Bladder Cancer Research Review™

Making Education Easy

Issue 8 - 2023

In this issue:

Abbreviations used in this issue:

BCG = Bacillus Calmette-Guérin; **DFS** = disease-free survival; **FDG-PET/CT** = fluorodeoxyglucose-positron emission tomography/computed tomography; **HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **LN** = lymph node; **OR** = odds ratio; **OS** = overall survival; **PD-1/PD-L1** = programmed cell death (ligand)-1; **PFS** = progression-free survival; **QOL** = quality of life; **RCT** = randomised controlled trial; **RR** = risk ratio; **SABR** = stereotactic ablative radiotherapy; **TURBT** = trans urethral resection of bladder tumour.

Welcome to the latest issue of Bladder Cancer Research Review

We begin this issue with the CHEERS phase 2 RCT which found that the combination of ICIs with stereotactic body radiotherapy had a limited, if any, abscopal effect in metastatic urothelial cancer. This is followed by an interesting retrospective analysis which showed that in patients with clinically node-positive bladder cancer, bladder-sparing treatment with trimodal radiotherapy is an effective alternative to radical cystectomy. The next paper reports that offshore petroleum workers with long-term exposure to benzene have an increased risk of bladder cancer. We conclude with a systemic review and meta-analysis which revealed that there was no difference in oncological outcomes with dose-reduced BCG, however there was a reduction in both local and systemic side effects. While this may help to overcome the global BCG shortage, I remain uncomfortable administering dose-reduced BCG, particularly for induction. Rather, I prefer to use alternate strains in maintenance – I would love to hear your approaches.

I hope you enjoy this update in bladder cancer research, and I encourage you to send in your thoughts and comments. But make sure you stay tuned for the upcoming issues that reflect the presentations we saw at ESMO. It's not everyday there is a standing ovation!!!

Warm regards,

Associate Professor Ben Tran
ben.tran@researchreview.com.au

Checkpoint inhibitors in combination with stereotactic body radiotherapy in patients with advanced solid tumors

Authors: Spaas M et al.

Summary: In the CHEERS phase 2 RCT, 96 evaluable patients with locally advanced/metastatic urothelial carcinoma, renal cell carcinoma, head and neck squamous cell carcinoma, non-small cell lung carcinoma or melanoma were randomised 1:1 to either standard of care (anti–PD-1/PD-L1 ICIs) with stereotactic body radiotherapy, or standard of care alone (control). At a median follow-up of 12.5 months, the primary endpoint was not met; the difference in PFS between the experimental and control arms was not statistically significant (4.4 vs. 2.8 months; p=0.82). There were also no significant between-group differences in median OS (14.3 vs. 11.0 months; p=0.47) or objective response rates (27% vs. 22%; p=0.56).

Comment: The radiation oncologists I work with keep harping on about the abscopal effect, which is a systemic immune response mediated by the effects of radiation on the immune system. The combination of radiation therapy and ICIs acts at several stages of the antitumour response, suggesting a mechanism of synergy between these two modalities. This study suggests that there is limited, if any, abscopal effect in the cancers tested here, including metastatic urothelial cancer. It may be that the mixed bag of tumour types makes it hard to analyse.

Reference: JAMA Oncol. 2023;9(9):1205-13
Abstract

Claim CPD/CME points Click here for more info.

Bladder-sparing treatment with radical dose radiotherapy is an effective alternative to radical cystectomy in patients with clinically node-positive nonmetastatic bladder cancer

Authors: Swinton M et al.

Summary: This was a multicentre retrospective analysis of survival outcomes in patients with clinically node-positive bladder cancer. Among a total of 287 patients, 87 were treated with bladder-sparing trimodal therapy and 76 underwent radical cystectomy. The overall median OS was 1.55 years. Compared to palliative treatment, patients showed significantly improved OS with radical treatment options (HR 0.32; p<0.001). According to multivariable analysis, choice of radical treatment modality had no significant impact on OS (HR 0.94; p=0.76) or PFS (HR 0.74; p=0.12).

