Ureteroscopy with High Power Laser Systems and Potential for Renal and Ureteral Complications

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Background and Evolution of Laser Lithotripsy

As urinary stone disease continues to increase in the United States and around the world, ureteroscopy (URS) with laser lithotripsy (LL) has become the most commonly used modality for stone treatment. More than 500,000 ureteroscopic stone cases are performed annually in the United States, based on extrapolation of data from the Urologic Diseases in America project. This increase in use of ureteroscopy is in part due to technological advances such as higher power laser systems, which have widely expanded the capabilities and efficiency of laser lithotripsy. Additional modes of laser lithotripsy, such as dusting and popcorning, can now be used in addition to traditional stone fragmentation to improve speed of treatment and better control stone particle size. However, these newer modes of laser lithotripsy are commonly applied at higher power and require increased irrigation to maintain a clear visual field. These laser and irrigation settings can substantially elevate fluid temperatures and intrarenal pressures, respectively.

Evidence of Complications from Elevated Temperature and Pressure

A number of in vitro studies, mathematical models and computer simulations have shown that laser energy applied at high power can elevate fluid temperature within the collecting system to dangerously high levels. The degree of temperature elevation is dependent on energy delivery (laser power, activation time and operator duty cycle) and the heat capacity of the system (fluid volume of calyx/ureter/collecting system, irrigation rate and irrigation temperature). Thermal tissue injury is dependent on both the degree of temperature elevation and the duration of exposure to elevated temperatures. This concept, developed by Sapareto and Dewey, is referred to as thermal dose and represents an accumulative measurement of temperature during the treatment period. Cellular injury occurs when a thermal dose threshold of 120 to 240 equivalent minutes (based on tissue type) is exceeded. So proper prediction of the thermal tissue injury requires calculation of thermal dose and not simply measurement of temperature. Gross evidence of tissue injury has been demonstrated during in vivo porcine URS LL studies in our laboratory when thermal dose thresholds were exceeded. Although there are limited human data, several studies have confirmed that significant temperature elevation can occur in the calyx and ureter during URS LL. In a study examining laser activation in the ureter, 63% of patients experienced temperatures greater than 37°C.

Evolution of Robotic Surgery in Pediatric Urology

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Nineteen years after the first pediatric robotic pyeloplasty with a da Vinci® Surgical System, robotic surgery in pediatric urology is well established and continuing to evolve. Initially developed for cardiac and potentially remote surgery, the da Vinci System has found its place solidly within urology and is used for numerous procedures with a high level of success. Controversy remains regarding its true value, and this is certainly the case in pediatric urology. With initial use beginning soon after the introduction of reconstructive laparoscopy, the robotic system offered the potential for much more efficient minimally invasive reconstructive procedures in children. As is often the case, early adapters rapidly explored the possibilities of this new technology. Initial results with pyeloplasty and ureteral reimplantation were generally very good, but currently the robotic system has been used primarily for reconstructive laparoscopy in pediatric urology. This is certainly the case in pediatric urology.
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Potential Complications of Ureteroscopy with High Power Laser

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than 56°C (exposure to 56°C for 1 second will produce cell death). Of this group of patients, 37% reported pain and/or had hydronephrosis on subsequent renal ultrasound concerning for ureteral stricture. While multiple factors can contribute to excessive heating, insufficient irrigation is perhaps the most important. However, what constitutes adequate irrigation has not been clearly defined. Laboratory studies have shown that temperature elevation can be well managed with room temperature irrigation delivered at 40 ml per minute for laser powers of 40 W applied continuously for 60 seconds.

High irrigation rates (see table) not only have been used to control intrarenal temperature, but also are necessary with advanced laser techniques, which produce dense clouds of stone fragments and debris that can obscure the endoscopic visual field. However, use of higher irrigation rate increases intrarenal pressure as measured during in vivo porcine studies (fig. 1). Pressures that exceed the threshold for pyelovenous backflow (30 mm Hg) increase the risk of tissue injury, fluid extravasation, systemic inflammatory response syndrome and sepsis. Ureteral access sheaths have been shown to reduce intrarenal pressure. This was confirmed in a recent human study that employed a wire pressure sensor during ureteroscopy. However, in a separate human study that also used wire pressure sensors, the pressure threshold for pyelovenous backflow was still dramatically exceeded in some cases, even with use of access sheaths. Furthermore, in many clinical circumstances, placement of an access sheath may not be possible or desirable.

Aside from the potential complications discussed above, we must also take a hard look at the current state of postoperative recovery following URS LL. While URS LL is commonly performed in the outpatient setting with patients discharged home after a typical 60-minute operative procedure, there is a stunning disconnect between the perceived minimally invasive nature of URS LL and the severity of postoperative pain, high postoperative emergency department visit rates (10% to 15%) and hospital readmission rates (5%). We must consider the possibility that elevated intrarenal temperature and pressure during URS LL produce tissue injury and inflammation (as seen with in vivo porcine studies), which in turn can lead to high postoperative pain, morbidity and readmission rates. Hence, one approach to decrease morbidity and improve the postoperative course for patients is to focus on better control and management of temperature and pressure during URS LL.

Current State and Future Directions

The introduction of high power lasers for lithotripsy occurred rapidly, without published evaluation of thermal or pressure risks. Currently, there is no guidance from industry, professional groups or regulatory bodies on selection of safe laser settings and irrigation rates. Recent bench and in vivo porcine studies have demonstrated that in certain circumstances clinical laser settings can induce dangerous temperature and pressure elevations and pathological injury (fig. 2). Although we perceive these events to be infrequent clinically, it is possible we are underestimating their prevalence. Thermal tissue changes may not be visually apparent at the time of URS LL. Although published human studies are limited at this point, they are not definitively reassuring.

Proper investigation of thermal and pressure risks is needed in order to enhance and ensure the safety and tolerability of URS LL. The first step is to develop a collective clinical awareness that elevated thermal dose and intrarenal pressure can occur during URS LL. Research is needed to rigorously examine the extent of injury and inflammation that results from temperature and pressure insults, and assess the relationships with postsurgical symptoms and complications. This work can further inform development of new URS LL systems capable of real-time monitoring of temperature and pressure to enhance patient safety without limiting the capabilities and efficiencies derived from recent technological advances in laser lithotripsy.

![Renal pelvis pressure readings](image)

**Figure 1.** In vivo porcine study of renal pelvic pressure during ureteroscopy (LithoVue ureteroscope) with irrigation applied at 0, 8, 15 and 40 ml per minute from peristaltic pump. 13Fr/15Fr access sheath was positioned with tip in proximal ureter.

![Table](image)

**Table.** Relationship between irrigation pressure and rate with 242 µm laser fiber in working channel of LithoVue™ ureteroscope

<table>
<thead>
<tr>
<th>Irrigation Configuration</th>
<th>Irrigation Bag Pressure (cm H₂O)</th>
<th>Irrigation Rate (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure bag at 150 mm Hg, 100 cm above ureteroscope tip</td>
<td>304</td>
<td>40</td>
</tr>
<tr>
<td>Bag 100 cm above ureteroscope tip</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>Bag 60 cm above ureteroscope tip</td>
<td>60</td>
<td>8</td>
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</tbody>
</table>

![Figure 2](image)

**Figure 2.** Gross appearance of bivalved porcine kidneys demonstrating thermal injury. Left panel, inner blanched and outer hyperemic rings of tissue injury are observed after in vivo holmium laser activation within middle calyx at 40 W settings for 60 seconds with no irrigation. Dashed arc designates outer margin of hyperemic zone. Right panel, similar, but less pronounced, tissue effects in calyx at center after 60 seconds of laser activation at 40 W with 8 ml per minute irrigation.

Robotic Surgery in Pediatric Urology


Continued from page 1

with success rates comparable to open surgery yet reduced hospital stays. Demonstration of significantly reduced morbidity, however, was difficult, particularly in younger children, where the recovery is often rapid no matter what surgical method is used. While the benefits could be debated, it was clear from initial reports that even small children could be successfully operated on for multiple renal surgeries (see figure), including ureteral, bladder and retrovesical procedures as well. As with any new technology, robotic surgery in pediatric urology had its early and late adaptors.1

While a small group of surgeons with access to the da Vinci System explored pediatric applications, overall adoption was relatively slow due to several factors.2 The system remained very costly both to purchase and maintain. While much easier to learn than conventional laparoscopic techniques, there was still a learning curve that in essence was a cost in itself. In pediatric urological practice, high volume procedures that could justify the cost to an institution are uncommon. Other pediatric specialties were even slower to take up robotic surgery and potentially spread the cost. At the same time, there was skepticism regarding its value, and several reports of alternative approaches including minimally invasive open surgery began to appear. In pediatric practice, there were few meaningful objective parameters to define surgical morbidity, and there has been no generally accepted threshold for morbidity reduction to justify the costs of robotic surgery. Performing rigorous prospective studies in children of highly variable ages can be quite difficult, and only through multicenter studies would adequate numbers be available.

