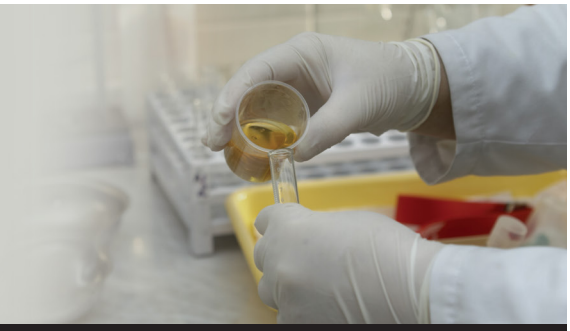
Urology RESEARCH REVIEW™



Making Education Easy

Issue 52 – 2023

In this issue:

Abbreviations used in this issue

BPH = benign prostatic hyperplasia
CI = confidence interval
COVID = coronavirus disease
ICI = immune checkpoint inhibitor
IV = intravenous
MI = minimally invasive
MIS = minimally invasive surgery
OAB = overactive bladder
OCD = obsessive-compulsive disorder
ORR = objective response rate
OS = overall survival
PFS = progression-free survival
QoL = quality of life
RCC = renal cell carcinoma
RCT = randomised controlled trial
SNP = single nucleotide polymorphism
TKI = tyrosine kinase inhibitor
UI = uncertainty interval

Welcome to Issue 52 of Urology Research Review.

First up we take a look at a review investigating the global burden of benign prostate hyperplasia and discover that the absolute burden of this disease is rising at an alarming rate in most of the world, particularly in low-income and middle-income countries that are currently undergoing rapid demographic and epidemiological changes. Following on, a study investigating the safety and efficacy of phenylephrine administration for the treatment of ischemic priapism informs that most patients responded to aspiration and phenylephrine without needing to proceed to surgical shunting, and that hypertension side effects were uncommon and manageable. Other topics covered in this issue include survival with lenvatinib plus pembrolizumab in advanced renal cell carcinoma, Australian trends in pelvic organ prolapse treatment, robotic versus open cystectomy for bladder cancer, robot-assisted retroperitoneal lymph node dissection, and repeat transurethral resection for pathological T1 bladder cancer.

I hope you enjoy reading this issue and look forward to any comments and feedback.

Kind regards,

Andrew Kennedy-Smith
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The global, regional, and national burden of benign prostatic hyperplasia in 204 countries and territories from 2000 to 2019: A systematic analysis for the Global Burden of Disease Study 2019

Authors: GBD 2019 Benign Prostatic Hyperplasia Collaborators

Summary: This study used Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 analytical and modelling strategies to estimate prevalence and global trends in benign prostatic hyperplasia (BPH) and the effect on disability-adjusted life-years (DALYs). There were an estimated 94.0 million (95% UI 73.2-118) prevalent cases of BPH in 2019 versus 51.1 million (95% UI 43.1-69.3) cases in 2000, while the age-standardised prevalence was 2480 per 100,000 people (95% UI 1940-3090); an increase in prevalent cases of 70.5% (95% UI 68.6-72.7), while the global age-standardised prevalence did not change (-0.770%; 95% CI -1.56 to 0.0912). Age-standardised prevalence ranged from 6480 per 100,000 (95% UI 5130-8080) in eastern Europe to 987 per 100,000 (95% UI 732-1320) in North Africa and the Middle East. The absolute DALY burden increased between 2000 and 2019 across all socio-demographic index (SDI) quintiles, with the most rapid increases in the middle SDI quintile (94.7%; 95% CI 91.8-97.6), the low-middle SDI quintile (77.3%; 95% CI 74.1-81.2), and the low SDI quintile (77.7%; 95% CI 72.9-83.2). Changes in age-standardised DALY rates were smaller, but the low, low-middle, and middle SDI quintiles saw small increases, while the high and high-middle SDI quintiles had small decreases.

