Update on the Postnatal Management of Antenatal Hydronephrosis

Gina M. Lockwood, MD, MS, FAAP
C. D. Anthony Herndon, MD, FAAP, FACS

Crowdfunding Campaign Characteristics in Patients with Urological Cancers

<table>
<thead>
<tr>
<th>2018</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Jason L. Lui, BA</td>
<td>$10,000</td>
</tr>
<tr>
<td>Nathan M. Shaw, MD</td>
<td>$12,000</td>
</tr>
<tr>
<td>Michael S. Leapman, MD</td>
<td>$50,000</td>
</tr>
<tr>
<td>Hannah S. Thomas, MBChB, MS</td>
<td>$100,000</td>
</tr>
<tr>
<td>Benjamin N. Breyer, MD, MAS</td>
<td>$200,000</td>
</tr>
</tbody>
</table>

Intravesical or Systemic Therapy for Bacillus Calmette-Guérin-Unresponsive Nonmuscle Invasive Bladder Cancer?

Mathieu Roumiguié, MD
Peter C. Black, MD

Robotic Cystectomy Has Not Lived Up to the Hype—Except Perhaps in One Very Important Way

Mark Tyson, MD, MPH

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Ben H. Chew, MD
Abdulghafoor Halawani, MD
Victor K.F. Wong, BSc

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Update on the Postnatal Management of Antenatal Hydronephrosis

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University of Iowa, Iowa City

C.D. Anthony Herndon, MD, FAAP, FACS
Children’s Hospital of Richmond at Virginia Commonwealth University

Perinatal urinary tract dilation (UTD), or hydronephrosis, occurs in approximately 1% of all pregnancies and may be attributed to transient dilation, vesicoureteral reflux (VUR) or an obstructive uropathy. There is a lack of evidence regarding the use of continuous antibiotic prophylaxis (CAP), postnatal imaging and the optimal interval for followup for these patients. The Urinary Tract Dilation classification system was developed in 2014 by specialists in multiple fields in an effort to standardize nomenclature for the grading of UTD across the prenatal and postnatal continuum. Additionally, a risk stratification system was developed to guide evidence-based recommendations for further evaluation and management.1

UTD Classification System

The UTD classification system combines the objective and subjective characteristics of the commonly used Society for Fetal Urology (SFU) grading system and the anteroposterior renal pelvic diameter (APD) system. Measured ultrasonographic parameters include APD, central calyceal dilation, peripheral calyceal dilation, appearance of kidney parenchyma, appearance of ureters and bladder, and unexplained oligohydramnios (see figure). Patients are stratified into three levels of risk: low (UTD P1), intermediate (UTD P2) and high (UTD P3).

Postnatal recommendations are based on this assigned level of risk and guide the use of CAP, need for subspecialist referral, appropriate interval of surveillance renal ultrasonography and the need for additional imaging (table 1). A shared decision-making model is endorsed, with guidance based on individualized patient risk and benefit assessment.

Postnatal Ultrasonographic Evaluation of Antenatal UTD

Renal bladder ultrasonography (RBUS) is the initial imaging of choice in a child with prenatally


Continued on page 4

<table>
<thead>
<tr>
<th>UTD Classification</th>
<th>Definition/Circumstance</th>
<th>Followup Ultrasound (2nd Ultrasound)</th>
<th>Antibiotic Prophylaxis</th>
<th>VCUG/CeVUS</th>
<th>MAG3/fMRU</th>
<th>Urology/Nephrology Consultation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolved</td>
<td></td>
<td>3–9 months of age</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Low Risk (P1)</td>
<td>APD ≤10 mm OR central calyceal dilation</td>
<td>3–6 months of age</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Intermediate Risk (P2)</td>
<td>APD ≥15 mm OR peripheral calyceal dilation</td>
<td>1–3 months of age</td>
<td>Consider upon discharge</td>
<td>May consider</td>
<td>May consider at &gt;6 weeks of age</td>
<td>Inpatient consult or expedited referral</td>
</tr>
<tr>
<td></td>
<td>APD ≥15 mm OR ureteral dilation</td>
<td>1–3 months of age</td>
<td>Recommended upon discharge if ureteral dilation ≥ 7 mm</td>
<td>Recommended</td>
<td>May consider at &gt;6 weeks of age</td>
<td>Inpatient consult or expedited referral</td>
</tr>
<tr>
<td>High Risk (P3)</td>
<td>Findings in P2 OR abnormal parenchymal thickness or appearance or abnormal bladder</td>
<td>1 month of age</td>
<td>Recommended upon discharge</td>
<td>Recommended</td>
<td>Recommended at &gt;6 weeks of age</td>
<td>Inpatient consult or expedited referral</td>
</tr>
</tbody>
</table>

CeVUS, contrast-enhanced voiding urosonography. fMRU, functional magnetic resonance urography. MAG3, mercaptoacetyl triglycine.
diagnosed UTD because of its availability, low cost, non-invasiveness and lack of radiation. For optimal assessment of UTD, RBUS should be performed after 48 hours of life, as studies during the first 48 hours might underestimate the degree of dilation. RBUS lacks diagnostic specificity although increased dilation does correlate with increased need for surgery. The timing of subsequent RBUS after discharge should be based on the degree of dilation of the initial postnatal RBUS.

**Risk of Urinary Tract Infection (UTI) and CAP: Assessment of Individual Risk**

Historically, patients with antenatal UTD were empirically prescribed CAP to prevent UTI, a practice that was not evidence based. Rates of UTI in patients with antenatal UTD range from 8%–22% with identifiable risk factors (table 2) that include high-grade hydronephrosis,5 distal ureteral dilation >7 mm,6 female gender,7 intact foreskin,8 presence of obstructive uropathy and renal scarring on renal scintigraphy.9

Historical data on the benefits of CAP in prevention of UTI in patients with UTD are conflicting and derived from retrospective or single-center reviews. Recent data from the multicenter prospective SFU hydronephrosis registry demonstrated two important findings which include a significant benefit of CAP in those patients with ureteral dilation ≥7 mm3 and no benefit for isolated ureteropelvic junction-like hydronephrosis.4 No studies to date have addressed the benefit of CAP on renal scarring in patients with UTD and those that have assessed benefits in subpopulations (eg VUR) are underpowered.10 Potential risks of long-term antibiotic prophylaxis include bacterial resistance and effects on the gut and urinary microbiome.

Some studies have shown circumcision to be an equally preventive alternative to CAP in prevention of UTI in boys with UTD.9 Amoxicillin is the primary antibiotic prescribed for CAP in the newborn, and after 2 months of life the most commonly prescribed antibiotic is trimethoprim-sulfamethoxazole. In general, the overall patient risk for UTI should be considered when deciding whether to initiate CAP.

### Adjunct Imaging for UTD: Assessment of Individual Risk

**Voiding cystourethrogram (VCUG) is the gold standard for diagnosis and grading of VUR.**

Frequent use of VCUG has been argued against given that VUR associated with prenatally diagnosed UTD has a high incidence of spontaneous resolution, and the clinical relevance of reflux in the absence of UTI with normal bladder function is unclear. Studies that assess whether or not patients with both UTD and VUR are at increased risk for UTI show conflicting results. It is largely acknowledged that diagnosis of VUR in this setting is to identify those patients at highest risk of recurrent pyelonephritis and its sequelae; UTD in isolation does not mandate performance of a VCUG in asymptomatic infants. Similar to CAP, a shared-decision making model that includes the risk of UTI should be used when determining the need for lower urinary tract imaging. A paradigm shift has taken place away from the indiscriminate use of VCUG.

Contrast-enhanced voiding urosonography is also used to detect VUR; this limits radiation and does have high sensitivity but does not allow for assessment of bladder and urethral morphology and is not available at most institutions.

Renal scintigraphy (RS) allows for the assessment of differential renal function and to differentiate between non-obstructive and obstructive UTD. A recent large review identified an APD cutoff of 15 mm to be predictive of the need for intervention.9 If warranted, RS should be deferred until after 6 weeks of age to allow for constitution of adequate renal blood flow. Its use should be considered in those in whom there is a high risk for decreased differential renal function (abnormal or thin parenchyma on ultrasonography). Indications for intervention include: deterioration of renal unit function to <40%, a decrease in differential renal function of ≥5% over time, symptoms (eg febrile UTI or feeding intolerance) or obstructive (flattened) drainage curve. Fortunately, a majority of patients with UTD will not need surgical correction and can be safely observed with serial RBUS imaging.10

In summary, the development of the UTD risk stratification system combined with recent prospective data from the SFU multicenter Hydronephrosis Registry has allowed providers to make evidence-based management decisions for patients.

#### Table 2. Risk factors for UTI in children with UTD and with known uropathies related to UTD

<table>
<thead>
<tr>
<th>Risk Factors for UTI</th>
<th>Children with UTD</th>
<th>Children with known uropathy at birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact foreskin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS UTD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal ureteral dilation &gt;7 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VUR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive uropathy (suggested by bilateral UTD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal scarring on renal scintigraphy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteropelvic junction obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior urethral valves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectopic ureter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duplex ureter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solitary kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicystic dysplastic kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder diverticulum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurogenic bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder extrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spina bifida</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral renal agenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horseshoe kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crossed-fused ectopia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cloacal extrophy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“The development of the UTD risk stratification system combined with recent prospective data from the SFU multicenter Hydronephrosis Registry has allowed providers to make evidence-based management decisions for patients.”

“**For optimal assessment of UTD, RBUS should be performed after 48 hours of life, as studies during the first 48 hours might underestimate the degree of dilation.”**

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Crowdfunding Campaign Characteristics in Patients with Urological Cancers

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University of Toronto, Ontario, Canada

Benjamin N. Breyer, MD, MAS
University of California, San Francisco


According to the National Cancer Institute, the cost of cancer care in the United States was $208.9 billion in 2020 and is expected to continue increasing (see figure). As treatment becomes more expensive, an array of economic burdens increasingly falls on patients. In addition to the direct expenses of cancer treatment, patients incur indirect costs—loss of work, family expenses and travel costs. These complex financial stressors contribute to the increasingly recognized financial toxicity of cancer. Financial toxicity, like other treatment toxicity (eg medication side effects), contributes to lower compliance with care and decreased medication adherence.

New strategies to fundraise for a person’s cancer care may provide a window into health care inequities by revealing the full scope of financial hardships encountered by patients and their support systems. In particular, online crowdfunding is now a common strategy for patients and their families to raise money to support their health care costs. Medical campaigns account for more than $650 million in donations annually through GoFundMe, the largest online crowdfunding platform. As the cost of health care continues to rise, crowdfunding serves as a means to cover health-related expenses. However, while raising funds may lessen individual financial pressures, crowdfunding does not fully address the broader unmet health care needs of patients.

Owing to the use of multiple advanced modalities and a protracted natural history, the survival rates of urological cancers have improved dramatically in the last few decades but these remain among the most expensive cancers to treat. There is a paucity of research exploring the characteristics of urological cancer crowdfunding campaigns. Understanding the financial needs of these patients guides clinical decision making for urologists and informs policy makers on the gaps in health care filled by crowdfunding. The highlighted study explores the characteristics of GoFundMe campaigns seeking financial relief for expenses related to urological cancers.

A total of 1,234 adult and pediatric patients with major urological cancers were included and narratives were reviewed to identify characteristics predicting campaign.

Figure. Estimates of national expenditures for cancer care (in billions of U.S. dollars [USD]) by cancer site and year. 1


The study found that campaign authorship is a key contributor to the financial success of a crowdfunding campaign. In the highlighted study, not only were most campaigns written by friends or family, but those campaigns also received more donations and higher donation amounts than self-authored campaigns (Table 2). Crowdfunding relies heavily on the size and depth of social networks. Campaigns written by others may better reach audiences outside the patient’s existing social network than those self-authored.

The emergence of online medical crowdfunding can help illuminate the scale of unmet financial needs encountered through contemporary urological cancer care. A closer look at the patterns of success may also reveal insights about prevailing social ideas on who is deserving of charity. In this study, campaign narratives that focused on one’s high moral character and contributions to society received more donations than those focused on disheartening circumstances, such as multiple negative events leading to the present devastating situation. Good character and past generosity draw on values of fairness and reciprocity, which are both strong motivators for collective action and charitable giving behaviors.

Primary malignancy type played a significant role in both the success, including demographic information, insurance status, campaign author identity and primary funding purpose (Table 1). The study found that campaign authorship, primary narrative appeal and cancer type were key factors to the financial success of a medical crowdfunding campaign.

“The cost of cancer care in the United States was $208.9 billion in 2020 and is expected to continue increasing.”

Table 1. Crowdfunding characteristics for patients with major urological cancers

<table>
<thead>
<tr>
<th></th>
<th>No. Kidney Ca (%)</th>
<th>No. Prostate Ca (%)</th>
<th>No. Bladder Ca (%)</th>
<th>No. Testicular Ca (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total campaigns</td>
<td>478 (39)</td>
<td>379 (31)</td>
<td>202 (16)</td>
<td>175 (14)</td>
</tr>
<tr>
<td>Child recipient (&lt;18 yrs)</td>
<td>77 (16)</td>
<td>0</td>
<td>3 (1)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Female gender</td>
<td>171 (37)</td>
<td>0</td>
<td>52 (27)</td>
<td>0</td>
</tr>
<tr>
<td>Primary wage earner</td>
<td>147 (31)</td>
<td>132 (35)</td>
<td>72 (36)</td>
<td>62 (35)</td>
</tr>
<tr>
<td>Loss of job/reduction of hrs due to illness</td>
<td>174 (36)</td>
<td>142 (37)</td>
<td>77 (38)</td>
<td>83 (47)</td>
</tr>
<tr>
<td>No insurance or underinsured</td>
<td>140 (29)</td>
<td>126 (33)</td>
<td>71 (30)</td>
<td>59 (34)</td>
</tr>
<tr>
<td>Campaign author:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self</td>
<td>63 (13)</td>
<td>55 (15)</td>
<td>29 (14)</td>
<td>30 (17)</td>
</tr>
<tr>
<td>Family</td>
<td>180 (38)</td>
<td>198 (52)</td>
<td>93 (46)</td>
<td>68 (39)</td>
</tr>
<tr>
<td>Friend</td>
<td>136 (29)</td>
<td>75 (20)</td>
<td>45 (22)</td>
<td>34 (19)</td>
</tr>
<tr>
<td>Unidentifiable</td>
<td>99 (21)</td>
<td>51 (13)</td>
<td>35 (17)</td>
<td>43 (25)</td>
</tr>
<tr>
<td>Purpose of funding:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical expenses</td>
<td>321 (67)</td>
<td>284 (75)</td>
<td>131 (65)</td>
<td>140 (80)</td>
</tr>
<tr>
<td>Nonmedical expenses</td>
<td>109 (23)</td>
<td>74 (20)</td>
<td>53 (26)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Medical + nonmedical expenses</td>
<td>175 (37)</td>
<td>158 (42)</td>
<td>70 (35)</td>
<td>100 (57)</td>
</tr>
<tr>
<td>Treatment status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active treatment</td>
<td>252 (53)</td>
<td>219 (58)</td>
<td>123 (61)</td>
<td>109 (62)</td>
</tr>
<tr>
<td>In remission</td>
<td>55 (12)</td>
<td>7 (2)</td>
<td>5 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>End of life or death</td>
<td>57 (12)</td>
<td>47 (12)</td>
<td>34 (17)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Primary appeal of campaign:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dishheartening circumstances</td>
<td>223 (47)</td>
<td>121 (32)</td>
<td>80 (40)</td>
<td>91 (52)</td>
</tr>
<tr>
<td>High moral character</td>
<td>167 (35)</td>
<td>142 (38)</td>
<td>71 (35)</td>
<td>55 (31)</td>
</tr>
<tr>
<td>Contributions to society</td>
<td>56 (12)</td>
<td>68 (18)</td>
<td>29 (14)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Unclear appeal</td>
<td>32 (7)</td>
<td>48 (13)</td>
<td>22 (11)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Reached financial goal</td>
<td>43 (9)</td>
<td>33 (9)</td>
<td>18 (9)</td>
<td>24 (14)</td>
</tr>
<tr>
<td>Median amount USD raised (IQR)</td>
<td>1,455 (575, 4,060)</td>
<td>1,515 (535, 4,100)</td>
<td>1,458 (620, 3,025)</td>
<td>3,400 (1,215, 8,380)</td>
</tr>
</tbody>
</table>

Table 2. Analysis of the number of campaign donations for major urological cancers

<table>
<thead>
<tr>
<th></th>
<th>Median No. (IQR)</th>
<th>% Difference after Adjustment (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca type:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular (referent)</td>
<td>43 (20, 88)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>17.5 (8, 43)</td>
<td>-19.5 (-31.8--5.1)</td>
<td>0.010</td>
</tr>
<tr>
<td>Prostate</td>
<td>20 (8, 43)</td>
<td>-18.8 (-30.9--4.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>Bladder</td>
<td>18 (8, 34)</td>
<td>-22.5 (-35.5--6.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Recipient age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (referent)</td>
<td>19 (8, 43)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Child (≤18 yrs)</td>
<td>44 (17, 107)</td>
<td>+42.0 (+16.8--72.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Campaign author type:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self (referent)</td>
<td>13 (6, 30)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td>18 (8, 43)</td>
<td>+21.2 (+4.1--41.2)</td>
<td>0.013</td>
</tr>
<tr>
<td>Friend</td>
<td>23 (10, 48)</td>
<td>+40.6 (+18.9--66.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unidentifiable</td>
<td>31 (12, 71.5)</td>
<td>+45.0 (+21.8--72.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary appeal of campaign:</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dishheartening circumstances (referent)</td>
<td>19 (8, 42)</td>
<td>+13.1 (+1.0--26.7)</td>
<td>0.033</td>
</tr>
<tr>
<td>High moral character</td>
<td>23 (10, 54)</td>
<td>+20.0 (+3.3--39.8)</td>
<td>0.019</td>
</tr>
<tr>
<td>Contributions to society</td>
<td>25 (10, 51)</td>
<td>-11.5 (-25.7--+5.4)</td>
<td>0.146</td>
</tr>
</tbody>
</table>

