patients with higher grade and stage disease were more likely to benefit, whereas older patients with increasing co-morbidities were less likely to benefit. Interestingly, almost 30% of patients with low/favourable intermediate risk prostate cancer were found to benefit from short course ADT, highlighting again the vagaries of trying to force continuous risk into a small number of categories.

Reference: Eur Urol. 2024;85(4):373-381
Abstract

A prospective randomized trial of neoadjuvant chemohormonal therapy vs hormonal therapy in locally advanced prostate cancer treated by radical prostatectomy

Authors: Qian H et al.

Summary: This randomised controlled trial examined whether docetaxel-based neoadjuvant chemohormonal therapy (NCHT) could improve biochemical PFS versus neoadjuvant hormonal therapy (NHT) in 141 patients with locally advanced prostate cancer. NCHT recipients experienced benefits in 3-year biochemical PFS versus NHT recipients (29% vs 9.5%; p = 0.002). After a median 53-month follow-up, NCHT recipients had a longer median biochemical PFS than NHT recipients (17 vs 14 months). There were no differences in pathological downstaging and minimal residual disease rates.

Comment: Although neo-adjuvant trials based on novel hormonal agents have shown some promising long-term results in patients achieving good pathological responses, results using neo-adjuvant chemotherapy have been generally disappointing (for instance the CALGB Alliance trial). In contrast, this randomised phase II study from China shows a significant but modest improvement in biochemical recurrence with neoadjuvant docetaxel/ADT compared to ADT alone. One clear difference is the much higher risk profile of this cohort (median PSA >90 ng/mL; ~50% cN1), suggesting the majority of patients had unmeasured metastatic disease at diagnosis. Still longer-term follow-up is needed to see if there is any meaningful effect on metastasis-free survival.

Reference: J Urol. 2024;211(5):648-655
Abstract

Intermittent versus continuous androgen deprivation therapy for biochemical progression after primary therapy in hormone-sensitive nonmetastatic prostate cancer: Comparative analysis in terms of CRPC-M0 progression

Authors: Salciccia S et al.

Summary: This retrospective study examined use of intermittent versus continuous ADT in 170 patients with biochemical progression after primary treatment in prostate cancer and the effect on development of nonmetastatic CRPC. There was no difference in CRPC progression between intermittent (25.8%) and continuous (30.5%) treatment after a mean of 32.7 and 35.6 months. Mean PSA at CRPC development was higher in intermittent ADT recipients (5.16 vs 3.1 ng/mL; p < 0.001). Univariate analysis suggested that continuous ADT administration increases the risk for CRPC progression (RR 3.48; 95% CI 1.66-7.29; p = 0.01) compared to intermittent administration; multivariate analysis confirmed an effect independent of other variables (RR 2.34; 95% CI 1.52-5.33; p = 0.03).

Comment: Intermittent ADT is a common strategy for men with biochemical progression after failed local treatment +/- salvage therapy based on decade old phase III data demonstrating non-inferior oncological outcomes (OS, disease specific survival and 'corrected' time to castration resistance) compared to continuous ADT post radiotherapy. These data are challenged by this small retrospective study which finds that continuous ADT was associated with a shorter time to non-metastatic CRPC but not metastatic CRPC compared to intermittent therapy. As well as having many methodological issues (particularly small numbers and high rates of missing data), the authors fail to 'correct' for the inherent delay in making a diagnosis of castration resistance in patients on intermittent ADT. So not particularly useful, except for confirming that in the real-world setting there is little difference between the two strategies, except perhaps the cost to the healthcare system.

Reference: Clin Genitourin Cancer 2024;22(2):74-83
Abstract

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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.

Risk factors for prostate cancer: An umbrella review of prospective observational studies and mendelian randomization analyses

Authors: Cui H et al.