Comment: Health-disease trends parallel wealth and socio-economic trends, and studies like this help to forecast outcomes and provide an opportunity for us to consider what might be anticipated both locoregionally and globally. The authors document the exponential rise of BPH over two decades from the turn of the millennium, primarily in low-, low/middle- and middle-income populations, and primarily attributable to aging and population growth. Some of the greatest increases of BPH morbidity have been in the South Pacific. Over the two decades, global wealth grew significantly and middle-income countries are catching up to high-income countries. Human capital is measured as the population's expected lifetime earnings and the largest source of worldwide wealth. Middle-income countries saw significant increases in their share of global human capital wealth over this period. So, the solutions to the problem of increasing BPH disease burden in these middle-income populations, requiring treatment and human resource, might be available within the populations themselves. But global wealth inequality is growing, with low-income countries' share of global wealth little changed over the two decades, despite population growth. In addition, the effects of the COVID pandemic are expected to translate to an up to 14% projected loss of total human capital in low-income countries going forward. All this is of course at the expense of declining wealth in renewable natural capital, both globally and most notably in low-income countries. The challenge going forward will be how to address growing health needs in the face of widening wealth inequality and unsustainable management of natural assets globally. Both urgently need correcting. And we may need to refocus on delivering BPH management to poorer folks and defocus on costly techy novel treatment options for mild disease in the wealthy and the frail and elderly, which is a bit of a moral challenge.

Reference: Lancet 2022;3(11):E754-E776
Abstract

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Survival by depth of response and efficacy by International Metastatic Renal Cell Carcinoma Database Consortium subgroup with lenvatinib plus pembrolizumab versus sunitinib in advanced renal cell carcinoma: Analysis of the phase 3 randomized CLEAR study

Authors: Grünwald V et al.

Summary: This exploratory analysis of the open-label, multicentre, randomised, phase III CLEAR trial assessed OS by tumour response after 6 months treatment with oral lenvatinib 20 mg/day plus IV pembrolizumab 200 mg every 3 weeks or sunitinib 50 mg/day for 4 weeks and 2 weeks off. Landmark analyses by tumour shrinkage indicated that patients receiving lenvatinib/pembrolizumab with a confirmed complete response or >75% target-lesion reduction after 6 months had a 24-month OS probability of ≥91.7%. Landmark analysis by disease progression indicated that patients who had no progression by 6 months had a reduced likelihood of death in both arms. Patients with an International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification of intermediate/poor had longer median PFS (22.1 vs 5.9 months) and a higher ORR (72.4% vs 28.8%) with lenvatinib/pembrolizumab than with sunitinib. Results also favoured lenvatinib/pembrolizumab in IMDC-favourable patients and in those with or without target kidney lesions.

Comment:

I take two messages from this paper:

1. ICI-based combination regimens have become the standard of care for management of metastatic renal cell carcinoma, and achieved significantly greater clinical response across all IMDC risk groups, than did TKI alone.
2. Tumour shrinkage and especially complete response at 6 months after starting anticancer treatment portend very good longer-term cancer-specific survival.

I have three observations:

1. Renal cancer cell type is not specified anywhere in the paper and then supplementary data, and it seems non-clear cell tumour was included in both study groups.
2. 75% of patients in each group had nephrectomy prior to starting systemic anti-cancer treatment.
3. 70% had lung metastases and 45% had lymph node metastases.

I have just one wish:

1. That Pharmac considers this paper and considers funding ICIs in addition to TKIs for at least 6 months for patients with metastatic clear cell or non-clear cell renal cell carcinoma.

Reference: Eur Urol Oncol. 2023;S2588-9311(23)00028-7
Abstract

Independent commentary by Mr Andrew Kennedy-Smith FRACS, MB BCh

Andrew is a full-time consultant urologist at Wellington Hospital, with commitments in both private and public urology practice. He grew up in Zimbabwe and South Africa, undertook his specialist surgical and urological training in New Zealand and Australia, and Fellowship training in Cardiff, Wales and Paris, France. His interests include general adult urology, laparoscopic and minimally invasive urologic surgery, surgical management of kidney cancer, kidney transplantation, evaluation and treatment of urinary incontinence and prolapse, laparoscopic pelvic floor reconstruction and urology prosthesis surgery.

Urinary analysis of *FGFR3* and *TERT* gene mutations enhances performance of Cxbladder tests and improves patient risk stratification

Authors: Lotan Y et al.

