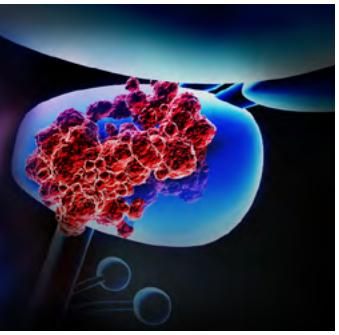
AUA Annual Meeting
2023 Conference Review™
Focus on Prostate Cancer



Making Education Easy

28 April – 1 May, 2023

In this review:

Abbreviations used in this issue:

ARSI = androgen-signalling inhibitor; **BCG** = bacillus Calmette–Guérin; **BOO** = bladder outlet obstruction; **BPH** = benign prostatic hyperplasia; **CN** = cytoreductive nephrectomy; **DAC** = prostatic ductal adenocarcinoma; **DFS** = disease-free survival; **DU** = detrusor underactivity; **GFP** = green fluorescent protein; **HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **IPSS** = International Prostate Symptom Score; **(m)RCC** = (metastatic) renal cell carcinoma; **(n)MIBC** = (non-) muscle-invasive bladder cancer; **OR** = odds ratio; **PAC** = acinar adenocarcinoma of the prostate; **PARPi** = poly (ADP-ribose) polymerase inhibitor; **PD-L1** = programmed death ligand-1; **PHI** = Prostate Health Index; **TURP** = transurethral resection of prostate.

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Welcome to our review of the 2023 American Urological Association (AUA) Conference held in Chicago, USA.

This year the annual AUA meeting offered over 100 hours of seminars and plenary sessions exploring the very latest advances in urology medicine, research, innovative technologies and updates in clinical guidelines. Here we share some of the highlights, including the exciting new Break Wave™ lithotripsy device, which could transform outpatient stone management by providing an effective, well-tolerated and non-invasive office-based treatment option. Another innovative device was LithoVue Elite™, a single-use flexible ureteroscope which provides real-time reporting of intrarenal pressure which may help to reduce the risk of adverse outcomes during ureteroscopy. Continuing with further technological developments, researchers in the US presented data on how the heterogenous group of patients with bladder pain have been broken down into helpful clinical phenotypes by machine learning techniques. Another paper of interest details the significant differences in concentrations of *Lactobacillus* detected in the tumour microbiome of patients with nMIBC who do and do not respond to BCG therapy, with co-cultures finding that *Lactobacillus* increased BCG internalisation in vitro.

We hope you find these and the other presentations detailed below interesting and informative, and we encourage you to send in your thoughts and feedback.

Kind Regards,

Dr Fairleigh Reeves
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Break Wave™ lithotripsy for urolithiasis

Authors: Dr Ben H Chew (Vancouver, Canada)

Summary: The safety and efficacy of the non-invasive SonoMotion Break Wave™ lithotripsy device for the treatment of urolithiasis were evaluated in this first-in-human, international, multicentre clinical trial. Eligible patients (n=44) with renal (59%) or ureteral stones (41%) received 30 minutes of Break Wave™ therapy (doses up to 8MPa) under continuous ultrasonography targeting in the emergency department, operating room or office/clinic. The procedure was completed in all patients; 50% received no medication and 36% received minor analgesics such as ketorolac 15-30mg. Most procedures (88%) achieved stone fragmentation, and CT revealed that 70% of patients had fragments ≤4mm or were stone-free. Among 36 patients who received the optimal dose setting, 75% had fragments ≤4mm and 58% were stone-free, while 71% of lower-pole patients had fragments ≤4mm and 29% were stone-free, and 89% with distal ureteral stones were stone-free. Within 90 days, 7% of patients were retreated with ureteroscopy or shock wave lithotripsy. Across all dose levels, no serious AEs, sepsis, cardiac arrythmia or haematomas were recorded. Ongoing trials are continuing to evaluate the use of Break Wave™ technology.

Comment: This is an exciting new technology. Early results suggest Break Wave™ Lithotripsy offers an effective and well-tolerated office-based treatment for stones. In most cases the procedure could be completed under local anaesthetic, and success rates for the stones treated in this study (6-10mm, ≈850HU) were similar to traditional extracorporeal shock wave lithotripsy (ESWL). Creative solutions are required to deal with the ever-growing pressure on our surgical waitlists. Availability of an effective 'pocket lithotripter' could substantially reduce the number of patients needing to be waitlisted for surgery. Given that many of the patients who come to the operating room require stenting, and often repeat procedures, the potential impact that this technology could have would be enormous. If upcoming research with the Generation 2 device lives up to expectations, this could transform outpatient stone management.

