# Bladder Cancer Research Review™

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## In this issue:



**Abbreviations used in this issue:**

**HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **(N)MIBC** = (non–)muscle-invasive bladder cancer; **OR** = odds ratio; **OS** = overall survival; **PFS** = progression-free survival; **PRMT5** = protein arginine methyltransferase 5; **RCT** = randomised controlled trial; **TURB** = transurethral resection of the bladder; **UCS** = urothelial carcinoma with squamous differentiation.

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## Welcome to the latest issue of Bladder Cancer Research Review

We begin this issue with a fascinating RCT which showed that selenium supplementation did not alter the risk of recurrence in NMIBC, while vitamin E supplementation actually increased patients' risk of recurrence. This is followed by a study from Italy which found that oncological outcomes following radical cystectomy for bladder cancer did not differ according to gender. The next paper reports on a retrospective analysis that explored the OS impact of neoadjuvant chemotherapy prior to radical cystectomy according to lymph node status. We conclude with a retrospective analysis which demonstrates that patients with urothelial carcinoma with squamous differentiation have a unique genomic profile relative to pure urothelial carcinoma, and significantly poorer outcomes following both ICIs and enfortumab vedotin.

We hope you find this update in bladder cancer interesting and informative, and we always welcome your comments and feedback.

Warm regards,


**Associate Professor Ben Tran**
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### Selenium and vitamin E for prevention of non–muscle-invasive bladder cancer recurrence and progression

**Authors:** Bryan RT et al., for the SELENIB Investigators


**Summary:** In this multicentre RCT from the UK, 270 patients with newly diagnosed non-muscle-invasive bladder cancer (NMIBC) were randomised 1:1:1:1 to one of four groups (selenium + placebo; vitamin E + placebo; selenium + vitamin E; placebo + placebo). After a medium treatment duration of 1.5 years and a median follow-up of 5.5 years (84% followed for >5 years), there was no significant difference in the recurrence-free intervals between selenium versus no selenium (HR 0.92; p=0.065). Moreover, recurrence-free interval was significantly worse with vitamin E versus no vitamin E (HR 1.46; p=0.04). There were no between-group differences in progression-free intervals or OS, even after adjustments for known prognostic factors.


**Comment:** Over-the-counter supplements are all the rage now. You can pick up anything and be convinced that you are making yourself healthier, and in some cases, you can be convinced that it is helping to prevent or fight cancer. Data regarding selenium in cancer has been around for years. Even our colleague Niall Corcoran was investigating a form of selenium in prostate cancer, and then later in Alzheimer's disease! This study looked at selenium and vitamin E in NMIBC. Not only did they show that these supplements did not reduce the risk of recurrence, but they found that vitamin E was detrimental! I think that recommending patients spend their extra money on exercise physiology instead of supplements is the best way to improve their wellbeing!

***Reference: JAMA Netw Open. 2023;6(10):e2337494***
Abstract

### Gender and cystectomy for bladder cancer: A high-volume tertiary urologic care center experience

**Authors:** Mariotti A et al.


**Summary:** The objective of this study conducted at a university hospital in Italy was to evaluate whether surgical options and clinical outcomes differ according to gender. A total of 447 patients with bladder cancer undergoing radical cystectomy were enrolled, including 362 males and 85 females. At a median follow-up of 28.3 months, there were no significant gender differences in pathological stage at diagnosis, type of surgery offered, surgical time, early postoperative complications or OS, even after adjustments for tumour stage and treatment modalities.


**Comment:** Bladder cancer is more common in biologically male patients. Some data have previously suggested that female patients have poorer outcomes. This single centre study suggested that there are no differences in outcomes for male versus female patients undergoing radical cystectomy.

***Reference: Eur J Surg Oncol. 2023;49(10):107034***
Abstract

## Influence of neoadjuvant chemotherapy on survival outcomes of radical cystectomy in pathologically proven positive and negative lymph nodes

**Authors:** Kaczmarek K et al.

**Summary:** It is unclear as to whether the survival benefits of neoadjuvant chemotherapy prior to radical cystectomy for MIBC vary according to lymph node status. This retrospective study examined data from 1395 treated patients between 1991-2002, of whom 481 had node-positive cancer. Patients with node-positive bladder cancer experienced no improvement in OS with neoadjuvant chemotherapy (HR 0.927; 95% CI 0.713—1.205), whereas those without lymph node involvement did derive a benefit in OS from neoadjuvant chemotherapy (HR 0.692; 95% CI 0.524—0.915).

