Urology Research Review™



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Issue 38 – 2019

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Abbreviations used in this issue

CI = confidence interval
CI = credible interval (Bayesian equivalent of CI)
DHB = District Health Board
ED = Emergency Department
HR = hazard ratio
MRI = magnetic resonance imaging
MUS = mid-urethral sling
NMIBC = non-muscle invasive bladder cancer
OS = overall survival
PFS = progression-free survival
PSA = prostate-specific antigen
RALP = robot-assisted laparoscopic radical prostatectomy
RR = relative risk
WBC = white blood cells

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Welcome to Issue 38 of Urology Research Review.

A recent US population-based cohort study has shown that 5α-reductase inhibitors may hide low-risk cancers from diagnosis and result in worse cancer-specific outcomes in men with prostate cancer. An informative, large systematic review and economic evaluation on surgical treatments for women with stress urinary incontinence is also an interesting read. Other topics covered in this issue include erdafitinib in locally advanced or metastatic urothelial carcinoma, transvaginal surgery using self-cut mesh for pelvic organ prolapse, bone fractures following urinary intestinal diversion, and asymptomatic bacteriuria in hospitalised patients.

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

Kind regards,

Andrew Kennedy-Smith
andrewkennedysmith@researchreview.co.nz

Association of treatment with 5α-reductase inhibitors with time to diagnosis and mortality in prostate cancer

Authors: Sarkar RR et al.

Summary: This US population-based cohort study used data from the Veterans Affairs Informatics and Computing Infrastructure and the National Death Index (2001-15) to determine whether pre-diagnostic use of 5α-reductase inhibitors (5-ARIs), which can reduce serum PSA levels by 50%, affected diagnosis delay, disease stage at diagnosis, or risk of prostate cancer-specific or all-cause mortality in 80,875 men with stage I-IV prostate cancer. Over a median follow-up of 5.90 years, the median time from first adjusted (adjusted by doubling the value) elevated PSA to diagnosis was greater among 5-ARI users than nonusers (3.60 vs 1.40 years; $p < 0.001$); the median adjusted PSA level at biopsy was also higher in 5-ARI users (13.5 vs 6.4 ng/mL; $p<0.001$). Multivariate regression analysis indicated that 5-ARI recipients had higher prostate cancer-specific (sub-distribution HR 1.39; 95% CI 1.27-1.52; $p<0.001$) and all-cause (HR 1.10; 95% CI 1.05-1.15; $p<0.001$) mortality than non-users. 5-ARI users were also more likely than nonusers to have Gleason grade ≥8 (25.2% vs 17.0%; $p<0.001$), clinical stage ≥T3 (4.7% vs 2.9%; $p<0.001$), node-positive (3.0% vs 1.7%; $p<0.001$), or metastatic (6.7% vs 2.9%; $p<0.001$) disease.

Comment: Far from being a disadvantage, or risk, as the conclusion from this paper suggests, my take from this report and dataset is that 5-ARIs hide low-risk cancers from diagnosis by halving the PSA level and probably by altering the pathological interpretation of biopsies. What is changed here is the denominator, leaving only the small subset of higher-risk tumours detected and available for inclusion in the study. We've learnt much from the prostate cancer prevention trials, only not what we expected to: that 5-ARIs don't prevent prostate cancer; that PSA is next to useless as a screening test; and that low-risk prostate "cancer" really isn't cancer; that 5-ARIs protect well people from becoming patients. Seems like it was a successful endeavour.

Reference: JAMA Intern Med. 2019;179(6):812-9
Abstract

Inclusion of a molecular marker of bladder cancer in a clinical pathway for investigation of haematuria may reduce the need for cystoscopy

Authors: Davidson PJ et al.

Summary: This modelling analysis of data from 571 patients with haematuria was conducted to assess the use of a urinary biomarker of bladder cancer (Cxbladder Triage™, CxbT) to a clinical pathway using CxbT and imaging where only test-positive patients would undergo secondary urological assessment and cytoscopy. In total, 44 transitional cell carcinomas were diagnosed after cystoscopy; two low-risk cancers were missed by CxbT, one of which was not detected by imaging. Combined imaging and CxbT had a 97.7% sensitivity and 99.8% negative predictive value.