Univariate testing with Kruskal-Wallis and Wilcoxon rank-sum tests. Adjustment accounts for cancer type, age, gender, author type, financial purpose, cancer stage, amount of time online, number of social media shares and fundraising goal. P values in bold are statistically significant.
Table 3. Analysis of the campaign donation amount for major urological cancers

<table>
<thead>
<tr>
<th>Category</th>
<th>USD Median (IQR)</th>
<th>% Difference after Adjustment (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca type:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular (referent)</td>
<td>77 (59, 100)</td>
<td></td>
<td>0.613</td>
</tr>
<tr>
<td>Kidney</td>
<td>77 (56, 110)</td>
<td>+9.3 (–2.4 to 22.5)</td>
<td>0.121</td>
</tr>
<tr>
<td>Prostate</td>
<td>79 (53, 118)</td>
<td>+9.2 (–2.2 to 22.0)</td>
<td>0.119</td>
</tr>
<tr>
<td>Bladder</td>
<td>85 (55, 119)</td>
<td>+17.0 (3.1 to 32.6)</td>
<td>0.015</td>
</tr>
<tr>
<td>Recipient age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (referent)</td>
<td>79 (56, 116)</td>
<td></td>
<td>0.018</td>
</tr>
<tr>
<td>Child (≤18 yrs)</td>
<td>70 (54, 92)</td>
<td>–12.5 (–23.4 to 0.0)</td>
<td>0.052</td>
</tr>
<tr>
<td>Campaign author type:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self (referent)</td>
<td>71 (47, 109)</td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Family</td>
<td>76 (55, 115)</td>
<td>+11.9 (1.0 to 24.0)</td>
<td>0.031</td>
</tr>
<tr>
<td>Friend</td>
<td>58 (84, 118)</td>
<td>+17.4 (4.7 to 31.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Unidentifiable</td>
<td>83 (64, 110)</td>
<td>+21.7 (8.1 to 37.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Primary appeal of campaign:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disheartening circumstances (referent)</td>
<td>65 (49, 100)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High moral character</td>
<td>76 (51, 109)</td>
<td>+18.6 (5.4 to 33.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Contributions to society</td>
<td>84 (60, 121)</td>
<td>+25.7 (11.4 to 41.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unclear appeal</td>
<td>88 (68, 119)</td>
<td>+25.1 (8.9 to 43.7)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Univariate testing with Kruskal-Wallis and Wilcoxon rank-sum tests. Adjustment accounts for campaign type, age, gender, author type, financial purpose, cancer stage, amount of time online, number of social media shares and fundraising goal. P values in bold are statistically significant.

number of donations and average donation amount in campaigns. Testicular cancer campaigns received the highest number of donations; however, bladder cancer campaigns received the largest average donation amount (tables 2 and 3). Excluding testicular cancers, only 9% of all other urological cancers reached their financial goals (table 1). Compared to all other cancer patients, those with bladder cancer incur the highest lifetime treatment costs due to the diagnostic and therapeutic tools necessary to manage the illness. As a result, these campaigns received the most money, most campaigns did not reach their stated fundraising goal, reflecting potentially unmet financial burdens.

In the last 30 years, while new techniques, pharmacological options and treatment modalities have improved survival in patients faced with urological cancers, it has become increasingly difficult to improve health while maintaining reasonable costs and affordable care. Urological cancer patients, representing a substantial portion of all cancer cases in the U.S., face a large burden of cancer-related financial toxicity. The rising popularity of medical crowdfunding is concerning as it is a reflection of the unmet financial needs experienced by this population. As therapy improves, an important consideration must be placed on developing cost-effective approaches to lessen the financial toxicity for these patients. Clinicians can also focus on minimizing the financial toxicity of cancer care by involving financial counselors, insurance eligibility workers and social workers to address patient needs when appropriate.

“Urological cancer patients, representing a substantial portion of all cancer cases in the U.S., face a large burden of cancer-related financial toxicity.”

Robotic radical cystectomy has mostly failed to live up to the hype. Robotic approaches were originally developed as an alternative to open cystectomy in an effort to mitigate the risk of complications and expedite convalescence, but it hasn’t done either. In fact, the only 2 veritable benefits to emerge from a panoply of retrospective studies and 5 randomized trials are blood loss and wound complications. In the RAZOR study 25% of robotic patients required transfusion compared to 43% of open patients, and in the Memorial trial the estimated blood loss was about 24% lower.5,6 Wound complications were about half as common in both studies.1,2

However, with respect to most other outcomes related to length of stay and convalescence, the robot is not associated with meaningful improvement. In average terms, robotic cystectomy may facilitate an earlier discharge from the hospital by 12 to 24 hours, but in an era where most cystectomy patients are being entered into enhanced recovery protocols this advantage is diminishing.3 With respect to quality of life, non-wound related complications, cancer outcomes and readmissions, there does not appear to be much difference between the 2 approaches when one considers the totality of the evidence.4 This seems to hold true even with intracorporeal diversion.2

On the other hand, there are several advantages of open cystectomy that are readily apparent. The open approach is faster and less costly in terms of operating room time and expenditures.2 Some data suggest open cystectomy may be associated with fewer anastomotic strictures.8 When one considers all these factors on balance, it’s easy to see why many skilled open surgeons have not adopted robotic techniques for bladder cancer like many have for prostate or kidney cancer.

Yet, there is an important point worth making regarding the comparative effectiveness of robotic and open cystectomy. Even though robotic surgery has mostly failed to significantly improve perioperative outcomes to date, these innovations are potential steppingstones in the developmental pathway toward better systems. Had the evolution of the electric vehicle stopped with the hybrid models because of short battery life and cost, we would have never had the Tesla. To the extent that robotic surgical systems have facilitated next generation surgical tools, the robot has undoubtedly achieved some level of success, even while failing to empirically improve outcomes in the short term for bladder cancer patients.

One potential advancement is the Da Vinci® single-port (SP) platform. Introduced in late 2018, the SP robot has been adopted for prostate and kidney surgery, but radical cystectomy may be a more suitable application. The main problem with multiport robotic cystectomy is the catch-22 one faces when deciding whether to open for the diversion to save time, particularly for neobladders. However, when one considers the aggregate length of all the robotic ports, laparoscopic assistant ports and the incision to perform the extracorporeal diversion, this ends up being just as invasive as open cystectomy. The SP robot overcomes this challenge by joining together the benefits of both the robotic and open approaches through a single 4 cm periumbilical incision (see figure).7 The robotic cystectomy and lymphadenectomy is completed in the usual fashion robotically, and the neobladder (or conduit) is constructed through that single incision in an open fashion and then returned to the abdomen for intracorporeal urethral and ureteral anastomoses, similar to what has been described for the Xi.8

This hybrid robotic-open SP approach has several theoretical advantages over existing robotic approaches. First, the incisional footprint is smaller than the Xi robot and limited to what would otherwise be required for extraction anyway. Theoretically this may reduce pain and expedite convalescence but further study is obviously required. Second, and more importantly, it more closely replicates open neobladder reconstructive techniques without requiring a laparotomy incision. There are longstanding principles of neobladder reconstruction that are sometimes abandoned with intracorporeal techniques. While the importance of these principles can be reasonably debated, forgoing them for the sake of staying intracorporeal runs counter to the ostensible goal of minimally invasive surgery to replicate open techniques.

It’s important to note that hybrid SP cystectomy has numerous disadvantages and potential contraindications. The disadvantages mostly pertain to the SP instrumentation such as lack of variation in grip strength, lack of advanced energy devices such as vessel sealers and lack of different sizes for the robotic clips. The learning curve is also very steep, and our first few cases were exceptionally long. At this stage of development, the SP robotic approach is not ideal for locally advanced carcinomas or patients with extreme obesity.

Taken together, a sober reading of the literature suggests that the existing robotic techniques for cystectomy have not substantially improved most patient outcomes. It’s possible, and maybe even likely, that the SP robot will also fail to improve outcomes for bladder cancer patients. But this doesn’t mean that we should abandon ship. Given that there is so much room for improvement in the cystectomy population, any progress, even if only incremental, is preferable to the status quo. Forging a new frontier might be the only meaningful contribution that robots has made to bladder cancer patients to date, but it is an important one.

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Intravesical or Systemic Therapy for Bacillus Calmette-Guérin-Unresponsive Nonmuscle Invasive Bladder Cancer?

There has been a boom in clinical trial activity in patients with bacillus Calmette-Guérin (BCG)-unresponsive high risk nonmuscle invasive bladder cancer (NMIBC) since the AUA/U.S. Food and Drug Administration (FDA) Workshop on this disease state in 2013. This workshop and the ensuing dialogue led to the 2018 FDA Guidance document, which defined this disease state specifically and laid the foundation for clinical trial design.1 Clear definitions and trial design parameters, as well as a clear pathway to drug registration and a large unmet clinical need, have encouraged many sponsors to test their drugs in these patients who otherwise face radical cystectomy.

The results of single-arm registration trials in patients with BCG-unresponsive carcinoma in situ (CIS) have been reported or published for 5 different agents (summarized in the table), including 2 systemic immunotherapies (pembrolizumab and atezolizumab) and 3 intravesical therapies (nadofaragene fradenovec, oprotuzumab monatox, and N-803 plus BCG).2-6 Pembrolizumab has been approved by the FDA and is now only the second drug after valrubicin to be approved in this disease state. Oprotuzumab monatox was declined approval by the FDA in August 2021 pending additional data and analyses, and nadofaragene is currently under review. Parallel to these rigorous trials, we have observed an increased popularity of sequential gemcitabine/docetaxel in North America, which has arguably become the de facto standard of care in these patients based on multicenter retrospective evidence.7,8

While all these agents are welcome additions to the treatment armamentarium of urologists and medical oncologists, and they represent important options for patients who are truly ineligible for cystectomy or wish to pursue other options over cystectomy, the trial results raise many questions. How do we decide which agent to administer first in patients with BCG-unresponsive NMIBC? What should be the next line therapy if not cystectomy?

Five factors are most likely to guide drug selection in patients with BCG-unresponsive NMIBC:

1. Toxicity: Adverse event profiles, as summarized in the table, favor the use of intravesical agents over systemic immunotherapy. This is likely the most clinically significant difference between intravesical and systemic therapies.

2. Treatment burden: The agents summarized in the table are administered with widely variable schedules. Oprotuzumab monatox, for example, is administered 18 times in the first 3 months, during which nadofaragene fradenovec is administered only once. Treatment burden is associated also with additional financial toxicity for the patient.

3. Patient preference: Patients may seek out specific therapies, including systemic immunotherapy, based off perceived benefits. It is important to recognize that some patients may prefer systemic therapy over repeated catheterization of the bladder and instillation therapy, and some patients may not be able to hold intravesical drugs long enough to allow these agents to have optimal efficacy.

4. Efficacy: It is challenging to compare outcomes across the various single-arm trials, but these trials were designed with strict inclusion criteria with the intent of being compared to historical controls, so a cross-trial comparison is not unreasonable, although certainly to be viewed with caution. We also need to reserve judgement until we see publication and/or after FDA review. Given these significant caveats, N803 plus BCG appears to have better early efficacy than the other agents.

5. Practice patterns: Patients with NMIBC have been managed solely by urologists up until recently. The advent of systemic therapy for NMIBC has brought medical oncologists into this domain, and multidisciplinary care is now important across the bladder cancer spectrum. However, without evidence suggesting that systemic therapy is better than intravesical therapy and in the absence of a contraindication to intravesical therapy, practice patterns will likely determine that intravesical therapy is the default treatment for BCG-unresponsive NMIBC. It is nonetheless essential to inform the patient of all options.

6. Cost: The cost of systemic immunotherapy is established, but the cost of novel intravesical therapies has yet to be determined. A cost comparison is therefore not possible. However, intravesical gemcitabine/docetaxel will cost a small fraction of any novel therapy since both agents are generic. Nonetheless, this needs to be balanced against the absence of clinical trial results for the use of gemcitabine/docetaxel.

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**Table.** Clinical trial results for novel agents in patients with BCG-unresponsive CIS

<table>
<thead>
<tr>
<th>Drug/Protocol</th>
<th>Nadofaragene fradenovec</th>
<th>Oprotuzumab monatox</th>
<th>N-803 + BCG</th>
<th>Pembrolizumab</th>
<th>Atezolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>% 3-mo complete response</td>
<td>53</td>
<td>40</td>
<td>55</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>% 12-mo complete response</td>
<td>24</td>
<td>17</td>
<td>40</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>% Grade 3–5 treatment-related adverse event</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>Every 3 mos x 4 yrs</td>
<td>1-2/wk x 12wk + every 2 wk x 2 yrs</td>
<td>Induction + maintenance per SWOG protocol</td>
<td>Every 3 wks x 2 yrs</td>
<td>Every 3 wks x 1 yr</td>
</tr>
</tbody>
</table>

---

“While the trials suggest a low risk of progression of BCG-unresponsive NMIBC in the short term, we know that this risk will increase over time if multiple courses of bladder-preserving medical therapy are used in sequence, and great caution is advised for patients who could pursue cystectomy as the most definitive option.”

Continued on page 10
Questions about drug sequencing are even more challenging, and there is no compelling evidence to select one agent over another in subsequent lines of therapy. While the trials suggest a low risk of progression of BCG-unresponsive NMIBC in the short term, we know that this risk will increase over time if multiple courses of bladder-preserving medical therapy are used in sequence, and great caution is advised for patients who could pursue cystectomy as the most definitive option. It is also important to recognize that these novel drugs are approved only for CIS with or without papillary disease (Ta/T1), but additional randomized trials will be required before they can be used in patients with BCG-unresponsive Ta/T1 without CIS. Furthermore, trimodal therapy remains an option for patients with T1 bladder tumors. The treatment of NMIBC continues to evolve rapidly and the future is impossible to predict. Future systemic therapy could include also oral fibroblast growth factor receptor inhibitors (NCT04172675), while novel delivery mechanisms are being developed for the intravesical delivery of immunotherapy in an attempt to avoid systemic toxicity (NCT03120622). Several other novel intravesical agents are under development. Combination therapies (eg NCT03519256) appear to be a logical next step, which may make the debate about systemic vs intravesical therapy moot because we could be combining both (eg NCT04164082). Furthermore, there is a lot of discussion about moving to randomized controlled trials for BCG-unresponsive NMIBC, although that has not been mandated by the FDA.


Since its introduction in the late 1970s, shock wave lithotripsy (SWL) has been the gold standard for the treatment of small renal calculi. However, in recent years there has been a significant shift towards the use of ureteroscopy (URS) for the treatment of stones that could be amenable to SWL. This shift can be attributed to improvements in surgical training and experience, as well as technological improvements of both the ureteroscopes themselves as well as the supporting equipment.

Given the accelerated pace of development in endoscopic instruments and significant laser improvements, the role of SWL becomes questionable. One of the undisputed arguments in favor of URS over SWL is the higher stone-free rates (SFRs) achieved. However, is the stone-free rate the only measure of success when it comes to treating urolithiasis patients? We think not. Instead of writing off SWL in favor of URS, the choice between SWL and URS is a complex decision that depends on multiple factors, eg the number of treatments required to obtain a stone-free status, the duration of the hospital stay, the need for anesthesia and auxiliary procedures, and the experience and equipment of the center.

One of the important things for SWL is patient selection. In the properly selected patient, up to 91.5% of stones <10 mm in the kidney were successfully treated with SWL. One other consideration is the location of the stone. Current AUA guidelines recommend URS as primary management of distal ureteral stones and SWL as a secondary option. Data from our center show that 78.8% of patients with distal ureteral stones treated with SWL were stone-free following 1 session of SWL and required no subsequent procedures. Similar SFRs have been reported by groups who conduct routine SWL on distal ureteral stones. SWL is still very relevant and effective for distal ureteral stones.

Patient quality of life (QOL) is an important factor to be considered. How often have you come across a patient with anxiety about undergoing URS and the subsequent ureteral stent placement? Such worries from patients are common when URS is proposed and can affect QOL. In a prospective longitudinal study by Hamamoto et al, SWL and URS patients were followed to assess their QOL over 6 months. The SWL group had higher physical function, role-physical function and social function, in addition to better emotional and mental health despite the stone-free rate being significantly lower in the SWL group (72.1 vs. 93%). Interestingly, this improved QOL was seen not only at 4 weeks postprocedure, but also present at 6 months postoperatively, suggesting that there is more to QOL than the stone-free rate.

Ureteral stent placements following URS are common practice but severely impact patient QOL in up to 80% of patients. This begs the question: Is treating the stone more important, or is treating the patient more important? These findings suggest that the higher SFR associated with URS compared to SWL comes with a patient with anxiety about undergoing URS and the subsequent ureteral stent placement. Such worries from patients are common when URS is proposed and can affect QOL. In a prospective longitudinal study by Hamamoto et al, SWL and URS patients were followed to assess their QOL over 6 months. The SWL group had higher physical function, role-physical function and social function, in addition to better emotional and mental health despite the stone-free rate being significantly lower in the SWL group (72.1 vs. 93%). Interestingly, this improved QOL was seen not only at 4 weeks postprocedure, but was also present at 6 months postoperatively, suggesting that there is more to QOL than the stone-free rate.

The clinical setting and experience of the urologist are crucial factors in determining the appropriate treatment. The World Health Organization states that climate change is the number one public health challenge of the 21st century. Canada’s health care system produces over 33 million tons of carbon dioxide equivalents each year, representing 4.6% of all greenhouse gas emissions in Canada. Health care waste is the second leading contributor in the U.S., with more than 6,600 tons/day and 4 billion pounds of waste annually. Operating rooms combined with labor and delivery suites account for approximately 70% of hospital waste. The manufacturing cost of a flexible ureteroscope was 11.49 kg of CO2 per 1 kg of ureteroscope. Furthermore, the single-use nature of the materials used in the operating room for URS results in vast amounts of plastic, metal and paper waste. As stated by Dr. Bodo Knudsen, “Surgeons, as end-users of devices, play a critical role in changing the current equipment used in surgery.” Although there have been no comparisons between SWL and URS in terms of carbon footprint generated, the idea that SWL produces much less waste is not far-fetched and can be agreed upon by many.

