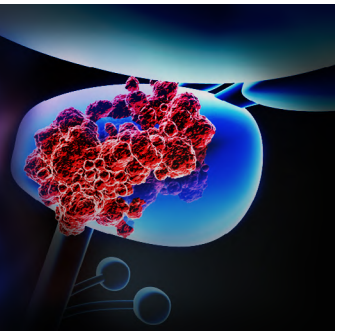
Prostate Cancer Research Review™



Making Education Easy

Issue 95 - 2026

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **CI** = confidence interval; **CT** = computed tomography; **DRE** = digital rectal examination; **Gy** = Gray; **HR** = hazard ratio; **HSPC** = metastatic hormone-sensitive prostate cancer; **mpMRI** = multiparametric magnetic resonance imaging; **MRI** = magnetic resonance imaging; **OR** = odds ratio; **OS** = overall survival; **PET** = positron emission tomography; **PFS** = progression-free survival; **PI-RADS** = Prostate Imaging-Reporting and Data System; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RCT** = randomised controlled trial; **RT** = radiotherapy; **SBRT** = stereotactic body radiotherapy.

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Welcome to Issue 95 of Prostate Cancer Research Review.

A meta-analysis suggests that the addition of ADT does not provide any significant benefit in OS over postoperative radiotherapy alone in patients with recurrent prostate cancer with a PSA <0.5 ng/mL. A single-centre study has shown that although PI-RADS 1 and 2 lesions are typically considered low-risk, clinical factors such as suspicious DRE and family history can enhance the detection of prostate cancer in this population. We conclude this issue with a prospective study evaluating the diagnostic accuracy of fluorescence confocal microscopy for real-time assessment of surgical margins in radical prostatectomy.

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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Hormone therapy use and duration with postoperative radiotherapy for recurrent prostate cancer: An individual patient data meta-analysis

Authors: Kishan AU et al.

Summary: This systematic review and meta-analysis assessed the benefit of adding hormonal therapy to postoperative radiotherapy after radical prostatectomy based on six RCTs including 6057 patients over a median follow-up of 9.0 years. Adding hormone therapy to postoperative radiotherapy did not improve OS (HR 0.87; 95% CI 0.76-1.01) and there was no interaction with postoperative radiotherapy duration. However, there was an interaction with pre-postoperative radiotherapy PSA levels >0.5 ng/mL versus ≤0.5 ng/mL (p = 0.02). Across all pre-postoperative radiotherapy PSA levels, the 95% CI upper bounds for HR of OS crossed 1.0 among those receiving postoperative radiotherapy with or without short-term hormone therapy, while among those receiving postoperative radiotherapy with or without long-term hormone therapy the 95% CI upper bound fell below 1.0 when the PSA level was >1.6 ng/mL.

Comment: The use of adjuvant ADT in the context of post-prostatectomy salvage radiotherapy remains controversial, with only one of several trials demonstrating a benefit. To provide a definitive answer, this meta-analysis used individual patient data from all published phase III trials to investigate if the use of adjuvant ADT improved OS, and whether this was affected by treatment duration and/or salvage PSA level. Overall, the use of adjuvant ADT did not provide any significant benefit for OS to salvage radiotherapy in patients with a PSA ≤0.5 ng/mL regardless of treatment duration. A small effect on metastasis-free survival was noted for pre-salvage PSA levels above this; however, this was not predicted to translate into a meaningful impact on OS unless pre-salvage PSA levels were >1.6 ng/mL. So, a definitive answer of sorts.

Reference: Lancet 2026;407(10533):1059-1071
Abstract

Prostate Cancer Research Review™

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.

Predicting prostate cancer in PI-RADS 1-2 lesions: The role of prostate-specific antigen density, digital rectal examination, and family history

Authors: Serkan Özcan et al.

Summary: This single-centre retrospective analysis assessed the diagnostic value of PSA density, DRE, and family history in predicting prostate cancer among 153 patients with low-risk PI-RADS 1 and 2 lesions undergoing prostate biopsy. Overall, prostate cancer was detected in 16 (10.5%) patients and these patients were more likely to have a higher PSA density, abnormal DRE findings, and a family history of prostate cancer. Independent predictors of cancer detection were an abnormal DRE (OR 0.062; p = 0.009) and family history (OR 0.211; p = 0.014). A combined model had moderate diagnostic performance (area under the receiver operating characteristic curve 0.711; p = 0.006).

