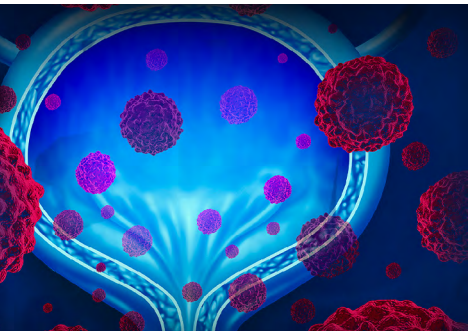
Bladder Cancer Research Review™



Making Education Easy

Issue 6 - 2023

In this issue:

Abbreviations used in this issue:

ACB = adenocarcinoma of the bladder; **BMI** = body mass index; **BSC** = best supportive care; **CHT** = chemohyperthermia; **CT** = computed tomography; **EAU** = The European Association of Urology; **(^{18}F-)FDG** = (18F-) fluorodeoxyglucose; **HR** = hazard ratio; **ICB** = immune checkpoint blockade; **MIBC** = muscle-invasive bladder cancer; **OS** = overall survival; **MDM** = multidisciplinary meeting; **PET** = positron emission tomography; **RCT** = randomised controlled trial; **re-TURBT** = restaging transurethral resection of bladder tumour; **TMB** = tumour mutational burden; **UBC** = urothelial bladder cancer.

Welcome to the latest issue of Bladder Cancer Research Review

We begin with a large retrospective study from the US which found a slight yet significantly increased risk of bladder cancer among Vietnam veterans who have been exposed to Agent Orange. This is followed by evidence that robot-assisted radical cystectomy for bladder cancer is not cost-effective in publicly funded health systems, however it may be cost-effective for certain subgroups. The next paper reports an OS benefit for trimodality therapy versus radical cystectomy in MIBC, which suggests that we should be offering this to all patients - not only those who are ineligible for surgery. We conclude with a study which explored the role of re-TURBT after neoadjuvant chemotherapy prior to radical cystectomy.

We hope you enjoy this update in bladder cancer research, and we always welcome your comments and feedback.

Warm regards,

Associate Professor Ben Tran
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Exposure to Agent Orange and risk of bladder cancer among US veterans

Authors: Williams SB et al.

Summary: This US-based, nationwide, retrospective study assessed the association between bladder cancer risk and exposure to Agent Orange among 2,517,926 male Vietnam veterans (median age 60.0 years). Investigators matched exposed (25.0%) and non-exposed (75.0%) veterans for age, race, ethnicity, year of service and military branch. Veterans who had been exposed to Agent Orange had a slight yet significant increased risk of bladder cancer (HR 1.04; 95% CI 1.02—1.06). There was a significant association between Agent Orange exposure and bladder cancer among veterans younger than the median age (HR 1.07; 95% CI 1.04—1.10), yet this interaction was not significant in those older than the median age (HR 1.03; 95% CI 0.99—1.05). There was no association between exposure to Agent Orange and bladder cancer aggressiveness.

Comment: As the Vietnam vets are ageing, the likelihood that we will see them in our clinics with bladder cancer is increasing. A question I am often posed is whether Agent Orange has had an impact. This retrospective study examined the risk of bladder cancer in those exposed to Agent Orange and demonstrated that it did in fact increase the risk of bladder cancer significantly, albeit only very slightly. Interestingly, the risk was greater in young veterans with bladder cancer which does make sense from a risk factor perspective, as older patients are at greater risk already, and perhaps Agent Orange isn't a strong enough factor amongst those other risks. These data will also apply to the many Vietnamese refugees in Western society who were also affected by Agent Orange, let alone all of those still in Vietnam. In the words of Jerry Seinfeld, "*War, what is it good for?*"

Reference: JAMA Netw Open. Published online 27 June, 2023.
Abstract

Cost-effectiveness of robot-assisted radical cystectomy vs open radical cystectomy for patients with bladder cancer

Authors: Dixon S et al.

Summary: The cost-effectiveness of robot-assisted radical cystectomy with intracorporeal urinary diversion versus open radical cystectomy for bladder cancer were compared in this analysis of a UK, multicentre RCT. A total of 305 patients were randomised 1:1 to undergo either robot-assisted or open radical cystectomy. Patients who received robot-assisted surgery had significantly reduced rates of admissions to intensive care and readmissions to hospital, however these patients also experienced longer times in theatre. Per quality-adjusted life-year gained, robot-assisted surgery had an incremental cost-effectiveness ratio of £100,008, which investigators state was higher than many publicly funded health system thresholds. Robot-assisted surgery was more likely to be cost-effective among patients aged ≥70 years, those with a BMI ≥25, and those with large tumours or a poorer performance status.