Reference: LBA01-14
Abstract

Impact of medical treatment on storage vs voiding symptoms and nocturia frequency

Authors: Dr Claus Roehrborn (Texas, USA)

Summary: This presentation shared a dynamic nomogram which was used to predict the risk of progression in men with benign prostatic hyperplasia (BPH) or lower urinary tract symptoms. The study enrolled a total of 9167 men across three trials who received either placebo, dutasteride, tamsulosin or dutasteride/tamsulosin combination therapy. Patients who received combination therapy had significant improvements versus either therapy alone in nocturia, voiding and storage symptoms. For patients administered dutasteride, better outcomes overall were associated with higher prostate-specific antigen and prostate volume levels versus placebo. Across all treatments, higher prostate-specific antigen levels were associated with greater improvements in nocturia and higher maximum urine flow rate levels were associated with improvements in voiding scores and nocturia. Higher post-void residual urine was associated with smaller improvements in voiding scores, and α-blocker use within 12 months was associated with smaller improvements in nocturia with tamsulosin versus combination therapy. Patients with higher prostate volume levels had poorer voiding scores with tamsulosin versus dutasteride and combination therapy. It was noted that the data illustrates the need for personalised treatment strategies for BPH management.

Comment: One of the challenges in managing patients with benign prostatic hyperplasia (BPH) is guiding patient choice amongst the ever-expanding list of available therapeutic options. In a world where one size does not fit all, the role of the urologist in patient counselling is essential. In his late-breaking abstract, Dr Roehrborn reported on an interactive web-based nomogram (www.bphtool.com), which considers multiple clinical parameters to predict the impact of medical treatment on likelihood of urinary retention and IPSS. Unsurprisingly, post-void residual urine played a dominant role in influencing outcomes. While these sorts of nomograms may not alter our recommendations as clinicians, they can be powerful educational tools to illustrate the rationale for treatment to patients. Practical decision aids in BPH will be important for clinicians and patients alike as the field of BPH management continues to grow.

Reference: LBA01-02
Abstract

The bladder tumor microbiome may augment response to BCG in non-muscle invasive bladder cancer

Authors: Zaeem Lone (Ohio, USA)

Summary: Formalin-fixed bladder tumours from 47 patients with non-muscle-invasive bladder cancer (nMIBC) were analysed in this clinical study, to compare differences in the urinary microbiome prior to intravesical bacillus Calmette–Guérin (BCG) therapy. Overall, 23 patients responded (no recurrence 2 years after BCG therapy), while 24 did not, and the microbiome of these two cohorts differed significantly according to both next-generation sequencing (p=0.042) and shotgun metagenomics (p=0.047), with significantly higher concentrations of *Lactobacillus* present in those who responded. Increasing concentrations of *Lactobacillus* concentrations in co-cultures significantly improved the internalisation of BCG-GFP in urothelial carcinoma versus controls (16% vs. 6% p<0.001).

Comment: A significant proportion of patients will fail BCG treatment, but we don't currently have reliable clinical markers to predict treatment response. Rather than analysing urine culture (as previous studies in this field have done), this study analysed fresh and formalin-fixed tumour samples to characterise the bladder tumour microbiome. When they compared BCG responders and non-responders there was a significant difference in the tumour microbiome. In particular, *Lactobacillus* was enriched in responders. Nuanced tools to predict BCG response will allow us to better counsel our patients, but more importantly it will hopefully lead to the development of strategies to mitigate mechanisms of non-response. In their co-culture experiments, Lone et al. found that *Lactobacillus* increased BCG internalisation in vitro. Of note, administration of oral *Lactobacillus* in combination with intravesical Epirubicin was associated with improved progression-free survival in a previous clinical study. Lone's study provides justification for clinical trials to investigate *Lactobacillus*-BCG combination therapy.

