# Genitourinary Cancers RESEARCH REVIEW™

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Issue 6 – 2026


## In this issue:



**Abbreviations used in this issue**

**ADT** = androgen deprivation therapy
**ccRCC** = clear cell renal cell carcinoma
**DFS** = disease-free survival
**EFS** = event-free survival
**GnRH** = gonadotropin-releasing hormone
**HR** = hazard ratio
**ICI** = immune checkpoint inhibitor
**MFS** = metastasis-free survival
**OR** = odds ratio
**ORR** = objective response rate
**OS** = overall survival
**PET** = positron emission tomography
**PFS** = progression-free survival
**PSA** = prostate-specific antigen
**RCC** = renal cell carcinoma
**SABRT** = stereotactic ablative body radiotherapy
**TKI** = tyrosine kinase inhibitor

# Welcome to Issue 6 of Genitourinary Cancers Research Review.

A meta-analysis has suggested that adding either short- or long-term hormone therapy to post-operative radiotherapy for men with localised prostate cancer and a PSA ≤0.5 ng/mL provides no meaningful OS benefit, but there might be an advantage in higher-risk patients. A phase II study undertaken in New Zealand, Australia and the Netherlands has demonstrated the long-term safety and efficacy of SABRT in non-surgical patients with primary renal cell carcinoma. We conclude this issue with a study investigating the use of transdermal estradiol patches in locally advanced prostate cancer.

I hope you find this update in Genitourinary Cancer research interesting and informative, and look forward to reading your comments and feedback.

Kind regards,


**Dr Carmel Jacobs**
carmeljacobs@researchreview.co.nz


## 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 patient-data level meta-analysis of six randomised, phase III trials including 6057 patients assessed the benefit of adding hormone therapy, short-term hormone therapy (4-6 months), or long-term hormone therapy (24 months) to post-operative radiotherapy (PORT) after radical prostatectomy. Over a median follow-up of 9.0 years, hormone therapy did not improve OS over PORT alone (HR 0.87; 95% CI 0.76-1.01; p = 0.06); there was an interaction between this effect and pre-PORT PSA >0.5 ng/mL versus ≤0.5 ng/mL (p = 0.02). Across all pre-PORT PSA values, the HR upper 95% CI limit for OS crossed 1.0 in PORT recipients with or without short-term hormone therapy (n = 3938), while for PORT recipients with or without long-term hormone therapy (n = 1088), the upper 95% CI limit was below 1.0 at PSA >1.6 ng/mL.


**Comment:** As stated by the authors of this meta-analysis, adding hormone therapy to radiation therapy for the primary treatment of prostate cancer has shown an OS benefit when given to higher-risk patients. However, the trials evaluating adding hormone therapy to PORT had mixed results. Hence the individual patient meta-analysis presented above. Whilst the conclusion is that there appears to be no consistent evidence for an OS benefit in adding hormone therapy to PORT for all patients, just like primary radiation therapy, there probably is a benefit seen when restricted to higher-risk subgroups (in this analysis largely defined by level of PSA at the time of therapy). The primary endpoint of OS as used in this analysis is absolutely what you want to be seeing an effect on with any adjuvant therapy, but given the long natural history of prostate cancer, this can be difficult to achieve. Metastasis-free survival (MFS), a surrogate for OS, was improved by the use of combination therapy across multiple subgroups. In summary, the treatment offered needs to be tailored to the patient and disease characteristics of the individual. Biomarkers, such as genomic classifiers, may be able to further define patients who will benefit from combined PORT and hormonal therapy.


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


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## Long-term outcomes of stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II): A multicentre, non-randomised, phase 2 study

**Authors:** Siva S et al.

**Summary:** This report provides the final long-term trial outcomes of the non-randomised, phase II TransTasman Radiation Oncology Group 15.03 FASTRACK II trial assessing stereotactic ablative body radiotherapy (SABRT; 26 Gy for tumours ≤4 cm diameter, or 42 Gy in three fractions for tumours >4 cm) in 70 patients (median age 77 years, 70% male) with primary renal cell carcinoma (median tumour size 46 mm; 34% T1a; 56% T1b, 9% T2a, 1% T3a). Over a median follow-up of 62 months SABRT provided 100% local control at 36, 60, and 84 months. At least one grade 3 adverse event possibly, probably, or definitely related to treatment occurred in 10% of patients within 9 months of SABRT; nausea and vomiting (4%), abdominal, flank or tumour pain (6%), colonic obstruction (3%), and diarrhoea (1%).