In our opinion, we do not believe SWL is dead. SWL remains an attractive, noninvasive procedure for the treatment of renal calculi, which has similar degrees of SFRs compared to URS, better patient QOL and can assist the world on a path towards net-zero emissions in health care. SWL is still relevant and should maintain a spot in the urologist’s armamentarium.
AUA Announces 2022 Award Winners

Each year the AUA recognizes physicians, researchers, educators and other individuals for their outstanding career contributions to the field of medicine, the specialty of urology and the AUA. For decades, these individuals have served as innovators, mentors, leaders and pioneers within urology, and I am honored to celebrate their achievements during the 59th annual AUA Awards Program ceremony in New Orleans during the 2022 Annual Meeting—congratulations!

Ramon Guiteras Award

The Ramon Guiteras Award is presented annually to an individual for outstanding contributions to the art and science of urology. Glenn M. Preminger, MD will receive this award for outstanding service to the AUA, and for pioneering and innovative work in the field of endourology.

Hugh Hampton Young Award

The Hugh Hampton Young Award is presented annually to an individual for their outstanding contributions to the study of genitourinary tract disease. Arthur L. Burnett II, MD, MBA will receive this award for groundbreaking advances in male sexual health, as well as advocacy, diversity and humanitarian contributions.

Gold Cystoscope Award

The Gold Cystoscope Award is presented annually to a urologist distinguished by outstanding contributions to the profession within 10 years of completing residency training. Angela M. Smith, MD, MS will receive this award for outstanding leadership and contributions in bladder cancer and outcomes research.

Lifetime Achievement Award

The Lifetime Achievement Award is presented annually to an individual for outstanding contributions to advancing the mission and goals of the AUA. Barry A. Kogan, MD will receive this award for outstanding leadership and contributions to the practice, science and education of pediatric urology.

Eugene Fuller Triennial Prostate Award

The Eugene Fuller Triennial Prostate Award is given once every 3 years to an individual who has made outstanding contributions to the study of the prostate gland and all its associated diseases. Claus G. Roehrborn, MD will receive this award for numerous contributions to the scientific study of benign prostatic hyperplasia and its treatment.

Victor A. Politano Award

The Victor A. Politano Award is presented annually to an individual for outstanding research and work in the field of incontinence, and for enhancing the treatment of incontinent patients, thereby helping to improve their quality of life. Craig V. Comiter, MD will receive this award for a defining career centered on investigation, innovation and education in treating incontinence.

William P. Didusch Art and History Award

The William P. Didusch Art and History Award promotes and recognizes contributions to urological art, including but not limited to illustrations, sculpture, still photography, motion pictures and television productions. Kevin R. Loughlin, MD, MBA will receive this award for demonstrating a passion for medical history and

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extensive publications on urological history.

Mid-Career Award

The Mid-Career Award is presented to a urologist distinguished by outstanding contributions to the profession in research, clinical urology or advocacy between 10 and 20 years after completing residency training. Kirsten L. Greene, MD, MS will receive this award for inspired institutional leadership, clinical expertise and service in the development of AUA clinical guidelines.

Distinguished Contribution Awards

The Distinguished Contribution Awards are presented annually to individuals who have made outstanding contributions to the science and practice of urology, including but not limited to contributions made in a subspecialty area or military service. The following individuals will be recognized with this award:

Aria F. Olumi, MD, for exemplary service as AUA Research Chair, strengthening the pipeline of surgeon-scientists and researchers.
Chandru P. Sundaram, MD, MS, for outstanding contributions in endourology and as a member of the AUA Board of Directors.

Distinguished Service Awards

The Distinguished Service Awards are presented annually to individuals for outstanding service in advancing the goals of the AUA. The following individuals will receive this award:

Toby C. Chai, MD, for exemplary contributions to the science of urology and advocacy for urological research.
Barbara B. Hartford, MS, for innovative and impactful management of AUA finances, especially during the worldwide pandemic.

Gold-Headed Cane Award

The Gold-Headed Cane Award is presented to a senior urologist distinguished by outstanding contributions to the profession and to the AUA. The inspiration for the AUA Gold-Headed Cane dates back to a highly respected tradition that began in the 17th century. The gold-headed cane was first carried by Dr. John Radcliffe from 1689 to 1714, and it accompanied him on many consultations in London, England. He was known by royalty for his medical skills and was considered an outstanding practitioner. Dr. Radcliffe was the first to pass the cane along to a successor whom he considered to be the greatest English physician of his time. The AUA continues this tradition by presenting this award to Julio M. Pow-Sang, MD for a superlative career dedicated to advancing urologic oncology, resident education and physician development.

Presidential Citations

Presidential Citations are presented to individuals deemed to have significantly promoted the cause of urology. Each recipient is chosen by the AUA President. This honor will be bestowed upon the following individuals:

Patricia M. Banks, MS, for outstanding leadership in advancing AUA programs during the worldwide pandemic.
Diane E. Bieri, Esq., for outstanding service and teamwork in navigating AUA operations during the worldwide pandemic.

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“For decades, these individuals have served as innovators, mentors, leaders and pioneers within urology, and I am honored to celebrate their achievements during the 59th annual AUA Awards Program ceremony in New Orleans during the 2022 Annual Meeting—congratulations!”

Christian G. Chaussy, MD, for world-renowned leadership and unsurpassed contributions in shock wave lithotripsy and high-intensity focused ultrasound.

Rodney Davis, MD, for dedicated military service and for outstanding contributions to minimally invasive techniques for the treatment of urological malignancies.

Inderbir S. Gill, MD, for scientific innovations in robotic and laparoscopic oncologic surgery.

Victor W. Nitti, MD, For outstanding contributions as the AUA Education Chair, advancing the Urology Core Curriculum and AUA University.

For more information on the upcoming meeting, visit AUA2022.org.

Impact of Technique on Outcomes of Botulinum Toxin Injection for Idiopathic Overactive Bladder

Ekene Enemchukwu, MD, MPH, FACS, FPMRS
Stanford Multidisciplinary Pelvic Health Center, Stanford University School of Medicine, California

Overactive bladder (OAB) is a chronic, debilitating condition that significantly impacts both individual quality of life and societal health care expenditures. Characterized by urinary urgency, with or without urinary incontinence, urinary frequency and/or nocturia, OAB is complex, with various amalgamations of presenting symptoms that have been described as phenotypes, including OAB-dry and OAB-wet. Published evidence-based guidelines recommend treatments including behavioral therapy, pharmacotherapy and advanced therapies. However, one of the significant challenges in OAB management is the wide range of symptom combinations and patient factors, which often necessitate a tailored approach.

Intradetrusor botulinum toxin A (BTXA) injection is an effective treatment for medication-refractory OAB that received U.S. Food and Drug Association approval in 2013. Advances in our understanding of the mechanism of action (MOA) of BTXA at the cellular level have prompted a resurgence of interest in BTXA injection paradigms in an effort to tailor and improve overall therapy outcomes. During the 2021 SUFU (Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction) Plenary Session on this topic, Dr. Francisco Cruz gave a robust primer on the basic science concepts and the corresponding clinical implications of BTXA MOA. Dr. Michael Kennelly followed with a tailored BTXA injection paradigm based on an assimilation of the literature, over 20 years of clinical experience with BTXA, and attention to individual OAB symptoms and patient factors (see table). These intriguing concepts warrant further study to validate the proposed BTXA injection paradigms.

MOA

OnabotulinumtoxinA exerts its effect at the neuromuscular junction

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by binding to SV2 (synaptic vesicle glycoprotein 2), a high-affinity protein receptor. After entering the neuron, BTXA light chain cleaves the SNAP-25 protein, preventing SNARE complex formation, membrane fusion and release of acetylcholine. This cascade of events occurs in the ganglia and the nerve terminals in the detrusor muscle, reducing bladder contractility. The distribution of SV2 has important implications for BTXA efficacy and its potential adverse events (e.g., elevated post-void residual). In the human bladder, SV2 is found on over 90% of parasympathetic nerve fibers, which are most abundant in the detrusor muscle. However, approximately half of human bladder sensory fibers express SV2, identifying potential targets (the sensory nerve fiber-rich suburothelium and bladder trigone) for tailored therapy in OAB-dry patients with sensory urgency and those at high risk for urinary retention.

BTXA also affects the sensory nerves through adenosine triphosphate (ATP), suburothelial neuropeptide release and sensory nerve receptor expression. Mechanical stretch and chemical irritation both stimulate the release of ATP from urothelial umbrella cells, thereby activating purinergic P2X3 receptors on sensory nerves (fig. 1). In animal studies, BTXA blocks this release of ATP, thereby reducing activation of P2X3 receptors and diminishing bladder sensory stimulation. BTXA further minimizes sensory transmission by disrupting transient receptor potential vanilloid-1 channel (TRPV1) and P2X3 receptor transport to the suburothelial sensory nerve membrane, consequently reducing activation of the micturition reflex. Finally, in rat models, BTXA inhibits the release of calcitonin gene-related peptide (CGRP) and substance P, both neurogenic components of bladder inflammation.

Clinical Implications of BTXA MOA

In the literature, several factors are thought to impact BTXA therapy outcomes with varying levels of evidence.

### Dose

In an onabotulinumtoxinA phase 2 randomized, placebo controlled trial, Dmochowski et al demonstrated a dose-dependent relationship between BTXA and therapy efficacy, quality of life and adverse events. This dose-response curve identified 100 U as the most effective dose with the lowest risk of side effects. In the phase 3 trials, Nitti et al confirmed therapy efficacy using trigone sparing injections at the 100 U dose, noting a clean intermittent catheterization (CIC) rate of approximately 6%. Subsequent clinical trials have evaluated various injection techniques to reduce the risk of urinary retention.

### Location and injection depth

Given the impact of BTXA on both the motor efferent and sensory afferent nerves, multiple studies have evaluated the impact of trigonal injections versus nontrigonal injections. Early studies avoided trigonal injections due to concern for vesicoureteral reflux. However, subsequent studies failed to demonstrate reflux. To evaluate the impact of an alternative injection pattern (8 peritrigonal with 2 trigonal injections), Glazier et al conducted a multicenter randomized controlled trial in 120 patients randomized 2:1 to the alternative onabotulinumtoxinA injection pattern (100 U) versus placebo (fig. 2). Although this trial was not intended to represent a direct comparison to the phase 3 trials, the authors reported 14.3% dry rates (versus 23% in the trigone sparing techniques used in the phase 3 trials) at 12 weeks with a 2.6% CIC rate (versus 6% in the phase 3 trials). In another study, Kuo evaluated the impact of both injection depth and location (suburothelial, lateral wall and trigonal/bladder base) in 45 patients (fig. 3). The author observed...
IMPACT OF TECHNIQUE ON OUTCOMES OF BOTULINUM TOXIN INJECTION FOR IDIOPATHIC OVERACTIVE BLADDER

Continued from page 15

significant subjective improvements in urgency severity in all 3 groups, with a higher proportion and longer duration of clinical success in the detrusor and suburothelial groups. However, there were no urinary retention episodes in the trigonal/bladder base group, while 2 participants in the suburothelial and the detrusor groups experienced urinary retention. In summary, these findings suggest that trigonal injections have less effect on bladder contractility and may be beneficial for patients with OAB-dry with sensory urgency or detrusor hyperactivity with impaired contractility.

However, this alternative injection paradigm may negatively impact the duration of therapy.

Volume and number of injections.

In animal studies, higher volume injections increased BTXA distribution and increased expression of cleaved SNAP-25 in the parasympathetic nerves, suggesting a single injection is more effective if diluted in a larger volume of saline. In another study, Liao et al evaluated the therapeutic effect of receiving 10, 20 or 40 injections of BTXA 100 U, and observed similar therapeutic and adverse effects based on validated questionnaires (Urgency Severity Scale, OAB Symptom Score, Patient Perception of Bladder Condition) and objective outcomes (post-void residual, urodynamics, bladder diary). These findings suggest that the number of injections is less impactful than the dose and volume of injection.

In summary, identifying opportunities for tailored therapy continues to be a priority in OAB management. The various mechanisms by which BTXA impacts bladder function present opportunities to individualize therapy for our diverse patient populations. However, data are currently lacking to support standard use of these injection paradigms. Further studies are needed to evaluate these concepts and validate these emerging techniques to improve BTXA injection outcomes.

Figure 3. Injection paradigm. A, suburothelial and detrusor injection template (40 injections). B, suburothelial injection depth. C, detrusor injection depth. D, bladder base and trigone injection template.
Medicare Physician Payment Reform and the Impact on Urologists

Avinash Maganty, MD
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Following passage of the Affordable Care Act, the Centers for Medicare and Medicaid Services (CMS) have undertaken numerous efforts to change how physicians are paid. Two of the more notable initiatives include reform of the Medicare Physician Fee Schedule and implementation of the Quality Payment Program. Both initiatives will alter physician incentives, which could influence practice patterns.

The revisions to the Medicare Physician Fee Schedule took effect on January 1, 2021, altering how physicians are reimbursed for office visits. One of the most common services physicians provide are office visits, which are billed as Evaluation and Management (E/M) services. Previously, CMS reimbursed office visits using 5 levels of codes that were meant to capture degree of complexity, medical decision making and time. The higher the level billed, the more a physician was reimbursed. However, documentation guidelines for these office visits had strict requirements that many viewed as burdensome. Physician organizations commented that this system led to unnecessary documentation that obscured the relevant information for patient care and hastened physician burnout. To simplify the documentation and reimbursement system, CMS implemented Physician Fee Schedule Reform. The reform outlines several key features that will impact urology office visit reimbursement:
1. New patient visit E/M codes will be reduced to 4 levels, and established visits will remain at 5 levels.
2. The work relative value units (RVUs) will be increased for each E/M code (table 1). However, to remain budget neutral and offset the E/M price increases, the RVU conversion factor will be reduced by 3.32%. The reduction, which was intended to be almost 10%, was mitigated by the Consolidated Appropriations Act, although this is expected to decrease an additional 3.89% beginning in 2022.
3. Documentation requirements for History and Physical Examination will be eliminated, requiring only pertinent information to be documented.
4. Physicians may choose a visit level based on either time or medical decision making. If time is chosen, the reported time may include all physician effort on the day of the encounter, even effort that is not necessarily face to face. If medical decision making is chosen, the level will depend on the number/complexity of diagnoses addressed, amount of data reviewed and morbidity associated with further testing or treatment.
5. New codes to capture physician work effort exceeding the maximum visit time expectations (G2212).
6. Add-on code G2211 may be used for primary care and certain specialty providers (including urologists) for added complexity associated with ongoing/chronic care for serious or complex conditions. Although payment for this code is delayed until 2024, it will result in an additional 0.49 total RVUs.

The changes implemented by CMS may have varying impact on physicians depending on their practice mix (eg mostly office based vs mostly procedural). The largest increase in E/M payments occurs for high-level established visits (table 1), thereby benefiting those who provide this service frequently (eg primary care and medical subspecialties). However, for procedural-oriented specialties, if the decrease in RVU conversion factor is not balanced with a corresponding increase in total RVUs, they may see decreased payments. As surgical specialists who perform office-based care, urologists may not be impacted to the same degree as other procedural-based specialties. From recent prior analyses, we see that the new payment reform may differentially impact physicians depending on their practice organization. For example, E/M visits accounted for 37% of Part B payments for physicians in solo practices, compared to 30%-31% for those in larger group practices (calculated using CMS public files from 2019; table 2). Based on the 2019 number of E/M services and distribution of visit levels (fig. 1), we find that physicians in solo practices will see the largest increase in payments from E/M payment reform (7.1%) compared to larger groups (5.8%; table 2). However, the net change in revenue for physicians may vary given the reduction in the RVU conversion factor and change in RVUs for other services. Importantly, CMS estimates

Table 1. Estimates of total payments for E/M visits using CMS Physician Fee Schedule and RVU conversion factors (36.04 for 2019, 34.89 for 2021, 33.59 for 2022)^2

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>2019 Work RVU</th>
<th>2019 Total Payment</th>
<th>2021 Work RVU</th>
<th>2021 Total Payment</th>
<th>% Change in Total Payment</th>
<th>2022 Work RVU</th>
<th>2022 Total Payment</th>
<th>% Change in Total Payments</th>
<th>% Change with G2211</th>
</tr>
</thead>
<tbody>
<tr>
<td>99201</td>
<td>New patient, level 1</td>
<td>0.48</td>
<td>46.49</td>
<td>Not applicable*</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>0.93</td>
<td>73.96</td>
<td>−4.5</td>
<td>0.93</td>
</tr>
<tr>
<td>99202</td>
<td>New patient, level 2</td>
<td>0.93</td>
<td>77.12</td>
<td>0.93</td>
<td>73.96</td>
<td>−4.5</td>
<td>0.93</td>
<td>71.19</td>
<td>−8.1</td>
<td>13.1</td>
</tr>
<tr>
<td>99203</td>
<td>New patient, level 3</td>
<td>1.42</td>
<td>109.20</td>
<td>1.6</td>
<td>113.74</td>
<td>3.5</td>
<td>1.6</td>
<td>109.47</td>
<td>−0.38</td>
<td>14.5</td>
</tr>
<tr>
<td>99204</td>
<td>New patient, level 4</td>
<td>2.43</td>
<td>166.86</td>
<td>2.6</td>
<td>169.91</td>
<td>1.8</td>
<td>2.6</td>
<td>163.53</td>
<td>−2</td>
<td>7.8</td>
</tr>
<tr>
<td>99205</td>
<td>New patient, level 5</td>
<td>3.17</td>
<td>207.75</td>
<td>3.5</td>
<td>224.34</td>
<td>6.9</td>
<td>3.5</td>
<td>215.92</td>
<td>3</td>
<td>10.7</td>
</tr>
<tr>
<td>99211</td>
<td>Established patient, level 1</td>
<td>0.18</td>
<td>23.43</td>
<td>0.18</td>
<td>23.03</td>
<td>−1.7</td>
<td>0.18</td>
<td>22.16</td>
<td>−5.4</td>
<td>64.8</td>
</tr>
<tr>
<td>99212</td>
<td>Established patient, level 2</td>
<td>0.48</td>
<td>45.77</td>
<td>0.7</td>
<td>56.87</td>
<td>24.3</td>
<td>0.7</td>
<td>54.73</td>
<td>19.6</td>
<td>55.5</td>
</tr>
<tr>
<td>99213</td>
<td>Established patient, level 3</td>
<td>0.97</td>
<td>75.32</td>
<td>1.3</td>
<td>92.46</td>
<td>22.7</td>
<td>1.3</td>
<td>88.98</td>
<td>18.2</td>
<td>40</td>
</tr>
<tr>
<td>99214</td>
<td>Established patient, level 4</td>
<td>1.5</td>
<td>110.28</td>
<td>1.92</td>
<td>131.18</td>
<td>19</td>
<td>1.92</td>
<td>126.26</td>
<td>14.5</td>
<td>29.4</td>
</tr>
<tr>
<td>99215</td>
<td>Established patient, level 5</td>
<td>2.11</td>
<td>147.76</td>
<td>2.8</td>
<td>183.17</td>
<td>24</td>
<td>2.8</td>
<td>176.30</td>
<td>19.3</td>
<td>30.4</td>
</tr>
</tbody>
</table>

Percent change in payments are relative to 2019 payments. For G2211 estimates, the 2022 RVU conversion factor is used, which assumes G2211 will receive 0.49 total RVUs and estimated changes are relative to 2019 payments.

that on average urologists will see an 8% increase in total reimbursements for 2021.²

The new E/M payment reform has the potential to alter physician behavior and change practice patterns in at least 2 ways. First, due to increased payment for high-level established visits and the additional addition of add-on code G2211 for chronic complex care, there will be incentives to maintain longitudinal care for urological patients. Therefore, rather than referral back to primary providers, urologists may opt to maintain routine visits with complex patients, such as those on active surveillance for prostate cancer or those with bladder pain syndrome. These incentives appear to better align with providing patients with quality care. Second, further reduction of the RVU conversion factor by 3.89% in 2022 and proposed reductions to practice expense RVUs will likely result in decreased payments for procedures commonly performed by urologists.³ This may influence physicians who primarily obtain revenue from procedures to preferentially pursue office-based care, potentially impacting access to surgery. Overall, urologists may benefit from the proposed changes; however, the impact on patient care remains to be determined.