Nonetheless, the appeal of the robotic system is strong relative to either conventional laparoscopic reconstructive surgery or open surgery. While the difference in outcome may be less evident in a 6-month-old patient, a 15-year-old undergoing robotic pyeloplasty clearly has a faster recovery than one undergoing open pyeloplasty. Having struggled with conventional laparoscopic reconstructive surgery, including pyeloplasty, for several years, the introduction of the robot was a true epiphany. Visualization of the anatomy with a stable 3-dimensional image and wide exposure was exceptional, and the precise and smooth movements provided by the system permitted a sense of control and accuracy far beyond what was possible with conventional laparoscopy, and even open surgery. With mastery of the basic procedures such as pyeloplasty, approaching more complex cases such as reoperative pyeloplasty, partial nephrectomies, ureterocalicostomies and even intrarenal infundibuloplasies became progressively more feasible. It is this natural progressive expansion of capability that must be recognized as an integral part of the evolution of this technology and its potential use in pediatric urology.

At present, application of robotic surgery in pediatric urology is relatively widespread at children’s hospitals and in many pediatric units.3 It is slowly expanding internationally, there is no doubt, pyeloplasty is the most useful technique and is relatively widely used. With experience and dedicated teams, surgical times are very acceptable and can be comparable to open surgery. More complex renal surgery is well described and reported outcomes are very good. Exploration of novel areas such as partial nephrectomy for malignancies in children has begun. Robotic management of vesicoureteral reflux remains less developed, with variable success rates and less enthusiastic uptake. It seems this reflects greater variability in the surgical techniques and in outcome assessment. This is combined with ongoing evolution of the surgical management of reflux as well. One of the most useful applications of the robotic system is in retrovesical procedures, particularly excision of a prostatic urethra or seminal vesicle cysts. This provides a minimally morbid procedure for what used to be quite difficult and uncomfortable for the patient. Complex reconstruction, including augmentation cystoplasty, continues to be explored but the efficiency remains limited and there is a clear need for more efficient operative algorithms.

These challenges and concerns provide direction for the future of pediatric urological robotics. There is a clear need for refinement of surgical algorithms combined with careful assessments and comparisons. Different techniques need to be examined and consensus developed regarding optimal methods to achieve the desired outcome. This speaks to the need for consistent educational efforts with careful

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Figure. Horseshoe kidney with upper pole ureteropelvic junction obstruction (left panel) due to stenotic short upper pole ureter is repaired robotically with upper-to-lower pyelopyelostomy and upper and lower pole pyeloplasty (right panel). Pelves have been joined, and ureter is being anastomosed to both.

[Image] Horseshoe kidney with upper pole ureteropelvic junction obstruction (left panel) due to stenotic short upper pole ureter is repaired robotically with upper-to-lower pyelopyelostomy and upper and lower pole pyeloplasty (right panel). Pelves have been joined, and ureter is being anastomosed to both.

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Contemporary Role of Cytoreductive Nephrectomy: Carpe Diem Meets Primum Non Nocere

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Alexander Kutikov, MD
Philadelphia, Pennsylvania

Similar to treatment paradigms in patients with stage IV disease with most malignancies, before 2001 the removal of the affected renal unit in patients with metastatic kidney cancer was largely reserved for those in need of palliation. Yet after a report of 2 landmark trials in 2001 that demonstrated an approximately 6-month overall survival advantage, cytoreductive nephrectomy (CN) seized the therapeutic scene and became an essential element of metastatic kidney cancer management.

Yet the last 2 decades have seen the introduction of a number of novel agents into the kidney cancer space, which include vascular endothelial growth factor pathway targeted therapeutics, immune checkpoint inhibitors and more recently combinations of the 2 (fig. 1). As the efficacy of systemic therapy has improved, the role of CN has undergone a major and rapid evolution (fig. 2).

Patients who enrolled into the 2001 SWOG and the European Platform of Cancer Research (EORTC) randomized trials received either upfront nephrectomy followed by interferon-alpha (INF) or INF alone without surgery. It is important to note that in these trials, nearly all patients (331) received systemic therapy. For instance, only 3 of 163 (1.8%) in the INF only arms and 9 of 161 (5.6%) in the CN+INF arms did not get INF. Yet in real world clinical practice far from every patient ended up receiving systemic therapy after CN. For instance, in one series 30% of patients did not receive systemic therapy for a variety of reasons with nearly half succumbing soon after CN without INF or targeted therapy due to rapid disease progression or perioperative mortality.1 In other words, in clinical practice CN at times prevented patients from receiving systemic therapy. As such, as systemic therapy became more effective over the years, the question regarding the harms of CN was appropriately raised.

In this context, the CARMENA trial was launched in 2009 to explore the continued role of CN in the targeted therapy era.2 The trial enrolled and randomized 450 patients to nephrectomy followed by the targeted agent sunitinib vs sunitinib alone. Randomization was stratified by International Metastatic RCC Database Consortium (IMDC) risk groups with the primary end point being overall survival. At a median followup of 30.9 months and at that time of analysis in 2017, patients in the sunitinib alone group exhibited a longer median overall survival than those in the CN + targeted therapy group (18.4 months vs 13.9 months).

Overall, the trial demonstrated noninferiority of sunitinib without surgery and demonstrated that some patients appear to be harmed by upfront CN. However, the study’s findings have been interpreted with a degree of caution, as CARMENA was enriched with poor risk patients, who made up 43% of the overall cohort. Also, unlike the 2001 SWOG and EORTC trials, a large proportion of patients did not receive systemic therapy (17.7% in CN+sunitinib arm) or nephrectomy (7.1% in the CN+sunitinib arm). Indeed, when one compares median overall survival (OS) of patients in the sunitinib only arm of CARMENA (18.4 months) to median OS in sunitinib only arms of other recent trials such as CABOSUN (21.8 months), CheckMate 214 (26 months), and KEYNOTE-426 (median OS not reached >18 months), the severity of disease for patients who were enrolled into CARMENA becomes apparent.

Given CARMENA’s poor risk disease case mix, clinicians have questioned whether patients who were most likely to benefit from CN never enrolled into CARMENA. To that end, the updated results presented at the 2019 annual meeting of the American Society of Clinical Oncology (ASCO) focused on the intermediate risk patient group [low risk patients are those who metastasize following treatment of localized disease and therefore do not undergo CN by definition]. Intention-to-treat analysis again demonstrated a clear survival benefit of sunitinib alone vs CN for patients who had 2 risk factors (31.2 months vs 17.6 months, p=0.033). However, this benefit

Figure 1. Targeted Therapy
- Systemic therapy: Tyrosine kinase inhibitors
- Key Trials: CARMINA & SURTIME
- Upfront CN not associated with survival benefit; can harm some patients

<table>
<thead>
<tr>
<th>1990’s</th>
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<th>Today</th>
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<td>Immunotherapy Era</td>
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- Systemic tx: Interferon alpha
- Key Trials: EORTC 30947 & SWOG 8949
- CN associated with ~6 month survival benefit in RCT |

Novel Immunotherapy Era
- Systemic tx: Immune Checkpoint Inhibitors and combination therapy
- Key Trials: NORDIC-SUN & PROBE

Figure 2. Male patient who presented with gross hematuria and weight loss found to have locally advanced and oligometastatic sarcomatoid clear cell RCC to lung. Patient underwent CN with concurrent distal pancreatectomy, splenectomy and left colectomy followed by treatment with chemotherapy/TKI combination and then checkpoint inhibitor for 2 years. Currently, NED x 2 years. Today’s clinical trials are seeking to establish appropriateness and sequencing of CN in such patients.
was no longer evident for patients who harbored only 1 risk factor, with a trend favoring CN (51.4 months vs 25.2 months, p=0.232). Furthermore, 29% of patients in the sunitinib only arm underwent an interval nephrectomy, with those patients experiencing the highest magnitude of a survival benefit (48.5 months vs 15.7 months, HR 0.34 [0.22–0.54]), supporting the idea of systemic therapy as a litmus test to guide CN patient selection.3

Concurrently, the EORTC conducted the SURTIME trial, which evaluated immediate vs delayed CN after a trial of 3 cycles of sunitinib.4 Given poor recruitment, this treatment sequencing trial was unable to meet its primary end point, and the results were presented as exploratory. While there was no difference in 28-week progression-free survival, the deferred CN approach resulted in more patients receiving sunitinib and indexing a higher overall survival rate. As such, pretreatment with sunitinib allowed for identification of patients who either would not benefit from or be harmed by surgery.