Summary: This umbrella review sought to identify factors modifying the risk of prostate cancer reported in 92 meta-analyses of prospective observational studies and 64 Mendelian randomisation (MR) analyses. Overall, 45 significant observational associations and 55 significant causal associations were categorised into lifestyle; diet and nutrition; anthropometric; biomarkers; clinical variables, diseases and treatments; and environmental factors. Meta-analyses identified five highly suggestive, 36 suggestive, and four weak associations, and Mendelian randomisation studies identified 10 robust, 24 probable, four suggestive, and 17 insufficient causal associations. There were 26 overlapping factors between meta-analyses and MR studies identified, with consistent effects for physical activity in meta-analyses (OR 0.87; 95% CI 0.80-0.94) and Mendelian analyses (OR 0.49; 95% CI 0.33, 0.72), height (OR 1.09; 95% CI 1.06-1.12; OR 1.07; 95% CI 1.01-1.15 for aggressive prostate cancer), and current smoking (OR 0.74; 95% CI 0.68-0.80) or smoking initiation (OR 0.91; 95% CI 0.86-0.97).

Comment: The strongest risk factors for prostate cancer (age, family history etc.) are generally unalterable. However, in the face of rising prostate cancer incidence globally with increasing life expectancy, identification of weak but modifiable risk factors could play a major role in disease prevention. This study synthesised data from multiple meta-analyses of prospective observational studies and Mendelian randomised studies to identify robust and consistent modifiable risk factors associated with prostate diagnosis. Only 3 factors showed consistent associations with prostate cancer across the analysis, including physical activity and smoking, which were both associated with a decreased incidence (the latter possibly related to decreased testing), as well as height, which was associated with an increased incidence. Associations were reasonably weak, and apart from a recommendation to maintain physical activity throughout life, hard to implement clinically.

Reference: PLoS Med. 2024;21(3):e1004362
Abstract

A phase I study of acapatamab, a half-life extended, PSMA-targeting bispecific T-cell engager for metastatic castration-resistant prostate cancer

Authors: Dorff T et al.

Summary: In this first-in-human study, the safety and efficacy of acapatamab, a PSMA x CD3 bispecific T-cell engager (BiTE) were evaluated in patients with mCRPC refractory to androgen receptor pathway inhibitor therapy and taxane-based chemotherapy. Patients received IV acapatamab 0.003 to 0.9 mg in dose exploration (7 dose levels; n = 77) or 0.3 mg (recommended phase II dose; n = 56) in dose expansion every 2 weeks. The most common treatment-emergent adverse event was cytokine release syndrome (CRS), observed in 97.4% of patients in the dose exploration group and 98.2% of patients in the dose expansion group, with grade ≥3 CRS observed in 23.4% and 16.1%, respectively. Antidrug antibodies were seen in 55% of patients and impacted serum exposures in 36% of patients in the dose expansion group. The incidence and severity of CRS reduced after cycle one. PSA50 responses (PSA decrease of >50% compared to baseline) were observed in 30.4% of the dose expansion group and radiographic partial responses were observed in 7.4% (Response Evaluation Criteria in Solid Tumors 1.1). The median radiographic PFS (Prostate Cancer Clinical Trials Working Group 3) was 3.7 months (95% CI 2.0-5.4) and the PSA PFS was 3.3 months (95% CI 3.0-4.9). Induction of T-cell activation and a several-fold increase in cytokine production was observed within 24 hours of starting acapatamab.

Comment: BiTEs are agents that recruit endogenous anti-tumour T cells to cancer cells independent of the major histocompatibility complex leading to tumour cell kill. This phase I study led by Ben Tran from Melbourne, investigated the safety and efficacy of a CD3 specific BiTE targeting PSMA in patients with mCRPC. In the dose expansion cohort, PSA responses were seen in 30% of patients, although radiological responses were infrequent and of limited duration. Cytokine release syndrome was almost universal, although was usually mild. Although probably not relevant for this agent, I can't help thinking that the best clinical setting for immunotherapy (and potentially long-term disease control) is in patients with minimal residual disease (PSA persistence or rapid biochemical recurrence) after prostatectomy.

Reference: Clin Cancer Res. 2024;30(8):1488-1500
Abstract

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