**Comment:** Node-positive bladder cancer remains a contentious topic. If there is clinical N1 disease, should we still be adopting a curative approach? How sure are we that a node seen on a CT (or even a PET) is actually a tumour, and not just reactive? It is possible to cure node-positive bladder cancer with neoadjuvant chemotherapy and surgery. However, if there are nodes involved with cancer following neoadjuvant chemotherapy, that is definitely a poor prognostic factor. This retrospective study showed that in all of the patients with negative nodes within a surgical specimen, the use of neoadjuvant chemotherapy prior was linked to improved survival. This is definitely a selection bias, given that negative nodes following neoadjuvant chemotherapy rule out most of the primary platinum-resistant patients. The study also showed that in all of the patients with positive nodes within a surgical specimen, the use of neoadjuvant chemotherapy did not improve survival. Again, this is selection bias! We're hoping to get some access to adjuvant nivolumab for these patients in the near future!

***Reference: Cancers (Basel). 2023;15(19):4901***
Abstract

## En bloc versus conventional resection of primary bladder tumor (eBLOC)

**Authors:** D'Andrea D et al., on behalf of the eBLOC Study Team

**Summary:** This prospective, multicentre, open-label, phase 3 RCT investigated whether en bloc transurethral resection of the bladder (TURB) improved the surgical management of NMIBC versus conventional TURB. Eligible patients with up to three tumours 1-3cm (n=384) were randomly assigned 1:1 to either en bloc or conventional TURB; 452 tumours were resected. Compared to conventional TURB, en bloc TURB resulted in greater retrieval of detrusor muscle (80.7% vs. 71.1%; p=0.01) and lower rates of bladder perforation (5.6% vs. 12%; 95% CI -12.2 to 0.6), and obturator reflex (8.4% vs. 16%; 95% CI -14.3 to -0.9). There was no between-group difference in surgical time. Fewer patients in the en bloc arm underwent second-look TURB (n=24 vs. n=34), with no difference in residual papillary disease (56% vs. 55.9%). At a follow-up of 13 months, bladder cancer recurrence was comparable between treatment arms.

**Comment:** Dear urologists, I need your help here! Is en bloc TURBT a standard approach to NMIBC? How do you fit a 3cm papillary pTaG3 lesion through the urethra en bloc? Ouch? Anyway, this study suggested that there was a greater rate of detrusor muscle sampled when using the en bloc method… is this just another selection bias of a better surgeon?

***Reference: Eur Urol Oncol. 2023;6(5):508-15***
Abstract

## Cell-free DNA methylation as a predictive biomarker of response to neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer in SWOG S1314

**Authors:** Lu Yi-Tsung et al.

**Summary:** Given that the benefit from neoadjuvant chemotherapy for MIBC is small, and treatment is intense, these investigators sought to identify cell-free DNA methylation signatures which predicted pathological response at radical cystectomy. Blood samples from 72 patients in the prospective SWOG S1314 trial were collected before and during neoadjuvant chemotherapy. Investigators developed a methylation-based response score predictive of pathologic response, based on prechemotherapy plasma cell-free DNA, and comparable predictability scores were produced from plasma samples collected after the first cycle of neoadjuvant chemotherapy. The circulating bladder DNA fraction also showed an independent, albeit modest predictive ability for treatment response. Utilising plasma collected at baseline and following one cycle of chemotherapy, investigators were able to correctly predict the pathologic response for 79% of patients by combining the methylation-based response score and circulating bladder DNA fraction.

**Comment:** There have been several studies examining predictors of response to neoadjuvant chemotherapy. The presence of *ERCC2* mutations, *RB1* mutations, *ATM* mutations and *FANCC* mutations within tumours have all been shown to be associated with pathological complete response from neoadjuvant chemotherapy. This study examined pre-chemotherapy plasma from patients and developed a score that predicted pathological response. It was a small study, and if validated in a larger dataset, it might help us to identify patients who should go straight to cystectomy instead of having neoadjuvant chemotherapy.

