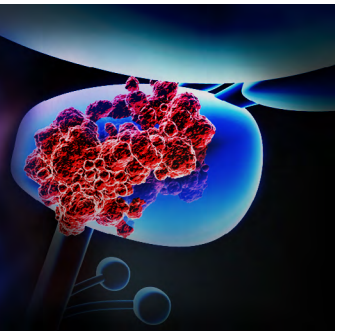
# Prostate Cancer Research Review™



Making Education Easy

Issue 74 - 2024


## In this issue:



**Abbreviations used in this issue:**

**ADT** = androgen deprivation therapy;
**ANZUP** = Australian and New Zealand Urogenital and Prostate;
**ASCO** = American Society of Clinical Oncology; **CI** = confidence interval;
**EAU** = European Association of Urology; **EBRT** = external beam radiation therapy;
**Gy** = Gray; **HR** = hazard ratio;
**ISUP** = International Society of Urological Pathology;
**MRI** = magnetic resonance imaging; **OS** = overall survival;
**PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen;
**RARP** = robotic-assisted radical prostatectomy.

## Welcome to Issue 74 of Prostate Cancer Research Review.

According to the findings of the open-label, phase II TheraP trial, $^{177}$Lu-PSMA does not significantly change overall survival in men with metastatic castration-resistant prostate cancer compared with cabazitaxel, however, given the better tolerability of $^{177}$Lu-PSMA, this should still be considered as a treatment of choice in eligible patients. In a safety analysis from the Prostate Cancer Study-5 trial in men with high-risk prostate cancer, it appears that moderately hypofractionated radiation therapy is well-tolerated, similar to standard fractionated radiation therapy at 2 years, and could be considered an alternative to standard fractionated radiation therapy. We conclude this issue with a study showing that darolutamide reduces the risk of death by up to 41% in men with non-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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## Overall survival with [$^{177}$Lu]Lu-PSMA-617 versus cabazitaxel in metastatic castration-resistant prostate cancer (TheraP): Secondary outcomes of a randomised, open-label, phase 2 trial

**Authors:** Hofman MS et al.


**Summary:** This secondary analysis of the Australian randomised, open-label, phase II, TheraP study of PSA responses to $^{177}$Lu-PSMA-617 (n = 99) or cabazitaxel (n = 101) in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel, examined OS and updated imaging biomarker analyses. After treatment, 20 (20%) cabazitaxel and 32 (32%) $^{177}$Lu-PSMA-617 recipients subsequently received the alternate regimen. Over a median follow-up of 35.7 months, 77 (78%) $^{177}$Lu-PSMA-617 recipients and 70 (69%) cabazitaxel recipients died, with no difference in OS restricted mean survival time (RMST; 19.1 months; 95% CI 16.9-21.4; vs 19.6 months; 95% CI 17.4-21.8; difference -0.5 months; 95% CI -3.7 to 2.7). Prior to study commencement, 80 men were excluded after $^{68}$Ga-PSMA-11 and 18FDG PET imaging, in 61 of these men RMST was 11.0 months (95% CI 9.0-13.1).


**Comment:** The ANZUP-sponsored TheraP trial previously reported that in patients with progressive PSMA-PET positive mCRPC (and no discordant FDG-PET positive lesions), treatment with $^{177}$Lu-PSMA led to better PSA and objective response rates as well as more prolonged progression-free survival compared to cabazitaxel in the third-line setting. This follow-up reports on OS, a secondary endpoint in the study, which was not significantly different between the two arms with a median OS of 35.7 months. However, given the better tolerability of $^{177}$Lu-PSMA, this would still be the treatment of choice in eligible patients. Interestingly, although the intensity of PSMA avidity was not predictive of treatment response to $^{177}$Lu-PSMA, it was an independent prognostic factor for OS, suggesting it as a novel biomarker in this phase of the disease.


***Reference: Lancet Oncol. 2024;25(1):99-107***
Abstract



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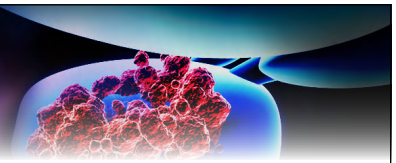

**Independent commentary by Professor Niall Corcoran.**

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.