In view of CARMENA and SURTIME results, is upfront CN ever appropriate in 2021? In the opinion of many the answer is a resounding “yes,” but for a very select group of patients. Indeed, not all patients with stage IV disease require immediate systemic therapy. A previously published phase II trial of patients with oligometastatic disease who underwent CN demonstrated that patients can stay off systemic therapy for a median time of 14.9 months with a significant proportion of patients being able to avoid treatment for 2 years.5 Therefore, in those patients with stage IV disease who present with oligometastatic disease and for whom observation off of systemic therapy is appropriate, upfront CN should be strongly considered (fig. 3).

As therapeutic options for kidney cancer patients continue to evolve, checkpoint inhibitors have become the gold standard for metastatic renal cell carcinoma (RCC), requiring a further appraisal of CN. Therefore, prospective clinical investigations continue. The PROBE trial [SWOG 1931] and NORDIC-SUN trial [NCT03977571] are phase III randomized clinical trials designed to evaluate the role of CN in the era of checkpoint inhibitors (see Appendix). While we await results from these studies, retrospective reports appear to be following the trends established in the targeted therapy era. Bakony and colleagues recently presented a retrospective analysis of survival in patients receiving checkpoint inhibitors with (143) and without surgery (55) at the 2020 GU ASCO.6 In this cohort, investigators identified improvement in overall survival associated with CN [HR 0.369 [0.19–0.83]], suggesting that CN may continue to play a role in properly selected patients. Nevertheless, as we have learned, such retrospective reports from preselected cohorts can be a self-fulfilling prophecy and must be validated via prospective trials.

In conclusion, patients who require systemic therapy should forgo upfront CN in order to avoid patient harm. CN should then be deployed as necessary based on systemic therapy response and patient clinical course. In patients with oligometastatic disease who do not require urgent systemic therapy, CN should still be strongly considered.

Update on Transvaginal Mesh

Approximately 50% of women who are 50 years old or older will experience pelvic organ prolapse (POP) during their lifetime.1 Of those women affected, 1 in 5 will require corrective surgery. Prior to the 1990s, native tissue repair was the gold standard approach for POP. However, this approach was associated with high recurrence rates, leading clinicians to search for alternative methods. Physicians widely began using synthetic mesh for POP repairs in the 1990s, but it was only approved by the U.S. Food and Drug Administration (FDA) for that indication in 2002 (fig. 1). Considered to be similar to mesh used for abdominal hernia surgery, synthetic mesh for POP was approved without the completion of a premarket approval (PMA) application.

After the FDA approval, transvaginal mesh quickly gained popularity, as it was associated with shorter surgical time, length of stay and recovery time, and a lower recurrence rate for high grade POP. Despite the benefits of mesh, a host of complications have been reported, including severe chronic pelvic pain, dyspareunia, infection, bleeding, organ perforation, vaginal mesh exposure and urinary problems from mesh eroding into surrounding tissues.1

In 2008, the FDA released warnings about the frequency of serious complications related to transvaginal mesh for POP. As more reported mesh related adverse events were filed, a new FDA safety update was released in 2011, reiterating potential complications (fig. 2). Subsequently, in 2016, the FDA recategorized transvaginal mesh from a class II (moderate risk) to a class III (high risk) device. Moreover, mesh instrumentation kits, including trocars, needle passer and guides, fixation tools and tissue anchors, were reclassified from class I (low risk) to class II. The FDA also ordered manufacturers to submit PMAs to formally evaluate their safety and efficacy.1

In April of 2019, the FDA ordered immediate cessation of the distribution of surgical mesh products for transvaginal repair of POP, stating that manufacturers failed to provide evidence that mesh prolapse repairs were superior to native tissue repairs. It is noteworthy the 2019 recall did not apply to the use of mesh for stress urinary incontinence (SUI) or transabdominal repairs of POP. This ban aroused significant controversy, as the decision was made before completion of the required PMAs.

In response to the 2019 ban of transvaginal mesh for POP, the Ibero-American Society of Neurourology and Urogynecology (SINUG) issued a position statement declaring that transvaginal mesh should not be offered routinely but should be reserved for high risk patients, such as those with recurrent prolapse, in whom the benefits of mesh outweigh the risks.1 Other professional societies also released official statements, but most only addressed the use of transvaginal mesh for SUI. The Society of Urodynamics, Female Pelvic Medicine and Urogynecologic Reconstruction (SUFU)/American Urogynecologic Society (AUGS) joint statement declared that polypropylene mesh is the gold standard for treating SUI and is safe and effective to use.2 The American Urological Association (AUA) reaffirmed this sentiment in their statement, adding that physicians who perform synthetic sling surgery should be highly experienced in doing so, and must discuss the risks and benefits of mesh with patients.3

Since the 2008 and 2011 warnings, there has been a significant reduction in mesh-augmented transvaginal POP surgeries, although the total number of POP repairs performed remains unchanged.4 There has also been a significant increase in mesh revision surgeries.

Despite these trends, the clinical data surrounding the efficacy of transvaginal native tissue compared to synthetic mesh repairs of POP are limited and variable, subject to differences in study design, surgical technique, surgeon experience and classification of prolapse. A few trials have recently been published comparing outcomes between transvaginal mesh and native tissue prolapse repairs.

A 2020 multicenter trial randomized 122 women with severe POP to undergo synthetic mesh repair or native tissue repair. After 5 years of followup, significantly higher cure rates in all compartments, defined as a Pelvic Organ Prolapse Quantification (POP-Q) System point of <0, and improvements in quality of life scores were seen in the mesh group. The mesh group also experienced a higher complication rate, with extrusion being the most common treatment related adverse event.5 PROSPECT (PROlapse Surgery: Pragmatic Evaluation and Randomised Controlled Trials) reported somewhat conflicting results for recurrent POP.6 In this study, Glazener et al randomized 155 women with recurrent prolapse to undergo repair with either native tissue, synthetic mesh or a mesh kit. After 1 year, the majority of women indicated improvement in prolapse symptoms and prolapse on physical examination, although there were no differences between treatment cohorts. All groups had similar rates of serious adverse events, other than mesh exposure, which occurred in 13% of the mesh inlay and 8% of the mesh kit arm participants.

While these trials give some insight into the risks and benefits of each surgical approach, many questions remain. Variables that should be factored in during the evaluation of transvaginal mesh complications include study design, patient comorbidities and tissue quality, surgeon experience and level of training, and product quality, among others. Ultimately, more randomized data with larger cohorts are needed to fully evaluate the safety and efficacy of transvaginal mesh for POP repair, especially in comparison with native tissue repair. For now, in order to optimize patient outcomes and minimize complications, POP surgery is best performed by skilled surgeons with experience in managing short and long-term complications.3


Figure 1. Regulatory history of transvaginal mesh for POP.

Figure 2. Postoperative extrusion (top) and erosion (bottom) of transvaginal mesh in POP cases.
Every year, children’s hospitals nervously await results of the U.S. News and World Report (USNWR) rankings, realizing that overall and specialty specific rankings may dictate how colleagues and patients view their institutions. Top programs are heartily congratulated, and programs who rank lower than expected feel defeated. Enormous amounts of time and resources are spent within institutions across the United States to collect USNWR data, and hospital initiatives are prioritized based on how closely they align with anticipated USNWR metrics.

Goals of USNWR Rankings

The USNWR Best Hospital rankings aim to provide publicly available information for patients with complex or high risk conditions to facilitate informed choices based on hospital quality.1 However, the rankings are often interpreted as a directive about where patients who want quality care should go for any condition, regardless of risk or severity. In reality, the ranking systems are highly imperfect, may be irrelevant for common, lower risk conditions and may be outweighed by myriad other factors including patient travel distance and culture. Although it is implied that USNWR rankings improve health care quality, it is unclear whether ranking programs and hospitals using the present scoring systems actually promotes better care.

Pediatric Urology Ranking Methodology

As pediatric urologists we are most familiar with the USNWR methodology for our specialty. The table shows relative contributions of different hospital and program attributes to calculating the USNWR score. Close examination of the pediatric urology ranking system illustrates concerns about methodology of objective data collection. Furthermore, the reputation score is completely subjective.