Comment: Professor Choudhury recently visited us in Australia when she attended for the ANZUP Annual Scientific Meeting. She is clearly a global thought leader when it comes to radiotherapy in bladder cancer. These data examine the role of radiotherapy for locally advanced bladder cancer that is clinically LN-positive. Certainly, the risk of metastatic disease in this patient subgroup is high. For that reason, radical cystectomy is often avoided, to optimise QOL for these likely incurable patients…assuming that having a functional bladder that is at risk of local progression, complicated by haematuria and ureteric obstruction, is in fact a better QOL than an ileal conduit (Controversial statement? Just making sure the urologist perspective is represented!). This study shows that trimodal therapy has similar survival outcomes to a radical cystectomy. I think these results were expected.

Reference: J Clin Oncol. 2023;41(27):4406-15
Abstract

Exposure to benzene and other hydrocarbons and risk of bladder cancer among male offshore petroleum workers

Authors: Shala NK et al.

Summary: After tobacco smoking, the second leading cause of urinary bladder cancer is occupational exposure. This prospective case-cohort study included individuals from the Norwegian Offshore Petroleum Workers group (189 with cancer, 2065 without). Expert-developed job-exposure matrices were used to calculate petroleum-related hydrocarbon exposure levels. Compared to workers who were unexposed, workers with long-term (≥18.8 years) exposure to the benzene fraction of the petroleum stream had an increased risk of bladder cancer (HR1.89; p=0.044), and these risks remained 20 years later. The risk of bladder cancer was not increased with exposure to diesel exhaust, mineral oil or crude oil.

Comment: I think it is always important to be aware of data around risk factors for cancer. A Google search reveals that occupations that may be exposed to benzene include steel workers, printers, rubber workers, shoemakers, lab technicians, firefighters and petrol station employees. But the most common source of exposure to benzene is tobacco smoke!

Reference: Br J Cancer. 2023;129(5):838-51
Abstract

Clinical characteristics of secondary bladder cancer developing after low-/high-dose-rate brachytherapy to treat localized prostate cancer

Authors: Miyajima K et al.

Summary: The objective of this retrospective review was to investigate the associations between brachytherapy and secondary bladder cancer. The analysis included 2163 evaluable patients with localised prostate cancer who had undergone low- or high-dose-rate brachytherapy with or without external beam radiation therapy, or radical prostatectomy. According to age-adjusted regression analyses, the incidence of secondary bladder cancer was not significantly altered with brachytherapy compared to radical prostatectomy. However, a higher incidence of invasive bladder cancer was observed in patients who underwent brachytherapy. The authors recommended close follow-up in these patients to support early detection of disease.

Comment: Radiation works for prostate cancer. But if you listen to the urologists…it has problems! One of these is a risk of secondary bladder cancer. This is one of the reasons we stopped adjuvant radiotherapy in stage 1 testicular seminoma! Interestingly, this retrospective study suggested that brachytherapy (when compared to radical prostatectomy) did not increase the incidence of secondary bladder cancer, however it was linked to a higher incidence of invasive bladder cancer.

Reference: Int J Clin Oncol. 2023;28(9):1200-6
Abstract

Impact of surgical margin and extent of lymphadenectomy on oncologic outcomes in plasmacytoid urothelial carcinoma

Authors: Davaro F et al.

Summary: These researchers retrospectively examined the outcomes of 67 patients (median age 71 years; 79.1% male) with plasmacytoid urothelial carcinoma who underwent radical cystectomy with pelvic LN dissection. Patients showed improved OS (p=0.02) and DFS (p=0.05) with optimal LN dissection. Multivariable regression analysis also showed that OS was improved with optimal LN dissection (p=0.03) as well as negative soft tissue margins (p=0.01). The optimal LN count cut point for OS and DFS was 19. OS was not improved with perioperative chemotherapy (p=0.46). The researchers concluded that surgical intervention should aim to remove ≥20 LNs, with negative soft tissue margins.