Comment: As many NZ DHBs have now integrated CxbT testing into clinical practice, either for evaluation of haematuria or for follow up of low-risk bladder cancer patients, this is welcome data supporting the clinical utility of this test. It's not perfect, cystoscopy isn't perfect, nothing's perfect, but it is very good at excluding significant bladder cancer in patients with haematuria. The exclusion rate is lower than ours in Wellington, but we've not applied CxbT to patients with macroscopic haematuria. The positive diagnosis rate in microhaematuria in Wellington is quite low anyway, and a negative CxbT in the context of normal imaging is additionally reassuring. It's not yet clear what the exclusion rate must be to achieve cost benefit to the service, but the clinical benefits, patient acceptance and delivery closer to home are obvious.

Reference: N Z Med J. 2019;132(1497):55-64
Abstract

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Reference: 1. KEYTRUDA Data Sheet.

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Surgical treatments for women with stress urinary incontinence: the ESTER systematic review and economic evaluation

Authors: Brazzelli M et al.

Summary: This analysis used an evidence synthesis, a discrete choice experiment and an economic decision model to assess the use of nine different surgical treatments in 120 studies of stress urinary incontinence (SUI) in women and women's preferences. Most of the studies had 'high' or 'unclear' risk of bias. A network meta-analysis suggested that retropubic mid-urethral sling (MUS), transobturator MUS, traditional sling, and open retropubic colposuspension were more effective than other procedures for the primary outcomes of 'cure' or 'improvement'. The rate of tape and mesh exposure was higher after transobturator versus retropubic MUS or single-incision sling. The discrete choice experiment in 789 women using an anonymous online questionnaire, suggested that women prefer surgical treatments with no pain or mild chronic pain and shorter length of hospital stay, and those that have a smaller risk for urinary symptom reoccurrence. Cost-effectiveness analysis over a lifetime indicated that retropubic MUS is the least costly and most effective surgery.

Comment: It's a chunky abstract, 803 words, almost a manuscript. Perhaps this journal acknowledges clinician reality that the full paper is rarely read. They have therefore included enough content in the abstract to allow consideration of the work and included a self-editorial. I like it. Moreover, the paper is timely: mesh slings are under fire and now restricted; fascial slings are on the recovery; but (alas) I see defunct vaginal application procedures are also being revived. Denied access to mesh slings and unfamiliarity with the technique of fascial sling, it's inevitable that some surgeons will turn the clock back. This review is limited to mesh slings (single incision laparoscopic surgery, trans-obturator-tape [TOT] and retropubic), fascial slings, and open colposuspension. Retropubic mesh slings come out in the lead, with TOT and fascial slings close behind. This largely supports the data and practice we had prior to the mesh-down-under debacle and why those vaginal application procedures and colposuspension were replaced. The call for better data and further research is optimistic, the furore surrounding pelvic mesh likely to scupper new trials and block recruitment on these existing treatment options. We must accept that the opportunity to robustly study the panoply of surgeries was lost. Only new treatments, perhaps stem cells and biologicals, can hope for high-quality evaluation. At least we have a reasonable current gold standard for comparison – retropubic mesh or fascial sling. Provided we have the patients and the confidence to train the new generation of surgeons in these surgeries.

Reference: Health Technol Asssess. 2019;23(14): 1-306
Abstract

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Surgical interventions for women with stress urinary incontinence: systematic review and network meta-analysis of randomised controlled trials

Authors: Imamura M et al.

Summary: This network meta-analysis of 175 randomised controlled trials evaluated surgical interventions for stress urinary incontinence in a total of 21,598 women. The interventions with the highest 'cure' rates were traditional sling (89.4%), retropubic MUS (89.1%), open colposuspension (76.7%) and transobturator MUS (64.1%). The OR for cure versus retropubic MUS were 1.06 (95% *CI* 0.62-1.85) for traditional sling, 0.85 (95% *CI* 0.54-1.33) for open colposuspension, and 0.74 (95% *CI* 0.59-0.92) for transobturator MUS. Women were more likely to experience an 'improvement' after retropubic MUS or transobturator MUS versus other procedures. The OR versus retropubic MUS for 'improvement' were 0.76 (95% *CI* 0.59-0.98) for transobturator MUS, 0.69 (95% *CI* 0.39-1.26) for traditional sling, and 0.65 (95% *CI* 0.41-1.02) for open colposuspension. Mesh procedures had a higher repeat surgery and groin pain rate, but lower rates of suprapubic pain, vascular complication, bladder or urethral perforation and voiding difficulties after transobturator versus retropubic MUS.