Summary: This retrospective pooled analysis of two multicentre, prospective studies in US patients aged ≥18 years and Singaporean patients aged >21 years with haematuria (gross haematuria n = 484, microhaematuria n = 320) assessed an enhanced Cxbladder test that incorporated DNA analysis of six single nucleotide polymorphisms for the *FGFR3* and *TERT* genes. In the pooled cohort, the enhanced Cxbladder-Detect (risk stratifies patients and detects positive patients) for detection of urothelial carcinoma had a sensitivity of 97% (95% CI 89-100), specificity of 90% (95% CI 88-92), and negative predictive value of 99.7% (95% CI 99-100). Overall, 83% of patients were negative and required no further work-up. Among 133 enhanced Cxbladder-Detect-positive patients, 59 patients had a confirmed tumour, with 19 having low-grade non-invasive papillary carcinoma or papillary urothelial neoplasm with low malignancy potential, while 40 tumours were high-grade Ta, T1-T4, and Tis, including concomitant carcinoma in situ. Among 74 patients with normal cystoscopy, 41 tested positive by SNP analysis. Enhanced Cxbladder-Triage (risk stratified patients) and Cxbladder-Detect had greater specificity than first-generation Cxbladder tests ($p < 0.001$).

Comment: Cxbladder has become established in evaluation of haematuria across New Zealand and increasingly elsewhere in the world. The request form isn't quite plug-and-play-for-dummies, a challenge for generalists. And funders have grappled with appreciating the cost savings from using these tests. Early in the COVID pandemic, and needing to reduce face-to-face contact, the value of a non-invasive test delivered close to home was obvious. Cxbladder's sensitivity to detect urothelial cancer has been patently excellent, but specificity is somewhat lower and there is still quite a need for standard investigations following Cxbladder testing. The test is getting better though, with additional SNPs and new algorithms. This study pooled data from 900 patients from Singapore and centres in the US that applied the new enhanced tests, "detect+", "triage+" and "detect+ triage+". Performance improved across the board compared to the original Cxbladder tests, notably specificity to 78-90%. Miss rate (false negatives) were rare and all missed lesions were low grade or papillary urothelial neoplasm of low malignant potential and potentially clinically insignificant. This seems to me significant improvement, and is likely to progress Cxbladder uptake globally.

Reference: J Urol. 2023;209(4):762-772
Abstract

Safety and efficacy of phenylephrine administration for the treatment of ischemic priapism: An opportunity for quality improvement in periprocedural safety assessment

Authors: Scarberry K et al.

Summary: This retrospective review assessed the use of hourly, low- or high-dose phenylephrine (≤1000 µg or >1000 µg) for acute ischemic priapism (AIP) in 123 patients (median age 40 years) by monitoring adverse haemodynamic events amongst risk profiles. Median time from AIP onset to presentation was 11 hours; 97 (78.9%) men received phenylephrine and detumescence was achieved nonoperatively in 62 (63.9%) men with a mean priapism duration of 8.7 hours. Mean AIP duration was 8.8 hours for those resolving with phenylephrine versus 57.3 hours for those without resolution ($p < 0.001$). Among low- (500 µg) and high- (2000 µg) dose phenylephrine recipients, the median duration of AIP was 10 and 12 hours, without a significant difference in AIP resolution between the groups. Twenty-one patients (17.1%) were considered at risk of a phenylephrine complications and four (4.1%) discontinued the agent due to haemodynamic changes.

Comment: Priapism remains a true urological emergency, with potential for long-term morbidity and cavernosal fibrosis from delayed treatment. It is often a night-time call-back, and sometimes delegated to more junior team members to fix. The management is stepwise and detailed in guidelines, but somewhat ad hoc with a range of options and in particular various doses of intracavernosal sympathomimetics recommended. There are risks associated with injecting adrenaline and phenylephrine. This is a single-institution retrospective study over 10 years. Most patients had intervention, most patients responded to aspiration and phenylephrine without needing to proceed to surgical shunting, and hypertension side effects from phenylephrine were uncommon and manageable. The resolution with phenylephrine dosing above 1000 µg was similar to dosing less than 1000 µg. Presumably some patients in the higher-dose group had not responded to lower dosing and needed the higher dose. Aspiration and irrigation seems important. And for patients with delayed presentation, <36 hours, doing nothing and hoping for spontaneous resolution seems overly optimistic or nihilistic.