As outlined in our recent editorial, “Ability to Prevent Surgical Complications” is weighted heavily in the USNWR scoring system yet relies solely on administrative data and self-report.2 Pohl and colleagues also recently showed that outcomes requested by USNWR do not accurately reflect published hypospadias complication rates,3 yet hypospadias outcomes were used to calculate USNWR scores. Additional concerns about the current USNWR ranking methodology include lack of clear criteria determining which procedures should be included in outcomes assessment, a focus on surgical volume when surgery for certain conditions (eg vesicoureteral reflux) may not necessarily represent “best care,” a reliance on factors outside of the control of programs directly (eg nursing ratios) and reliance on the highly subjective reputation score. Improvements in outcomes assessment methodology are made each year, but it is not clear that USNWR scores accurately differentiate between the quality offered at different hospitals for pediatric urological procedures.

The USNWR ranking methodology has resulted in a situation where the “Top 10” programs are relatively geographically concentrated (see figure) such that most patients would incur significant travel burden to access care at one of these hospitals. Although access is far from perfect, excellent pediatric urological care is available in many areas not in the figure, and the travel burden implicated by the “Top 10” is likely not beneficial for most patients. In our own “Top 10” practice, we frequently care for patients who do not live near Chicago. Many live much closer to another high quality pediatric urology center and would have received care of identical quality without traveling. We also care for patients who went elsewhere for surgical reconstruction due to program reputation or ranking; living far from your reconstructive surgical team can create postoperative care challenges that outweigh a small technical benefit, even if present.

Adult Urology Ranking Methodology

As with pediatric urology, methodologic concerns related to reputation and outcomes scoring also exist for adult urology. A recent study showed that USNWR reputations scores are associated with presence of an active Twitter account.4 It is no secret why glossy mailers and reminders to sign up for Doximity (the voting platform for USNWR reputation scores) all come around the time of USNWR voting. Reputation scores likely reflect marketing ability and resources along with quality of care. Concerns about inappropriate attribution of poor patient outcomes to subspecialty care also exist, particularly because adult USNWR rankings rely heavily on administrative data. A 2020 study demonstrated that a minority of deaths attributed to urology and otolaryngology over a 5-year period actually occurred among patients on those services.5

Best Use of Limited Resources?

Through the upheaval of the COVID-19 pandemic, the year 2020 provided an opportunity for reflection and change. We have

Table. USNWR pediatric urology scoring calculation.

<table>
<thead>
<tr>
<th>Category</th>
<th>Components</th>
<th>Contribution to Overall Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes and Experience</td>
<td>• Ability to prevent surgical complications</td>
<td>42.5%</td>
</tr>
<tr>
<td></td>
<td>• Speed in treating testicular torsion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ability to prevent infections throughout hospital</td>
<td></td>
</tr>
<tr>
<td>Numbers of Patients and Procedures</td>
<td>• Number of patients</td>
<td>5.3%</td>
</tr>
<tr>
<td></td>
<td>• Number of surgeries</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Number of minimally invasive procedures</td>
<td></td>
</tr>
<tr>
<td>Key Programs, Services and Staff</td>
<td>• Nurse staffing</td>
<td>12.3%</td>
</tr>
<tr>
<td></td>
<td>• Advanced clinical services offered</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Clinical support services offered</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Advanced technologies available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Specialized clinics and programs available</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Has full-time subspecialists available</td>
<td></td>
</tr>
<tr>
<td>Professional Recognition</td>
<td>• Recognized as Nurse Magnet hospital</td>
<td>17.6%</td>
</tr>
<tr>
<td></td>
<td>• Reputition with physicians in specialty</td>
<td></td>
</tr>
<tr>
<td>Quality Improvement Efforts</td>
<td>• Commitment to best practices</td>
<td>18.4%</td>
</tr>
<tr>
<td></td>
<td>• Commitment to quality improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adoption of health information technology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Active fellowship programs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Commitment to clinical research</td>
<td></td>
</tr>
<tr>
<td>Patient Support</td>
<td>• Help for families</td>
<td>3.9%</td>
</tr>
<tr>
<td></td>
<td>• Enlists families in structuring care</td>
<td></td>
</tr>
</tbody>
</table>
examined and redesigned behaviors and routines once assumed fixed. Financial and personnel resources have been stressed and are still unstable for many. Children’s hospitals are facing unprecedented challenges, so important questions need to be asked. Should scarce resources be devoted to collecting large amounts of USNWR data when there is no evidence that rankings truly reflect differences in care? Are we misleading patients such that they are traveling long distances to higher ranked programs when local care is equally efficacious? At a time when American hospitals should be joining forces to provide coordinated improvement in children’s health care, should we be spending health care dollars on marketing materials designed to create competition? This is not to say that competition cannot be an important driver to improve care. However, the type of competition that is created by USNWR is not one that many would consider “healthy.” Therefore, shouldn’t we be spending more time and effort on determining how institutions can work together for the collective benefit for patient care?

**Final Thoughts**

In their current state, the USNWR rankings do not necessarily benefit patient care. They create an environment that generally encourages competition rather than collaboration. We strongly encourage all physicians to closely examine how USNWR rankings impact patient care in their own specialty. If it is determined that current methodology is flawed, as it is in pediatric urology, then discuss potential solutions with your colleagues. Solutions could include a coordinated effort to overhaul USNWR methodology or a decision to collectively opt out of USNWR. Until complete methodologic redesign or opting out occurs, hospitals will be under tremendous pressure to use precious resources to facilitate USNWR rankings. Now is the time to examine and change the narrative about what role the USNWR should play in determining public perceptions and where patients and families seek medical care.


Continence after Exstrophy Closure: What Does it Mean and is it Achievable?

Bladder exstrophy (BE) is widely recognized as one of the most challenging congenital urological conditions for the treating urologist, both because of its rarity as well as the technical challenges associated with surgical reconstruction. With a prevalence of approximately 1:40,000 live births, most pediatric urologists even at academic centers can expect to see only a handful of cases in a career. Therefore, collaborative models of care have becoming increasingly frequent. Starting with the Multi-Institutional Bladder Exstrophy Consortium (MIBEC) among Boston Children’s Hospital, Children’s Hospital of Philadelphia and Children’s Hospital of Wisconsin in 2012, pediatric urologists are increasingly joining forces to increase surgical volume to share clinical outcomes and to assess, define and evaluate the care and treatment of patients with BE.

Within the past 3 years, multiple recognized academic centers of excellence for bladder exstrophy have released long-term outcomes data detailing volitional voiding, dry intervals and use of clean intermittent catheterization (CIC) among BE patients. In 2019 Szymanski et al reported pooled data from the Pediatric Urology Midwest Alliance (PUMA) demonstrating a CIC rate of 67.4% at last known followup visit with median followup of 14.4 years.1 Patients in the study underwent primary reconstruction between 1980 and 2016. The majority of older patients in this cohort (70.1%) underwent bladder augmentation or other urinary diversion by age 18. Similarly, Maruf et al from Johns Hopkins recently reported volitional voiding per urethra with at least 3-hour dry intervals in 80 (23%) of their cohort of 350 patients with BE for whom continence could be assessed (median followup 14.8 years).2 We have similarly examined our BE cohort before the initiation of our MIBEC partnership, finding that 20.4% of patients met criteria for volitional voiding per urethra with dry intervals of at least 3 hours (median age at followup 12.1 years).3

While volitional voiding rates, dry intervals and use of CIC offer easily reportable metrics, they only hint at the end goal for BE patients and surgeons: urinary continence. There remains no standard definition of continence within the BE population or in the field of pediatric urology at large. Within this vacuum, the most commonly reported outcome is a binary differentiation between those who can be dry for 3 hours at a time and those who cannot. Whether patients utilizing CIC can be considered continent remains debated.4

As BE surgeons continue to study and refine BE reconstructive techniques, the need for a more nuanced and universal definition of continence continues to emerge. Our own experience within MIBEC has shown us that there is a significant subset of patients who achieve and are satisfied with a 2-hour to 3-hour dry interval with volitional voiding per urethra.3 Many of these patients express that further reconstructive surgery to achieve a longer dry interval with reliance on CIC would diminish their quality of life. We must listen to these patients when they tell us that dryness and continence are not the same. Additional work by Ellison et al in Seattle suggests that continence can be a process for BE patients after reconstruction with a proportion of patients attaining continence years after their last surgical reconstruction.5 Our multi-institutional experience mirrors this finding, and we often celebrate with patients and parents as they slowly achieve longer dry intervals with normal growth and development, often aided by physical therapy. Still, continence cannot be achieved without successful surgery to restore anatomic bladder and pelvic floor anatomy. Even more importantly, if we are impatient and rush to bladder augmentation and diversion we may inadvertently deprive a subset of patients from achieving true continence with volitional voiding per urethra.