Comment: We've had a couple of healthy debates regarding robot versus open radical cystectomy at Australian conferences this year, firstly at USANZ and then later at ANZUP. There are some benefits of the robot-assisted approach, which I have covered in previous reviews here, but one of the major drawbacks is cost. This cost-effectiveness study, based upon a RCT in the UK, indicated that on a population basis, the robotic approach was not cost-effective for publicly funded health systems. This was a UK study, so caution must be applied when applying it to the Australian setting. However, they did note that the cost-effectiveness was improved in selected patient subgroups, particularly those aged over 70 years and those with larger tumours (≥T3).

Reference: JAMA Netw Open. 2023;6(6):e2317255
Abstract

Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer

Authors: Zlotta AR et al.

Summary: This was a propensity score-matched and weighted retrospective analysis which evaluated the outcomes of 772 patients with muscle-invasive bladder cancer (MIBC) who underwent either radical cystectomy (n=440) or trimodality therapy (n=282; maximal transurethral resection of bladder tumour followed by concurrent chemoradiation). It was noted that all patients would have been eligible to receive either treatment approach. After propensity-score matching, there were no significant between-group differences in metastasis-free survival (primary endpoint), cancer-specific survival or disease-free survival. However, patients who received trimodality therapy had significantly longer OS than radical cystectomy (p=0.0078), and 13% of trimodality patients had a subsequent salvage cystectomy.

Comment: In Australia, MIBC is predominantly treated with radical cystectomy, hopefully preceded by neoadjuvant chemotherapy. Mostly, radiotherapy as part of a trimodality approach is reserved for proactive patients keen to avoid a cystectomy, or those unfit for surgery. This drives a substantial bias in the outcome data. In other countries, trimodality therapy is the preferred option. This retrospective analysis attempted to account for selection bias, using a propensity score-matched and weighted analysis. They found that there was no difference in metastasis-free survival for trimodality therapy versus radical cystectomy, however, there was an OS benefit for trimodality therapy, noting that 13% of patients did go on to have a salvage cystectomy. The authors suggest we should be offering this to all suitable patients and not only to those where surgery is not an option… Dear urology colleagues, I'm sure all the radiation oncologists and medical oncologists would be happy to see your patients!

Reference: Lancet Oncol. 2023;24(6):669-81
Abstract

Avelumab first-line maintenance for advanced urothelial carcinoma

Authors: Powles T et al.

Summary: This paper reports updated data from the JAVELIN Bladder 100 RCT with ≥2 years of follow-up, which initially demonstrated that avelumab + best supportive care (BSC) significantly prolonged OS and PFS versus BSC alone in patients with advanced urothelial carcinoma who remained progression-free after first-line platinum-based chemotherapy. At data cutoff, 67 patients (19.5%) in the treatment arm had received avelumab for ≥2 years. Maintenance first-line avelumab + BSC continued to show an improvement in OS versus BSC alone (HR 0.76; p=0.0036), with benefits also seen in PFS. No novel long-term safety signals were recorded.

Comment: The JAVELIN Bladder 100 study has cemented maintenance avelumab as a standard of care following response/stable disease on first-line platinum-based chemotherapy. This updated survival analysis only further supports this. We should be offering all of our suitable advanced urothelial cancer patients maintenance avelumab.

Reference: J Clin Oncol. 2023;41(19):3486-92
Abstract

Novel genetic subtypes of urothelial carcinoma with differential outcomes on immune checkpoint blockade

Authors: Sarfaty M et al.

Summary: In order to identify genetic and molecular factors indicative of a response to immune checkpoint blockade (ICB) therapy for bladder cancer, these investigators carried out whole-exome sequencing on tumours from 88 patients who had received ICB treatment. Factors that were associated with OS and PFS following ICB included mutations in the *ARID1A* gene, tumour cell purity, intratumoural heterogeneity, tumour mutational burden and ratio of synonymous to non-synonymous mutations in the immunopeptidome; OS was negatively associated with smoking history and neutrophil-to-lymphocyte ratio. Overall, investigators identified and validated four molecular subtypes which correlated with sensitivity to ICB therapy and ensuing clinical benefit.