Reference: Urology 2022;169:115-119
Abstract

Australian trends in the treatment of pelvic organ prolapse in the non-mesh era

Authors: Mollah T & Brennan J

Summary: This retrospective (2005-21) cohort study used three large Australian Government databases to assess contemporary trends in the types and incidence of pelvic organ prolapse surgery after the removal of transvaginal mesh for clinical use. Overall, 408,881 pelvic organ prolapse procedures were carried out with the number of procedures peaking in 2005-2006 at 537.8 per 100,000 age-standardised female population, and decreasing thereafter by an average 3.5% per year to 329.0 per 100,000 in 2018-19 (-38.8%; $p < 0.001$). There was a sudden increase (23.1%) in private operative procedures between 2019-20 and 2020-21, from 218.2 to 268.6 per 100,000 ($p < 0.001$). Laparoscopic and abdominal pelvic organ prolapse repair has increased 115.8% from 13.7 to 29.6 per 100,000 between 2005-06 and 2020-21. The most common age group to undergo a procedure has increased from 55-64 years to 65-74 years over the last 15 years.

Comment: This is a tidy retrospective review of prolapse management in Australia over the past 15 years or so. I have wondered what happened to all the patients who would have been considered for prolapse surgery prior to the mesh debacle, who are now not coming forward for mesh surgery. And this review provides some insights:

- Prolapse didn't go away, but overall surgical interventions declined following the public concerns about mesh, and its removal from the market in Australia (and New Zealand)
- We reverted to technically easy native tissue surgeries (and their well-recognised failure rates)
- We re-committed (somewhat) to the more invasive open abdominal and technically more challenging laparoscopic abdominal approaches for prolapse repair, that achieve apical support
- And we (or patients) deferred surgery by a decade.

The paper makes note of an uptick in surgery in private hospitals since 2019, and certainly I agree that the availability of the robotic platform in the private sector may have facilitated robot-assisted laparoscopic sacrocolpopexy. But interpretation is made difficult by the data from the public sector for 2019-2021 not being available to the authors at the time of writing. The authors also acknowledge that the constraints on public surgeries during the COVID pandemic may have shifted some elective surgeries into private. Whilst it has become fashionable to sound alarms about inexperienced surgeons performing unfamiliar surgeries, and the need for credentialing, it may be counterproductive to discourage provision of prolapse management and engagement with a more successful operation than native tissue repair. And it smells a bit of protectionism.

Reference: ANZ J Surg. 2023;93(3):469-475
Abstract

Robotic versus open cystectomy for bladder cancer: Synthesizing the data from current systematic reviews and meta-analyses

Authors: Aminoltejari K et al.

Summary: This summary of six systematic reviews and meta-analyses examined the use of robotic assisted radical cystectomy (RARC) versus open radical cystectomy (ORC) in patients with bladder cancer. RARC had lower estimated blood loss and transfusion rates, but longer operative time. There was also inconsistent evidence for an effect of RARC on hospital length of stay. Overall complication rate, major complication rate, and oncologic outcomes did not differ between groups. Health-related quality of life (QOL) outcomes could not be compared between studies because of statistical and methodological heterogeneity.

Comment: The review of the reviews that compare open with robot-assisted MIS cystectomy! The review captures several of the allures of robotic surgery and why urology has been so enthusiastic about it. Namely:

- We are inherently technophiles;
- The Emperor's New Clothes phenomenon means we believed the expert and corporate messaging that enhanced endoscopic vision and surgical ergonomics and control translates to improved clinical outcomes;
- We believed the experts that the long-term morbidities of incontinence and erectile dysfunction could be overcome by doing the procedure "better"; and
- That the only harms of robotics are limited to costs, and older men who have worked hard all their lives and paid taxes deserve a more expensive treatment.

Which is tough as robots are potentially useful, but we've struggled to clearly define just how useful. Open cystectomy has perioperative complications in some two-thirds of patients and an approach that mitigates some of these would be welcome. The authors found 43 papers that met their initial inclusion criteria and filtered these to 29 articles for analysis. This report indicates we're not there yet, with only blood loss and transfusion reduced in the robot patients. But three studies assessed QoL and although the differences did not reach statistical significance, there was a trend towards overall improved QoL in the robotic group compared with open cystectomy at 3- and 6-months post-surgery. For the present, whilst both approaches remain, at least they are oncologically equivalent and clinical outcomes are broadly similar.