While a universal definition of continence remains fleeting, the concept of continence after exstrophy closure continues to evolve as pediatric urologists continue to work collaboratively to examine and report long-term clinical outcomes. We acknowledge that there is great room for improvement in achieving continence after exstrophy closure as continence by current metrics is only achieved by a minority of patients in these studies. Nevertheless, there remains a persistent 20% to 30% of patients who demonstrate durable volitional voiding per urethra with significant dry intervals for years after initial surgical reconstruction regardless of institution or surgical technique. In our MIBEC cohort, analysis of 28 patients with at least 3 years of followup after initial surgical reconstruction demonstrated that 32% of patients were achieving dry intervals of at least 1 hour at a young age, the majority after a single surgery for continence.6 Therefore, we are heartened that continued refinement of BE reconstruction along with diligent long-term clinical care and physical therapy can lead to continued improvement in continence both in terms of our understanding of continence as well as the proportion of patients who achieve it.◆

Looking to the future, there are increasing calls to delay genitalia altering surgeries until after the age of assent. International bodies, like Human Rights Watch, Amnesty International and the European Union are already moving to legislate prevention of pediatric genital altering surgery. Concurrently, many cultures have shifted away from a binomial definition of sexuality and by association from a binomial acceptance of genital ideal. It still remains to be determined how changing political forces and societal norms will impact the ability of urologists to perform hypospadias repairs and the willingness of parents and patients to submit to them. However, it will be incumbent on urologists to better characterize long-term effects and understand differences in outcomes of repairs done before and after puberty so that parents and patients can make informed decisions.

The worldwide COVID-19 pandemic has caused a significant paradigm shift in the delivery of health care. A recent questionaire-based study found that urologists were significantly affected by the COVID-19 pandemic with decreased outpatient visits, outpatient procedures and surgeries (77%, 84% and 93%, respectively). There has been rapid implementation of telemedicine in urology due to these cancelations, inadequate personal protective equipment and shortage of personnel. Dubin et al found that before the COVID-19 pandemic only 15.8% of surveyed urologists were using telemedicine. However, this number increased to 46% during the pandemic.

Female pelvic medicine and reconstructive surgery (FPMRS) represents a subspecialty of urology that may be ideally suited for telemedicine. As the pandemic continues to rage, FPMRS providers may face increasing numbers of cancelations of in-person visits due to patients who have either contracted or have been exposed to COVID-19. Additionally, it may prove difficult to keep clinics staffed with appropriate personnel due to similar COVID-19 exposures and mandatory quarantines. FPMRS providers may be disproportionately affected by cancelation of clinic visits/surgeries, as many FPMRS-related issues are elective/non-emergent. Teoh et al found that treatment of benign urological conditions was most affected by COVID-19 related closures/cancelations. Outpatient visits and surgery for female urinary incontinence were reduced by 81% to 85%. Telemedicine will likely play a critical role in optimizing FPMRS patient care during the COVID-19 pandemic to overcome the above mentioned challenges.

Telemedicine can be a valuable tool for many FPMRS-related issues such as overactive bladder (OAB), urinary incontinence and urinary tract infections. Physical exam may be helpful but not absolutely necessary in many of these cases for diagnosis and initial management. Many FPMRS providers use clinical care pathways for these common diagnoses, and these pathways may lend themselves to telemedicine. For example, first line and second line therapies from the AUA/SUFU (Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction) clinical care pathways include behavioral modification (ie fluid intake, timed voiding) and pharmacotherapy.

Limited literature exists for the use of telemedicine in FPMRS-related conditions. Huang et al recently performed a systematic review and meta-analysis of the efficacy of telemedicine for urinary incontinence in women. Seven studies involving a total of 836 patients were included. The results revealed that telemedicine intervention significantly reduced the severity of urinary incontinence and improved quality of life compared to in-person visits. Descriptive analysis of this meta-analysis showed that telemedicine led to reduced patient anxiety and depression, which led to improved impression of improvement.

A randomized controlled trial comparing telemedicine to standard followup found that both types of visits yielded similar improvements in symptom bother while the telemedicine group exhibited improved medication compliance and higher progression to third line therapy (intradetrusor botulinum-toxin A injections, percutaneous tibial nerve stimulation and sacral neuromodulation). A limitation of this study was the small sample size and limited followup. Current literature regarding the use of telemedicine in FPMRS is sparse. However, by the time of this
Therapeutic Trends in the Treatment of Patients with Peyronie’s Disease

Landon Trost, MD
Provo, Utah

Like many things in life, management of medical conditions often trends from one therapy to another over time. This seems particularly true for certain conditions, such as Peyronie’s disease (PD), where an optimal treatment has not been clearly defined. However, as anyone with a silk shirt, fidget spinner, planking personal record, or PTSD from an ice bucket challenge can attest, some trends are good, while others are best left in the past.

Peyronie’s disease itself has become a notably trendy topic, with nearly a third of all manuscripts ever written on PD published within the past 5 years. Regarding therapies, arguably, the 3 most prominent trends with PD in the past several years have been with collagenase clostridium histolyticum (CCH), traction devices, and shockwave/restorative therapy. Each of these trends will be briefly reviewed regarding their prominence, efficacy and projected future role in the management of PD.

Since FDA approval of CCH, it has increasingly been used as a first line therapy for the management of PD [unpublished data]. Recent publications evaluating national CCH use demonstrated that while first line treatment with CCH was 1:1 with surgery after FDA release, by 2017 it had increased to 2:1 despite similar rates of PD diagnosis. Concomitantly, the use of intraligamental verapamil dropped from 11% in 2007 to <1% by 2018, with meta-analyses suggesting superiority of CCH over verapamil. With few exceptions, reported efficacy rates after FDA release have demonstrated similar or slightly improved success rates compared to original phase III randomized, controlled trials, suggesting ongoing efficacy when used in real-to-life clinical scenarios by PD specialists.

Independent of efficacy, a key debate with CCH has been its cost, which has contributed to the development of modified, shortened protocols and even withdrawal from select international markets. Several cost-effectiveness studies have been reported with varying conclusions as to superiority of one therapy over another due in part to differences in methodological rigor. However, recent data suggest that these debates are ultimately short-sighted as contemporary management of PD is often multifaceted with several categories of therapies often combined. Specifically, the previously cited trending data suggest that the introduction of CCH resulted in >50% more PD men seeking treatment rather than the cannibalization of other therapies. Otherwise stated, the introduction of CCH has created a novel treatment niche wherein more patients are receiving effective therapy compared to before CCH.

In this context, comparing surgery vs CCH for PD would be akin to debating the cost-effectiveness of docetaxel vs surgery for men with prostate cancer.

An additional trend and debate worth mentioning is the appropriate pattern of administration of CCH. Recent strategies and market forces have led more general urologists and even nonurologists to administer CCH, which represents a notable change from prior use predominantly among subspecialty urologists (andrologists). The long-term impacts of this change on patient safety, efficacy, and healthcare/insurance utilization restrictions are indeterminate. However, extrapolating data from other disease states would suggest that a change from more to less specialization is associated with poorer outcomes, worsened complications and eventual payer restrictions leading to reduced availability.

Penile traction therapy (PTT) is a second trending topic in the field of PD. Please also note my specific conflict of interest in this regard, as I was involved in the development of a new class of PTT device during my time at Mayo Clinic. Penile traction is being increasingly used in men with PD as a primary treatment for penile length and curvature as well as an adjunctive therapy in men undergoing surgery or CCH. In contrast to other therapies [ie vacuum devices], PTT has demonstrated more robust and consistent data on restoring or improving penile length in this population without long-term adverse events. Additionally, with newer technology, PTT may be effectively used for 30 to 60 minutes daily compared to a historical need for 3 to 9 hours, which has greatly improved use and expanded the clinical utility. Therefore, PTT is becoming one of a combination of treatments that are recommended in the management of PD.

The third notable trending topic with PD is with restorative therapies, including low intensity shock wave/ acoustic wave, stem cells and platelet-rich plasma. These treatments are increasingly among the most discussed therapies for several sexual conditions, including erectile dysfunction, PD and other sexual dysfunctions. Although these treatments have demonstrated some preliminary data in animal and in vitro models, none have gone through standard regulatory pathways to assess for clinical efficacy and are therefore off label.

From a broader guideline standpoint, the American Urological Association has specifically indicated that extracorporeal shock wave therapy should not be used for the reduction of penile curvature or plaque size (Statement 14). Similarly, the Sexual Medicine Society of North America (SMSNA) has released a position statement on the role of regenerative therapies for sexual conditions and has concluded, “shock waves or stem cells/SVF or platelet rich plasma [are] experimental and should only be conducted under research protocols in compliance with Institutional Review Board approval at little or no cost to the patient” (emphasis added; unpublished data). The statement goes on to indicate, “the SMSNA does not feel that it is appropriate or ethical for providers to advertise or otherwise make implicit or explicit claims of efficacy for these therapies pending further data. Similarly, patients considering such therapies should be fully informed as to the lack of data demonstrating clinically relevant efficacy and consented regarding the potential benefits and risks. In summary, at the current time, the SMSNA does not advocate for restorative therapies to be offered or used in routine clinical practice.”