## Hypofractionated, dose escalation radiation therapy for high-risk prostate cancer: The safety analysis of the Prostate Cancer Study-5, a Groupe de Radio-Oncologie Génito-Urinaire de Quebec led phase 3 trial

**Authors:** Niazi T et al.

**Summary:** This report provides a safety analysis of a noninferiority phase III clinical trial of hypofractionated (HF; 68 Gy; 2.72 Gy per fraction plus 45 Gy; 1.8 Gy per fraction to the pelvic lymph nodes) versus standard fractionated (SF; 76 Gy; 2 Gy per fraction) radiation therapy plus neoadjuvant, concurrent, and long-term adjuvant ADT in 329 patients with high-risk prostate cancer. Because of lower-than-expected toxicities in both arms, noninferiority analysis was dropped. More grade ≥1 acute gastrointestinal (GI) events occurred in the HF arm than SF arm (102 versus 83 events; p = 0.016), but this was not significant at 8 weeks of follow-up, and there were no differences in grade ≥1 or worse acute genitourinary (GU) events (105 vs 99). At 24 months, there was no difference in grade ≥2 delayed GI-related adverse events (15 vs 12 patients; HR 1.32; 95% CI 0.62-2.83), but more SF versus HF recipients had grade ≥2 delayed GU toxicities (3 vs 11; HR 0.26; 95% CI, 0.07-0.94; p = 0.037).

**Comment:** Reducing the number of fractions given during external beam radiation is desirable to decrease patient treatment burden as long as it's not at a cost of greater toxicity or poorer oncological outcomes. In this Canadian study, patients with high-risk disease were randomly assigned to receive either SF conventionally fractionated prostate radiation (76 Gy in 38 daily sessions over 8 weeks) or moderate HF radiation (68 Gy in 25 daily sessions over 5 weeks), with similar doses to the pelvic lymph nodes and concomitant ADT in both groups. The oncological outcomes have previously been presented at ASCO (similar outcomes at 7 years), and this report focusses on toxicity, which was reasonably low and similar in both groups. Good news for patients; bad news for radiation oncologists paid by the fraction.

***Reference: Int J Radiat Oncol Biol Phys. 2024;118(1):52-62***
Abstract

## Risk modeling for individualization of the FLAME focal boost approach in external beam radiation therapy for patients with localized prostate cancer

**Authors:** Menne Guricová K et al.

**Summary:** This analysis of the Focal Lesion Ablative Microboost in Prostate Cancer (FLAME) trial assessed whether there are identifiable risk factors associated with a benefit of isotoxic focal boosting to the intraprostatic lesion in 526 patients with intermediate- and high-risk prostate cancer. Patients with high-risk factors were highly represented in 120 patients that received the near-minimum dose to the gross tumour volume (D98%) >85 Gy and had fewer recurrences than those that received 77 Gy. Using a model simulating a standard dose of 77 Gy whole-gland radiation therapy, a high 5-year disease-free survival (DFS) was predicted for Grade Group 1 patients, but in those with high-risk characteristics a low 5-year DFS was identified. All risk groups had a high 5-year DFS in a simulation of D98% of 95 Gy.

**Comment:** The FLAME trial randomised men with intermediate- or high-risk prostate cancer to either standard external beam radiation (77 Gy in 2.2 Gy fractions) to the entire prostate, or the same with an additional focal boost of 95 Gy to any intraprostatic lesion visible on MRI. Focal boosting was associated with an improved biochemical DFS without additional toxicity. In this report the authors stratify the observed benefit by biopsy tumour grade, showing less benefit for low-grade tumours, which are adequately controlled using conventional treatment, whereas patients with high-grade tumours benefited most. Interesting, as it suggests 'treatment failure' (rather than occult dissemination prior to treatment) is a relatively common cause of disease progression following conventional external beam radiotherapy.