**Comment:** Whilst this is a phase II study, the demonstration of local control rates of 100% are going to compare well to any other treatment modalities. Likewise, not only is stereotactic radiotherapy to renal masses in this study providing excellent local control, the rate of cancer-related survival is also 100%. The toxicity and adverse effect profile seem reasonable and comparable to what might be seen with other methods of local control, either surgery or alternative ablation techniques. Importantly the rate of increase in creatinine level was low (2%). Therefore, SABRT to primary renal masses is an option for local control comparable to surgical excision and ablation in terms of efficacy. Patient selection, preference, and toxicity profiles will be important factors in choosing therapy for individual patients.

***Reference: Lancet Oncol. 2026;27(6):711-720***
Abstract

## Real-world outcomes in advanced clear cell renal cell carcinoma: A retrospective analysis comparing New Zealand and Australian cohorts

**Authors:** Harris W et al.

**Summary:** This retrospective (2010-19) cohort study compared New Zealand patients treated with systemic therapy for advanced clear cell renal cell carcinoma (ccRCC) in Auckland (n = 183) and Waikato (n = 101) with patients in Australia (Melbourne; n = 66). Median OS time was longer in Australian versus New Zealand patients (56 vs 17 months; HR 0.40; p < 0.0001). Australian patients received more subsequent-line therapies than New Zealand patients; 24% vs 11% received third line. More Australian patients received an immune checkpoint inhibitor (ICI)-containing regimen (41% vs 13%).

**Comment:** First a disclaimer, as the commentator is also an author on this paper. However, my opinion is this an exceptionally important piece of work highlighting the disparities that New Zealand patients face in terms of being able to access modern medications in a timely fashion. The treatment of advanced renal cancer (clear cell in particular) has changed dramatically with a multitude of newer life-prolonging treatments becoming available over the last 15 years. Unfortunately, New Zealand has been very slow to fund and make available these high-cost but life prolonging medicines. Thankfully, a change in funding in 2025 means that patients with ccRCC can now access newer life-prolonging therapies. It would be important to repeat this retrospective study in time to see if we have 'caught up'. We also need to acknowledge that drug development and improvements in care are incremental and ongoing, and whilst availability of drugs has improved, there is still progress to be made for this cohort of patients and many others living with alternate malignancies.

***Reference: JCO Glob Oncol. 2026;12(3):e2500384***
Abstract



## Real-world occurrence of adverse events associated with adjuvant pembrolizumab therapy for renal cell carcinoma: A multicenter retrospective study

**Authors:** Iinuma K et al.

**Summary:** This Japanese multicentre, retrospective, observational study examined the clinical safety of adjuvant pembrolizumab therapy in 35 patients with high-risk RCC. Over a median follow-up of 7.0 months, treatment-related adverse events (TRAEs) occurred in 13 patients, including two grade ≥3 events; five patients discontinued treatment due to TRAEs. Grade ≥3 TRAEs included erythema multiforme, myocarditis, gastrointestinal perforation, and myasthenia gravis. Median DFS and OS were not achieved.

**Comment:** Adjuvant pembrolizumab has recently been approved for patients with high-risk resected ccRCC (or for patients with completely resected metastatic disease). The landmark trial showed a PFS benefit of 1 year for adjuvant pembrolizumab, the follow-up publication showed an OS benefit for patients receiving pembrolizumab with an HR of 0.62 favouring the pembrolizumab group. This has led to approval and mainstream use of the therapy in some locations. However, there remains debate as to who should receive this therapy and where checkpoint inhibitors fit in the management of disease across the spectrum. With any therapy comes risk and what the above study shows, as did the original clinical trial, is that a proportion of patients will develop toxicity and adverse events secondary to the therapy, and a proportion of these will be high grade. When a therapy is designed to 'cure' patients of the disease, it is feasible that any toxicity could be permanent and for some, these adverse events can be devastating. This highlights the importance of patients being fully informed of the risk of any therapy in balance with the potential benefits.