Clearly, and as with other disease states, the management of PD is frequently changing, and the introduction of novel therapies offers new potential avenues for treatment. However, it is important to recognize that the trendiness of any particular therapy is not a surrogate for efficacy. Therefore, distinguishing providers must incorporate data and societal recommendations to develop optimal patient care pathways and identify which therapies are truly beneficial.

Disclosure. Dr. Landon Trost is the inventor of a penile traction therapy technology in coordination with Mayo Clinic Ventures. The technology has been licensed by PathRight Medical and is used with the RestoreX penile traction therapy device.

An Update on Novel Therapeutics for Premature Ejaculation

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Dapoxetine

Dapoxetine is a rapid acting SSRI with a short half-life developed specifically as an on-demand treatment for PE. While it is currently an approved first line agent in the guidelines, its utility has been limited by availability and thus providers may not be familiar with the drug. A meta-analysis by Yue et al. included 5 placebo-controlled trials and found a significantly increased intravaginal ejaculatory latency time (IELT) with dapoxetine. The analysis included a total of 6,576 subjects, aged ≥18 years, in monogamous heterosexual relationships for ≥6 months. Four of the trials involved subjects taking 30 mg or 60 mg on demand 1 to 3 hours prior to sexual intercourse, while one trial involved either 60 mg pm dosing or once daily. Across all studies, dapoxetine increased IELT by a weighted mean difference of 1.47 minutes (95% CI 1.22–1.71). In all 5 trials, patient reported outcomes were significantly improved in the treatment groups as compared to placebo. When comparing the 30 mg and 60 mg doses, the higher dose appeared to be more effective. Mild AEs where reported in around 50% of subjects in the treatment groups compared to 33% of the placebo groups, with the most frequent AEs being nausea (17%), dizziness (9%), headache (8%), and diarrhea (6%). Less than 1% of subjects experienced severe AEs with no reports of sexual dysfunction or suicide attempts, leading the authors to argue that dapoxetine is safer than SSRIs historically used to treat PE. While approved in over 50 countries for the treatment of PE, dapoxetine has not received marketing approval by the FDA.

Modafinil

Modafinil is a wake-promoting agent that has a complex and incompletely understood effect on the central nervous system, though it is thought to principally act on the dopaminergic and GABAergic systems. Murine studies demonstrate that modafinil increases ejaculatory latency without suppressing sexual behavior. A recent uncontrolled proof-of-concept study involving 55 patients with lifelong PE showed positive results. Using patient reported IELTs the authors demonstrated that 100 mg of on-demand modafinil (taken before noon the day of anticipated sex) doubled patient reported mean IELT from 25 to 50 seconds. This was associated with significant improvements in patient reported outcomes. The authors did not report any notable AEs. While this study does suggest a potential role for modafinil in the treatment of PE, placebo-controlled trials are needed.

Oxytocin Antagonists

Oxytocin has a prominent role in sexual response and is known to have a stimulatory effect on the ejaculatory process; therefore it is hypothesized that oxytocin antagonists could be used as a potential treatment for PE. Two recently published phase II randomized control trials of cligobisan, an oxytocin antagonist, have shown conflicting results. In one study, subjects were randomized to either 400 mg cligobisan 1 to 6 hours before planned sexual activity for 8 weeks with subjects allowed to adjust their dose to 200 or 800 mg during the trial. At the conclusion of the study, IELT increased by 61 seconds in the treatment vs 16.4 seconds in the placebo group, with corresponding significant improvements in ejaculation-related personal distress scores. The same authors performed a second phase II RCT randomizing 239 patients to either a fixed dose of cligobisan (400, 800, or 1,200 mg) vs placebo. However, in this trial no significant differences were observed in either IELT or patient-reported outcomes. Both trials showed cligobisan to be generally well tolerated with few severe AEs. The reasons for the conflicting outcomes of these two studies may be explained by differences in design. First, the negative study prescribed a fixed dose rather than allowing the patients to dose titrate.
An Update on Novel Therapeutics for Premature Ejaculation

Second, in the positive trial subjects with PE were selected from centers with specialists in sexual medicine, while the negative trial included subjects referred from generalist clinics and may not have as carefully screened for true lifelong PE. Although mechanistically oxytocin antagonists show promise, more research is needed before they can be established as a viable therapy for PE.

Conclusions

While topical anesthetics and daily SSRIs remain the most established pharmacologic treatments for PE, their side effect profile can be problematic. Though the guidelines state the most efficacious strategies are likely to involve a combination of both medications and behavioral approaches, having medications with fewer AEs is of paramount importance. As our understanding of the complex physiology underlying ejaculatory function improves, and our classification of men with PE becomes more standardized, it is likely that more robust clinical trials will follow. Our hope is that these advances will provide clinicians with an expanded repertoire of pharmacologic options to alleviate the distress experienced by patients with PE without unnecessary side effects.


Figure 1. Retrograde instillation of mitomycin hydrogel during office cystoscopy in patient with bifid renal pelvis and tumor in upper pole. After contrast injection, ureteral catheter is placed into upper pole (A) and hydrogel injected while pulling back ureteral catheter in order to primarily treat upper pole (B), while remainder is delivered into lower pole. Hydrogel is radiolucent and seen as filling defect displacing contrast material.
Urology Residency Applications during the COVID-19 Pandemic

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The residency application process in 2020–2021 was significantly affected by the COVID-19 pandemic. As it became clear that travel and in-person meetings were restricted, the urology residency community restructured the application cycle. Medical students applying to urology reported concerns about decreased exposure to urology, difficulty learning about different programs and fewer opportunities to obtain letters of recommendation.

As a result of the limitations imposed by the pandemic, there have been significant adaptations to the application process. These include virtual subinternships, virtual open houses, increased social media presence, standardized interview invitation process, virtual interview format, decreased letter of recommendation requirement and delayed match date.

External subinternships typically play a major role in urological education. They provide a platform for students to learn foundational knowledge, strengthen their residency applications and evaluate their degree of “fit” with a program. For 2020–2021, in accordance with the Coalition for Physician Accountability, the Society of Academic Urologists (SAU) recommended deferring in-person external rotations, except for medical students who did not have a urology program at their home institution. Because of the lack of external rotations, the SAU decreased the required number of letters of recommendation to 2, rather than the traditional 3 or 4.

With guidance from the SAU, urology programs saw an opportunity to develop virtual subinternships that could meet many of the same objectives as the traditional rotations. The SAU formed a committee of academic urologists to develop a standardized curriculum for the virtual subinternship. There were 17 virtual subinternships listed on the SAU website, with 8 others listed on the UroResidency website and several more promoted on social media. These were a combination of 2-week and 4-week electives ranging from part-time to full-time commitments. Many were accredited by their institutions and were listed on student transcripts. They consisted largely of small group didactic sessions and self-directed learning. Several programs also incorporated technical skills training and allowed students to engage in surgical and/or clinical care using videoconferences. Other programs added research and online modules. Many required grand rounds presentations, group projects and reflective writing pieces.

While these virtual subinternships had the obvious limitation of lacking hands-on surgical training, they were able to achieve many of the other goals of traditional subinternships. Most importantly, the virtual didactic and clinical sessions were able to convey foundational urological knowledge to prepare for residency. Additionally, the virtual subinternships gave students the opportunity to demonstrate their abilities through presentations and other deliverables, providing a platform for programs to evaluate students in a manner similar to the traditional rotation. Through a variety of interactive sessions that showcased each department’s faculty and residents, students were exposed to the culture of the program.

The interactive nature allowed these rotations to serve as “auditions” for students and programs to assess their compatibility and fit for a potential match. Students also had an opportunity to receive letters of recommendation from many of these subinternships that could strengthen their applications—a process that was largely standardized by the SAU committee.

Virtual subinternships have the advantage of eliminating the regional and financial biases that exist in the current system. Traditional subinternships have the obvious limitation of lacking hands-on surgical training, they were able to achieve many of the other goals of traditional subinternships. Most importantly, the virtual didactic and clinical sessions were able to convey foundational urological knowledge to prepare for residency. Additionally, the virtual subinternships gave students the opportunity to demonstrate their abilities through presentations and other deliverables, providing a platform for programs to evaluate students in a manner similar to the traditional rotation. Through a variety of interactive sessions that showcased each department’s faculty and residents, students were exposed to the culture of the program.