***Reference: Int J Radiat Oncol Biol Phys. 2024;118(1):66-73***
Abstract

## Peritoneal flap for lymphocele prophylaxis following robotic-assisted radical prostatectomy with lymph node dissection: The randomised controlled phase 3 PELYCAN trial

**Authors:** Neuberger M et al.

**Summary:** This investigator-initiated, prospective, parallel, double-blinded, adaptive, phase III randomised controlled trial (RCT; n = 551) examined the addition of peritoneal flaps (PFs; ventral peritoneum incised bilaterally and fixed to the pelvic floor) on postoperative symptomatic lymphoceles (SLCs). Over a 6-month follow-up, fewer SLCs (9.1% vs 3.7%; p = 0.005) and asymptomatic lymphoceles (ALCs; 27.2% vs 10.3%; p < 0.001) were observed in an intent-to-treat analysis. The operating time was 11 minutes longer (p < 0.001), but there were no differences in number (80 vs 103) or severity (p = 0.182) of postoperative complications.

**Comment:** Fewer and fewer surgeons perform lymph node dissections routinely at the time of prostatectomy in Australia, given the lack of firm evidence of oncological benefit and risk of additional morbidity. This is highlighted in this large German RCT, where 9.1% of patients undergoing pelvic lymph node dissection developed an SLC requiring intervention within 6 months of surgery, and a further 16.8% had an ALC at the time of discharge (day 7 postoperative). Rates were more than halved using the peritoneal flaps as described, but one can't help feeling it would be better just to avoid them completely.

***Reference: Eur Urol Oncol. 2024;7(1):53-62***
Abstract

## First-in-human evaluation of a prostate-specific membrane antigen-targeted near-infrared fluorescent small molecule for fluorescence-based identification of prostate cancer in patients with high-risk prostate cancer undergoing robotic-assisted prostatectomy

**Authors:** Nguyen HG et al.

**Summary:** This single-centre, dose-escalation phase I study assessed IS-002, a near-infrared PSMA-targeted fluorescence imaging agent intended for intraoperative prostate cancer visualisation, in 24 men with high-risk prostate cancer undergoing RARP. Adverse events (AEs) included discoloration of urine (n = 22; grade 1), and there were no grade ≥2 AEs. Maximum concentration ($C_{max}$) and area under the curve increased with increasing dose, while plasma concentrations decreased in a biphasic manner with median terminal half-lives ranging from 5.0 to 7.6 hours. At 25 µg/kg, exploratory efficacy for negative and positive predictive values for lymph nodes were 97% and 45%, and for residual/locoregional disease detection were 100% and 80%

**Comment:** The ability to directly visualise tumour intra-operatively could maximise sparing of the neuro-vascular bundles whilst minimising the risk of positive surgical margins. This small phase I investigated the safety, tolerability and pharmacokinetics of a novel, near-infrared fluorescently labelled PSMA-targeting peptide using the Firefly fluorescence imaging capability of the da Vinci surgical system. The authors report good locoregional/residual tumour detection at the lower doses, although sensitivity for lymph node metastases was less. Its main value appears to be detection of residual disease in the surgical bed (occurred in 7/24 patients), which was not suspected under white light vision. The main disadvantage is that, in this trial at least, it needed to be given as an infusion 24 hours prior to surgery, which might temper enthusiasm.

***Reference: Eur Urol Oncol. 2024;7(1):63-72***
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.

## Oncological outcomes after attempted nerve-sparing radical prostatectomy (NSRP) in patients with high-risk prostate cancer are comparable to standard non-NSRP: A longitudinal long-term propensity-matched single-centre study

**Authors:** Furrer MA et al.

**Summary:** This single-centre study examined long-term safety of nerve-sparing radical prostatectomy in 726 men with high-risk prostate cancer; 609 (84%) received nerve-sparing surgery. There was no difference in positive surgical margin rate between nerve sparing and non-nerve sparing groups (47% vs 49%) nor was there a difference in need for postoperative radiotherapy (HR 0.78; 95% CI 0.53-1.15). There was also no difference in risk of any recurrence (HR 0.99; 95% CI 0.73-1.34), nor for differences between groups in survival (HR 0.65; 95% CI 0.39-1.08), cancer-specific survival (HR 0.56; 95% CI 0.29-1.11) or PFS (HR 0.99; 95% CI 0.73-1.34).