Comment: This is another timely paper. It collates into a systematic review/meta-analysis the multiple existing trials on materials and surgical procedures that have directed and recorded the past 25 years of surgery for stress urinary incontinence in woman. The findings are similar to the Brazzelli paper: that the "traditional" mesh procedures and native tissue slings are as good as we thought they were, and somewhat better than colposuspension, and better than their predecessor surgeries that were abandoned for good reasons; and better than the even-less-invasive-mini-mesh-slings (why?) that most recently came to market, and largely disappeared again. Couldn't we have come to the same conclusions by employing common sense? Still, the anti-mesh tide seems now unstoppable and it's good to have a publication like this to balance the criticism, particularly in the event of a mesh-related complication case.

Reference: BMJ. 2019;365:l1842
Abstract

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Erdafitinib in locally advanced or metastatic urothelial carcinoma

Authors: Loriot Y et al.

Summary: This open-label, phase II study examined the use of the tyrosine kinase inhibitor of fibroblast growth factor receptor (FGFR)-4, erdafitinib 8 mg/day, in 99 patients with locally advanced, unresectable or metastatic urothelial carcinoma with pre-specified FGFR alterations. The erdafitinib confirmed response rate was 40% (3% complete response, 37% partial response). Among 22 patients who had received prior immunotherapy, the confirmed response rate was 59%. The median PFS duration was 5.5 months and the median OS duration was 13.8 months. 46% of patients reported treatment-related adverse events of grade ≥3, 13% of the patients discontinued treatment due to adverse events.

Comment: It must be statistics and lobbying that bamboozle the reviewers of reputable journals into accepting such a paper that demonstrates so very little clinical merit from an intervention, and at fierce financial cost and toxicity. Or perhaps it is that the journal publishes this paper to demonstrate the poor cost/benefit equation and discourage this intervention. This is a single arm study of advanced bladder cancer patients, unresponsive to standard chemotherapy. Half the patient group had moderate to severe side effects and almost 2/3 were unresponsive to the novel monoclonal antibody treatment. Median OS was just over 1 year. Amazingly, however, three patients had a complete response attributed to this treatment. Perhaps this is the positive and tantalising outcome from this study: if this outcome is truly a treatment response, deciphering what induced complete response in this tiny subset of poor prognosis patients, and how to extrapolate it to the larger group, is the scientific challenge.

Reference: N Engl J Med. 2019;381(4):338-48
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.

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Transvaginal surgery using self-cut mesh for pelvic organ prolapse: 3-year clinical outcomes

Authors: Gonocruz SG et al.

Summary: This retrospective analysis examined subjective and objective outcomes, complications, and recurrence and reoperation rates after transvaginal mesh surgery using self-cut mesh in 101 patients. Both 1- and 3-year follow up identified improvements in subjective and objective outcomes. Recurrences occurred in three patients and one patient required reoperation. One intraoperative complication (bladder injury) and four postoperative complications (two mesh exposure, one haematoma, one increase in post-voiding residual) occurred.

Comment: Not of direct clinical relevance to us now, but interesting to reflect on whether the anti-mesh lobby would have gained the momentum it has if there had not been a branded kit-based product promoted by a massive corporate to mount a class action against. The results from this small retrospective 3-centre Japan-Philippines study showed very good outcomes, actually quite similar to the reported outcomes from kit-based procedures for transvaginal mesh prolapse surgery. I'm impressed that this is a recent dataset, and that despite the negative publicity, their patients came forward for transvaginal mesh prolapse surgery. Follow-up is short and their results may deteriorate with longer follow-up as some patients report mesh-tenderness and contraction, and there are delayed mesh erosions. However, I suspect these authors are subspecialists, understand the tissue planes and procedure and how to limit complications, select patients appropriately and counsel them carefully. Perhaps the undoing of Prolift and friends was the unbridled enthusiasm to perform this procedure by almost anyone and in almost any patient. There is a broader lesson to be learnt here.

Reference: Int J Urol. 2019;26(7):731-6
Abstract

Risk of bone fractures following urinary intestinal diversion: A population based study

Authors: Richard PO et al.

Summary: This Canadian analysis of administrative databases examined whether patients undergoing intestinal urinary diversion for bladder cancer are at increased risk for bone fracture secondary to chronic metabolic acidosis and bone loss. The fracture incidence rate in the bladder cancer cohort (n = 4301) versus matched controls was 4.41 versus 2.63 fractures/100 person-years, while in the non-bladder cancer cohort (n = 907) there were 5.67 versus 3.51 fractures/100 person-years (both $p < 0.001$). Multivariate analysis indicated a shorter fracture-free survival than matched cohorts in patients receiving intestinal urinary diversion for bladder cancer (HR 1.48) or non-bladder cancer (HR 1.48) reasons.