***Reference: Eur Urol Oncol. 2023;6(5):516-24***
Abstract

## Sexual function after radical cystectomy in males with bladder carcinoma

**Authors:** Pronk CE et al.

**Summary:** This was a 6-year, longitudinal, single-centre study from the Netherlands which examined the course of sexual function among male patients following radical cystectomy for bladder cancer. Between 2008-22, 62 patients underwent radical cystectomy for bladder cancer, 12 of whom received sexual-preserving cystectomy. Across the 6 years of follow-up, patients demonstrated a decrease of sexual function following cystectomy, and this remained stable thereafter. On average, patients experienced moderate to severe erectile dysfunction both before and after radical cystectomy. A time-dependent difference in sexual health was found between patients who underwent sexual-preserving versus conventional cystectomy (p=0.015). Significantly better sexual function was reported by patients with an orthotopic ileal neobladder compared to those with a Bricker's ileal conduit (p<0.001), and in patients who were younger at the time of cystectomy (p=0.004). Quality of life was significantly associated with sexual functioning (p=0.004)

**Comment:** I am always discussing sexual function with my prostate cancer testicular cancer patients, but for whatever reason, I always forget to discuss it with my bladder cancer patients who have had a radical cystectomy-prostatectomy! This study reiterates that radical cystectomy can decrease sexual function. They show that neobladder can result in better sexual function. I think we have to do a better job of counselling our patients about this before surgery, and also discussing it afterwards.

***Reference: Front. Urol. 2023;3***
Abstract

## Preoperative risk classification for intravesical recurrence after laparoscopic radical nephroureterectomy for upper tract urothelial carcinoma in a multi-institutional cohort

**Authors:** Somiya S et al.

**Summary:** These investigators explored the preoperative risk factors for intravesical recurrence of nonmetastatic upper urinary tract urothelial carcinoma after laparoscopic radical nephroureterectomy, with the aim of developing a risk classification system. A retrospective analysis was conducted with 283 eligible patients treated between 2002-20. At a median follow-up of 33.3 months, intravesical recurrence occurred in 31.7% of patients; at 1 and 5 years, the cumulative incidences were 23.5% and 36.4%, respectively. Independent predictive factors for recurrence included ureter tumours and multiple tumours. Investigators used these data to create three risk categories. Within 5 years following surgery, the low-, intermediate- and high-risk groups showed cumulative incidence intravesical recurrence rates of 24.4%, 42.5% and 66.7%, respectively. It was recommended that these findings be used to create individualised surveillance or adjuvant therapy regimens.

**Comment:** I am big on intravesical chemotherapy after nephroureterectomy - I think the data are strong, and we should be doing it to prevent intravesical recurrence. This Japanese study examined almost 300 patients and found that the risk of intravesical recurrence was 31%. Could these have all been prevented with intravesical mitomycin C immediately after nephroureterectomy? Is there really any risk involved in administering it? Shouldn't everyone be getting it? Shouldn't we be working harder to remove the barriers that prevent it from happening routinely? Surely the medical oncologists and urologists can communicate better?!?!!? Or is the problem that most medical oncologists don't know about intravesical chemotherapy, and most urologists don't know a chemotherapy pharmacist?!

***Reference: Int J Urol. 2023;30(10):853-8***
Abstract

## International Bladder Cancer Group Intermediate-Risk Nonmuscle-invasive Bladder Cancer scoring system predicts outcomes of patients on active surveillance

**Authors:** Tan WS et al.

**Summary:** This paper reports on the utility of the International Bladder Cancer Group Intermediate-Risk NMIBC Scoring System in predicting the necessity for delayed transurethral resection in low-grade NMIBC under active surveillance. At a median follow-up of 33 months, 109 of 163 patients with low-grade Ta/T1 NMIBC underwent transurethral resection of bladder tumour. At 24 months, patients with ≥3 risk factors were significantly more likely to undergo transurethral resection versus those with no risk factors. Multivariable cox regression showed that after adjustments for age, tumour stage and gender, the scoring system could predict the risk of subsequent transurethral resection (≥3 risk factors HR 3.21 p<0.001).