**Comment:** The presence of high-risk disease has traditionally been considered a contra-indication to nerve sparing surgery, although with better definition of tumour location and burden, more and more men are considered candidates. This large, single-centre series from Switzerland reports on men with high-risk disease who underwent open radical prostatectomy. All patients had an attempted nerve sparing procedure except on the ipsilateral side of gross palpable disease or obvious extension into the bundle on MRI, with the majority having some form of nerve spare performed. There was no difference in long-term oncological outcomes in men undergoing a nerve sparing compared to those who had a non-nerving sparing procedure, in particular no difference in positive margin rate, indicating that men were carefully selected. No functional data is reported to assess the quality of nerve spare though.

***Reference: BJU Int. 2024;133(1):53-62***
Abstract

## Multiparametric magnetic resonance imaging in prostate cancer screening at the age of 45 years: Results from the first screening round of the PROBASE trial

**Authors:** Boschheidgen M et al.

**Summary:** This analysis of data from the PROBASE trial assessed the performance of multiparametric MRI (mpMRI) and MRI/transrectal ultrasound fusion biopsy (FBx) in 186 men aged 45 years who participated in a PSA screening trial; 114 patients underwent mpMRI and FBx. Prostate cancer was detected in 47 (41%) patients, with 33 (29%) having clinically significant prostate cancer (ISUP grade group ≥2). Interobserver reliability between radiologist Prostate Imaging-Data and Reporting System (PI-RADS) scores was moderate (k = 0.41). Using a PI-RADS cut-off of 4, reference radiologist readings were better for clinically significant cancer detection (sensitivity 79%, negative predictive value [NPV] 91%, accuracy 85%) than local reading (sensitivity 55%, NPV 80%, accuracy 68%). Reference reading did not miss any cases with a cut-off of PI-RADS <3. Using a PI-RADS ≥4 as a biopsy cut-off, mpMRI would reduce negative biopsies by 68% and avoid nonsignificant prostate cancer detection in 71% of cases.

**Comment:** The utility of prostate MRI in detecting clinically significant prostate cancer in older men with an elevated PSA is clear, but its performance in younger patients is less certain. This study from the PROBASE Trial (a multicentre German RCT comparing immediate PSA-based screening at age 45 with delayed PSA-based screening at age 50 years) reports on the test performance of MRI in the younger cohort of men with a persistent elevated screening PSA >3 ng/mL. Overall, MRI reading is less clear cut in younger men, with high rates of indeterminate lesions (PIRADS 3) and only moderate inter-observer agreement. Accuracy was greater with more experienced readers, re-enforcing the importance of knowing who is looking at the scans.

***Reference: Eur Urol. 2024;85(2):105-111***
Abstract

## European association of urology biochemical recurrence risk classification as a decision tool for salvage radiotherapy – A multicenter study

**Authors:** Preisser F et al.

**Summary:** This European multicentre retrospective analysis of 2379 patients between 1989-2020 who developed biochemical recurrence (BCR) after radical prostatectomy (RP), assessed whether European Association of Urology (EAU) risk stratification assists in selecting patients for salvage radiotherapy (SRT). Overall, 805 patients were classified as having EAU low-risk BCR and 1574 had high-risk BCR. Over a median follow-up of 54 months after BCR, 12-year OS in low-risk BCR did not differ between early versus no SRT (87% vs 78%), nor in cancer-specific survival (100% vs 96%). In high-risk BCR, 12-year OS after early versus no SRT was 81% versus 66% ($p < 0.001$) and cancer-specific survival was 98% versus 82% ($p < 0.001$). In multivariate analyses, early SRT decreased risk of death (HR 0.55; $p < 0.01$) and cancer-specific death (HR 0.08; $p < 0.001$), while late SRT predicted of cancer-specific death (HR 0.17; $p < 0.01$) but not death.