***Reference: Int J Urol. 2026;33(5):e70505***
Abstract

## Comparative efficacy of first-line immune checkpoint inhibitor-based combination therapies in patients with sarcomatoid renal cell carcinoma: A Japanese multicenter cohort study

**Authors:** Tamura K et al.

**Summary:** This Japanese real-world clinical study examined ICI-based, first-line, dual immunotherapy (IO-IO) versus IO plus tyrosine kinase inhibitor (IO-TKI) in 46 patients with sarcomatoid RCC. Overall, the ORR was numerically, but not statistically, higher with IO-TKI than IO-IO (64.3% vs 50.0%). In a comparative analysis of 43 intermediate-/poor-risk patients, PFS was similar (p = 0.071), while OS was longer (p = 0.016) with IO-TKI. Multivariate analysis adjusted for International Metastatic RCC Database Consortium risk categories favoured the IO-TKI regimen (HR 0.37; p = 0.061).

**Comment:** As the authors note, sarcomatoid RCC is an aggressive feature seen in both clear cell and non-clear cell variants of RCC. Patients in this cohort generally had sarcomatoid features, not pure sarcomatoid cancers (which is an even rarer occurrence). Whilst a small cohort, what the authors have shown is this subgroup of patients with sarcomatoid features respond generally in a similar way to the overall patient population. We know that (by cross-trial comparisons) an IO-TKI combination usually leads to higher initial response rates than an IO-IO combination. I think the numbers are too small to draw meaningful conclusions about survival, OS and PFS, but it is encouraging to see a response for these patients with aggressive disease and evidence to use standard treatment algorithms despite the aggressive pathology.

***Reference: Int J Urol. 2026;33(5):e70494***
Abstract

## Real-world effectiveness and safety of pembrolizumab-lenvatinib versus axitinib-based regimens in metastatic clear cell renal cell carcinoma: A multicenter retrospective study

**Authors:** Kobatake K et al.

**Summary:** This retrospective (2017-25) study compared pembrolizumab plus lenvatinib versus axitinib-based regimens (avelumab plus axitinib or pembrolizumab plus axitinib) in 42 propensity matched patient pairs with metastatic ccRCC. Pembrolizumab plus lenvatinib had a higher objective response rate than axitinib-based regimens. Any-grade and grade ≥3 adverse event incidence rates did not differ between regimens; however, pembrolizumab plus lenvatinib had higher rates of hypertension (including grade ≥3 hypertension), fatigue, rash, and appetite loss in a full-dose subgroup. PFS and OS did not differ between treatments. Pembrolizumab plus lenvatinib was an independent predictor of objective response on multivariate analysis; survival outcomes were associated with clinical factors rather than regimen.

**Comment:** In separate clinical trials the combination of either pembrolizumab with axitinib and pembrolizumab with lenvatinib both showed superiority to single-agent treatment with sunitinib. All three drugs, axitinib, lenvatinib and sunitinib are TKIs targeting the vascular endothelial growth factor pathways and all have similar yet slightly different toxicities. The pembrolizumab combinations have not been compared to each other head-to-head in a randomised trial. Therefore, the above trial is a useful real-world comparison of the two. The registration trial of pembrolizumab and lenvatinib did show the highest response rate of any first-line immunotherapy combination clinical trial, so this is not a surprising result. It is, however, reassuring that the PFS and OS results did not differ between the two regimens. However, toxicity did and as any clinician utilising the treatments will see, toxicity is difficult to predict for both combinations. This trial provides useful information if trying to choose between the two therapies for an individual patient.

***Reference: Int J Urol. 2026;33(4):e70461***
Abstract

## Clinical outcomes of the alternative GAMMA regimen in relapsed germ cell tumours

**Authors:** Aziz NA et al.

**Summary:** This retrospective (2012-23) single-centre study assessed use of the GAMMA regimen (granulocyte colony-stimulating factor [G-CSF], actinomycin-D, methotrexate, paclitaxel and oxaliplatin) as salvage therapy in 69 unselected patients (median age 39 years; 94% male) with relapsed germ cell tumours (GCT; 80% non-seminomatous, 74% gonadal primary tumour) after progression on cisplatin-based chemotherapy. Overall, 64% of patients completed all planned chemotherapy cycles with 10% discontinuing treatment due to toxicity; 91% had successful stem cell mobilisation. Partial response marker negative was the most common treatment response (38%). The 2-year PFS was 31% and OS was 49%. According to the International Prognostic Factor Study Group risk group, 2-year PFS ranged from 20-50% and OS ranged from 20-75%. Among those with lactate dehydrogenase ≥2.5 times the upper limit of normal, 2-year PFS was 38% and OS was 47%.