Comment: Is it safe to discharge men referred with an elevated PSA and no suspicious lesion on MRI? This small retrospective study investigated the rates of cancer diagnosis in men with PI-RADS 1-2 lesions who underwent transrectal prostate biopsy due to persistent clinical suspicion. Overall, 10.5% of patients were identified with prostate cancer, which was Gleason ≥3+4=7 in just over half. Family history and a positive DRE were associated with an increased risk of prostate cancer diagnosis, whereas an increased PSA density was not. These findings reinforce the need to consider additional clinical factors before patients can be safely discharged.

Reference: EMJ. 2025;10(3):66-72
Abstract

SBRT vs HDR brachytherapy for intermediate-risk prostate cancer

Authors: Udovicich C et al.

Summary: This *post hoc*, patient-level, pooled analysis of five prospective trials compared biochemical failure, late patient-reported quality of life (PR-QoL), and acute and late adverse events associated with stereotactic body radiotherapy (SBRT; n = 180) and high dose rate brachytherapy monotherapy (HDR-BT; n = 67). After a median follow-up of 9.5 years, HDR-BT was associated with a greater biochemical failure rate (7.8%; 95% CI 1.0-14.6) versus SBRT (3.0%; 95% CI 0.4-5.6). After 10 years, biochemical failure rate was 38.0% (95% CI 19.8-56.1) with HDR-BT versus 10.4% (95% CI 4.3%-16.6%) with SBRT (p < 0.001). HDR-BT recipients had a higher incidence of acute grade ≥2 genitourinary adverse events than SBRT recipients (74.6% vs 51.7%; p = 0.007).No differences were observed in other adverse events or late PR-QoL.

Comment: Ultra-fractionated radiotherapy is non-inferior to hypo- and conventional fractionated radiation for patients with intermediate-risk prostate cancer, with the advantages of reduced treatment burden and decreased costs. This analysis by a Melbourne-based radiation oncologist compares two different ultra-fractionation techniques (2 or 5 fraction SBRT versus 1-2 dose HDR-BT) using individual patient-level data from both randomised and non-randomised studies. The headline result is that HDR-BT was associated with higher rates of biochemical failure compared to SBRT. Whilst acknowledging the limitations of the study design, these data support SBRT as the preferred technique of ultra-fractionation in this setting. Although concerns about long-term toxicity linger.

Reference: JAMA Netw Open 2026;9(2):e260146
Abstract

[^{177}Lu] Lu-PSMA-617 in oligometastatic hormone sensitive prostate cancer (BULLSEYE): An open-label, randomised, phase 2 study

Authors: Privé BM et al.

Summary: The multinational, open-label, randomised, controlled phase II BULLSEYE trial assessed ^{177}Lu-PSMA-617 in 58 patients with recurrent PSMA-expressing oligometastatic HSPC after radical surgery or radiotherapy over a median follow-up of 27 months. In the initial 30 weeks, disease progression occurred in 7% of patients receiving ^{177}Lu-PSMA-617 versus 93% receiving deferred ADT as the standard-of-care control (p < 0.0001); median PFS was 25 months versus 5 months (HR 0.07; 95% CI 0.03-0.17; p < 0.0001). Adverse events included grade 3 dry eyes (3%) and grade 3 lymphocyte decrease (10%) in ^{177}Lu-PSMA-617 recipients, and grade 3 hypertension (17%), grade 3 lymphocyte decrease (3%), grade 4 gallbladder infection (3%), and grade 4 myocardial infarction (3%) in standard-of-care recipients. The most common adverse events were grade 1 dry mouth (66% vs 10%), fatigue (55% vs 21%), and nausea (48% vs 10%).