Comment: Cancer series mostly report on cancer outcomes, and early and direct complications of treatment. Older patients with poor risk bladder cancer proceeding to intestinal urinary diversion often die from the disease, or from old age and comorbidities. Chronic metabolic acidosis and osteoporosis aren't a major consideration. However, younger patients with more favourable disease NMIBC or post neoadjuvant chemotherapy T0 and those with benign disease enjoy survivorship. Bone complications become relevant and important. As with most complications, the best means to prevent this problem is not to have intestinal urinary diversion. Bladder conservation should be considered more frequently than it is, at present; better endoscopic surgery for NMIBC with en bloc resection in one, tri- and tetra-modal therapy for MIBC is another. On a more positive note, patients with bad bladder cancer are having better survival outcomes from current managements. Survivorship is a success. It behoves us to manage the patient holistically and actively address the unintended consequences of the reconstruction.

Reference: J Urol. 2019;202(2):319-25
Abstract

Preoperative MRI parameters predict urinary continence after robot-assisted laparoscopic prostatectomy in prostatic cancer patients

Authors: Fukui S et al.

Summary: This retrospective study assessed whether preoperative MRI could predict bladder neck location on postoperative cystography and the recovery of urinary incontinence after RALP in 270 consecutive patients. Pubic symphysis-prostate apex length (PAL) was shorter in patients with the bladder neck location above (higher group) versus below (lower group) the pubic symphysis (25.5 vs 29.1 mm; $p < 0.0001$). Those who were continent at 3 months had a longer membranous urethral length (MUL; 8.1 vs 6.7 mm; $p < 0.05$) and shorter PAL than those who were incontinent (26.0 vs. 28.1 mm; $p < 0.05$).

Comment: As I read this study, I thought "how useful"; many patients now coming forward for radical prostatectomy have had MRI in the diagnostic work-up and with a little more effort from radiology, we can better predict who is more likely to suffer postoperative urinary incontinence. Which may then assist patients in making decisions on treatment, choosing between options. But that thought in turn prompted recognition of certain assumptions. Surely this data can be extrapolated to open prostatectomy? Could the patients with short MUL and long PAL, at increased risk of urinary incontinence post RALP, also be at risk of worse urinary outcomes following radiotherapy? And so alas, this observation won't yet assist treatment choice, until the same MRI findings are studied in radiotherapy patients, and patients having open surgery. But it does refine the counselling of patients coming forward for RALP.

Reference: Diagnostics (Basel) 2019;9(3):pii:E102
Abstract

Risk factors and outcomes associated with treatment of asymptomatic bacteriuria in hospitalized patients

Authors: Petty LA et al.

Summary: This US retrospective cohort study examined factors associated with asymptomatic bacteriuria (ASB) treatment among hospitalised patients (n = 2733) and the association with clinical outcomes. In total, 2259 (82.7%) patients received antibiotics for a median of 7 days. ASB treatment was associated with older age (OR 1.10 per 10 years; 95% CI 1.02-1.18), dementia (OR 1.57; 95% CI 1.15-2.13), acutely altered mental status (OR 1.93; 95% CI 1.23-3.04), urinary incontinence (OR 1.81; 95% CI 1.36-2.41), leukocytosis (WBC >10,000/μL; OR 1.55; 95% CI 1.21-2.00), positive urinalysis (leukocyte esterase or nitrite, or >5 WBC per high-power field; OR 2.83; 95% CI 2.05-3.93), or a urine bacterial colony count >100,000 colony-forming units per high-power field (OR 2.30; 95% CI 1.83-2.91). ASB treatment was associated with longer hospitalisation after urine testing (4 vs 3 days; RR 1.37; 95% CI 1.28-1.47).

Comment: Bacteriuria is common in elderly patients admitted to hospital. It's probably common in elderly patients not admitted to hospital. And I agree that in the main, if asymptomatic, it doesn't warrant antibiotic treatment. And this study suggests that. However, before we set about removing the dipstix from the wards and ED, or rejecting laboratory-submitted urine samples from asymptomatic elderly inpatients, we should recognise the limitations on the conclusions of this study: it's a retrospective review and there may be non-apparent reasons why the treated patients were treated: their bacteriuria perhaps not truly asymptomatic; that the treated group stayed in hospital on average 1 day longer than the untreated group may not be causative; and the untreated group were just 17% of the total cohort. What I take from this paper is, think before ordering a test!

Reference: JAMA Intern Med. 2019;Aug 26 [Epub ahead of print]
Abstract

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