Comment: Biomarkers for response to immunotherapy for advanced urothelial cancer haven't progressed beyond PD-L1 expression and TMB. This study conducted in-depth molecular testing including whole-exome sequencing, and generated novel molecular subtypes that were linked to outcomes to immune checkpoint inhibitors. While such subtyping will be useful for future research, it is not something that is readily applicable in the clinic. For now, we should continue to offer all suitable patients immune checkpoint inhibitors while continuing to conduct research to better identify those who may not benefit, so that we might offer those patients new treatments such as antibody drug conjugates.

Reference: J Clin Oncol. 2023;41(17):3225-35
Abstract

Adenocarcinoma of the bladder: assessment of survival advantage associated with radical cystectomy and comparison with urothelial bladder cancer

Authors: Tappero S et al.

Summary: This study examined the cancer-specific mortality of patients with non-metastatic muscle-invasive adenocarcinoma of the bladder (n=1005; ACB) or urothelial bladder cancer (n=47,741; UBC), of whom 47% and 41% underwent radical cystectomy, respectively. Following propensity-score matching, radical cystectomy was associated with lowered cancer-specific mortality versus no cystectomy across all stages of organ-confined ACB (14% vs. 44%, respectively; HR 0.37) and organ-confined UBC (18% vs. 39%; HR 0.45), as well as non-organ-confined ACB (49% vs. 66%; HR 0.65) and non-organ confined UBC (44% vs. 56%; HR 0.68).

Comment: Every now and then we'll come across a bladder adenocarcinoma patient that is not a urachal cancer. We don't really know how best to treat these patients. We are nervous that they don't respond well to neoadjuvant chemotherapy, so often suggest that patients proceed directly to surgery. This study examined the role of radical cystectomy in MIBC (adenocarcinoma) compared to MIBC (urothelial). They demonstrated that radical cystectomy resulted in improved cancer-specific survival in the adenocarcinoma cohort, more so than in the urothelial cancer cohort. This perhaps speaks to the highly effective nature of chemotherapy and radiotherapy in urothelial cancer, which offers a good alternative to surgery compared to adenocarcinoma, where the effectiveness of these approaches is much lower.

Reference: Urol Oncol. 2023;41(7):326.e9-326.e16
Abstract

European Association of Urology guidelines on upper urinary tract urothelial carcinoma

Authors: Rouprêt M et al.

Summary: This paper outlined the updated 2023 EAU guidelines on the best management of upper urinary tract urothelial carcinoma, which were informed by a systematic literature review. It was noted that it is not yet possible to put forward informed recommendations in many areas due to the lack of robust data and evidence, although studies are continuing to make progress. Clinical examination, imaging and histology should inform patient stratification, and it is important to evaluate those who are at risk of Lynch syndrome. For patients with low-risk upper urinary tract urothelial carcinoma and two functioning kidneys, primary treatment should be kidney-sparing treatment. New treatments for high-risk disease include radical nephroureterectomy followed by platinum-based chemotherapy, or adjuvant nivolumab for those ineligible/unwilling to undergo chemotherapy. For cisplatin-ineligible patients with metastatic disease, the recommended first-line treatment is gemcitabine/carboplatin chemotherapy, while pembrolizumab or atezolizumab should be offered to those with PD-1/PD-L1-positive tumours.

Comment: Upper tract urothelial cancer used to be a disease state where data were limited and we never know the right thing to do. The POUT study changed all that. We now know that patients who have node-positive disease or pT2 and greater disease should be receiving adjuvant platinum-based chemotherapy. The EAU guidelines are always useful, so it is good to see these published. In Australia, adjuvant nivolumab, in those not fit for chemotherapy, is not currently reimbursed, so it is not an option for our patients - but it would be great to have it available to us. Fingers crossed for future access!

Reference: Eur Urol. 2023;84(1):49-64
Abstract

Adjuvant intravesical chemohyperthermia versus passive chemotherapy in patients with intermediate-risk non–muscle-invasive bladder cancer (HIVEC-II)

Authors: Tan WS et al.