Reference: PD25-08
Abstract

The role of cytoreductive nephrectomy with immune checkpoint inhibitor therapies in metastatic renal cell carcinoma murine model

Authors: Jee Soo Park (Sorokdo, South Korea)

Summary: The role of cytoreductive nephrectomy (CN) has been significantly reduced since the CARMENA trial demonstrated non-inferiority of sunitinib alone; however the trial showed that particular sub-groups of patients with metastatic renal cell carcinoma (mRCC) may still benefit from CN. The objective of this study was to examine the role of CN alongside ICI therapy in terms of the perspective tumour immune microenvironment. Pulmonary metastatic orthotopic murine mRCC models were developed for low- and high-tumour burden, with significant differences in median survival between these groups (p<0.05). Upfront CN plus ICI was associated with significantly improved survival outcomes in the low-tumour burden model versus deferred CN plus ICI. Similar findings were recorded in the high-tumour burden model, however there was no significant difference in survival between CN only and ICI only, or between upfront CN plus ICI and deferred CN plus ICI. The tumour microenvironment was altered by CN, with increases in M1 tumour-associated macrophages, and simultaneous decreases in M2 tumour-associated macrophages.

Comment: The role and timing of cytoreductive nephrectomy (CN) in the era of immunotherapy remains unclear. In their orthotopic pulmonary metastatic tumour models, Park et al. compared upfront and deferred CN in low- and high-tumour burden models receiving nivolumab + ipilimumab (NIVO+IPI). In the low-tumour burden group, upfront CN outperformed the control and ICI-only groups. They also demonstrated that a significant reduction in lung nodules was seen, simply with removal of the primary kidney. Differences in the immune landscape were seen depending on the timing of surgery. For example, in low tumour-burden models, CN conferred an increase in M1 tumour-associated macrophages, whereas in high tumour-burden models, CN resulted in a decrease in the same cells. Future clinical trials are needed to evaluate the effect that differences in timing of intervention have on these patients. Understanding the role of the immune system in RCC will underpin clinical study design in this space.

Reference: PD17-04
Abstract

Baseline Prostate Health Index risk category and risk category changes during active surveillance predict grade reclassification

Authors: Dr Claire de la Calle (San Francisco, USA)

Summary: The value of repeating Prostate Health Index (PHI) tests over time during active surveillance were assessed in this clinical study of 382 patients with Grade group 1 (GG1) prostate cancer. PHI risk category was found to be a predictor of grade reclassification, with higher scores associated with lower rates of grade-reclassification survival (p<0.001). More upgrading occurred in men with a consistently high-risk category PHI (3-4) or an increase in PHI risk category from baseline (32.1% vs. 20.9%; p=0.048).

Comment: As we expand our indication of active surveillance, particularly as we include a greater number of low-intermediate risk patients, we need better tools to risk-stratify patients. Evidence-based individualised approaches to surveillance strategies are needed. Active surveillance protocols cannot be one-size-fits-all. Although PHI is not routinely used by many Australian clinicians, it is a non-invasive test that may provide additional information to help identify patients that are at higher risk of reclassification. In this study, PHI was predictive of grade reclassification, however only patients with GG1 disease at diagnosis were included. Future studies in this space must include low-intermediate risk patients, as this is a particularly challenging group to classify.

Reference: MP38-04
Abstract

First-in-human experience using the LithoVue Elite™ single use ureteroscope to measure intrarenal pressure

Authors: Dr Ben H Chew (Vancouver, Canada)

Summary: This presentation reported on the first-in-human experience of the LithoVue Elite™ ureteroscope in Canada, involving 46 patients (median age 62.5 years; median BMI 29.4) undergoing ureteroscopic lithotripsy. Physicians were provided with a ureteral access sheath, a pressure bag set at 150mmHg and hand irrigation with 60cc syringe. At a median procedure time of 31.9 minutes, intrarenal pressure remained <60mmHg for 91.3% of the time, with a median intrarenal pressure of 30.0mmHg and maximum 177.0mmHg. Patients who did not require ureteral access sheath or with tight ureters experienced longer relative cumulative time ≥60mmHg, and patients with hypertension or Asian ethnicity had higher pressures and longer relative cumulative time ≥20mmHg. The 11/13 Fr and 12/14 Fr ureteral access sheaths decreased pressure significantly more than the 10/12 Fr sheath. Intrarenal pressure was not associated with body mass index, age, pre-stenting or preoperative α-blockade.