Beyond reimbursement for office visits, payment reform is occurring more broadly to transition health care from volume to value, further altering physician incentives. The Merit-based Incentive Payment System (MIPS) in fee-for-service Medicare, introduced as part of the Medicare Access and CHIP Reauthorization Act, is a payment model that aims to improve the value of care. Implemented in 2017, MIPS determines whether a physician’s subsequent Medicare reimbursement (assessed on a per-claim basis 2 years following the performance year) is reduced or enhanced based on performance in 4 categories: quality, practice improvement, promotion of information technology and spending. The overall MIPS score is calculated as a weighted average of the 4 category scores. As Medicare annually escalates the weight of the spending component, spending, which is measured at the beneficiary level, is becoming increasingly important in deciding winners and losers with respect to the policy. CMS is continuing to move forward with MIPS, albeit with the intent of bundling spending with quality through implementation of value pathways. However, of the 7 value pathways CMS has proposed for 2023, none is directly relevant to urologists. Therefore, urologists will continue to be subject to the traditional MIPS program until a specialty specific pathway (or an advanced payment model that would exempt participants from MIPS) is created. Based on our analyses of CMS Quality Payment Program data,⁷ urologists were performing better

Table 2. Physician-level Part B medical services and Part B Medicare price-standardized payments summarized from 2019 (most recent available data),⁴ stratified by practice type

<table>
<thead>
<tr>
<th>Organization Type</th>
<th>Solo</th>
<th>Single Specialty Urology Groups</th>
<th>Multispecialty Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. urologists</td>
<td>1,187</td>
<td>2,971</td>
<td>3,686</td>
</tr>
<tr>
<td>Total Part B medical services</td>
<td>2,809 (1,551–4,804)</td>
<td>3,621 (2,425–5,231)</td>
<td>1,770 (947–3,003)</td>
</tr>
<tr>
<td>% Medical services that are E/M</td>
<td>37 (29–47)</td>
<td>1,076 (721–1,540)</td>
<td>630 (344–1,028)</td>
</tr>
<tr>
<td>Total Part B payments</td>
<td>857 (419–1,415)</td>
<td>31 (26–37)</td>
<td>36 (30–46)</td>
</tr>
<tr>
<td>Total Part B payments for E/M services</td>
<td>241,221 (159,958–355,781)</td>
<td>38,995 (20,387–64,052)</td>
<td>127,744 (69,822–202,724)</td>
</tr>
<tr>
<td>% Payments that are E/M services</td>
<td>56,603 (28,056–95,468)</td>
<td>30 (23–37)</td>
<td>31 (23–39)</td>
</tr>
<tr>
<td>Estimated % change in allowed charges from 2019 to 2022</td>
<td>7.1 (5.4–9.2)</td>
<td>5.8 (4.3–7.3)</td>
<td>5.8 (4.2–7.7)</td>
</tr>
<tr>
<td>Estimated % change in allowed charges from 2019 to 2022</td>
<td>5.4 (4–7)</td>
<td>4.3 (3.2–5.5)</td>
<td>4.2 (3–5.7)</td>
</tr>
</tbody>
</table>

Values represent median (IQR). Estimated changes are calculated using table 1 E/M payments, the 2019 number and distribution of E/M services, and change is measured relative to 2019 Medicare total allowed charges. Hospital-based practices were not included. Data source: Medicare Physician and Other Practitioners by Provider and Service File⁴ and Medicare Data on Provider Practice and Specialty File.⁹

Figure 1. Percent of E/M visits billed by level, stratified by practice type. Level 1 visits represented <1% and actual values are not shown. Level 1: 99201 and 99212; level 2: 99202 and 99212; level 3: 99203 and 99213; level 4: 99204 and 99214; level 5: 99205 and 99215. Data source: Medicare Physician and Other Practitioners—by Provider and Service File.¹ MSG, multispecialty group. SSG, single specialty urology group.

Figure 2. Payment adjustments stratified by practice type for the 2017 performance year (A) and the 2019 performance year (B). Providers receive either bonus adjustment, positive adjustment, no adjustment or penalties depending on their overall MIPS performance. Data source: CMS Physician Compare Files 2017 and 2019.⁷ MSG, multispecialty group. SSG, single specialty urology group.
in MIPS in 2019 compared with 2017, with no physicians receiving penalties in 2019 (fig. 2). However, as incentives to decrease spending become stronger [ie as it is weighted more heavily in the overall score over time] and performance thresholds increase, it will be important to determine how patient care is impacted.

The 2 initiatives described above represent significant changes in how physicians are paid. The impact this will have on patient care, such as access to procedural based care, is yet to be determined. Most importantly, the initiatives represent an attempt to design a system that minimizes the burden of documentation and emphasizes value over volume.


The Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN): Working to Improve Care for Persons with Lower Urinary Tract Symptoms

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Lower urinary tract symptoms (LUTS) affect and afflict a huge portion of the population, with increasing prevalence with advancing age. The negative impact of LUTS is substantial and wide ranging: LUTS can pose a significant burden to affected individuals and caregivers and is associated with an enormous economic burden.1,2

In 2012, the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) created the Symptoms of Lower Urinary Tract Dysfunction Research Network, known as LURN, to address the gaps in understanding and treating LUTS. LURN is comprised of 6 academic research sites, scientific officers at NIDDK and a data coordinating center at Arbor Research Collaborative for Health. The goals of LURN are to increase understanding of lower urinary tract dysfunction by 1) improving the measurement of patient experiences of LUTS and 2) identifying and explaining the important subtypes of lower urinary tract dysfunction in men and women. Ultimately, the identification of new and distinct subtypes of these symptom conditions will lead to more effective therapeutic options and improved decision making for the affected patients. To achieve these goals, LURN leverages the resources of a multicenter, multidisciplinary network structure to gather and analyze data on large numbers of affected patients from around the United States. Over the course of 6 years, we enrolled close to 2,000 men and women with LUTS in LURN studies (see figure). The data from over 1,100 participants in the observational cohort study included medical history, physical examination, urological symptom assessments, treatments, sociodemographics and nonurological co-occurring symptom assessments. Other data collected included brain magnetic resonance imaging; quantitative sensory testing; biological samples for genetic, biochemical and microbiological analysis; and physiological data. Many of these data were collected longitudinally.

This rich and comprehensive collection of information allows investigators to examine the multitude of domains impacting the development of LUTS and mechanisms of dysfunction, and provides opportunities for multi-domain analyses above and beyond those of each of the individual components. At the time of this writing, there have been 27 manuscripts published, with many more in progress, and over 75,000 biological samples stored at the NIDDK Central Repository (https://repository.niddk.nih.gov/home/) for use by the broader urological research community.

Some of the immediately translatable findings from the first funding cycle of the network (2012–2018) include the following. LURN investigators devoted significant effort to developing self-reported measures for LUTS. The first product was CASUS, an acronym for Comprehensive Assessment of Self-Reported Urinary Symptoms. The almost 100-item instrument captures most of all LUTS and is the most comprehensive self-report LUTS measure to date.3 It was developed for research purposes to identify subgroups of persons with LUTS. Another research tool is the LURN Symptom Index-29, or LURN SI-29, a 29-item instrument to capture symptoms for measurement of clinical outcomes.4  The third product is the LURN Symptom Index-10, or LURN SI-10, a short, 10-item instrument for routine clinical use for symptom screening and monitoring.5 The instrument is appropriate for both men and women, unlike the currently used questionnaires (e.g AUA Symptom Index). It captures more urinary symptoms than other instruments, including stress urinary incontinence, urgency urinary incontinence, post-void dribbling, bladder pain/discomfort and symptom bother. These instruments are freely available for public use and download at the LURN website (https://nih-lurn.org/Resources/Questionnaires).

Another study addressed symptom recall, to answer the question: how reliable are patient recollections of their symptoms? A schedule of bladder diaries and symptom reporting was completed by participants over the course of 30 days. The findings indicated that recalled reports generally tracked pretty well with average daily reports of symptoms, for both men and women, supporting the use of both 7- and 30-day recall periods for the LURN instruments.6

A separate objective of LURN is to identify clinically relevant subtypes of LUTS patients, because current diagnostic groups and treatments do not seem to address the heterogeneity of these patients. The observational cohort study followed over 1,100 men and women for 12 months, and some of the findings include:

• increasing urinary incontinence severity, rather than the presence or type of urinary incontinence, was associated with increased depression, anxiety and stress7
• central and general obesity were key metabolic factors associated with urinary incontinence and overactive bladder8
• a large percentage of men seeking care for lower urinary tract symptoms report some incontinence. This is a particularly germane point, as questionnaires used for men, such as the AUA Symptom Index or International Prostate Symptom Score, do not query for stress and urgency urinary incontinence and post-void dribbling. This finding motivated the inclusion of certain items on the LURN SI-10.

As part of the effort to subtype patients with LUTS, a novel statistical technique that we are using is consensus cluster analysis. Without the bias of these patients’ actual clinical diagnoses, we are using the multi-domain data to see how this heterogeneous group of patients subdivides itself from an unsupervised mathematical standpoint.9 This work has not yet been clinically validated, but we believe...
that this new approach to identify subgroups of LUTS patients will result in impactful patient care.

In addition to continuing the work from LURN I on subtyping the broad spectrum of participants with LUTS, the second phase of LURN (LURN II, 2019-2024) focuses research efforts on the symptoms of urinary urgency. The International Continence Society defines urgency as the sudden onset of a sensation to void that is difficult to defer, which is the motivation for millions of persons worldwide to seek health care. Approximately 840 men and women with urinary urgency (with or without urgency incontinence) are being recruited for postoperative adjuvant RT to early salvage RT as the preferred approach. Three randomized trials comparing adjuvant RT to early salvage RT have recently been published (Table 2).6–8 RADICALS-RT recruited 1,396 patients in the United Kingdom, Denmark, Canada and Ireland (2007 to 2016); GETUG-AFU I7 recruited 424 patients in France (2008 to 2016); and RAVES recruited 333 patients in Australia and New Zealand (2009 to 2015). While the GETUG-AFU I7 and RADICALS-RT trials were designed to assess whether adjuvant RT was superior to salvage RT, the RAVES trial assessed whether salvage RT was noninferior to adjuvant RT. For all trials, patients randomized to receive adjuvant RT received it within 6 months after surgery. Salvage RT was triggered at low prostate specific antigen (PSA) level recurrences that differed slightly between the trials. The results of all 3 trials and a meta-analysis of the aggregate data (ARTISTIC)9 showed that the oncologic outcomes of early salvage RT were not inferior to adjuvant RT. In addition, all 3 trials reported increased side effects with adjuvant RT. While these results support early salvage RT as the preferred approach, it is noteworthy that these trials included only a small proportion of patients with high-risk disease. Men with pathological Gleason score 8–10 and/or pT3a or higher disease comprised only 9% to 17% of those enrolled.6–8 Since the majority had relatively favorable pathology, the potential

### Table 1. Three randomized trials of adjuvant radiotherapy after prostatectomy versus initial observation for men with adverse pathological findings

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>EORTC 22911</th>
<th>SWOG 8794</th>
<th>ARO 96-02</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2-3N0</td>
<td>pT2-3N0</td>
<td>pT3-4N0</td>
<td></td>
</tr>
<tr>
<td>EPE, SVI or +SM</td>
<td>EPE, SVI or +SM</td>
<td>EPE, SVI, ± SM</td>
<td></td>
</tr>
<tr>
<td>No. pts</td>
<td>1,005</td>
<td>425</td>
<td>307</td>
</tr>
<tr>
<td>Preop PSA (median)</td>
<td>12 ng/ml</td>
<td>≤10 ng/ml</td>
<td>9–10 ng/ml</td>
</tr>
<tr>
<td>Postop PSA</td>
<td>≤0.2 ng/ml in 70%</td>
<td>≤0.2 ng/ml in 66%</td>
<td>≤0.2 ng/ml in 100%</td>
</tr>
<tr>
<td>Radiation</td>
<td>60 Gy conventional within 4 mos</td>
<td>60–64 Gy conventional within 4 mos</td>
<td>60 Gy 3-dimensional conformal within 3 mos</td>
</tr>
<tr>
<td>Median followup</td>
<td>10.6 yrs</td>
<td>12.6 yrs</td>
<td>9.3 yrs</td>
</tr>
<tr>
<td>End points (adjuvant vs wait-and-see)</td>
<td>BCR-free survival: 61.8 vs 39.4% (HR 0.49), NNT 5; overall survival 54% (HR 0.71), NNT 10</td>
<td>Metastasis-free survival: 43% vs 54% (HR 0.71), NNT 10; overall survival 52% vs 41% (HR 0.72), NNT 10</td>
<td>BCR-free survival (10 yr): 56% vs 35% (HR 0.51), NNT 5; overall survival: not powered to detect difference</td>
</tr>
</tbody>
</table>

Adapted from Rodriguez et al.5,6 EPE, extraprostatic extension; SVI, seminal vesicle invasion.

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With the increasing use of active surveillance, a greater proportion of men undergoing radical prostatectomy (RP) have high-risk disease, and as many as 50% of these men will develop biochemical recurrence (BCR) within 10 years.1 Thus, an increasing number of men are being considered for postoperative radiotherapy (RT). Three randomized trials have demonstrated improved oncologic outcomes with adjuvant RT when adverse pathological findings are found at prostatectomy, specifically extracapsular extension, seminal vesical involvement and/or positive surgical margins (Table 1).2–4 However, the use of adjuvant RT has remained limited, at 10% to 15% at best.5 This low utilization is in large part due to the concern about overtreatment. About half of the patients in the control arms of these trials had no evidence of recurrence at 5 years. Thus, early salvage RT (given at the time of BCR) may be a preferable approach.

Three randomized trials comparing adjuvant RT to early salvage RT have recently been published (Table 2).6–8 RADICALS-RT recruited 1,396 patients in the United Kingdom, Denmark, Canada and Ireland (2007 to 2016); GETUG-AFU I7 recruited 424 patients in France (2008 to 2016); and RAVES recruited 333 patients in Australia and New Zealand (2009 to 2015). While the GETUG-AFU I7 and RADICALS-RT trials were designed to assess whether adjuvant RT was superior to salvage RT, the RAVES trial assessed whether salvage RT was noninferior to adjuvant RT. For all trials, patients randomized to receive adjuvant RT received it within 6 months after surgery. Salvage RT was triggered at low prostate specific antigen (PSA) level recurrences that differed slightly between the trials. The results of all 3 trials and a meta-analysis of the aggregate data (ARTISTIC)9 showed that the oncologic outcomes of early salvage RT were not inferior to adjuvant RT. In addition, all 3 trials reported increased side effects with adjuvant RT.

While these results support early salvage RT as the preferred approach, it is noteworthy that these trials included only a small proportion of patients with high-risk disease. Men with pathological Gleason score 8–10 and/or pT3a or higher disease comprised only 9% to 17% of those enrolled.6–8 Since the majority had relatively favorable pathology, the potential...
benefit of adjuvant RT in high-risk patients may have been missed. In addition, fewer men underwent salvage RT than adjuvant RT in these trials. Since androgen deprivation therapy (ADT) was used concomitantly with adjuvant RT in 2 of the trials, progression-free survival in the adjuvant RT group may have been favorably affected since ADT can delay time to progression. Immortal time bias, a well-recognized bias in observational studies, is another potential confounding factor. In the salvage RT arms of these trials, there was a period of time (salvage RT treatment planning and delivery) during which the outcome event (recurrence) could not occur. By scoring PSA failure on the salvage arm at a later time than the adjuvant arm, salvage RT could falsely appear superior to adjuvant RT.

If these trials were underpowered to address the adjuvant versus early salvage question in high-risk patients, could there still be a role for adjuvant RT? A recently published large retrospective analysis suggests a benefit to adjuvant RT in some cases. This analysis of 26,118 men from Germany and the United States, using propensity score matching to minimize treatment selection bias, found that in men with pN1, pathological Gleason score 8–10 and pT3a or higher disease, adjuvant RT was superior to early salvage RT with regard to all-cause mortality.12 In the salvage RT setting, multiple studies show better outcomes when radiation is administered at the lowest possible PSA level. Since PSA is proportional to the volume of residual disease, adjuvant RT would be delivered when there is the lowest microscopic disease burden (ie when PSA is undetectable).