**Comment:** The EUA have recently described a two-tiered BCR risk classification based on Gleason score and PSA doubling time (PSADT), which stratifies patients by their subsequent risk of metastasis. EAU low-risk recurrence is defined as Gleason score <8 and PSADT >12 months, and high-risk BCR is defined as Gleason score ≥8 or PSADT ≤12 months. This large multicentre retrospective study finds that in patients with high-risk BCR, early SRT (PSA <0.5 ng/mL) was associated with significant improvements in OS and cancer-specific survival compared to patients not receiving SRT, whereas a significant benefit was not observed in patients with low-risk recurrence. Although these findings come with all the caveats of a retrospective study, it suggests that the classification is useful to assist the appropriate selection of men for early SRT.

***Reference: Eur Urol. 2024;85(2):164-170***
Abstract

## Bone biomarkers and subsequent survival in men with hormone-sensitive prostate cancer: Results from the SWOG S1216 phase 3 trial of androgen deprivation therapy with or without orteronel

**Authors:** Lara PN Jr et al.

**Summary:** This prospective phase III study of ADT with or without the CYP17 inhibitor orteronel, assessed the use of bone resorption (C-telopeptide and pyridinoline) and bone formation (C-terminal collagen propeptide and bone alkaline phosphatase) biomarkers in patients with hormone-sensitive prostate cancer (HSPC) based on data from a training (n = 316) and validation (n = 633) set. Optimal cut-offs identified elevated levels of each biomarker (all $p < 0.05$) associated with worse OS. After adjustment for clinical risk factors, elevated bone biomarkers were associated with an increased risk of death (HR 1.37-1.92). Three risk groups were identified (low, intermediate, and poor) based on combinations of bone biomarkers with differential OS outcomes (median OS 8.2, 5.1, and 2.1 years). The results from the training set were confirmed in the validation set.

**Comment:** Markers of bone turnover are potential surrogate markers of bony metastatic disease burden and may have prognostic utility in patients newly diagnosed with advanced disease. This observation study used patient level data from a phase III trial of ADT with or without orteronel in newly diagnosed metastatic hormone-sensitive prostate cancer. Elevated markers of both bone resorption and formation were associated with worse OS independent of other clinical variables. However, clinical disease burden was just dichotomised as 'minimal' or 'extensive' based on conventional imaging, so it may not retain significance if a more quantitative measure of bony involvement (such as number of metastases) was included in the model.

***Reference: Eur Urol. 2024;85(2):171-176***
Abstract

## Effect of crossover from placebo to darolutamide on overall survival in men with non-metastatic prostate cancer: sensitivity analyses from the randomised phase 3 ARAMIS study

**Authors:** Shore ND et al.

**Summary:** This sensitivity analysis of data from the randomised, controlled phase III ARAMIS study assessed the effect of crossover from placebo to open-label darolutamide after study unblinding on OS in patients with non-metastatic castration-resistant prostate cancer (CRPC). Overall, 170 (30.7%) of 554 placebo recipients crossed over to darolutamide. At a median 11.2 months after unblinding, darolutamide improved OS by 31% versus placebo (HR 0.69; 95% CI 0.53-0.88; $p = 0.003$). After adjustment for crossover, the benefit was increased as identified by prespecified, rank-preserving structural failure time analysis (HR 0.68; 95% CI 0.51-0.90; $p = 0.007$), iterative parameter estimation (HR 0.66; 95% CI 0.51-0.84; $p < 0.001$), and *post hoc*, OS-adjusted censoring (HR 0.59; 95% CI 0.45-0.76) and inverse probability of censoring weighting (HR 0.63; 95% CI 0.480-0.81) analyses.

**Comment:** The ARAMIS trial showed that treatment of patients with non-metastatic CRPC with darolutamide improved metastasis-free survival (MFS) compared to placebo, which translated into a 31% decrease in risk of death when OS was analysed in a subsequent report on an intention-to-treat basis. Given almost one-third of patients in the placebo arm crossed over to active treatment following unblinding after initial observation of MFS superiority, this sensitivity analysis attempts to calculate OS benefit if no cross-over occurred, increasing the HR estimate to 0.59 (95% CI 0.45-0.76). However, interpretation of the results is unclear as apart from the 31% of patients in the placebo cohort who crossed over to darolatumide, only a small number of patients in the placebo arm received subsequent treatment with a novel agent.

***Reference: Eur J Cancer 2023;195:113342***
Abstract



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