Comment: We are all conscientious about limiting our intrarenal pressure to reduce the risk of adverse outcomes during ureteroscopy. However, until recently it has not been a parameter that we have been able to assess easily and practically during routine surgery. Several AUA abstracts reported on this topic using different devices. Chew et al. described their first-in-human experience with the LithoVue Elite™, a single-use flexible ureteroscope which provides real-time reporting of intrarenal pressure. A wide range of intrarenal pressures were recorded across the series. They found that a surgeon reported that a 'tight ureter' correlated with higher pressures, whereas access sheath use and pre-stenting was more likely to be associated with lower pressures. As this type of technology becomes more accessible, it will be great to see further research clarifying the magnitude and duration of 'safe pressures' and tips and tricks for achieving consistent low-pressure operating.

Reference: PD28-07
Abstract

Distinct phenotypes of bladder pain identified in the multidisciplinary approach to the study of chronic pelvic pain research network dataset

Authors: Dr Oluwarotimi Nettey (Texas, USA)

Summary: These researchers applied self-reported symptom data from 130 premenopausal female individuals in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain research cohort to unsupervised machine learning algorithms. The machine learning techniques identified three distinct symptom clusters, which showed concordance across a single cohort and a larger multi-site study: nonurological pelvic pain (localised pain unrelated to the urination cycle), myofascial pain (stranguria, sensation of incomplete bladder emptying, urinary urgency, high symptom bother/severity) and bladder-specific pain (worsened by bladder filling, relieved by emptying). Compared to the other phenotypic clusters, patients with myofascial pelvic pain were found to have an increased number of flares (p=0.009), greater pelvic floor tenderness (p=0.01), more diffuse body involvement (p=0.02) and greater pain severity (p<0.001), as well as anxiety, sleep disturbances, severe sexual dysfunction and decreased relationship scores. It was noted that further research into the associations between these phenotypes and their response to therapy targeting bladder pain is warranted.

Comment: Research utilising artificial intelligence featured in many benign and cancer abstracts. In this multicentre study, machine learning was used to break down the heterogenous group of patients with bladder pain into helpful clinical phenotypes. Analysis of validated symptom instruments demonstrated three distinct clusters of symptoms (myofascial pelvic pain, bladder-specific pain, non-urological pelvic pain). The authors suggest that this stratification may obviate the need for detailed pelvic examination. While I'm not sure that we're ready to give away clinical examination, this certainly serves as a reminder of the importance of detailed history-taking. Chronic pelvic pain is notoriously difficult to treat, and symptoms are not always urological in origin. Stratification tools like this will be particularly valuable once they can be used to predict treatment response.

Reference: PD05-01
Abstract

Detrusor ultrastructural study predicts long term voiding outcomes in male patients with detrusor underactivity who underwent transurethral resection of prostate (TURP)

Authors: Dr Amanda Chung (Sydney, Australia)

Summary: The detrusor ultrastructure features associated with long-term voiding outcomes were examined in this study of 27 men (mean age 78 years) with detrusor underactivity (DU; n=23) or bladder outlet obstruction (BOO; n=4) who have undergone TURP. The mean postvoid residual urine was 630mL in men with DU. Following TURP, all patients with BOO voided. At 3 months, 39% of patients with DU were catheter-free, while 61% were re-catheterised, and 29% were catheter-free at long-term follow-up. Voiding outcomes were not associated with bladder contractility index, voiding efficiency or postvoid residual urine. Ultrastructural studies revealed that in patients with DU, voiding outcomes were associated with collagenosis (p=0.041) and myocyte derangement/irregularity (p=0.034). In all patients, poorer long-term voiding outcomes and catheter dependence were associated with moderate-severe changes in myocyte size variation, increased cell separation, increased intercellular collagen and degeneration (p=0.029; OR for catheter dependence 5.5).

Comment: It was fantastic to see so many excellent abstracts presented by Australian Urologists. Out of Sydney, Dr Chung reported findings of a detrusor ultrastructural study assessing patients with detrusor underactivity (DU) or bladder outlet obstruction who underwent TURP. At long-term follow-up, less than one third of DU patients were catheter-free. Characteristic detrusor ultrastructural features were associated with poor long-term voiding outcomes and catheter dependence. Many patients with detrusor underactivity are frail. If a cystoscopy and biopsy can be used to accurately predict voiding outcomes following TURP we could potentially avoid futile surgery in a significant proportion of patients. However, we don't fully understand the capacity for detrusor remodelling. It will be interesting to see how relieving bladder outlet obstruction impacts on detrusor structure in follow-up studies.