The results of these trials establish early salvage RT as the standard of care in most cases, but adjuvant RT may still be preferable for some very high-risk patients. Prognostic nomograms such as the CAPRA-S scoring system (Cancer of the Prostate Risk Assessment–post-surgical) and/or the Stephenson nomogram can be used to accurately predict the probability of BCR.13,14 If these nomograms predict a near certain chance of recurrence, adjuvant RT could be considered. Postoperative PSA nadir has also been shown to be an indicator of recurrence. In one study, BCR was unlikely in those with postoperative PSA nadir ≤0.02 ng/mL, but almost all cases with PSA nadir above this level eventually recurred, especially those with PSA ≥0.05 ng/mL.15 Prognostic nomograms and nadir postoperative PSA levels could be used together to select men for adjuvant RT.

New tissue-based biomarkers will undoubtedly be developed to assist in identifying the best candidates for adjuvant RT. There is some evidence from retrospective studies that a tissue-based genomic classifier score (Decipher Prostate Cancer Classifier), based on the expression of 22 genes, may help predict who might be best suited for adjuvant versus salvage RT.16 Dalela et al developed a risk-stratification tool incorporating the Decipher score and pathological features to identify patients who would benefit most from adjuvant RT.17 In patients with 2 or more high risk factors, adjuvant RT was associated with a 10.1% 10-year clinical recurrence rate compared to a rate of 42.1% in those managed with initial observation. While positron emission tomography/computerized tomography imaging has improved detection of residual disease after RP, the sensitivity is limited at the very low PSA levels at which adjuvant RT would be given. Thus, although we now have good evidence from randomized trials that an early salvage RT approach is preferable in most cases, the role of adjuvant RT after RP will likely evolve and continue to be debated. 

Table 2. Randomized trials comparing adjuvant to early salvage radiotherapy after prostatectomy

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Randomization and timing of RT</th>
<th>Use of ADT</th>
<th>Trigger for early salvage RT</th>
<th>Primary outcome</th>
<th>RADICALS-RT</th>
<th>RAVES</th>
<th>GETUG-AFU 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>1,396 pts; Canada, UK, Denmark, Ireland</td>
<td>2007–2016</td>
<td>PSA ≥0.1 ng/mL and rising or 3 consecutive rising PSA levels</td>
<td>Freedom from distant metastases</td>
<td>Superiority</td>
<td>Superiority</td>
<td>Superiority</td>
</tr>
<tr>
<td>Enrollment dates</td>
<td>2009–2015</td>
<td>Immediate (within 6 mos of RP or early salvage RT (within 2 mos of trigger PSA)</td>
<td>Freedom from biochemical recurrence</td>
<td>Superiority</td>
<td>Superiority</td>
<td>Superiority</td>
<td>Superiority</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>pT2a/pT3a/pT3b/pT4a, Gleason 7–10</td>
<td>Immediate (within 6 mos of RP or early salvage RT (within 4 mos of trigger PSA)</td>
<td>Noninferiority</td>
<td>Freedom from distant metastases</td>
<td>Superiority</td>
<td>Superiority</td>
<td>Superiority</td>
</tr>
<tr>
<td>RADICALS-RT</td>
<td>pT2a/pT3a/pT3b and either pos margins or ECE</td>
<td>Immediate (within 6 mos of RP)</td>
<td>PSA ≥0.2 ng/mL and rising</td>
<td>PSA ≥0.2 ng/mL</td>
<td>Superiority</td>
<td>Superiority</td>
<td>Superiority</td>
</tr>
<tr>
<td>RAVES</td>
<td>pT3a/pT3b/pT4 and pos margins or ECE</td>
<td>Immediate (within 6 mos of RP)</td>
<td>Event-free survival</td>
<td>Event-free survival</td>
<td>Superiority</td>
<td>Superiority</td>
<td>Superiority</td>
</tr>
<tr>
<td>GETUG-AFU 17</td>
<td>Immediate (within 6 mos of RP)</td>
<td>Early salvage RT (as soon as possible after PSA relapse and before PSA=1 ng/ml)</td>
<td>All received ADT, both adjuvant and salvage RT</td>
<td>All received ADT, both adjuvant and salvage RT</td>
<td>Superiority</td>
<td>Superiority</td>
<td>Superiority</td>
</tr>
</tbody>
</table>

Adapted from Vale et al.9 ECE, extracapsular extension.

Factors Affecting Surgical and Nonsurgical Options in Patients with Peyronie’s Disease

Lawrence C. Jenkins, MD, MBA, FACS
Arizona Urology Specialists, Tucson

Current AUA guidelines for Peyronie’s disease published in 2015 recommend that only 2 types of treatments be offered: intraleisional injections or surgical therapies (plication, grafting, prosthesis). Numerous factors affect whether patients are candidates for these 2 options, some being patient specific and others being system based. Some of these factors include acute vs chronic phase, degree of curvature, associated deformities (ie indentation or tapering), multiplanar curves, baseline erectile function and presence of calcification. However, 2 overlying factors can affect decisions, cost and access to care.

Patient-centered factors will guide treatment recommendations. One would not want to perform corrective surgery if the deformity is still in the acute phase and actively changing. Associated deformities like indentation or tapering may cause some to choose surgical grafting rather than plication surgery, and poor baseline erections would push recommendations the opposite way. The presence of large calcifications has been shown to make intraleisional collagenase less effective, and providers may choose to recommend penile plication instead. Ultimately, an experienced provider can use a detailed history, physical examination and deformity assessment to determine the best course of action with shared decision making. Many patients can be divided into 2 personality groups. The first are those who are averse to surgery and want a more conservative option regardless of the longer treatment cycle and thus choose injections. The other personality group wants the fastest option with the least amount of interruption in their lives, and they often choose surgical repair.

Costs have increased since the release of intraleisional collagenase in 2013. A retrospective cohort study conducted using claims data from the Truven MarketScan database illustrates, in 2018, the mean cost of treatment with intraleisional collagenase was substantially higher than surgery ($20,260 and $10,930, respectively). From 2007 to 2018, the average treatment cost per patient increased almost six-fold from approximately $1,500 to $10,000 per patient. A 2017 cost analysis comparing intraleisional collagenase to penile plication found the mean costs for penile plication surgery were approximately $3,000 vs $25,000 for intraleisional collagenase. These costs can be prohibitive for some patients whose insurance does not cover costlier treatments like intraleisional collagenase.

Access to care is a growing problem, and with the current physician shortage this is increasingly evident in specialty care. According to the 2020 AUA Census, of the more than 13,000 practicing urologists, only about 5% report having a primary subspecialty area in either erectile dysfunction or male genitourinary reconstruction (the closest subspecialty areas that might include Peyronie’s disease treatment). This does not fully represent all the urologists who treat Peyronie’s disease, but it does illustrate how difficult it may be for patients to find proper care. This only gets worse in the rural areas. As shown by the Census report, only 10% of practicing urologists report their primary practice location in nonmetropolitan (population less than 50,000) areas while 20% of the population lives in these areas. In addition, 62% of U.S. counties have 0 urologists with a primary practice located within them. Access to care will increasingly be more of a problem as fewer physicians enter rural practice, necessitating patients to travel further for care.

In summary, many factors contribute to the treatment of Peyronie’s disease. With the help of a careful history, focused exam and in-office deformity assessment, a properly experienced provider can navigate the patient through these patient-centered factors. However, some factors are more systems based and rely on major changes to the delivery of health care to decrease costs and increase access to care.

“One would not want to perform corrective surgery if the deformity is still in the acute phase and actively changing.”

“Costs can be prohibitive for some patients whose insurance does not cover costlier treatments like intraleisional collagenase.”

References:

Urology Care Foundation
The Official Foundation of the American Urological Association

Humanitarian Grant Program
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UROLOGYHEALTH.ORG/HUMANITARIANISM
Among women who are experiencing GSM symptoms less than 10% are prescribed therapies; this discrepancy between prevalence and treatment is due in part to lack of patient education regarding GSM and the lack of physician initiated assessment.”

We are the leaders in managing erectile dysfunction and hormone deficiency in men, and the leaders in managing urinary problems in women.”

Have you ever tried to put a square peg in a round hole? No matter how hard or straight that peg is, it’s not going to fit. It won’t fit even if the peg is made by Boston Scientific or Coloplast, contains 2 pieces, 3 pieces or is semi-rigid.

Square peg. Round hole.

As urologists we have the unique privilege of being able to take care of all genders. We have proclaimed ourselves the sexual medicine experts, and our field’s encouragement of quality-of-life medicine is the exact thing that drew me in all those years ago.

As a society, the AUA has partnered with the Sexual Medicine Society of North America to publish pioneering guidelines for erectile dysfunction, disorders for ejaculation, testosterone deficiency and priapism.

When a guideline gets published the whole field listens, and a framework is developed for incorporating new standards to urology practices worldwide.

I propose a new guideline: one for Genitourinary Syndrome of Menopause (GSM).

GSM is a relatively new term that was established around 2014 to replace the diagnosis of vulvovaginal atrophy/atrophic vaginitis. Not shockingly, women don’t like to be told their vagina is atrophic, and just as important, the term atrophy doesn’t describe the signs and symptoms of what actually happens to the genitals and urinary tract after hormone withdrawal.

GSM is essential for urologists to understand, diagnose and treat. In fact, I would argue it is essential for urologists to take ownership of this condition as the urinary implications of this disease are quite serious.

Unlike hot flashes and night sweats in menopause which often diminish over time, GSM is a chronic and progressive condition that has the potential to pose significant morbidity to our patients. Think about the 90-year-old nursing home patient with urosepsis. The source of the urosepsis is much more likely from her GSM than her 2 mm nonobstructing stone. And you can bet I would place her on Food and Drug Administration approved vaginal estrogen or prasterone with refills lasting forever.

Without circulating estrogens and androgens there is a loss of collagen and elastin, diminished blood supply, and a loss of an acidic environment which changes the entire ecosystem of the genital and urinary tract. Because of these changes women develop urinary frequency, urgency, dysuria, pelvic pain and recurrent urinary tract infections (UTIs). Additional symptoms include vaginal dryness, dyspareunia and difficulties with desire, arousal and orgasm.²

Approximately 50% of postmenopausal women experience GSM symptoms³ and 10%–15% of women over 60 years old have recurrent UTIs.⁴ Among women who are experiencing GSM symptoms less than 10% are prescribed therapies; this discrepancy between prevalence and treatment is due in part to lack of patient education regarding GSM and the lack of physician initiated assessment.⁵

The urological community has been slow to integrate GSM assessment into its treatment of postmenopausal patients.

A promising development is the 2019 guidance of the American Urological Association; Canadian Urological Association; and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction to include vaginal estrogen as a prophylaxis for peri- and postmenopausal women with recurrent UTIs to reduce the future UTI risk (Moderate Recommendation; Evidence Level: Grade B).⁶ These treatment guidelines are an important initial step toward the urology community introducing the assessment and treatment of GSM in their clinical practice.

We are the leaders in managing erectile dysfunction and hormone deficiency in men, and the leaders in managing urinary problems in women. If we place penile implants and care about satisfaction outcomes with these devices, we must also start thinking about where that device is often being inserted. No matter the quality of the implant, or the high volume center where it was placed, if the partner suffers from GSM, satisfaction will not be maximized.

If we have guidelines in place for the urological community to screen and manage GSM (it’s the easiest and most rewarding thing I do in my practice) then not only will quality of life improve for both our male and female patients, but calls to your office for urgent urine cultures will dramatically decrease, as will hospital admissions for urosepsis. ■

References


Enhanced Recovery After Surgery (ERAS®) is a perioperative framework that uses evidence-based strategies to reduce physiologic stress from anesthesia and surgery via standardized care before, during and after surgery. The protocol has increasingly become the standard of care for many adult specialties, yet its uptake in pediatric urology has been behind the adult curve. This is not entirely surprising; as a subspecialty within urology, we practice and train differently and increasingly separately from our adult counterparts. Dissemination of innovation in medicine occurs over long timespans, and ERAS’s entry into pediatric urology is no different, trailing approximately 10 years behind its introduction in adult surgical practice in North America. Early pediatric ERAS outcomes have shown positive effects similar to their adult counterparts, namely reduced length of stay, reduced opioid use in and out of the operating room, reduced complications, and improved time to return to baseline function. Although data in pediatric urology are limited, there are efforts underway to remedy this as outlined below.

First, several studies in pediatric surgery and pediatric urology have been published recently that demonstrate improved outcomes and raise the level of knowledge regarding ERAS. A literature review from Shinnick et al in 2016 regarding ERAS. A literature review from Shinnick et al in 2016 demonstrated significantly fewer complications in patients who received ERAS care vs standard practice (1.3 vs 2.1 events per patient, OR 0.71, 95% CI 0.51–0.97), which is in line with results from numerous adult studies. Another study from Purcell et al showed ERAS pathways decreased opioid usage in their pediatric patients undergoing colorectal surgery.

Second, societal efforts have come to bear recently to improve the representation of pediatric surgical specialties. The First World Congress on Enhanced Recovery After Surgery in Pediatrics convened on November 30, 2018 at Virginia Commonwealth University in Richmond, Virginia. Global experts gathered here to bring the key concepts of ERAS to the pediatric community. This was a major step in acknowledging the future of pediatric care and catapulting ERAS into this new arena. In 2019, ERAS USA agreed to create a formal subsection for pediatrics, where leaders in surgical specialties and anesthesiology are working to develop new protocols, put forth best practice statements and curate resources to aid in improving ERAS knowledge and experience. As members of ERAS USA and ERAS Pediatrics, we encourage providers interested in pediatric ERAS to get involved and consider attending a meeting to learn more and hear from national experts.

And third, prospective multicenter studies are underway that relate to pediatric urology. PURSUING, or Pediatric Urology Recovery after Surgery, is an observational, prospective, propensity-matched study comparing patients who have lower urinary tract reconstructive operations (including bladder augmentation, creation of catheterizable channels and bladder neck surgeries) to patients not under an ERAS pathway. Investigators are examining protocol compliance, length of stay, complications, opioid usage and patient-reported outcomes. Results are expected in the next year or so. ENRICH-US (ENHanced Recovery In CHildren Undergoing Surgery) is a pediatric surgery multicenter collaboration with a stepped-wedge cluster randomized design examining ERAS implementation and outcomes for pediatric patients undergoing colonic resection. While not directly relevant to urology, understanding implementation of pediatric ERAS in a variety of centers and settings lends itself to new, more efficient implementations within our specialty. Finally, PORTS (Pediatric Oncology Recovery Trial after Surgery) is a multicenter effort to examine surgical and oncologic outcomes for pediatric cancer patients after surgical resection.

We believe the time is now to make ERAS the standard of care for pediatric urology. Any patient can benefit from a framework of standardized practices to reduce physiologic stress, but pediatrics has many factors that lend itself well to adoption. For example, having patients who are generally healthy and a high proportion of procedures that are relatively short ambulatory cases make things like minimizing nil per os (NPO) times, standardizing anesthetic and surgical care, minimizing opioids accomplishing, and accruing additional benefits to patients. In a time when we are seeing record numbers of mortalities in the opioid epidemic, protecting our youth by using multimodal pain control and minimizing opioid exposure is all the more important.

At our center, ERAS has become the standard for all urological procedures. Whether a patient is undergoing reconstructive surgery or a simple biopsy, the goal is to reduce the patient’s physiologic stress and promote recovery. The protocol has increasingly become the standard of care for all urological procedures.

### Appendix

ERAS process measures with applicability in pediatric urology. Adaptation to specific operations is common, allowing for more precise definitions that lend themselves to auditing a protocol or pathway implementation to allow for constructive feedback to a clinical team to continue to improve care. These elements are also not meant to be rigidly adhered to, as clinical circumstances of a patient may take precedent. However, we encourage providers to apply as many other principles as possible, even if 1 or more are not or cannot be applied.

<table>
<thead>
<tr>
<th>Phase of Care</th>
<th>Process Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative/clinic</td>
<td>Counsel about ERAS</td>
</tr>
<tr>
<td></td>
<td>Clear-liquid complex carbohydrate load</td>
</tr>
<tr>
<td></td>
<td>Avoid prolonged fasting</td>
</tr>
<tr>
<td></td>
<td>No bowel preparation</td>
</tr>
<tr>
<td></td>
<td>Antibiotic prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Regional analgesia</td>
</tr>
<tr>
<td></td>
<td>Avoid excess drains</td>
</tr>
<tr>
<td></td>
<td>Euvolemia</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
</tr>
<tr>
<td></td>
<td>Minimize opioids</td>
</tr>
<tr>
<td></td>
<td>Minimally invasive assisted (if feasible, safe)</td>
</tr>
<tr>
<td></td>
<td>Venous thromboembolism prophylaxis</td>
</tr>
<tr>
<td></td>
<td>No nasogastric tube</td>
</tr>
<tr>
<td></td>
<td>Nausea/vomiting prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Early ambulation</td>
</tr>
<tr>
<td></td>
<td>Early feeding</td>
</tr>
<tr>
<td></td>
<td>Scheduled nonopioid pain meds</td>
</tr>
<tr>
<td></td>
<td>Discontinue intravenous fluids early</td>
</tr>
<tr>
<td></td>
<td>Early removal of excess drains</td>
</tr>
<tr>
<td></td>
<td>Minimize opioids</td>
</tr>
</tbody>
</table>

Continued on page 26
Urethral stricture disease (USD) is a common urological problem that drives many men to seek treatment from a urologist. Currently, treatment options include endoscopic management (eg urethral dilation or direct visual internal urethrotomy) and urethroplasty, with the latter being considered the standard of care by the AUA.1 Despite this recommendation, the ubiquitous implementation of urethroplasty is hindered by barriers such as variations among clinical sites, including in physician training, access to specialty care and patient populations.2 In order to overcome these barriers and promote care compliant with AUA guidelines, it is imperative the urologic community understand diverse urologic practice and how standards apply in real world situations.