Comment: Plasmacytoid urothelial carcinoma is an unfavourable variant. It is generally rapidly progressive and is widely infiltrative. It is known to spread along fascial planes and into the peritoneum. Most patients are upstaged at re-resection. Data does suggest that they can be chemo-responsive, with reasonable pathological complete response and downstaging rates following neoadjuvant chemotherapy - albeit lower than for standard urothelial cancer. This retrospective study showed that optimal LN dissection was associated with improved survival, but peri-operative chemotherapy was not. My experience is that moving quickly is the key to this subtype. If you are opting to move direct from TURBT to radical cystectomy, this should be done within weeks. If you are opting for neoadjuvant chemotherapy, then restaging should be done during and at completion, with a plan for surgery within weeks of completion. My experience is that this subtype can progress very quickly, even after a good response to treatment.

Reference: Urol Oncol. 2023;41(9):389.e7-13
Abstract

Sequential intravesical gemcitabine-docetaxel vs. Bacillus Calmette-Guérin (BCG) in the treatment of non-muscle invasive bladder cancer

Authors: Bukavina L et al.

Summary: Recent data have shown that intravesical sequential gemcitabine-docetaxel is an effective and well-tolerated option for treatment-naïve high-risk non-muscle-invasive bladder cancer. This preliminary cost-effectiveness analysis compared intravesical sequential gemcitabine-docetaxel with BCG in this setting. Gemcitabine-docetaxel was found to be as effective as BCG, with both treatment regimens resulting in a gain of 1.76 QALYs. At 2 years, gemcitabine-docetaxel was less costly than BCG, with a substantially lower mean cost per patient ($7090 vs. $12,363). The cost-effectiveness of gemcitabine docetaxel persisted after one-way sensitivity analyses.

Comment: Momentum for sequential intravesical gemcitabine/docetaxel chemotherapy in BCG-resistant/treated/refractory patients is growing. This is now being administered in Australia on a semi-regular basis, particularly following the disappointing results for hyperthermic mitomycin C. These data here confirm that it is a cost-effective option. I have given atropine prior to dosing in several patients, which has helped them retain both drugs for an hour, as specified in the protocol.

Reference: Urol Oncol. 2023;41(9):391.e1-4
Abstract

Staging fluorodeoxyglucose-positron emission tomography/computed tomography for muscle-invasive bladder cancer

Authors: Richters A et al.

Summary: These researchers used data from a nationwide population-based study to explore the use of staging FDG-PET/CT in patients with muscle-invasive bladder cancer. Among a total of 2731 patients, 69.1% underwent CT only, 22.2% underwent CT and FDG-PET/CT and 8.6% did not undergo CT. A larger proportion of patients were staged as cN+ with CT and FDG-PET/CT than with CT only (35.8% vs. 10.6%). Of the patients who were staged with CT as cN0, 21.9% were upstaged to cN+ following FDG-PET/CT. Patients with cN+ disease and those who were staged with FDG-PET/CT had higher rates of preoperative chemotherapy. Patients staged as cN+ with CT and FDG-PET/CT had higher concordance with pathological LN stage after radical cystectomy than those who were staged as cN+ with CT only (50.0% vs. 39.3%).

Comment: This is tricky. I certainly use a fair bit of FDG-PET in staging bladder cancer patients, but there is no doubt that there will be some false positives. Inflammation and infection are possible reasons for FDG uptake in a regional LN. In this very large retrospective study, in the cohort with both PET and CT, PET upstaged 22% of patients from cN0 to cN+ disease. And interestingly, in those who did not proceed with neoadjuvant chemotherapy, but went direct to radical cystectomy, only 50% of the positive LN on PET were confirmed by histopathology. However, this was higher than using CT, where only 39% of positive LN were confirmed by histopathology. Additionally, sensitivity of both approaches was also poor. For those with pN+ in histopathology, PET/CT detected only 40%, while CT alone detected only 7%. So, if you are like me and use a lot of PET, don't overly rely on the results. Someone once said to me that an anagram of nuclear medicine is 'unclear medicine'!

Reference: BJU Int. 2023;132(4):420-7
Abstract

Definition and diagnosis of oligometastatic bladder cancer: A Delphi consensus study endorsed by the European Association of Urology, European Society for Radiotherapy and Oncology, and European Society of Medical Oncology Genitourinary Faculty

Authors: Bamias A et al.