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subinternships impose a significant financial burden on medical students, who are already strained by educational debt as well as the other expenses of the residency application process. Virtual subinternships offer an alternative to make this process more accessible and less biased.

While virtual subinternships were offered by a minority of programs, many organizations held virtual sessions to showcase their program and get to know the medical students through town halls, open houses etc (see figure). The SAU and UroResidency websites listed a total of 103 programs that offered these virtual events, and there were likely more programs that were not listed. Some meetings had more of a lecture format that displayed the structure of the urology department and residency structure. Some meetings were more casual, with open question-and-answer sessions and/or happy hours with just the residents. Zoom has a breakout function that divides participants of a large meeting into many small sessions; these small sessions can be timed and then reverted back to the large group to then divide into different small groups again.

Social media and especially Twitter became very prevalent this year, both for the urology programs as well as applicants. The Twitter urology world previously was more research and clinically inclined. This year, many programs created residency-specific Twitter and Instagram accounts to offer a closer glimpse of the residents and residency programs, as well as posting pictures of residents, attendings and staff. Resident bios were more prevalent this year. Announcements were made online publicly. A number of Twitter accounts were created to help compile application resources and mentorship opportunities for students and programs, notably @UroResidency, @UrologyList, @Uro_Stream and @Uro_Res.

The interview invitation process is a potentially enduring part of this cycle’s restructuring. In years past, invitations were given on a random rolling schedule. Applicants waited for an email from the programs and had to respond within minutes to secure a spot. As other programs released interview invitations, students shuffled their interview schedules constantly. This past year, all invitations were sent out on the weekend to decide which interviews to accept. Acceptances were due on Monday, November 9. This one cycle of interview invitations may be a method to keep for future application cycles. The interview dates were slightly delayed, ranging from November through January. The match date was similarly slightly delayed from mid January until early February.

Interviews were also recommended to be all virtual by the SAU. Traditionally, urology applicants met multiple people in the department separated into small groups (1 to 3 people). This translated readily to virtual interviews.

The urology match application cycle for 2020–2021 was significantly affected by the pandemic, with a transition to virtual learning, communication and networking. While it is unclear which of these changes will endure in future years, these modifications provide opportunities for permanent change to streamline the application process. The match was February 1. Congratulations to everyone; welcome to the urology world!

Our study sought to examine the readability of kidney stone educational materials present on the most popular websites. Using the top 10 results of a search for “kidney stones” on the most popular search engine (Google), readability was determined using 6 widely used readability assessment tools (Flesch Reading Ease, FORCAST Readability Formula, Fry Graph, Gunning Fog Index, Raygor Readability Estimate and Simple Measure of Gobbledygook, or SMOG). Readability of specific subsections was then analyzed, paying particular attention to content on the prevention and treatment of kidney stones.

Our results found that for all 10 websites, text was written above the 6th grade reading level, with a range from grade 7 to 13. As shown in the Fry Graph (see figure), 8 of 10 websites contained words with a high number of syllables, thereby resulting in readability above the 9th grade level. Similarly, for the prevention and treatment subsections,
Online Kidney Stone Educational Materials

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all websites contained text written well above recommended reading levels, ranging from the 9th to above the 12th grade.

With the recent COVID-19 pandemic and the subsequent increase in telehealth visits, it is reasonable to expect that even more patients may be seeking health information from the Internet. The results of this study should serve as a sobering reminder to urologists that a large percentage of patients might not be able to understand the readily available kidney stone information being provided to them. It is unwise for clinicians to assume that patients can simply “Google” kidney stones and understand the information contained on the resulting websites. Hopefully, this work brings attention to the need for updated online kidney stone educational materials that use simpler language to improve patient understanding.

Figure. Graph for estimating readability: extended.


Outpatient Robotic Sacrocolpopexy in the ERAS Era

Jacqueline Zillioux, MD
Cleveland, Ohio

Howard Goldman, MD

Several years ago, as we made evening rounds on patients status-post robot-assisted sacrocolpopexy (RASC), we began to wonder, why are we routinely keeping these patients overnight? Often, we found them sitting in bed or a chair, having coffee and reading the newspaper, as if at home relaxing on a weekend. Our colleagues in urologic oncology had begun decreasing length of stay and complications using minimally invasive techniques and enhanced recovery after surgery (ERAS) protocols for more invasive, lengthy and complex cases in sicker patients. Gynecologists had begun publishing data to support same-day discharge (SDD) following laparoscopic hysterectomy. It was time to reevaluate the need for standard postoperative admission following RASC.

ERAS protocols were first developed and popularized by colorectal surgeons in the early 2000s to optimize perioperative care. Although details of various protocols differ, core principles include preoperative optimization and counseling, minimization of perioperative stress, opioid-sparing multimodal analgesia and early mobilization. In concert with advances in minimally invasive techniques, ERAS protocols have significantly reduced length of stay and improved outcomes across specialties.

Compared to other subspecialties such as urologic oncology, female pelvic medicine and reconstructive surgery (FPMRS) cases have fewer complications and faster recovery at baseline. Minimally invasive techniques are now the norm. A logical target for perioperative improvement using ERAS protocols within FPMRS is therefore SDD in minimally invasive reconstructive surgery, particularly RASC. RASC cases often also include supracervical hysterectomy, additional transvaginal pelvic floor reconstruction or placement of a synthetic mid urethral sling for stress urinary incontinence, but are nevertheless 2 to 4 hours in length with patients traditionally discharged the next day, with few complications.

In 2015, we began discharging patients home following robotic pelvic floor reconstruction on the day of surgery as part of a feasibility study. Initial results in the first 10 patients were encouraging, with 80% successful SDDs and no increase in unplanned postoperative encounters or complications compared to historical controls. These initial promising results led to a collaboration with our urogynecology colleagues in 2018 to perform a prospective cohort study of a SDD ERAS protocol following minimally invasive sacrocolpopexy with or without hysterectomy or mid urethral sling. Among 47 women in the study SDD was accomplished in 37 (79%). There were few emergency department (ED) visits (2, or 4.3%) or readmissions (1, or 2.1%) and, compared to historical controls, no difference in rates of adverse events or unplanned health care encounters following SDD. Patient satisfaction was also extremely high with SDD (96%).

The prospective trial used a formal SDD ERAS protocol including a preoperative educational video, cefoxitin and gabapentin, and specific anesthesia protocols. However, we in the urology department have pared down our practice to what we believe to be its essential components, including detailed preoperative patient education and counseling regarding perioperative course, minimization of opioids and standardized postoperative Foley plans (see Appendix). Our anesthesia teams follow general best practices in the ERAS era: liberalized nothing-by-mouth (NPO) guidelines, postoperative nausea

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Robotic Sacrocolpopexy

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prophylaxis, minimization of intraoperative opioids and fluids, and use of preoperative acetaminophen and postoperative ketorolac when safe. Following these practices, our last 50 RASC cases (April 2019 to October 2020) have resulted in a SDD rate of 84%. There were no readmissions, and just 2 ED visits at 5 and 6 days postoperatively for urinary tract infection and subjective shortness of breath, respectively.

Our experience demonstrates that SDD is safe and feasible for RASC in the ERAS era. Benefits of SDD include avoidance of theoretical risks of medical error and hospital-acquired infections, financial savings and reduced burden on the health care system. During the COVID-19 pandemic, we have been able to continue to offer RASC even during local COVID-19 surges with limited hospital bed availability due to standardized SDD. With these apparent benefits and as evidence of safety and feasibility grows, we believe SDD should become routine for most RASC patients.

Appendix. Cleveland Clinic RASC SDD protocol

<table>
<thead>
<tr>
<th>Preop</th>
<th>Standard preop surgical counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>Clears at midnight NPO 2 hrs prior to surgery</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Preop—1,000 mg acetaminophen orally Intraop—bupivacaine for local analgesia, 30 mg ketorolac intravenously at closure Postop—opioid-sparing</td>
</tr>
<tr>
<td>Postop nausea/ vomiting</td>
<td>Per anesthesia team discretion</td>
</tr>
<tr>
<td>Fluids</td>
<td>Per anesthesia team discretion</td>
</tr>
<tr>
<td>Diet</td>
<td>Early advancement as tolerated</td>
</tr>
<tr>
<td>Foley</td>
<td>If no sling—home with catheter, self¬removal at home on postop day 1 If sling—home with catheter, trial of void in office on postop day 2</td>
</tr>
<tr>
<td>Disposition</td>
<td>Discharge when tolerating fluids, pain adequately controlled and ambulating Observed overnight if not meeting above</td>
</tr>
<tr>
<td>Discharge prescriptions/instructions</td>
<td>5 mg oxycodone (5–10 tabs) with instructions for prioritizing nonsteroidal anti-inflammatory drugs (NSAIDs), bowel regimen</td>
</tr>
</tbody>
</table>

Elevated PSA and Normal MRI: Can Biopsy Be Omitted?