One way to accomplish this goal is to utilize databases such as the AUA Quality (AQUA) Registry. The AQUA Registry collects information from 171 urology practices from all geographic regions, representing 48 states, 1,343 practitioners and 5,504,296 patients. The included practices are primarily community-based groups that range from single-provider to large organizations with dozens of urologists. The registry is derived from electronic health records and manual analysis of provider reports, and designed specifically to report health care outcomes.3

Our group aimed to quantify variation in USD care through the use of data from the AQUA Registry. In all, 77,742 patients in the registry had a history of USD diagnosis. These patients were separated into groups based on whether they were treated with urethroplasty alone (430), 1 trial of endoscopic management (eg urethrotomy), or ≥2 endoscopic treatments (repeat endoscopic management; 6,218). Independent variables included characteristics of the patient (eg age, race, ethnicity, comorbidities), provider (eg age, gender) and practice (eg metropolitan status, location and number of providers). The authors studied how variations in the aforementioned characteristics impacted treatment patterns in individual patients. Ultimately, older provider age, older patient age and higher patient comorbidities such as bladder cancer and benign prostatic hyperplasia were predictive for repeat endoscopic management. Practice variability was also evident when controlling for patient characteristics, as anywhere between 5% and 100% of patients at each studied practice underwent ≥2 or more endoscopic procedures. Additionally, patients were more likely to undergo repeat endoscopic management in 2018 compared to 2014, despite the AUA guidelines recommending against this in 2016.4

This study was the first of its kind published using the excellent resource of the AQUA Registry. Ideally, this database will thrive as a urology specific tool for high quality, impactful research for decades to come. We highlight the need for continued quality improvement in USD care and suggest AQUA as a potential tool for promoting change. Given the unique population available to study, AQUA allows policymakers to meet providers where they are and address barriers to guideline-based care in the community. The findings of this study demonstrate that many urologists continue to pursue repeated endoscopic treatments, despite the wealth of evidence indicating the futility of such treatments.

While this study is novel in its use of the AQUA Registry, quality improvement research in urology is not limited to USD care. The Michigan Urological Surgery Improvement Collaborative (MUSIC) is a quality collaborative that comprises 42 practices representing 85% of Michigan urologists. MUSIC investigated baseline rates of bone and computerized tomography in prostate cancer patients in 2012 and 2013 before developing imaging criteria in 2014. Inappropriate use of both imaging modalities significantly decreased in 2015 and has remained stable, demonstrating the success of the initiative.5 Further, data from MUSIC registries were used to create a machine learning model that was able to accurately predict treatment decisions for men newly diagnosed with prostate cancer.
There Is No Role for a Low Oxalate Diet in Current Era Stone Management

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Clinical Nutrition Services, UW Health/University of Wisconsin Hospitals and Clinics, Madison

Introduction

Patients depend on us to prescribe tested and effective treatments. In the current era, as public skepticism about science and medicine is rising, patients’ trust in us is more important than ever. This applies to medical and nutritional management of kidney stone disease. Therapeutic dietary changes may reduce stone recurrence risk provided they 1) address (an) identified etiological factor(s) contributing to the patient’s stone disease, 2) are achievable and sustainable over time, 3) cause no or limited unwanted side effects and 4) have ample evidence to support their use. A low oxalate diet, including when prescribed within a blanket regimen of dietary therapies to all patients with stones, fails these tests and is thus not appropriate in the current era stone management.

What Is a Low Oxalate Diet?

There is no consensus definition. In theory, it limits oxalate-rich foods to below some cutoff expressed in mg per day. This cutoff is variable, depending on providers’ beliefs, but is typically 50–100 mg per day. There are problems with this approach. For example, it is possible for individuals to consume the same foods but to calculate different oxalate content. Factors related to this variability are shown in Table 1.1–3 For these reasons, cutoffs for a low oxalate diet are practically meaningless. The low oxalate diet is a treatment with no standard definition and varies widely in its application and practice.

Etiology

Determining the etiological factor(s) in any disease is the first step in medical management. While patients with kidney stones may present with similar physical symptoms and renal imaging (flank pain, lower urinary tract symptoms, visualized calculi in kidneys or lower urinary tract), causative factors can differ. This is not unique among medical conditions. In anemia, for instance, the etiology for the generally shared sequelae (fatigue, shortness of breath, low hemoglobin or hematocrit, low red blood cells) must be correctly identified in order to develop an effective response—iron supplementation does not address anemia caused by vitamin B12 or folate deficiency. Similarly, patients whose calcium oxalate (CaOx) stone disease is not caused by high urine oxalate will not be helped by a low oxalate diet. There are many potential contributors to hyperoxaluria; oxalate intake is not always primary. Consider the patient who consumes virtually no or only a little plant material. Recommending a low oxalate diet to this patient, whose oxalate intake is already low, is meaningless therapy. Moreover, in such a case, the recommendation of a more appropriate strategy, ie one that correctly addresses the etiology, is obviated.

Achievability and Sustainability

To be successful, nutrition therapy must be achievable. Challenges in undertaking a specifically defined low oxalate diet were already addressed. Very diligent patients frequently end up eliminating more foods than necessary in pursuit of the goal: “I haven’t eaten a tomato in 20 years.” This patient did not believe me when I told her that available evidence suggests that tomatoes are not actually high for oxalate. But she was given the information decades ago by her urologist (“He has treated all my stones,” she said), who she insisted knew more about nutrition than I. Even after pointing out she had continued to form primarily CaOx stones all these 20 years and that her 24-hour urine results demonstrated other treatable risk factors (low citrate and magnesium), she

could not be convinced to eat a tomato. By avoiding tomatoes all these years, not to mention many other fruits and vegetables, the patient had not achieved a lower oxalate diet.

What about sustainability? Patients who don’t like to eat fruits, vegetables and whole grains find a low oxalate diet quite sustainable. But if you’ve ever heard a patient ask, “What can I eat?” or express some other frustration about following dietary recommendations, sustainability must be questioned. Dietary restrictions of any kind have a poor history of sustainability. For those who want to incorporate a healthy variety of plant-based foods into their diets, a low oxalate diet is not sustainable.

**Side Effects**

A diet low in plant-based foods, particularly when practiced zealously, is insufficient for antioxidants, which are primarily plant-derived phytochemicals conferring many health benefits, including those related to cardiovascular disease, inflammation, degenerative diseases and many cancers. The benefits of fiber, nearly exclusively provided by foods of plant origin, are lost. Potential digestive tract effects of low fiber consumption include altered bowel function (eg constipation, diarrhea, loss of colonic lubrication) and dysbiosis. Patients with diabetes on a lower fiber diet sacrifice a dietary strategy to control blood glucose. Table 2 lists other side effects. In sum, the risk-to-benefit ratio for a low oxalate is high, rendering it of questionable therapeutic value.

**Evidence**

The kind of evidence we typically require prior to implementing a clinical therapy is lacking for a low oxalate diet. One controlled nutrition study among CaOx stone formers demonstrated a reduction in urinary oxalate excretion on a low oxalate diet. However, this same study revealed higher CaOx stone risk due to lower urine citrate and magnesium and higher urinary CaOx supersaturation. A short-term study demonstrated lower urine oxalate and a longer-term study demonstrated lower recurrence rates among CaOx stone formers on low oxalate diets, but there are no high-quality, well-designed, appropriately controlled, long-term trials to confirm these findings. In contrast, evidence for reducing the bioavailability (absorption) of dietary oxalate is robust. In clinical nutrition, the bioavailability of nutrients and other food-derived components is frequently manipulated. While the aim is usually to enhance bioavailability (eg by pairing consumption of nonheime iron with ascorbic acid, dietary fat with carotenoids and fat-soluble vitamins), the opposite can be accomplished, such as by pairing fat, fiber and/or protein with meals to reduce glucose absorption.

Few other widely practiced “therapies” in medicine have so little evidence as the low oxalate diet for stone prevention. In patients whose CaOx stone risk is diet-related, evidence supports 1) balanced dietary patterns that are ample for fruits, vegetables and fiber, and, if needed, 2) calcium consumption sufficient to reduce oxalate bioavailability.

### Table 2. Potential side effects of a low oxalate diet

<table>
<thead>
<tr>
<th>Restricted Foods</th>
<th>Dietary Effect of Restriction</th>
<th>Specific Stone Risk</th>
<th>Mechanism for Stone Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most all fruits and vegetables</td>
<td>Lower intake of bicarbonate precursors</td>
<td>Calcium (all types), uric acid</td>
<td>Lower urine citrate, lower urine pH</td>
</tr>
<tr>
<td>Leafy green vegetables, beans, nuts, seeds, whole grains, chocolate</td>
<td>Lower magnesium intake</td>
<td>Calcium oxalate</td>
<td>Lower urine magnesium</td>
</tr>
<tr>
<td>Whole grains, nuts, seeds, some fruits and vegetables</td>
<td>Lower consumption of prebiotics from fiber</td>
<td>Calcium oxalate</td>
<td>Higher urine oxalate due to lower oxalate degrading capacity of gut microbes</td>
</tr>
<tr>
<td>Nuts, seeds, tubers, some whole grains</td>
<td>Lower phytate intake</td>
<td>Calcium (all types)</td>
<td>Lower urine phytate</td>
</tr>
</tbody>
</table>

Key Historical Developments and Milestones in the Founding of the Associated Journals of the International Society for Sexual Medicine

Ronald W. Lewis, MD
Medical College of Georgia at Augusta University

Beginning with 2 early key meetings in New York City in 1978 and Monaco in 1980 on sexual medicine in men, the third meeting held in Copenhagen, Denmark, in 1982 led to the formation of the International Society for Impotence Research (ISIR), later to eventually become the International Society for Sexual Medicine (ISSM). The key early leaders were Adrian Zorgniotti, a urologist from the United States, Gorm Wagner, a sexologist from Denmark, and Vaclav Michal, a vascular surgeon from Czechoslovakia.

Milestone 1 occurred when 2 key people, Gorm Wagner and William (Bill) Furlow, a urologist from the United States, decided there was a need to share the new scientific findings occurring in this field of male sexual dysfunction—not just at the biennial meetings of the fledgling society, but also in a formal peer-reviewed journal format. Another function of the journal was to publish summaries and abstracts
of other scientific meetings in the realm of sexual medicine. The first issue of the journal, titled *International Journal of Impotence Research (IJIR)* appeared in August of 1989 with 3 issues in that volume. The 2 individuals named above served as the first editors. The journal was owned by the publisher Smith-Gordon and Company and printed in London. At first the journal consisted of 4 issues per year. Details of the scope of the early articles appearing in IJIR can be found in an extensive comprehensive history of the publications and other communication methods recently published in one of the families of journals of ISSM, *Sexual Medicine Reviews.*

Arnold Melman, another urologist from the United States, replaced Bill Furlow as co-editor-in-chief along with Gorm Wagner in 1993 with volume 5 of the early journal. In the year 1995 the journal was sold to Stockton Press, and volume 8 the first published by the new group. In volume 11 in 1999 the number of issues was increased to 6 per year. In 2000 Nature Publication Group, a division of McMillan Publishers, took over ownership of the journal. In 2003 a new editor was chosen after interviewing several candidates. The Publication Committee recommended Irwin Goldstein, a urologist from Boston, as the new editor-in-chief of IJIR. He was appointed to that position by the executive board of ISIR. For the first time, a budget for the editorial office was included in the contract with the publisher.

Milestone 2 came with a major change occurring in 2004, at which time the publication committee and the executive board of the International Society for Sexual and Impotence Research (ISSIR) decided to become owners of the journal with a contract with a publisher producing the product. An attempt to purchase IJIR from Nature Publishing was rejected. After interviewing 3 companies interested in such a partnership, in Amsterdam in March 2004 Blackwell Publishing was chosen as the partner by the executive board of ISIR and the first issue was published in July 2004 under the title, *Journal of Sexual Medicine (JSM).* All the editorial board resigned from IJIR and became the editorial team for the society-owned journal. In addition, the 5 regional sexual medicine societies adopted JSM as their official journal. (Similarly, the International Society for the Study of Women’s Sexual Health adopted it as their official journal in 2007.) The journal was published in 6 issues per year, increasing to a monthly publication in 2008. In 2015 a new editorial team took over the journal with John Mulhall, urologist from New York City, selected as editor-in-chief. Publisher affiliations have included Wiley/Blackwell, Wiley and, currently, Elsevier.

“Milestone 1 occurred when 2 key people, Gorm Wagner and William (Bill) Furlow, a urologist from the United States, decided there was a need to share the new scientific findings occurring in this field of male sexual dysfunction—not just at the biennial meetings of the fledgling society, but also in a formal peer-reviewed journal format.”
Milestone 3 occurred in 2012, when ISSM and its publication committee decided, along with the publisher Wiley, to help curtail the size of JSM by spinning off 2 sister journals, Sexual Medicine Reviews and Sexual Medicine Open Access, in 2013. The page number of JSM was set to be 3,200 per year with an adoption of an increase in rejection rate. Sexual Medicine Reviews’ aim would be to highlight exceptional science and analysis within the field of sexual medicine by an entirely commissioned peer-reviewed content consisting of 4 issues per year. Culley Carson, a urologist from the United States, served as the first editor-in-chief, and the current editor-in-chief is Irwin Goldstein, appointed in 2014. Open Access was to be online only and included a publication fee that was deeply discounted for those from developing nations and significantly reduced for members of ISSM. Its contents would allow for rapid publication and publication of articles more limited to regional or less general audiences. The first editor-in-chief was Alan Shindel, a urologist from the United States, followed by Kwangsung Park, a urologist from Korea in 2015. Currently the editor is again Alan Shindel, reappointed in 2020. An online video journal was started in 2013, under industrial sponsorship. The journal is titled, Video Journal of Prosthetic Urology and has been under 2 editors-in-chief, Steve Wilson from 2013-2019 and Rafael Carrion since 2020, both urologists from the United States. See the table and figure for a list of editors-in-chief of the journals of ISSM and cover representations over the years.

ISSM strives to be the leader for publishing in the field of sexual medicine through its family of journals. This effort has led to publication of major breakthroughs in the field and has expanded over the years to include all aspects of sexual medicine in all genders.
NSQIP and Reconstructive Urology: Has It Informed Decision Making?

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With the introduction of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) in 2001, surgeons across all specialties have utilized NSQIP as a comprehensive representation of individual hospital systems and operational improvement. Urologists and particularly urologic oncologists have frequently relied on NSQIP to compare complication rates during the transition from open to primarily minimally invasive surgery (MIS). Despite its presence for the last 2 decades, its influence on clinical decision making, particularly genitourinary reconstruction, is uncertain. With rising numbers of fellowship-trained reconstructive urologists, both academic and private practice settings have seen compensatory increases in reconstructive case volume. Still, in the context of quality, the role of NSQIP in reconstructive urology is not clear.

Given the breadth of reconstructive urology, it is difficult to assess the influence of NSQIP without narrowing the scope to specific subsets of CPT codes. Studies such as Armstrong et al have attempted to utilize NSQIP to assess 30-day complications after urethroplasty. Their study highlighted an overall complication rate of 8.6% among 1,136 patients over 10-year period. Predictors of complications were identified as age >55 years, preoperative sepsis and length of procedure. Despite statistical significance, the clinical implications were limited by the overall low number of complications associated with urethroplasty. Additionally, variables intrinsic to urethroplasty were either unavailable (perioperative hematoma) or not differentiated (patients who underwent EPA vs substitution urethroplasty). In urethroplasty, limited granularity of operative data within NSQIP proved to be a significant barrier for successful change within a clinical setting.

In contrast to urethroplasty, which will continue to rely on open technique, minimally invasive robotic ureteral reconstruction has been quickly adopted over the last decade. As such, discrete CPT codes within NSQIP may be able to identify differences between open and MIS interventions. This was demonstrated by Hebert et al, who compared outcomes in open and MIS patients undergoing upper and lower ureteral reconstruction. Of the 3,042 patients identified over a 10-year period, patients undergoing an open approach had increased risk of minor and major complications, transfusion and hospital stay. Packiam et al similarly looked at open and MIS approaches for ureteral reimplantation in a NSQIP population. Their conclusions rang similar with increasing complications in those undergoing an open approach, particularly transfusions and urinary tract infections. Use of NSQIP in this setting provides a clear difference in complication rates and actionable data, but in terms of novelty this information falls on deaf ears.

Use of NSQIP appears to be most effective at modifying clinical decision making when the question asked is small or an event is rare. Shelton et al showed that there was no difference in risk of postoperative complications between early (<24 hr) and late (>24 hr) discharges after artificial urinary sphincter placement. Theo-

CASE REPORT

Allium® Stent to Treat Urinary Leak Post-Partial Nephrectomy

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Introduction and Background
Most ureteral injuries occur by iatrogenic trauma.1,2 Ureteral injury during partial nephrectomy is an uncommon iatrogenic lesion, but there is a higher risk of injury with lower pole and medially located tumors.3 Many ureteral injuries go unrecognized at the time of surgery. In fact, of all recognized iatrogenic ureteral injuries, 50% to 70% are not recognized acutely, resulting in further complications.1,3

Ureteral injury at the time of partial nephrectomy may be successfully treated with ureteral stent placement; however, in some cases more complex procedures may be required.1 Our aim is to show resolution of a urinary leak after laparoscopic partial nephrectomy with the placement of an Allium® stent.

Case Report

In our center, a 49-year-old male patient with a 20-year history of smoking was assessed after presenting with gross hematuria. A computerized tomography (CT) with contrast demonstrated a 6 cm lower pole right renal mass with central necrosis. The opposite kidney was normal. Laparoscopic right partial nephrectomy was performed, and during the procedure a proximal ureteral injury occurred due to an incision with cold cutting scissors. This was repaired with spatulation and an end-to-end tension-free ureteral anastomosis over a 6Fr internal ureteral stent. The pathology demonstrated a renal cell carcinoma ISUP 2 with clear surgical margins.

Sixty days after surgery, a retrograde pyelogram was performed at the time of ureteral stent removal to evaluate the site of ureteral injury, and a urinary fistula was evidenced with contrast leak (fig. 1).

Given the findings, an Allium ureteral stent was placed with cystoscopically under fluoroscopic control. Six months after placement, the Allium stent was removed and semirigid ureteroscopy was conducted using a 7.5Fr ureteroscope. Access to the upper urinary tract was easily achieved, and the Allium stent was removed with grasping forceps. Retrograde pyelography demonstrated no contrast leak, and the patient was discharged from hospital 6 hours postprocedure. A CT with contrast performed 3 months after Allium removal and demonstrated no calcification, extravasation or hydronephrosis. Six months after stent removal the patient is clinically well with no urinary leak recurrence.