**Comment:** The treatment of testicular cancer is undoubtedly one of the greatest successes of the discipline of medical oncology. Yet despite the high cure rates, a small proportion of people will relapse after first-line therapy and require further treatment. Second-line and above therapy for the most remains platinum-based treatment, either in standard dose or utilising high-dose chemotherapy with stem cell support. There are no randomised trials to guide management for relapse after first-line therapy, though this may change with results from the much-anticipated TIGER trial (comparing paclitaxel, ifosfamide, and cisplatin standard-dose chemotherapy with taxane, ifosfamide, carboplatin, and etoposide high-dose chemotherapy with stem cell support). Platinum-based chemotherapy does require reasonable renal function, the treatment is both nephrotoxic and ototoxic. The GAMMA regimen avoids cisplatin and includes actinomycin-D, paclitaxel, methotrexate, oxaliplatin and G-CSF support. What this trial shows is that response rates and outcomes reflect reasonable activity, it is feasible to deliver prior to stem cell collect and as a non-platinum-based therapy, and it may be an option for patients who cannot receive cisplatin.

***Reference: Cancer Med. 2026;15(5):e71964***
Abstract

## Impact of prior primary tumor resection on long-term prognosis in patients with metastatic renal cell carcinoma treated with nivolumab plus ipilimumab: A multicenter analysis

**Authors:** Yamashita S et al.

**Summary:** This Japanese, retrospective, multicentre study assessed the use of nivolumab plus ipilimumab in 135 patients with intermediate-risk and poor-risk metastatic RCC after primary tumour resection (cytoreductive nephrectomy; metachronous distant metastases developed after nephrectomy; synchronous metastases at diagnosis underwent upfront resection). Compared with no resection, both metachronous and synchronous resection provided longer PFS (median 18 and 19 vs 6 months; $p < 0.01$) and OS (median not reached and 52 vs 22 months; $p < 0.01$). Multivariate analysis suggested that absence of prior resection was associated with shorter PFS ($p = 0.02$) and OS ($p < 0.01$). Objective response rate and disease control rate were highest with metachronous resection and lowest without resection.

**Comment:** Prior to the current era of checkpoint inhibitor combination therapy as standard-of-care first-line therapy for advanced ccRCC, several randomised trials attempted to answer the question of if cytoreductive nephrectomy benefits patients with metastatic disease in combination with systemic therapy. Previous retrospective studies have suggested that patients who underwent cytoreductive nephrectomy had better outcomes. However, the answer in the TKI era was somewhat inconclusive and the decision for cytoreductive nephrectomy really comes down to patient and disease variables. Likewise, this study tries to answer the same question and probably comes up with the same result in the immunotherapy era. We know that patients who present with metastatic disease requiring systemic therapy quickly have higher-risk disease; when stratifying for this variable, it appeared that patients who underwent cytoreductive nephrectomy did better, even if they did present with synchronous metastatic disease. Despite attempts to control for the many variables at play here, the retrospective nature of this study gives risk of selection bias, hence randomised trials are needed to really answer this question.

***Reference: Int J Clin Oncol. 2026;May 19 [Epub ahead of print]***
Abstract

INDEPENDENT COMMENTARY BY

### Dr Carmel Jacobs

Dr Carmel Jacobs is a Medical Oncologist at Auckland City Hospital and Canopy Cancer Care. Carmel specialises in the treatment of genitourinary and prostate cancers. Carmel graduated from the Otago University School of Medicine in 2001 with Distinction. She completed training in oncology in 2011 with dual specialist training in Internal Medicine in 2012. Between 2013 and 2015 Carmel completed a clinical research fellowship at The Ottawa Hospital, Canada, focussing on breast cancer, genitourinary malignancies and melanoma. Carmel is a principal and co-investigator on a number of clinical research trials in the area of genitourinary oncology. She is an honorary clinical lecturer at Auckland University.