Summary: A consensus group of 29 experts used a modified Delphi method to formulate a consensus statement on the definition and staging of oligometastatic bladder cancer. The proposed definition was "*A maximum of three metastatic sites, all resectable or amenable to stereotactic therapy*". The only organs not included in the definition were the pelvic lymph nodes. No consensus was reached on the role of FDG-PET/CT for staging. Experts proposed that if a patient shows a favourable response to systemic treatment, they are likely to be suitable for metastasis-directed therapy.

Comment: Most clinicians treating bladder cancer also treat prostate cancer, and have been immersed in the oligometastatic treatment paradigm. Many of us adopt a metastasis-directed approach for oligometastatic prostate cancer, but bladder cancer is not the same! It is important to define oligometastatic disease in bladder cancer, which this paper has done. Several consensus statements were made. One important one was that metastasis-directed therapy should follow a favourable response of oligometastatic disease to systemic therapy. Unlike prostate cancer, bladder cancer can progress rapidly, and treating oligometastatic disease with SABR and then reassessing in 3 months may result in the patient being undertreated and having developed widespread symptomatic metastatic disease before restaging. I agree that if there is truly oligometastatic bladder cancer, systemic treatment should be given first, and then SABR reserved for residual oligometastatic disease.

Reference: Eur Urol. 2023;84(4):381-9
Abstract

Robot-assisted radical cystectomy versus open radical cystectomy

Authors: Khetrapal P et al.

Summary: This was a systematic review with meta-analysis which compared the perioperative, oncological and QOL outcomes following robot-assisted versus open radical cystectomy for bladder cancer. A total of eight RCTs enrolling 1024 patients were included in the review. While both treatment approaches had similar complication rates, robot-assisted surgery was associated with a shorter length of stay in hospital (p=0.02). Patients who underwent open radical cystectomy had a shorter operative time (-76min; p<0.001), yet they also experienced greater blood loss (233mL; p<0.001) and had a higher chance of experiencing a thromboembolic event (OR 1.84; p=0.04) or receiving a transfusion (OR 2.35; p<0.001). There were no significant differences in positive surgical margin or lymph node yield rates. Following surgery, patients who underwent robot-assisted surgery showed significantly improved physical functioning/wellbeing (p<0.001) and role functioning (p=0.007), however, no improvement in overall health-related QOL was recorded. PFS and OS were similar between treatment groups.

Comment: Here we go again! Who doesn't love a robot? Well, this meta-analysis examined eight trials including 1024 patients. They found that robot radical cystectomies were associated with a shorter hospital stay but similar complication rates. However, venous thromboembolism was more common and blood loss requiring transfusions were higher in open surgery. Does this come down to surgeon preference and cost?

Reference: Eur Urol. 2023;84(4):393-405
Abstract

The impact of dose reduction of Bacillus Calmette–Guérin on oncological outcomes and toxicity in non-muscle invasive bladder cancer

Authors: Azuri W et al.

Summary: The objective of this systematic review with meta-analysis was to explore the impact of dose-reduced BCG in patients with non-muscle invasive cancer. A total of 13 RCTs including 2963 patients were identified. There was no significant difference between a full dose and any dose reduction for recurrence (p=0.7) or progression (p=0.93). Compared to dose-reduced BCG, those who received a full dose had more local (RR 0.81; p<0.01) and systemic (RR 0.53; p<0.01) side effects. Oncological outcomes did not differ across the various BCG strains included in the analysis.

Comment: The global BCG shortage continues to wax and wane. One way to overcome the shortage is to give less BCG. This has been done with minimal data. This meta-analysis aims to provide some data to support the use of BCG dose reduction. They found that in 13 randomised trials including almost 3000 patients, there was no difference in oncological outcomes with dose-reduced BCG, but there was a reduction in both local and systemic side effects. I think I'm still not comfortable administering dose-reduced BCG, particularly for induction. My approach during the BCG shortage is to use alternate strains in maintenance and to give full dose oncotice for induction. What are other people's approaches?

Reference: Bladder Cancer. 2023;9(3):227-36
Abstract

Bladder Cancer Research Review™

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.

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.