Summary: In HIVEC-II, the phase 2, open-label RCT, 259 patients with intermediate-risk non-MIBC were randomised to receive either adjuvant intravesical chemohyperthermia (CHT) with mitomycin C at 43°C (n=131; treatment) or mitomycin C at room temperature (n=128; control). Within 24 months, 32% and 38% of patients in the CHT and control arms experienced recurrence, respectively. Compared to the control arm, patients who received CHT showed no significant improvement in 24-month disease-free survival (primary endpoint; p=0.8) or OS (p=0.09), however, intention-to-treat analysis revealed that patients in the control arm had longer PFS (p=0.02). A markedly lower proportion of patients who were administered CHT completed their treatment than those in the control arm (59% vs. 89%, respectively).

Comment: There have been several papers on hot mitomycin for bladder cancer. This study reported here is a phase 2 study of hot mitomycin C versus standard mitomycin C in patients with intermediate-risk non-MIBC. Consistent with the other studies recently reported, hot mitomycin C did not result in any improvement. In fact, standard mitomycin C was associated with improved PFS. This may relate to the fact that patients receiving hot mitomycin were less likely to complete their treatment. I think we can put hot mitomycin to bed. There are other more exciting options for this patient population coming to the clinic soon.

Reference: Eur Urol. 2023;83(6):497-504
Abstract

Added clinical value of ^{18}F-FDG-PET/CT to stage patients with high-risk non-muscle invasive bladder cancer before radical cystectomy

Authors: van Ginkel N et al.

Summary: This retrospective analysis examined the value of adding ^{18}F-FDG-PET-CT to enhanced CT prior to radical cystectomy in 92 patients with high-risk non-MIBC. All patients received both enhanced CT and FDG-PET-CT, and investigators compared the clinical disease stage and treatment recommendations from before and after the FDG-PET/CT scan. Additional FDG-PET/CT findings informed a change in disease stage for 11 patients (12%) and led to a change in treatment for 9 patients (10%). The reference standard stated that 25 patients (27%) had metastases, however FDG-PET/CT identified metastases in 14 patients (15%). FDG-PET/CT versus enhanced-CT showed sensitivities, specificities and accuracies of 36% versus 12%, 93% versus 97% and 77% versus 74%, respectively, while the ROC curves were 0.643 versus 0.545 (p=0.036).

Comment: I'm a Peter Mac doctor, so we use A LOT of PET scans!!! Probably too many. In my practice, I have found it very helpful in urothelial cancer, as the FDG uptake in urothelial cancer metastases is quite high. It is much more difficult for primary bladder cancer, given that urine can mask the bladder primary, however, the use of Lasix to dilute urine can often overcome this problem. This study reported here was a retrospective study from Amsterdam. They had 92 patients and demonstrated that FDG PET did upstage 12% of patients and led to treatment changes in 10%. Now in Australia, with the altered Medicare criteria for PET scans, I would encourage clinicians to consider PET at initial staging - but I am a Peter Mac doctor, so take it with a grain of salt!

Reference: Clin Genitourin Cancer. 2023;21(3):342-8
Abstract

Is there a benefit of restaging transurethral resection of bladder tumor prior to radical cystectomy with or without neoadjuvant chemotherapy?

Authors: Mehr JP et al.

Summary: These investigators explored whether restaging transurethral resection of bladder tumour (re-TURBT) after neoadjuvant chemotherapy improved staging accuracy versus re-TURBT without neoadjuvant chemotherapy prior to radical cystectomy. A total of 129 patients who underwent re-TURBT were included in the retrospective analysis, of whom 53 received neoadjuvant chemotherapy between their initial and re-TURBT, while 76 did not receive neoadjuvant chemotherapy. Overall, 34.9% of patients were upstaged from re-TURBT to radical cystectomy, however there was no significant difference in the rate of upstaging between those who did and did not receive neoadjuvant chemotherapy.

Comment: I may be a mere medical oncologist, but I do listen at MDMs! One of the issues I hear is the role of re-TURBT. This is often encouraged, but in some scenarios it might be unnecessary. This small retrospective study examined if re-TURBT was helpful after neoadjuvant chemotherapy. I have never seen this done, as patients should be proceeding quickly to radical cystectomy anyway. There is a lot of potential selection bias in this study, and I am not sure how much it actually adds. Patients without muscle in the specimen and who do not have clearly clinically/radiologically evident muscle invasion should have a re-TURBT to determine if there is muscle-invasive disease which can then guide the use of neoadjuvant chemotherapy prior to radical cystectomy. I don't see a need for re-TURBT post neoadjuvant chemotherapy – but please reach out if I'm missing something!

Reference: Bladder Cancer. 2023;9(1):41-8
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.