Reference: Ann Surg Oncol. 2023;30(5):2976-2987
Abstract

Real-time documentation of the effect of onabotulinumtoxin A detrusor injection in OAB patients – preliminary results

Authors: Schulte-Baukloh H et al.

Summary: This study used an app-controlled automated diary pod to document the onset and course of the effect of detrusor injection with onabotulinumtoxin A (OnabotA-DI) for overactive bladder in 17 patients (15 women; mean age 64.6 years). Analysis of reliably documented micturitions showed a continuous reduction in frequency each day after the first day. For 24-hour voiding, from a mean frequency of 12.83 in the 3 days before injection, the frequency declined from 9.17 on day 5, 8.75 on day 10, 7.17 on day 15, and 5.75 on day 20 (all $p < 0.05$).

Comment: It isn't uncommon for patients having intravesical Botox injections for the first time to make contact early after the procedure to report no improvement or worsening of symptoms, but that things are much more settled by the time the repeat urine culture is back and they return to clinic for review. Patients having repeat treatments seem more attuned to expecting a delay in benefit. And yet science tells us that at a cellular level the Botox binds almost immediately and the direct effects are similarly instantaneous. However, we now appreciate that the effects of Botox are complex with release of several neurotransmitters in addition to blockade of neuromuscular transmission. Overactive bladder is a symptom disease, and we have relied on patient-reported symptoms to assess outcome from interventions, which is important. But additionally useful, for both clinician and patient, is objective measurement. This paper presents data from a small patient group using a cool novel device that automatically records a bladder diary on an app, and demonstrated a significant reduction in voiding frequency from day 3 post treatment and continued reduction in frequency out to 3 weeks. And it's a cool bit of tech. Depending on costs for the device, it may be a useful adjunct in the clinic when asking patients to chart a bladder diary. Not everyone (OCD patients excluded) finds the recording of a bladder diary to be an easy exercise, and their efforts are sometimes overlooked in a busy clinic setting, with the paper diary being left unviewed in a bag.

Reference: Toxins (Basel) 2023;15(1):30
Abstract

Reduced versus standard intradetrusor onabotulinumtoxinA injections for treatment of overactive bladder

Authors: DiCarlo-Meacham AM et al.

Summary: This study examined whether a reduced injection technique of five OnabotA-DI injection sites was noninferior to standard technique 20 injection sites for treatment of overactive bladder in 77 patients. Overactive Bladder Questionnaire-Short Form (OBQ-SF) and International Consultation on Incontinence Questionnaire scores ($p < 0.001$) improved in both treatment arms. Overall treatment success was 68% with no difference between treatments, and the study arm did not demonstrate noninferiority to the control arm. There was a difference on the OBQ-SF quality of life survey favouring the control arm (CI 0.36-20.5; $p = 0.04$), but not in any other validated questionnaires. Subjects in the study arm were more likely to express a willingness to undergo the procedure again (OR 3.8; 95% CI 1.42-10.67; $p = 0.004$).

Comment: It seems to me that almost everyone has a different technique for intravesical Botox injections:

- operating theatre or office
- rigid or flexible cystoscopy
- pre-procedure local anaesthetic/analgesia/antibiotics or not
- Botox dose
- volume of dilution and number of injections
- depth of injections
- trigone or trigone sparing.

And the permutations of these combinations are numerous. Perhaps this is understandable as bladder Botox is relatively novel. This prospective RCT in non-neuropathic patients with OAB focusses on one of these variations, namely the optimal number of injections. From the diagrams, it appears the investigators did trigone-sparing. Either flexible or rigid cystoscopy was performed and all procedures were performed in the office on awake patients without sedation. What we can say with confidence is that Botox works, procedure-related pain is common, but other significant adverse events are low. What can't be determined from this study is the optimal number of injections. There appears to be greater improvement in OAB symptoms and QoL at 4-12 weeks in patients having 20 injections compared with patients having five injections. However, UTI rate in the 20 injection group was double that in the five injection group. And willingness to undergo re-treatment in the five injection group was double that of the 20 injection group. Perhaps the most important but missing outcome is durability of response. How were the patients faring at 6 and 12 months?

Reference: Neurourol Urodyn. 2023;42(1):366-374
Abstract

Robot-assisted retroperitoneal lymph node dissection: A systematic review of perioperative outcomes

Authors: Garg H et al.