Comment: Small randomised phase II study investigating the potential utility of ^{177}Lu-PSMA-617 in patients with biochemically recurrent disease (PSA ≥1 ng/mL and a doubling time <6 months) after definitive local therapy and at least one (but <5) metastatic lesion (nodal or bony) on PSMA-PET. The primary endpoint was clinical progression, a composite of symptomatic, radiographic and PSA progression. Unsurprisingly, 2-4 cycles of ^{177}Lu-PSMA-617 significantly delayed disease progression compared to deferred ADT with active monitoring, particularly as most progression events in the control arm were biochemical. Of more interest is the small group of men in the intervention arm who achieved complete biochemical response, four of whom still had an undetectable PSA at data cut-off (median follow-up 17 months). Cure? Time will tell.

Reference: Lancet Oncol. 2026;27(4):461-469
Abstract

Nomogram-based risk classification for predicting response to metastasis-directed stereotactic body radiotherapy in PSMA PET-staged oligorecurrent prostate cancer (PORTAL): An international, retrospective cohort study

Authors: Soeterik TFW et al.

Summary: This European multinational, retrospective cohort study sought to develop and validate a nomogram to predict ADT-free survival in patients with oligorecurrent hormone-sensitive prostate cancer after curative-intent local therapy. Overall, 586 men formed the development cohort (52% pelvic nodal; 48% distant metastases) with a median follow-up of 37 months, while an external validation cohort included 131 men (44% pelvic nodal; 56% distant metastases), with a median follow-up of 43 months; 1 year ADT-free survival was 84.3% (95% CI 81.4-87.3) versus 92.8% (88.4-97.4). Predictors of earlier ADT initiation were distant metastases (HR 1.45; 95% CI 1.18-1.78), higher pre-treatment PSA (HR 1.05; 95% CI 1.03-1.08), shorter PSA doubling time (0.97; HR 0.95-0.98), and presence of 3-5 lesions (HR 1.74; 95% CI 1.33-2.28). Model discrimination using Harrell's concordance index (C-index) in the development cohort was 0.66 (95% CI 0.65-0.68) and in the external validation cohort was 0.65 (95% CI 0.55-0.75). Risk stratification identified low-risk, intermediate-risk, and high-risk prognostic groups (p < 0.0001).

Comment: Metastasis-directed therapy has been shown to defer commencement of ADT in patients with metachronous oligometastatic disease; however, defining who is most likely to respond favourably remains to be clarified. This European-based multicentre retrospective cohort study investigates the association of various clinical and radiological features with ADT-free survival at one year. Patients had five or fewer PSMA-PET avid nodal and/or bony metastases and were treated by SBRT to all lesions without concomitant ADT. ADT was commenced predominantly for radiographic progression. Interestingly PSA doubling time and pre-treatment PSA had a greater relative effect on ADT-free survival than the number of lesions and metastatic site, broadly supporting previously published data. The accompanying nomogram (albeit with poor individual discrimination) may be useful in selecting appropriate patients.

Reference: Lancet Oncol. 2026;27(3):383-392
Abstract

Stereotactic body radiation therapy to the prostate with focal boost: Analysis of the primary endpoint in the DELINEATE trial cohort E

Authors: Murray J et al.

Summary: The single-centre, prospective phase II DELINEATE cohort E pilot study assessed toxicity associated with focal boost SBRT (36.25 Gy, simultaneous integrated boost to tumour(s) of up to 45 Gy in 5 fractions) in 49 patients with intermediate- or high-risk prostate cancer. Over a median follow-up of 48.8 months, the highest rate of acute Radiation Therapy Oncology Group (RTOG) gastrointestinal (GI) and genitourinary (GU) toxicity (grade ≥2) was observed at 3 and 4 weeks, returning to baseline levels by 12 weeks. Cumulative 1-year RTOG grade ≥2 GI late toxicity incidence was 6.1% (90% CI 2.4-15.1); 4.1% of patients reported 1-year RTOG grade 3 GU toxicity. Cumulative 1-year RTOG grade ≥2 GU toxicity incidence was 10.2%.

Comment: Analysis of patients with intra-prostatic recurrence after definitive radiotherapy usually occurs at the site of visible disease on the pre-treatment MRI. This has led to the concept of focal boosting of the dominant lesion(s) during whole gland therapy with improvements in disease control; however, as whole gland treatment is delivered in fewer and fewer fractions, is it still safe to continue to escalate the dose to visible disease? This phase II study examines the feasibility of concurrent dose escalation (up to 45 Gy in to up to 3 lesions) in men undergoing five-fraction SBRT (36.25 Gy) to the whole prostate, showing that it is safe at least with medium-term follow-up, although late GU toxicity was higher than in other studies. So, although boosting with ultra-hypofractionation is possible, whether it is necessary remains to be determined.