Discussion and Literature Review
Allium stents are designed for temporary use in urology with the concept of rebuilding a normal epithelium with resulting healing and improved drainage.3 The stent is composed of nitinol and coated with a co-polymer, which reduces the rate of encrustation. In order to overcome migration, stents are connected to an anchor, which significantly reduces the risk of migration and helps at the time of stent removal.5

The Allium ureteral stent was originally designed for the treatment of ureteral strictures, caused by any etiology, with a wide range of stricture lengths.4 Successful experience with this device has encouraged use of the stent in other pathologies such as urinary fistula.6

Prolonged urinary leakage at the site of a previous anastomosis is the most common acute genitourinary complication after repair of ureteral injuries. The incidence of complications after repair of the iatrogenically injured ureter is not well reported, but there are data regarding complication rates after repair of traumatic ureteral injuries; this rate is approximately 25%.6

As is well documented in trauma literature, delayed recognition of any traumatic injury leads to an increased complication rate, including urinoma formation, urosepsis and a more complicated subsequent repair.7 Bahouth et al have reported the use of Allium stents to treat benign and malignant ureteral strictures and urinary fistulae. They documented feasible, safe and effective results with stents placed in 107 ureters. A total of 21 patients died of their primary disease carrying the stent. Stent migration was seen in 11 patients within 8 months after its insertion, and these stents were removed. In 4 patients with early stent migration, the stents were replaced. In 18 patients, the stents were removed as planned after 1 year of indwelling time, and these patients were asymptomatic in a follow-up period of up to 59 months.

The Allium stent represents an important tool that may allow effective treatment for postoperative urinary fistulae. In our case, a 6-month period of stenting resulted in resolution of the fistula and ureteral healing without obstruction or stricture formation.7


Figure 1. Retrograde pyelography showing proximal ureter contrast leak.

Figure 2. Allium stent placed in right ureter.

Figure 3. No contrast extravasation on CT scan.
A 37-year-old man presented with exhaustion and reduced strength in his right arm. Physical examination showed marked anemia and a hard, large tumor of the left testicle, which the patient had been observing for several months. There was a history of extensive cocaine and nicotine consumption. Scrotal ultrasound confirmed a large testicular tumor. Serum tumor markers were increased (α-fetoprotein [AFP] 15.9 ng/ml [<5.8 ng/ml], human chorion gonadotropin [β-HCG] 128,292 IU/ml [<2 IU/ml], lactate dehydrogenase 363 U/L [<250 U/L]). Computerized tomography scan of the thorax, abdomen and pelvis showed multiple metastases in the retroperitoneal lymph nodes, liver and lungs. Magnetic resonance imaging (MRI) of the head showed 3 supra- and infratentorial lesions with pronounced perifocal edema and displacement of the hemispherical gap.

The patient was offered sperm cryoconservation and systemic chemotherapy with cisplatin, etoposide and ifosfamide (PEI) was started, with a dose reduction during the first cycle. With chemotherapy, there was a marked improvement of the neurological symptoms. Blood transfusions were given, but anemia persisted. Further evaluation showed iron deficiency anemia, and the patient also reported repeated rectal blood discharge. Upper gastrointestinal endoscopy was normal, but on colonoscopy an ulcerated tumor of the ileocecal valve was seen (fig. 1). Biopsy confirmed a poorly differentiated, pleomorphic cell carcinoma with mononuclear and multinucleated giant cells and very strong expression of β-HCG (fig. 2).

A total of 4 cycles of PEI polychemotherapy were given and well tolerated. Under chemotherapy, the rectal bleeding stopped, the hemoglobin level normalized and the patient had better appetite and gained 17 kg in body weight. The reduction in serum tumor markers was adequate (AFP 1.7 ng/ml, β-HCG 110 IU/ml, lactate dehydrogenase 264 U/L). After the 4 cycles, computerized tomography scanning showed a clear regression of the intra-abdominal and thoracic metastases. Repeat colonoscopy could no longer detect the previously seen tumor of the ileocecal valve.

Then the left testicle was surgically removed and a still large, but largely devitalized, germ cell tumor was seen with the only still vital tumor tissue described as mature teratoma. Cerebral MRI did, however, show only a mixed treatment response. There was stable disease noted in the previously seen cerebral lesions, but both supra- and infratentorially, several new, small metastases were detected (fig. 3). After extensive multidisciplinary discussions, high-dose chemotherapy of PEI with subsequent autologous stem cell transplantation and additive stereotactical radiotherapy of the cerebral metastases were started. For this purpose, blood stem cells were taken from the patient before chemotherapy, which will be transferred after the treatment is completed. High-dose chemotherapy is currently only performed in special centers.

**Discussion**

This case is unique in that intermittent rectal bleeding occurred in metastatic testicular tumor disease caused by an ileocecal valve metastasis leading to marked iron-deficiency anemia. Intestinal metastasis of testicular cancer is rare and is seen in less than 5% of germ cell tumors. It occurs more often with nonseminomas and especially with embryonal carcinoma. Presumably
Mini-Percutaneous Nephrolithotomy with Ultrasound-Assisted Fluoroscopy Puncture in Horseshoe Kidney and Retrorenal Colon

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Introduction

The horseshoe kidney (HSK) is the most common renal fusion anomaly, with a prevalence of 0.25% in the general population.1,2 In most cases, this fusion occurs at the lower end or base, and it is associated with lack of ascent and malrotation, which cause a high incidence of urinary tract infections and stone formation (around 21%–60% of patients).2 Percutaneous nephrolithotomy (PCNL) is currently considered the first line of treatment in HSK with stones greater than 2 cm in diameter due to its higher stone-free rate.1 The colon has been reported to be posterior or posterolateral to the renal units in 3%–19% of patients with HSK. The incidence of colonic injury during PCNL in horseshoe kidneys is 5.9%, compared to less than 1% in patients with orthotopic kidneys.2,4,5 In this case report, we present a patient with an HSK, staghorn kidney stone and retrorenal colon.

Case Presentation

A 52-year-old male patient from the Peruvian jungle was referred to our hospital due to a left renal lithiasis found on ultrasound. The patient had no significant background and a 3-month illness time, characterized by intermittent left lumbar pain without urinary infections. Noncontrast computerized tomography showed a left staghorn kidney stone on an HSK with fusion at the lower poles, with a volume of 3,456 mm³ (12×24×24 mm) and a density of 1,100 HU. In addition, a retrorenal colon and multiple bilateral renal cysts were evidenced (fig. 1). Nephrolithometric scale scores were as follows: Guy’s, III; STONE (stone size, tract length, obstruction, number of involved calyces and essence/stone density), 8; CROES (Clinical Research Office of the Endourological Society), 230. Admission laboratory results included hemoglobin 14 gm/dl, platelets 280,000/μl, leukocytes 7,500/μl, creatinine 0.56 mg/dl, sodium 142 mEq/l, potassium 4.2 mEq/l and urinalysis without alterations.

Faced with the possibility of colonic injury, we initially performed flexible ureteroscopy, treating only 40% of the stone, near the renal pelvis. Since the desired stone-free rate was not obtained, a consensus meeting was held with the Urology Department, and it was decided to perform a mini-PCNL with ultrasound support to minimize the risk of colonic injury and to be able to access all renal cavities.

The patient was scheduled for mini-PCNL 1 week after the first surgery. He underwent general anesthesia and was placed in a prone position. After placing the ureteral catheter retrogradely by cystoscopy, we performed pyelography.

Figure 1. Anteroposterior computerized tomogram without contrast. A, coronal plane shows calculus spanning lower calyx. B, axial plane shows the interposition of the colon (white arrow) on the way to the upper calyx (yellow arrow). C, 3-dimensional reconstruction of the staghorn calculus.
The puncture was performed with a bull’s-eye technique, directing the puncture toward the upper calyx using fluoroscopic guidance. An ultrasound scan was performed using a 4 mHz curved ultrasound transducer (BK Medical®) to define the adjacent structures to the puncture area and avoid possible inadvertent colonic injury. After puncturing with a Chiba 18 gauge needle (Rocamed®) and passing through it a 0.035 inch × 145 cm hydrophilic guidewire (Roadrunner®), a 1-step candle dilator (Karl Storz, Tuttlingen, Germany) was placed, through which a second guide was passed (safety guidewire), and the 16.5Ch/17.5Ch surgical sheath (Karl Storz) was passed over the latter (fig. 2). After identifying the exit of liquid through the sheath, we proceeded to place the mini-percutaneous 12Ch equipment, with a 6Ch/7Ch working channel and 12° optics (Karl Storz). Nephroscopy was performed and a clear medium was evidenced, with the presence of the residual stone, which was located mainly in the lower calyx. Laser lithotripsy was then performed using high-power holmium P100 equipment (Lumenis®) with a 365 micron laser fiber and laser settings of 0.6 J and 15 Hz, respectively, for energy and frequency. The last stone fragments were removed with an extractor forceps or spontaneously expelled (Venturi phenomenon). The immediate radiological stone-free status was verified under fluoroscopy and by mininephroscopy, navigating all the cavities (fig. 3). Finally, the sheath was removed under vision, leaving the safety guide, and since no bleeding was observed along the way or in the Foley drainage catheter, we opted for a total tubeless procedure.

The postoperative course was unremarkable and the patient was discharged on postoperative day 2. After 3 months, during followup, noncontrast computerized tomography was requested in his city of origin, verifying the stone-free status, which was defined as the presence of no fragments or residual fragment <4 mm.

Conclusions

It is a challenge for the urologist to perform PCNL through a path that has a retrorenal colon interposed. Initially, flexible ureteroscopy was considered to be the best approach, but ultimately PCNL with ultrasound guidance yielded a stone-free outcome. Using intraoperative ultrasonography during mini-PCNL reduces the risk of colon injury, especially in the case of a retrorenal colon.

Cross-Discipline Technology Transfer: A Thankful Urologist

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In the 1970s the German aviation giant, Dornier, in partnership with German urologists, went out of their scope of industry practice and experimented with shock-wave-induced fragmentation of urinary calculi. In 1980, Christian Chaussey et al reported the first clinical use of the prototype HM3 lithotripter to treat renal stone disease.1 Four years later, in March 1984, the first HM3 unit arrived in the United States at the Methodist Hospital in Indianapolis, Indiana and soon thereafter to 4 additional U.S. academic centers. These centers immediately became a magnet for patients seeking a noninvasive method for the treatment of their kidney stones. The approach to this common problem was changed forever. Soon technology modified the bulky HM3 to smaller units.

So why this abbreviated history of the seismic shift in the treatment of urinary calculus disease? The ability to disrupt calcific aggregates has found another home far from the urinary tract, namely to calcifications in the coronary arteries. As in so many areas, miniaturization is key. In this case it made possible the incorporation of shockwave technology to catheters that transverse the coronary arteries.

How did such a catheter address my problem? I experienced the crushing chest pain that I had experienced several times in the past and which had been successfully treated with balloon angioplasty and stent placement. Current coronary angiography revealed "instant stenosis" in an area of prior stenting of the left anterior descending coronary artery. Furthermore, this region had developed dense arterial wall calcification in this previously stented area. This rigidity of the calcified artery prevented balloon expansion from dilating the lesion to allow stent placement. The procedure was terminated. The interventional cardiologist then presented me with the choice of coronary artery bypass surgery or the possibility of an intervention using a catheter with shockwave lithotripter capability (Shockwave Medical, Inc., Santa Clara, California). The intravascular lithotripsy catheter contains integrated lithotripsy emitters for the localized delivery of acoustic pressure pulses within the target treatment site. This disrupts calcium within the coronary artery lesion allowing it to yield to dilatation using low balloon pressure. Stents can then be successfully placed. While traditionally studied and approved for dilation of complex, calcified vessels prior to stent placement, off-label use has included treating previously stented lesions, as in my case.2,3

I expressed wonder and disbelief. I fell back on a familiar statement: “You can’t be serious!” But we are encouraged to listen to our doctors. The catheter was deployed and activated. The calcification within the arterial wall was fragmented and softened, permitting balloon expansion and placement of stents. Interventional cardiology has applied technology born to fragment urinary calculi to a successful cardiac intervention. For innovation, cross-discipline technology and a skilled interventional cardiologist, I am an ever-thankful urologist.


Cross-Discipline Technology Transfer: A Thankful Urologist


Special thanks to Drs. Hari Vigneswaran and Daniel Moreira at the University of Illinois at Chicago.

Positron emission tomography (PET) in prostate cancer helps urologists diagnose patients with biochemical recurrence after local therapy. Choline and fluorocholine were conventionally used, but prostate specific membrane antigen (PSMA) PET has shown promising results and appears to be replacing the more conventional imaging modalities.

The authors of this multicenter prospective phase 3 imaging trial evaluated the role of PSMA PET in the initial staging of localized prostate cancer to identify those with pelvic nodal metastasis. Patients with either intermediate- or high-risk prostate cancer were studied. In total 764 men were recruited from 2015 to 2019 and underwent 68Ga-PSMA-11 PET scans. The primary end points of the study evaluated the accuracy of PSMA PET compared to the pathological specimen at time of surgery.

Of the 764 who underwent PET imaging, 277 underwent surgery, and the others underwent radiation, systemic therapy, surveillance or were lost to followup. In the surgical group, 40 (14%) had regional pelvic node metastasis on PSMA PET, and 75 (27%) had metastases by pathological evaluation. The sensitivity of PSMA PET was modest at 40% but with a high specificity of 95%. The positive predictive value was 75%, and the negative predictive value was 81%. These results were used for U.S. Food and Drug Administration application of PSMA PET for initial prostate cancer staging. If approved, urologists may soon use this evidence when considering PET evaluation in their own patients for initial staging of prostate cancer.


Special thanks to Drs. Kareim Khalafalla and Samuel Oklader at the University of Illinois at Chicago.

Urologists who treat men with azoospermia due to spermatogenic dysfunction are keenly interested in predictors of successful surgical sperm retrieval. Many studies have tried, but few have succeeded in identifying clear factors that forecast success. In this study, the authors evaluated the correlation between testicular histopathological heterogeneity and surgical sperm retrieval rate (SRR) in patients undergoing microdissection testicular sperm extraction over a 10-year period ending in 2020. A total of 918 men with microdissection testicular sperm extraction were included. The median testis volume was 8 cc and the median follicle stimulating hormone was 21 miU/ml. Of
these, 391 men (43%) had 1 pathology, 388 men (42%) had 2, 108 (12%) had 3 and 31 (3.4%) had 4 different pathologies. Sertoli cell-only was the most common histopathology detected, followed by maturation arrest. The overall SRR was 42% with a clinical intrauterine gestation rate of 30%. Increasing histopathological variety was associated with higher SRRs: SRR of 33% was observed when 1 histopathological subtype was present, 41% with 2 subtypes, 64% with 3 subtypes and 94% with 4 subtypes. Men with any foci of spermatogenesis had higher SRRs.

The authors concluded that the presence of multiple heterogeneous histopathology specimens correlated with higher surgical sperm retrieval rates in men with azoospermia due to spermatogenic dysfunction. Proper uniformreporting of histopathology pattern and percent is thus critical for patient management and followup. Despite how small an area with spermatogenesis is, it truly makes a difference in a patient’s hope in fathering children.


Special thanks to Drs. Susan Talamini and Omer Acar at the University of Illinois at Chicago.

The diagnosis of cancer is life changing. Life expectancy is a vital component in determining which men will obtain the most benefit from treatment and aids in selecting therapy. These investigators assessed the patient perspective in the communication of life expectancy in prostate cancer.

A total of 26 men were interviewed after consultation for prostate cancer treatment. The importance of life expectancy, if or how it had been discussed, barriers to discussing life expectancy, and ideal modes of communication were assessed. Of the participants, 19 (73%) recalled discussing life expectancy. Of these men, three-quarters recalled the discussion as a generalization such as “long” or “short” or a numerical survival probability, and the remainder discussed life expectancy as number of years. The majority of men (6 of 7) who did not discuss life expectancy felt that it would have been helpful.

Regarding preferences for life expectancy discussion, men preferred either number of years as it was easily understandable and concrete, or survival probability as it provided hope. Generalizations were felt to reduce patient involvement in shared decision making. The main barrier to discussing life expectancy was anxiety (15 of 26, or 58%), which could be ameliorated by using life expectancy ranges, depersonalizing language and assessing patient’s desire to know life expectancy.

This article demonstrates evidence that patients diagnosed with prostate cancer want to be informed about their life expectancy and would like specifics rather than generalizations. The authors also provide a framework for conducting life expectancy conversations using patient-centered language in a way that enhances shared decision making in the treatment of prostate cancer.

FROM THE UROLOGY CARE FOUNDATION PRESIDENT

The Humanitarian Grants Program Delivers

Harris Nagler, MD, FACS
President, Urology Care Foundation

Give a man a fish and he will eat for a day. Teach a man how to fish and you feed him for a lifetime.

In early 2021, the Urology Care Foundation proudly launched a new humanitarian initiative designed to support the humanitarian efforts of AUA members. Endowments were created with funds donated by our many generous donors and matched by the AUA. In its first year, we were able to provide funds for 2 individuals of the 17 who applied. We are proud to recognize and share with you the accomplishments of our first 2 grant recipients.

In November of 2021, Dr. Una Jeanie Lee from Virginia Mason Franciscan Health Urology, Seattle, Washington served as teaching faculty with the nonprofit organization Medicine for Humanity, a group she has been volunteering with for more than a decade. This year, after careful COVID-19 risk mitigation planning, 9 team members including urologists, urogynecologists, anesthesiologists, nurses and surgical technicians successfully completed the annual Medicine for Humanity surgical educational program at MUST (Mbarara University of Science and Technology) in Mbarara, Uganda. Forty-five surgeries were performed with Ugandan and American surgeons working side by side. In addition to the surgical care provided, the education of Ugandan and American residents and fellows was one of the program’s main goals. “I’m most proud of being part of an organization that has committed to empowering the surgeons of Mbarara and building their capacity to help women with obstetric fistula,” said Dr. Lee. “Medicine for Humanity and MUST [have] established the second Urogynecology Fellowship in East Africa, and now their team of trained surgeons and nurses does outreach fistula surgery in other parts of Uganda with unmet needs. We help teach the Ugandan doctors to ‘fish’ and these doctors are teaching others to ‘fish,’ and these surgeries have downstream positive impacts as changing women’s lives lifts up families and communities.”

The Urology Care Foundation has recognized the importance of supporting programs and initiatives that lead to sustainable progress in establishing equity of care and access. The proverb, “Give a man a fish and he will eat for a day. Teach a man how to fish and you feed him for a lifetime” continues to hold true.