Summary: This systematic review assessed robot-assisted retroperitoneal lymph node dissection (R-RPLND) versus open RPLND (O-RPLND) for management of testis cancer based on data from 4222 patients (single-arm studies n = 459; comparative studies n = 3763). For primary R-RPLND, operative time ranged from 175-540 minutes and the major complication rate was 4.1%, while for post-chemotherapy R-RPLND, the operative time ranged from 134-550 min with a major complication rate of 8.5%. Conversion to open surgery was required in 2.2% of primary R-RPLND and 9.0% of post-chemotherapy R-RPLND recipients. R-RPLND was associated with a lower transfusion rate (14.5% vs 0.9%; p = 0.0001) and a lower complication rate (18.5% vs 7.8%; p = 0.002) than O-RPLND.

Comment: RPLND is one of Urology's Great Big Surgeries. And particularly in the post-chemo setting is technically quite demanding. These are young patients and post open surgery complications, particularly wound- and bowel-related, are troublesome. Hence the interest in a minimally invasive approach. Initially reported with pure laparoscopy, and now using a robotic platform to achieve MIS, this international systematic review looks at published outcomes from minimally invasive R-RPLND compared to O-RPLND. Inevitably with a small volume complex surgery, robust comparative data is lacking. Of the 42 studies assessed, 37 were single-arm series, but there were five studies that directly compared open with R-RPLND, one of which was prospective, and the comparative studies included most of the patients for the review. There's a fair mix of primary and post-chemo RPLND in both groups. The authors note that O-RPLND is performed widely and in low-volume centres, whereas R-RPLND tended to be from higher-volume centres. That said, robotic surgery appeared to be oncologically as effective as open surgery, but with fewer complications and earlier discharge from hospital. Whilst pure laparoscopic RPLND struggled to be more than a niche procedure, because of technical difficulty, it seems the robotic approach, in a younger generation of surgeons, may come to replace O-RPLND. For the patients' good.

Reference: BJU Int. 2023;Feb 8 [Epub ahead of print]
Abstract

Do we need repeat transurethral resection after en bloc resection for pathological T1 bladder cancer?

Authors: Yanagisawa T et al.

Summary: This Japanese, retrospective, multicentre analysis of 106 patients who underwent *en bloc* resection of bladder tumour (ERBT) for pathological T1 (pT1) bladder cancer assessed the clinical significance of repeat transurethral resection (n = 50) and surgical margin status. There was no difference between those undergoing repeat transurethral resection and those who did not in either 2-year recurrence-free survival (55.1% vs 59.9%) or 3-year PFS (80.6% vs 82.6%). No patients were upstaged to pT2 on repeat transurethral resection. There were no recurrences at the original site in 51 patients with negative horizontal surgical margins. A positive vertical margin was an independent prognostic factor of worse PFS. Repeat transurethral resection identified six pTa/is residues in patients with a positive horizontal margin, and three pT1 residues in one patient with a positive vertical margin or other adverse pathological features.

Comment: Non-muscle-invasive bladder cancer is our most expensive cancer because of high rates of recurrence and invasive and costly long-term follow-up surveillance. So at least we can understand the challenge. *En bloc* transurethral resection of bladder tumour (TURBT) respects the principles of cancer surgery:

- To achieve a complete excision when technically possible, and
- To allow the pathologist to comment on margins.

As residual disease at the primary site is much less common following *en bloc* resection than following traditional TURBT, one of the costly interventions, namely early repeat transurethral resection (TUR), may be unnecessary and could be omitted. Particularly for Ta lesions, but also for T1, which is reported in multicentre trials. There remain naysayers to this approach, and international guidelines still support re-TUR for T1 tumours. But the guidelines don't distinguish between initial TURBT performed en bloc and TURBT performed traditionally. What this paper looks to define in patients having *en bloc* TURBT is who might benefit from early re-TUR. And it is patients with positive surgical margins, particularly at the tumour base, and those with adverse pathology features of invasion beyond the muscularis mucosae (pT1c) or lymphovascular invasion. Giving the pathologist a complete specimen makes their job more feasible. Inevitably T1 disease is more common post *en bloc*, as the muscularis mucosae is detectable and detrusor muscle is present, so the staging is accurate. I sense a revision to the guidelines.

Reference: BJU Int. 2023;131(2):190-197
Abstract

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