**Comment:** Intermediate-risk NMIBC can manifest as frequent low-grade recurrences. This can be frustrating for both patients and their treating clinician alike. The use of intravesical mitomycin C is an option for these patients. This study developed a scoring system that can predict the risk of recurrence. Factors in this scoring system included number of bladder tumours, tumour size, gross haematuria and urinary cytology. While this is interesting, I am not sure what clinical application it might have, as patients will still get check scopes on a regular basis, won't they?

***Reference: J Urol. 2023;210(5):763-70***
Abstract

## Prospective evaluation of functional outcomes in 395 patients with an ileal neobladder 1 year after radical cystectomy

**Authors:** Bahlburg H et al.

**Summary:** The functional outcomes for patients with an ileal neobladder after radical cystectomy were explored in this study conducted in a high-volume German urologic rehabilitation centre. Among a total of 842 patients, prospective data for 395 patients (38 female) were included in the analysis. At 12 months after radical cystectomy, 78.3% of men and 64.0% of women reported using only one safety pad every 24 hours for social continence, whereas a respective 27.3% and 64.0% reported severe incontinence. An independent predictor for no pad use at 12 months was male gender (OR 4.11; p=0.029). Nerve-sparing surgery was an independent predictor for good erectile function at 12 months (OR 4.377; p=0.004) and only requiring a safety pad (OR 1.918; p=0.040).

**Comment:** Neobladders might help in some ways, but I am beginning to understand that a lot of work is needed from the patient to train the neobladder and make full use of it. This study of almost 1000 patients examined continence and sexual function in those who had a neobladder. It showed that incontinence was more common in women. Like the study discussed earlier, more in-depth discussion of functional outcomes is important prior to surgery.

***Reference: World J Urol. 2023;41(9):2367-74***
Abstract

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**Independent commentary by Associate Professor Ben Tran**

Ben is a medical oncologist in Melbourne, Australia with appointments at Peter MacCallum Centre and Walter and Eliza Hall Institute. He is actively involved in clinical trials and translational research, with special interests in genitourinary cancers, drug development and real-world evidence. Ben is currently the chair of the Phase 1 group within Cancer Trials Australia (CTA), and is also the Chair of the germ cell subcommittee within the Australian and New Zealand Urological and Prostate Cancer Trials (ANZUP) Group.

## Impact of squamous histology on clinical outcomes and molecular profiling in metastatic urothelial carcinoma patients treated with immune checkpoint inhibitors or enfortumab vedotin

**Authors:** Jindal T et al.

**Summary:** Patients with urothelial carcinoma with squamous differentiation (UCS) show increased resistance to chemotherapy, however there is a paucity of data on outcomes following newer therapies. This was a retrospective analysis of the clinical outcomes and molecular profiling of UCS treated with an immune checkpoint inhibitor (ICI) or enfortumab vedotin. A total of 160 patients were identified, of whom 40 had UCS and 120 had pure urothelial carcinoma. An ICI was administered to 151 patients (38 UCS, 113 pure urothelial carcinoma), while 37 received enfortumab vedotin (12 UCS, 25 pure urothelial carcinoma). ICI therapy was associated with a shorter PFS among UCS patients compared to those with pure urothelial carcinoma (1.9 vs. 4.8 months; p<0.01), and shorter OS (9.2 vs. 20.7 months; p<0.01). Similarly, enfortumab vedotin treatment was associated with a lower objective response rate in UCS patients versus pure urothelial carcinoma (17% vs. 70%; p<0.01) and shorter PFS (3.4 vs. 15.8 months; p<0.01). Patients with UCS showed enrichment of *CDKN2A*, *CDKN2B* and *PIK3CA* alterations, whereas those with pure urothelial carcinoma showed enrichment of *ERBB2*.

**Comment:** Squamous cell carcinoma of the bladder is rare and has a poor prognosis. Urothelial carcinoma with squamous differentiation is regularly encountered. This study included 40 patients with this histological subtype and demonstrated that these patients have poorer survival and lower response rates to enfortumab vedotin. It would be interesting to see if they have lower expression of Nectin-4. Molecularly, *CDKN2A* was enriched in these cancers. These mutations are associated with *MTAP* loss, which is a possible biomarker for benefit from PRMT5 inhibitors, and these are in early clinical development…maybe this is a histological subtype that might benefit from these novel agents.

***Reference: Clin Genitourin Cancer. 2023;21(5):e394-e404***
Abstract