Dr. Lee goes on to say, “I’m humbled by their resilience and their courage in the face of hardship. They each taught me about gratitude, what really matters in this world, and how connected we all are.” The Foundation support was invaluable for this program, given the multifactorial challenges related to COVID in low-income countries and the tremendous need for surgery, education and training on urological and urogynecologic women’s health and repair of childbirth injury.

Also in November, Dr. David Rapp, University of Virginia and founder of Global Surgical Expedition, led a surgical trip to Belize where combined mission teams treated 37 patients and provided 31 surgeries and procedures to patients coming from all regions of the country. In an effort to reach more patients, separate surgical teams were organized to provide focus on both general urology and Female Pelvic Medicine and Reconstructive Surgeries. Care was provided at Corozal Community Hospital in the Corozal region. A total of 8 members participated in

HAVE YOU READ?

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the trip, including surgical, anesthesia and nursing professionals. Combined, Global Surgical Expedition teams performed surgeries to correct vesicovaginal fistula, benign prostatic hyperplasia, urethral stricture disease, pelvic organ prolapse, urinary incontinence and bladder stones, as well as provided surgical training to local Belizean surgeons and gynecologists. Also as part of the trip, more than $1,000 in surgical supplies was provided to facilitate future surgery by Belizean surgeons. Dr. Rapp commented, “Our group of medical volunteers continue to be both humbled and thankful for the support we have received to conduct our ongoing surgical trips. The work of the team during our most recent mission included treatments of urogenital fistula, pelvic organ prolapse, urinary incontinence, prostate obstruction, urethral strictures, and numerous other debilitating illnesses. We are truly excited about continuing to provide care and develop the surgical infrastructure in Belize during future missions.”

The Urology Care Foundation is on the move with this new humanitarian component of our vision and mission, and these trips exemplify how the Foundation is becoming stronger through the dedication and vision of volunteers, in this case with international horizons. We are excited to say in 2022 we will be offering 7 humanitarian grants. For more information, visit UrologyHealth.org/Humanitarian.

FROM THE AUA SCIENCE AND QUALITY COUNCIL

Science & Quality Update: Guidelines

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Despite ongoing challenges due to the COVID-19 pandemic, 2021 was a strong year for the AUA Guidelines program with the release of 3 new guidelines and related educational content. The AUA membership showed continued support for the program through use of guidelines products available on the AUA website as well as programming accessed via the 2021 virtual Annual Meeting. In line with the AUA mission, such dedication highlights the commitment of the field of urology to promoting the highest standards of care through evidence-based medicine.

The Acute Ischemic Priapism Guideline, developed in partnership with the Sexual Medicine Society of North America, provides a clinical framework for the diagnosis, evaluation, and treatment (nonsurgical and surgical) of this condition. This guideline joins the AUA’s robust stable of guidelines focused on sexual and reproductive health, which also includes titles on erectile dysfunction, Peyronie’s disease, testosterone deficiency, male infertility, disorders of ejaculation and vasectomy.

Developed in partnership with the Society of Urodynamics, Female Pelvic Medicine & Urogential Reconstruction, adult neurogenic lower urinary tract dysfunction is a new topic for AUA Guidelines. Focused on abnormal function of the bladder, bladder neck, and/or its sphincters due to neurologic disorder, this guideline provides discussion of available treatment options and emphasizes the importance of shared decision making in optimizing patient quality of life as it relates to bladder management.

Following previous iterations of the Surgical Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms and now includes detailed discussion of medical therapy options as well as updated content related to surgical management.

“As new topics are assessed for potential guideline development, AUA members are reminded that they are able to nominate topics for consideration by visiting www.auanet.org/guidelines.”

“Following previous iterations of the Surgical Management of Benign Prostatic Hyperplasia Guideline, this guideline was revised in 2021 as the AUA Guideline on Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms and now includes detailed discussion of medical therapy options as well as updated content related to surgical management.”

Localized Prostate Cancer as well as an expansion of the Priapism Guideline. Development will also continue on early detection of prostate cancer, which will expand on the current AUA Guideline, which is largely focused on the use of prostate specific antigen in cancer detection, as well as a new topic on upper tract urothelial carcinoma. The latter is the first AUA Guideline to undergo development using the AUA’s new policy on open nominations for panel membership. This significant update to the paneling process allows for the creation of multidisciplinary panels of subject matter experts while further underscoring the AUA’s commitment to promoting diversity within the program.
As new topics are assessed for potential guideline development, AUA members are reminded that they are able to nominate topics for consideration by visiting www.auanet.org/guidelines. Members are also encouraged to visit the AUA Guidelines webpage for updates on future opportunities to engage with the Guidelines team through activities such as panel participation and peer review. The Guidelines webpage also houses all freely available, full-text guidelines and selected translations. Members will also find links to order Guidelines-at-a-Glance books and download the AUA Guidelines smartphone application, which is available for both Apple® and Android™ devices. As use of AUA Guidelines grows, the AUA will continue to review the program to ensure compliance with the most current accepted standards in guideline development to guarantee production of the quality documents that AUA members have come to expect and trust.

The implications of the COVID-19 pandemic have affected every facet of society, and professional organization meetings are no exception. With meeting participants gathering from around the country and around the world to exchange ideas and innovations, it is only natural that an exchange of germs could follow. Indeed, one of the earliest and most publicized COVID-19 outbreaks was connected to such a meeting, when, after a biotechnology conference in Boston in February 2020, over 100 people were sickened with COVID-19, and the chain of transmission started to spread. Indeed, in-person professional society meetings were one of the first things to be halted in the pandemic, and there has been substantial trepidation related to their return.

While the pandemic has exacted a massive human cost and has had unprecedented economic impacts, its silver lining is that it has led to the development and expansion of numerous innovative digital platforms to facilitate virtual collaboration and socialization. These platforms allowed for a transition from in-person to virtual meetings, which maintained much of the core academic and educational content. The recent all-virtual AUA2021 meeting is a notable example. However, these virtual meetings are often lacking in formal and informal networking opportunities. These social and networking elements are particularly crucial for residents, for whom these events facilitate making connections that can be critical in securing a job or fellowship. Additionally, from a resident wellness perspective, these meetings also offer a rare opportunity to gather and socialize with co-residents and residents from other programs, building camaraderie and helping foster career and lifelong friendships.

Now, nearly 2 years into the pandemic, a number of successful vaccines and public health measures have helped turn the tide on COVID-19, permitting incremental transition back to normalcy. Urological professional organizations such as the AUA and its regional sections; the Society of Urology; and the Society of Urologic Oncology are starting to cautiously plan and execute in-person meetings again.

The AUA South Central Section (SCS) recently held its 100th meeting in Scottsdale, Arizona, which marked the first in-person urology meeting since the start of the pandemic. While there was some degree of uncertainty regarding the risks of hosting a meeting in the era of COVID-19, studies have been conducted of experimental indoor mass gathering events, which have demonstrated that such events can be safely executed in a properly ventilated facility with appropriate measures such as mask wearing and testing or vaccination. The SCS meeting adopted many of these safety measures, including mandatory vaccination, indoor masks, and primarily outdoor networking and social events.

Participants from across the nation attended the SCS meeting, and there was even attendance from an international delegation from Mexico. Thanks to technology honed during the pandemic, speakers who were unable to attend in person were able to virtually participate in the meeting, an innovation that is here to stay.

Although there were extensive educational opportunities available at the SCS meeting, it was the informal, in-person interactions that made the meeting exceptional and refreshing in the post-COVID-19 era. Thanks to the safety measures mentioned above, we are not aware of any ill effects from the meeting.

While there will certainly be a place for virtual meetings and collaboration going forward, it is clear that in-person meetings have substantial advantages, and their return will be of great benefit to our field, particularly its trainees.

Adverse reactions occurring more frequently in the NUBEQA arm (6% vs 3%) and rash (3% vs 1%).

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs 11%), pain in extremity (6% vs 3%) and rash (3% vs 1%).

Clinically significant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs 3.4% on placebo) and heart failure (2.1% vs 0.9% on placebo).

Drug Interactions
Effect of Other Drugs on NUBEQA – Combined Pgp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use. Combined Pgp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the prescribing information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

Please see the following pages for brief summary of full Prescribing Information.
NUBEQA® 
(darolutamide) 300 mg tablets

Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled, international, multicenter, phase III study (ARAMIS) in nmCRPC patients with a prostate-specific antigen doubling time of ≤10 months. 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA twice daily (n=955) or matching placebo (n=554). All patients received concurrent ADT (treatment with GnRH analog or previous bilateral orchiectomy). The primary endpoint was MFS, defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, 99mTc bone scan by BICR, unacceptable toxicity, or withdrawal. The final analysis of OS and time to initiation of cytotoxic chemotherapy was event-driven and conducted after 254 OS events had occurred and 14 months after MFS analysis.1,2

1In patients treated with NUBEQA + ADT, the most frequent adverse reactions requiring dose reduction included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%); the most frequent adverse reactions requiring dose interruption included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

2The most frequent adverse reactions requiring permanent discontinuation in patients treated with NUBEQA + ADT included cardiac failure (0.4%) and death (0.4%).

3All-grade laboratory abnormalities in patients treated with NUBEQA + ADT vs ADT alone were, respectively, decreased neutrophil count (20% vs 9%), increased AST (23% vs 14%), and increased bilirubin (16% vs 7%). Grade 3-4 for same lab abnormalities were, respectively, 4% vs 0.6%, 0.5% vs 0.2%, and 0.1% vs 0%.

4The NUBEQA Free Trial Program provides 1 month’s supply of NUBEQA at no cost to patients who meet the program eligibility requirements and agree to the terms and conditions. For full terms and conditions and to enroll patients, please call Access Services by Bayer at 1-800-288-8374 or visit NUBEQAhcp.com.

PFS=prostate-specific antigen; ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; NE=not estimable; GnRH=gonadotropin-releasing hormone; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging; AST=aspartate aminotransferase.

Start new NUBEQA patients with a 1-month free trial† / Visit NUBEQAhcp.com

**Adverse Reactions occurring more frequently in the NUBEQA arm**

Please see the following pages for brief summary of full Prescribing Information.

(≥2% over placebo) were fatigue (16% vs 11%), pain in extremity (0.2%), and pulmonary embolism (0.2%) for NUBEQA. Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.3%), and hypertension (0.3%) for NUBEQA and for 1 week after the last dose.

IMPORTANT SAFETY INFORMATION

INDICATION

NUBEQA is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

**Serious adverse reactions**

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.3%), and hypertension (0.3%) for NUBEQA and for 1 week after the last dose.

**Prescribing Information**

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Monitor more frequently for adverse reactions, and consider dose reduction of these substrates.

**Concomitant use**

Concomitant use may increase plasma concentrations of OATP1B1 or moderate CYP3A4 inducers decrease NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Review the prescribing information of drugs that are BCRP , OATP1B3 substrates. Monitor more frequently for adverse reactions, and consider dose reduction of these substrates.

**Drug Interactions**

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of BCRP substrate-related toxicities. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of NUBEQA adverse reactions. Avoid concomitant use.

**Powerful Efficacy, Extend patient survival with NUBEQA**

3.4% on placebo) and heart failure (2.1% vs 0.9% on placebo). In patients treated with NUBEQA + ADT, the most frequent adverse reactions requiring dose reduction included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%); the most frequent adverse reactions requiring dose interruption included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

**Most NUBEQA patients did not report any fatigue (84%)**

Three adverse reactions occurred more frequently with NUBEQA + ADT (≥2% over ADT alone): fatigue (16% vs 11%), pain in extremity (6% vs 3%), and rash (3% vs 1%).

**Reduced risk of death by nearly a third**

31% reduction in the risk of death with NUBEQA + ADT vs ADT alone (HR: 0.69; 95% CI: 0.53-0.88; P=0.003)

**Prescribe with confidence**

~19 out of 20 patients started on and stayed on full dose

Low rates of dose reduction (6%) and interruptions (13%) with no increase in permanent discontinuation due to adverse reactions when NUBEQA was added to ADT (9% vs. 9% with ADT alone).
NUBEQA® (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

BRIEF SUMMARY OF PRESCRIBING INFORMATION
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
NUBEQA is indicated for the treatment of patients with nonmetastatic castration-resistant prostate cancer (nmCRPC).

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Embryo-Fetal Toxicity
The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Clinical Pharmacology (12.1)].
Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
ARAMIS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nonmetastatic castration-resistant prostate cancer (nmCRPC). In this study, patients received NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.
Overall, serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA included urinary retention, pneumonia and hematoma. Overall 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.
Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%) and death (0.4%).
Dosage interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).
Dosage reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).
Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

Table 1: Adverse Reactions in ARAMIS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades ≥ 3</td>
</tr>
<tr>
<td>Fatigue¹</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

¹ Includes fatigue and asthenia
² Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).

Table 2: Laboratory Test Abnormalities in ARAMIS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (N=954)</th>
<th>Placebo (N=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades¹</td>
<td>Grade 3-4²</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>AST increased</td>
<td>23</td>
<td>0.5</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16</td>
<td>0.1</td>
</tr>
</tbody>
</table>

¹ The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.
² Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on NUBEQA
Combined P-gp and Strong or Moderate CYP3A4 Inducer
Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity [see Clinical Pharmacology (12.3)]. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Combined P-gp and Strong CYP3A4 Inhibitors
Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see Clinical Pharmacology (12.3)] which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see Dosage and Administration (2.2)].

7.2 Effects of NUBEQA on Other Drugs
Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates
NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and Cmax of BCRP substrates [see Clinical Pharmacology (12.3)], which may increase the risk of BCRP substrate-related toxicities.
Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug.

NUBEQA is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA [see Clinical Pharmacology (12.3)].

Review the prescribing information of the BCRP, OATP1B1 and OATP1B3 substrates when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1)]. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

Risk Summary
The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males
Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (8.1)].

Infertility

Males
Based on animal studies, NUBEQA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

Safety and effectiveness of NUBEQA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m²) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30–89 mL/min/1.73 m²). The effect of end stage renal disease (eGFR <15 mL/min/1.73 m²) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see Clinical Pharmacology (12.3)].

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

Darolutamide was clastogenic in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the in vivo combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hyposperma, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose [see Dosage and Administration (2.1)].

Embryo-Fetal Toxicity

Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy [see Use in Specific Populations (8.1)].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)].

Infertility

Advise male patients that NUBEQA may impair fertility [see Use in Specific Populations (8.3)].

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SECTION AND SPECIALTY MEETINGS

Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction 2022 Winter Meeting

Imagine escaping the dreary February winter frost to meet up with your urology friends and colleagues from across the country in sunny San Diego for a fantastic scientific meeting. The meeting has the right mix of basic science talks, informative thought-provoking poster and podium presentations, insightful discussion during debates and breakout sessions, networking, empowering Zumba, clinical pearls, useful updates, camaraderie and fun for both the general urologist as well as the urologist specializing in urodynamics, incontinence, female pelvic medicine, neurourology and urogenital reconstructive surgery. The meeting I am describing is the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) 2022 Winter Meeting that will be held at the Marriot Marquis San Diego Marina.

Many of us have fond memories of the SUFU 2020 Winter Meeting, which was held in Arizona the week before the country locked down for COVID. The SUFU 2021 Winter Meeting was very successful but virtual. I am very much looking forward to the in-person SUFU 2022 Winter Meeting February 22–26, which boasts a stellar program and venue, as well as diverse speakers and participants.

Some of the meeting highlights include updates in the basic science behind bladder and pelvic pain, focus on the social aspects of pelvic floor conditions, challenging treatment debates, surgical pearls, awards, ABU and coding updates and a session on how to use the excellent (but not well known) SUFU resources. As usual, there will be video, moderated podium and poster sessions focused on incontinence, neurogenic bladder, basic science, pelvic organ prolapse, reconstruction, neuromodulation, benign prostatic hyperplasia, interstitial cystitis and geriatrics. This year’s meeting also features some great opportunities for fellows and residents to network.

Some of the basic science talks at this year’s meeting that would interest all urologists include a lecture by Lisa Karstens, PhD discussing the role of bacteria in overactive bladder and urinary incontinence. A panel (moderated by Michel Pontari, MD) will discuss signaling in bladder pain (Pedro Vera, PhD), the effect of aging on immune activity (Indira Mysorek, PhD) and neuro-immune interactions in chronic pelvic pain (Praveen Thumbikat, PhD). Keynote lectures by Stuart Brierly, PhD and Min Dong, PhD will discuss mechanisms underlying noxious bladder pathways and new frontiers in therapeutic toxins for urological disease.

Here are some of the challenging treatment debates at this year’s SUFU meeting: bulking vs mid-urethral sling vs autologous fascial sling for which patient? Bariatric surgery/weight loss vs surgery for the obese patient with stress urinary incontinence? Oral medications vs neuromodulation for a patient with fecal incontinence and overactive bladder? Mid-urethral sling vs bulking agent for primary stress urinary incontinence?

There are sessions focused on physician wellness and practice management. Mark Painter will give a coding update for 2022. There are breakout sessions to discuss physician burnout, optimization of advanced practice providers in practice and even a session where you can bring your own complex cases for discussion.

As always, there will be valuable expert talks about surgical management. One session, chaired by SUFU President Sandip Vasavada, MD, focuses on tips and tricks when things go wrong during female pelvic medicine and reconstructive surgery (panelists Jason Kim, MD, Ja-Hong Kim, MD and Larissa Rodriguez, MD). The expert surgical theater (moderated by Michael Albo, MD) will focus on native tissue pelvic organ prolapse repair (Christian Twiss, MD) and robotic hysterectomy (Nirit Rosenblum, MD).

Female cosmetic genital surgery (Linda Cardozo, MD) and flaps in female pelvic medicine (Schlomo Raz, MD) will also be highlighted. An expert lecture by Dr. Philippe Zimmer will detail transvaginal native tissue repair for pelvic organ prolapse.

There are so many other outstanding sessions during the 2022 SUFU Winter Meeting that I have not mentioned in this article.

Dr. David Ginsberg is the head the program committee and has worked tirelessly to put together this program. The other program committee members are Benjamin Dillon, MD, Stuart Reynolds, MD and me, Doreen Chung. We hope to see you all there in sunny San Diego.