Reference: Clin Investigation 2026;125(1):P193-202
Abstract

Does addition of multiparametric MRI to PSMA PET/CT improve diagnostic accuracy for biochemical recurrence after radical prostatectomy?

Authors: Khanna Y et al.

Summary: This Australian, single-centre, retrospective analysis assessed the addition of mpMRI to ^{68}Ga- PSMA PET/CT for detection of local and distant recurrence in 117 patients with biochemical recurrence after radical prostatectomy. ^{68}Ga-PSMA PET/CT had better detection rates than mpMRI for distant recurrence at PSA levels of <0.2 (6.1% vs 3%), 0.2-0.5 (10% vs 6.7%), 0.5-1.0 (25% vs 6.3%; p = 0.039), and >1.0 ng/mL (36% vs 24%), while mpMRI provided better detection of local recurrence (30.3% vs 0% [p < 0.001]; 33.3% vs 13.3% [p = 0.001]; 40.6% vs 18.8%; 40% vs 32%), respectively. Multivariate analysis suggested that PSA velocity was a predictor of both local and distant recurrence on MRI alone, PSMA alone, and paired PSMA and MRI; International Society of Urological Pathology grade was a predictor of distant recurrence on MRI.

Comment: PSMA-PET/CT is the go-to imaging modality for patients with biochemical recurrence after prostatectomy, but prior to its widespread adoption, pelvic mpMRI to detect local recurrence was commonly used to assist treatment decision-making. So, in this era does mpMRI still have a role? This report from Melbourne analyses the diagnostic performance of concurrent mpMRI and PSMA-PET in patients with postoperative biochemical recurrence. mpMRI was found to detect more local recurrences (particularly at lower PSA levels) than PSMA-PET, whereas PSMA-PET was better at detecting distant disease. Recent improvements in PET techniques to reduce urinary contamination (early injection of frusemide, multiphase scanning) have probably closed this gap. Also given similar rates of response to salvage radiotherapy in patients without distant disease on PET with or without a detectable local recurrence, the additional mpMRI is probably not necessary in most patients.

Reference: BJU Int. 2026;137(4):619-628
Abstract

Active surveillance for patients with prostate cancer aged ≥75 years: The Prostate Cancer Research International: Active Surveillance (PRIAS)-JAPAN study

Authors: Kato T et al.

Summary: This Japanese nationwide, multicentre, prospective cohort study used data from Prostate Cancer Research International: Active Surveillance (PRIAS)-JAPAN study to examine clinical outcomes, treatment, and survival rates in 1274 men aged <75 years (n = 1043) or ≥75 (n = 231) years with prostate cancer. Older patients had larger prostate volumes, a higher proportion of Gleason Score 3+4, and more T2 disease than younger patients at diagnosis. Protocol biopsy acceptance rate decreased with time (1 year 82.9%; 4 years 63.6%, 7 years 42.2%; 10 years 22.4%), with no difference with age. The 10-year active surveillance persistence rate was 8.8% in older patients. OS was lower in older patients (HR 0.32; 95% CI 0.14-0.74); however, 10-year cancer-specific survival and metastasis-free survival rates were both 100% in older patients.

Comment: As healthy aging increases, a strict age cut-off at which radical treatment of localised prostate is no longer considered necessary becomes harder to define. This report from Japan (which has similar life expectancy for men as Australia) of men enrolled within the PRIAS study shows that older men with low- or intermediate-risk prostate cancer are as willing to persist with active surveillance, including interval biopsies, as younger men. However, fewer older men progress to radical treatment during surveillance, even with upgrading on interval biopsies. There was no difference in metastasis-free survival at 10 years between the groups. Interesting observations; however, with the widespread availability of prostate MRI the continued practice of routine interval biopsies (as opposed to 'for cause') in patients on active surveillance is becoming harder to justify, particularly in older men.