## Perioperative apalutamide in high-risk localized prostate cancer

**Authors:** Taplin ME et al., for the PROTEUS Investigators

**Summary:** This double-blind, placebo-controlled phase III trial compared ADT plus apalutamide versus ADT plus placebo before and after radical prostatectomy in 2109 patients with newly diagnosed, high-risk, localised or locally advanced prostate cancer. Over a median follow-up of 61.7 months, the rate of pathological complete response (pCR) or minimal residual disease (MRD) was higher with apalutamide than in the placebo group (8.9% vs 1.0%; OR 10.17; 95% CI 5.27-19.64; $p < 0.001$), as was the rate of MFS at 5 years (78.2% vs 73.5%; HR 0.80; 95% CI 0.67-0.96; $p = 0.02$). Apalutamide was also favoured for EFS, time to the first subsequent treatment, and time to distant metastasis (all $p < 0.001$). Grade 3/4 adverse events were observed in 39.6% of apalutamide and 31.0% of placebo recipients, primarily due to a higher incidence of rash with apalutamide.

**Comment:** Current treatment algorithms for localised prostate cancer include surgery alone or radiation therapy in combination with ADT for selected (higher risk) cases. The PROTEUS trial attempts to define a role for perioperative intensified ADT in high-risk patients undergoing surgery. Intuitively, systemic therapy in this population does make sense, with higher-risk prostate cancer, the higher the risk of systemic disease and subsequent progression and death. We know that the intensified ADT with GnRH analogues and androgen receptor pathway inhibitors is more active than GnRH analogues alone. The PROTEUS trial demonstrates an improvement in its primary endpoints of pCR/MRD and MFS as determined by either conventional or PET imaging in patients receiving the intensified therapy. However, pCR/MRD is not a validated endpoint in prostate cancer, as it is in other cancers, nor is MFS by PET imaging (it is if by conventional imaging alone). So, the trial is positive in these primary endpoints, but secondary endpoints, MFS by conventional imaging and OS are not. Some other secondary endpoints such as time to subsequent therapy also favour the experimental arm. The trial is a positive trial, but the significance of, and relevance to, patients today is uncertain. Potentially, with further follow-up, longer-term benefits of intensified ADT may become more certain. Quality of life data will also be important to understand, for some men, avoidance of hormonal therapy (and avoidance of its side effects) can be a primary driver of treatment decisions. We also see intensified ADT has a higher rate of adverse events and these can be high grade. The PROTEUS trial is a large, randomised surgical trial and it's a great achievement to have completed. It's answered a number of questions, but left a number unanswered as of yet.

***Reference: N Engl J Med. 2026:May 31 [Epub ahead of print]***
Abstract



## Transdermal estradiol patches in locally advanced prostate cancer

**Authors:** Langley RE et al., for the STAMPEDE-1 and PATCH Investigators

**Summary:** This non-inferiority, randomised phase III trial tested transdermal oestradiol (tE2) versus luteinising hormone-releasing hormone (LHRH) agonists in 1360 patients (median age 72 years) with prostate cancer. Overall, the 3-year MFS with tE2 was 87.1% versus 85.9% with LHRH agonists (HR 0.96; upper limit of 1-sided 95% CI 1.11, meeting non-inferiority criterion). Castrate levels of testosterone were sustained over the first year in 85% of participants in each group. Observed 5-year OS was 81.1% versus 79.2% (HR 0.90; 95% CI 0.75-1.07). Hot flashes were reported by 44% of tE2 and 89% of LHRH agonist recipients (grade ≥2 events 8% vs 37%), while gynaecomastia was seen in 85% versus 42% (grade ≥2 events 37% vs 9%).

**Comment:** Suppressing testosterone is the cornerstone of management of locally advanced and metastatic prostate cancer. Exogenous oestrogen delivery does this, as a downstream product of testosterone metabolism, oestrogen inhibits testosterone production via a negative feedback loop. Oestrogen can be delivered orally or via transdermal application. In previous trials and use, oral oestrogen was associated with a high risk of thromboembolic events. tE2 does not have this effect, likely due to an absence of first-pass metabolism. The PATCH trial therefore compared standard LHRH agonist therapy with tE2 in men with locally advanced prostate cancer. The trial was a non-inferiority trial and showed the tE2 was non-inferior in respect to 3-year MFS between the two treatment groups. The adverse event profile between the two agents differed, with less hot flushes and fatigue with tE2, more gynaecomastia and a more favourable effect on bone and metabolic markers. The PATCH trial offers tE2 as an alternate method of testosterone suppression for men with locally advanced prostate cancer.

***Reference: N Engl J Med. 2026;394(16):1595-1607***
Abstract

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