Reference: LBA01-20
Abstract

Using genomic and transcriptomic properties to determine androgen response in ductal prostate cancers and determine efficacy of poly(ADP-ribose) polymerase inhibitors with androgen signalling inhibitors therapy in vitro

Authors: Assoc Prof Weranja Ranasinghe (Melbourne, Australia)

Summary: The genomic and transcriptomic characteristics of prostatic ductal adenocarcinoma (DAC) were analysed in this clinical study, as well as the androgen response and efficacy of PARPi plus androgen-signalling inhibitor (ARSI; enzalutamide) therapy. A total of 20 (DAC) and 10 acinar adenocarcinoma of the prostate (PAC) tumours were dissected from radical prostatectomy tissue, and matched for volume, grade and stage. Analyses revealed that PAC tumours had lower rates of mutations than DACs. A distinct DAC cluster was detected, with enrichment of HR pathways and downregulation of AR pathways in comparison to PAC. PARPi plus ARSI reduced DAC organoid viability of HR proficient (287R) and *BRCA2* heterozygous-mutated (201.1A-Cx) cells more effectively than either of the therapies alone, regardless of HR status.

Comment: We know that treating ductal cancer is difficult, as androgen deprivation therapy is not as effective. As treatment options for prostate cancer continue to expand, we must be able to establish which treatments are likely to be successful or futile for individual patients so that we don't expose them to unnecessary interventions, or waste precious healthcare resources. Personalised treatment will rely on understanding the molecular subtyping of cancers. This will no doubt be incorporated into routine clinical practice before we know it. Raanasinghe et al. demonstrated that the mutational profiles of ductal cancers were distinct from acinar adenocarcinoma. They also reported synergy between PARPi and ARSIs in ductal patients. We eagerly await their planned neoadjuvant clinical trial.

Reference: PD04-02
Abstract

Results from the extended follow-up in patients with muscle-invasive bladder cancer in the CheckMate 274 trial

Authors: Professor Matthew Milowsky (North Carolina, USA)

Summary: Professor Milowski shared these updated results from extended follow-up of the CheckMate 274 trial, which found a DFS benefit with nivolumab versus placebo following radical resection in high-risk muscle-invasive urothelial cancer and MIBC. At a median of 36.1 months, patients in the trial with MIBC continued to demonstrate improvement in DFS (HR 0.44 [PD-L1 ≥1% HR 0.44]; [PD-L1 <1% HR 0.74]), non-urothelial tract recurrence-free survival (HR 0.64) and distant metastasis-free survival (HR 0.70). A total of 17.3% of patients in the nivolumab arm and 5.8% in the placebo arm experienced grade 3-4 treatment-related AEs, which was consistent with previous findings. It was concluded that these data support the use of nivolumab as standard of care in this population.

Comment: Extended follow-up (3-year) results were presented for CheckMate 274, a phase 3 randomised controlled trial of adjuvant nivolumab versus placebo in high-risk muscle-invasive urothelial cancer. 40-50% of the patients included had received prior neoadjuvant chemotherapy. Trial treatment was administered for up to 1 year. 14% of patients discontinued treatment due to AEs in the nivolumab group, and there were three treatment-related deaths. A sustained response was seen in this latest update. A significant difference was observed in median DFS in nivolumab versus placebo (22 vs. 10.9 months). The DFS benefit was particularly pronounced in patients with PDL1 ≥1% (52.6 vs. 8.4 months). Updated subgroup analysis stratified by neoadjuvant treatment status was not presented, however in the original 2021 NEJM publication, a larger effect size was seen in those who had previously received neoadjuvant chemotherapy.

Reference: LBA02-08
Abstract

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Independent commentary by Dr Fairleigh Reeves

Dr Fairleigh Reeves is a urological surgeon with a subspecialty interest in prostate cancer diagnosis and management. She is a fellow of the Royal Australasian College of Surgeons and has completed a fellowship in Uro-Oncology and Robotic surgery at Guy's and St Thomas's Hospital in London. Fairleigh has a PhD in prostate cancer from The University of Melbourne and is passionate about providing evidence-based, patient-centred care.