Reference: BJU Int. 2026;137(4):650-658
Abstract

[18F]-Fluciclovine or [68Ga]-PSMA-11 molecular imaging to guide dose escalation of salvage radiotherapy after radical prostatectomy for prostate cancer: The EMPIRE-2 trial

Authors: Jani AB et al.

Summary: EMPIRE-2 was a randomised trial of ^{18}F-fluciclovine-PSMA-11 PET versus ^{68}Ga-PSMA-11 PET imaging to guide salvage radiotherapy (RT) for prostate cancer recurrence after prostatectomy in 140 men with biochemical progression after prostatectomy. After a median follow-up of 2.6 years, event-free survival (EFS) rates were 87% in the EMPIRE-2 cohort versus 80% in the ^{18}F-fluciclovine EMPIRE-1 comparison cohort (difference 7.7%, 95% CI 4.7-12; p = 0.01); propensity weighted analysis suggested the corresponding 2-year EFS rates were 84% versus 73% (difference 11%; 95% CI 3.6-24; p = 0.01). EMPIRE-2 EFS rates at 2 years were 87% with ^{18}F-fluciclovine versus 88% with ^{68}Ga-PSMA-11 (difference 0.7%; 95% CI 0.3-1.3; p > 0.09).

Comment: Focal boosting of MRI detectable lesions improves disease control in patients undergoing primary radiotherapy, but whether boosting visible pelvic lesions (prostate bed or pelvic nodes) improves outcomes in the salvage setting is unclear. This prospective cohort study compared disease control in men with post-prostatectomy biochemical recurrence undergoing salvage radiotherapy with focal boosting to all PET-detectable pelvic lesions, to the results of an earlier study in which PET was performed for treatment planning, but no focal boost delivered. Within the study, patients were randomised to either ^{18}F-fluciclovine or ^{68}Ga-PSMA for imaging. Overall, patients assigned to the cohort with focal boosting of PET visible lesions (if present) had better disease control at 2 years than those assigned to PET-imaging for treatment planning only with no focal boosting. Not an RCT, but provocative data.

Reference: Eur Urol. 2026;89(4):368-377
Abstract

IP8-FLUORESCE: A prospective paired cohort study evaluating the diagnostic accuracy of fluorescence confocal microscopy for real-time assessment of surgical margins in radical prostatectomy

Authors: Mayor N et al.

Summary: This UK multicentre, prospective, blinded, paired cohort study evaluated diagnostic performance of fluorescence confocal microscopy for detecting positive surgical margins in 156 men undergoing radical prostatectomy for localised or locally advanced prostate cancer. Across multiple definitions of positive surgical margins, the prevalence of positive surgical margins was 30.8%. For all lengths of positive surgical margins, including focally positive and <1 mm margins, sensitivity was 48% (95% CI 33-63%), specificity was 94% (95% CI 88-98%), positive predictive value (PPV) was 79% (95% CI 60-92%), and negative predictive value (NPV) was 80% (95% CI 72-87%). For positive surgical margins of ≥3 mm, fluorescence confocal microscopy had sensitivity of 79% (95% CI 54-94%), specificity of 94% (95% CI 89-97%), PPV of 71% (95% CI 48-89%), and NPV of 96% (95% CI 91-99%). Among false negative cases, 84% of positive surgical margins were ≤2 mm, with 52% being at the apex.

Comment: Intraoperative frozen section analysis of margin status with secondary resection as required (NeuroSAFE), expands patient eligibility for nerve-sparing and improves postoperative erectile function; however, it is both time-consuming and resource intensive. High resolution surface imaging using fluorescent confocal microscopy of fresh uncut specimens can generate images in a shorter time, but it is not clear if it is as good as frozen sections for assessing margin status. This cohort study investigated the accuracy of intraoperative margin assessment using the Histolog Scanner (although fluorescence confocal microscopy images were read postoperatively) using standard pathology as the gold standard. Sensitivity was reasonably low, but did get better as margin length increased. Of perhaps more concern was the high rate of false positives, which if acted upon would have led to unnecessary secondary resections. Also still requires a pathologist!

Reference: Eur Urol. 2026;89(3):223-232
Abstract