Pre-biopsy magnetic resonance imaging (MRI) is negative in 20% to 40% of cancer-naïve patients with elevated prostate specific antigen (PSA) suspicious for prostate cancer (PCa). European Association of Urology (EAU) guidelines recommend that prostate biopsy be discussed with the patient in case of negative MRI and low clinical suspicion of PCa. MRI has been suggested as a “triage test” for the indication of biopsy to decrease the number of unnecessary biopsies, as well as overdiagnosis and overtreatment of nonclinically significant (noncs) PCa. MRI has been shown to have a negative predictive value between 85% and 95% for PCa. In addition to MRI results, other clinical (prostate volume, age, body mass index [BMI], family history of PCa, T-stage) or biological factors (PSA kinetics, PSA density [PSAd]) with negative MRI can increase the diagnostic accuracy of MRI by reducing the risk of false-negatives. Validation of the negative predictive value of MRI and other factors can be performed by correlation of MRI result to histopathological reference standards, such as template prostate biopsies or radical prostatectomy specimens. It can also be assessed by longitudinal evaluation of clinically significant PCa incidence over time.

In this study, we observed what would have happened if, in the case of a negative MRI in a biopsy-naïve population, we would have omitted biopsy. What would have been the clinically significant PCa cumulative incidence after long-term followup?

We conducted a single center, retrospective cohort study of consecutive cancer and biopsy-naïve patients referred with PSA or digital rectal examination (DRE) suspicious for PCa who underwent biopsy series after pre-biopsy MRI.

was at metastatic stage. Overall incidence at the end of analysis was 13% (66/503, 95% CI 7–21) for csPCa-1, 7% (36/503, 95% CI 5–9) for csPCa-2 and 2% (12/503, 95% CI 1.1–3.7) for high risk PCa.

At multivariate analyses, family history of PCa OR 2.31 (95% CI 1.12–5.26), abnormal DRE OR 2.43 (95% CI 1.12–5.26) and PSAd OR 1.06 (95% CI 1.03–1.10) were significantly associated with csPCa-1 diagnosis at first biopsy series in men with negative MRI (see table). Use of PSAd threshold ≥0.15 ng/ml/ml in negative MRI patients would have reduced the risk of missing clinically significant PCa from 9% to 4.6%, while avoiding biopsy in 56% of the negative MRI cases. Then he would need to be followed by PSA, which may with time lead to a diagnosis of clinically significant cancer in 2% to 5% of cases. To add confidence to these results, our results supported this diagnostic pathway, which was previously promoted by Panebianco and Norris et al.

Yes, we can omit biopsies, telling the patient that his risk of missing a clinically significant PCa in case of no biopsy is less than 3% if PSAd is less than 0.15 ng/ml/ml, DRE is normal and he has no family history, in addition to negative MRI. This situation concerns roughly 20% of our patients. Then he would need to be followed by PSA, which may with time lead to a diagnosis of clinically significant cancer in 2% to 5% of cases. To add confidence to these results, we need a longer median followup and detailed oncologic outcomes after treatments for the clinically significant cancers diagnosed during followup. This approach of triage tests before biopsy, combining MRI and biological or clinical factors, minimizes harms of screening.


### Table. Univariate and multivariate analyses of predictive factors for clinically significant prostate cancer

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>459</th>
<th>0.99 (0.95–1.04)</th>
<th>0.71</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²):</td>
<td>369</td>
<td>Overall: 0.95 (0.87–1.04)</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥30: 0.79 (0.32–1.96)</td>
<td>0.61</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>457</td>
<td>2.38 (1.10–6.16)</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.31 (1.03–5.21)</td>
<td>0.043</td>
</tr>
<tr>
<td>Prostate vol (ml)</td>
<td>459</td>
<td>1.03 (0.97–1.09)</td>
<td>0.4</td>
</tr>
<tr>
<td>CT stage (≥CT2a)</td>
<td>457</td>
<td>0.99 (0.97–1.01)</td>
<td>0.072</td>
</tr>
<tr>
<td>PSA doubling time (mos)</td>
<td>297</td>
<td>3.32 (1.69–6.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA velocity (ng/ml/yr)</td>
<td>297</td>
<td>1.02 (0.98–1.06)†</td>
<td>0.29</td>
</tr>
<tr>
<td>PSA density (ng/ml/ml):</td>
<td>445</td>
<td>1.00 (0.9–1.06)</td>
<td>0.87</td>
</tr>
<tr>
<td>Overall</td>
<td>1.06 (1.03–1.09)‡</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>≥0.15</td>
<td>2.43 (1.19–4.21)</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>≥0.14</td>
<td>3.14 (1.64–6.00)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>≥0.10</td>
<td>3.2 (1.39–7.34)</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

Values in bold indicate statistical significance. *Data were not available for all patients (missing data or only 1 pre-biopsy PSA result). †OR calculated for 10 unit increase. ‡OR calculated for 0.01 unit increase.

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### Postprostatectomy Recurrence Diagnosed Using MRI/Ultrasound Fusion Transperineal Biopsy

**RADIOLGY**  
**Corner**

**Postprostatectomy Recurrence Diagnosed Using MRI/Ultrasound Fusion Transperineal Biopsy**

**Joshua S. Jue, MD**  
**Ardeshir R. Rastinehad, DO**  
New York, New York

An 82-year-old Caucasian male with a history of prostate cancer underwent robotic assisted laparoscopic radical prostatectomy in 2007 with Gleason Grade Group 3 surgical pathology (T1C, N0, M0) and later underwent salvage radiation in 2009 due to prostate specific antigen (PSA) recurrence with negative metastatic workup. The patient was then lost to followup and was referred to our institution with a PSA of 6.62. A positron emitting tomography (PET)/computerized tomography (CT) Axumin scan demonstrated focal Axumin uptake in the region of the left prostatectomy bed posteriorly, seen in the region of surgical clips, highly suspicious for recurrent malignancy. A magnetic resonance imaging (MRI) of the pelvis showed a 2.4 cm × 1.1 cm ill-defined signal of soft tissue thickening and enhancement appearing to be left seminal vesicle remnant (fig. 1). A CT guided percutaneous biopsy was deemed challenging due to its location adjacent to the prostatectomy bed deep within the pelvis. The patient agreed to proceed with a MRI/ultrasound (US) transperineal biopsy to obtain a tissue diagnosis of this suspicious area.

Pelvic MRI segmentation was performed using a DynaCAD® workstation. The MRI/US fusion systems need a central point of reference to align both 3D datasets, which is typically the prostate. We segmented the prostate as the external urinary sphincter, the pubic

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**Figure 1.** Axial T2 weighted MRI and PET/CT Axumin scan of suspicious ill-defined soft tissue mass appearing to be left seminal vesicle remnant in left posterior prostatectomy bed.

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Continued on page 20
bone as a second point of reference and suspicious MRI lesion as the target (fig. 2). This was performed using the new Philips UroNav 4.0 system, which can be used to perform prostate biopsies and focal ablations.

A hypoechoic lesion in the left posterior prostatectomy bed surrounded by hyperechoic clips was visualized using live transrectal ultrasound, once colocalized by fusion imaging. This hypoechoic lesion correlated well with the MRI segmentation. Multiple cores were obtained from this lesion (fig. 3). The live ultrasound imaging was particularly useful to visualize needle deflection from the lesion’s rigidity, which would not have been appreciated during a CT guided biopsy.

The pathology was Gleason 4+3 prostate adenocarcinoma, extensively involving fibromuscular and adipose tissue. Large nerve invasion was present, with tumor permeating around ganglion cells. The patient has started a planned 6-month course of luteinizing hormone releasing hormone agonist with radiation, since the prior treatment field did not treat the area of recurrence due to the location.

To our knowledge, this is the first use of MRI/US fusion technology to diagnose prostate cancer recurrence in the postprostatectomy bed. Although this technology was first designed to better target clinically significant prostate cancer within a prostate gland, we used stationary fiducials as landmarks to localize the region of interest in 3D. Lesions suspicious for prostate cancer recurrence after radical prostatectomy are typically percutaneously biopsied using CT guidance, which can be used for histologic confirmation and molecular analyses for treatment planning.1 The overall success rate of obtaining a histologic diagnosis of prostate cancer from CT guided bone biopsies is 69% to 77% but can decrease to 42% for lesions that are ~8.8 cm³ in size, such as ours.1,2 A mobile soft tissue mass is also technically more challenging to biopsy than a fixed bony lesion. We obtained a tissue diagnosis through the perineum with the same sterility as a CT guided biopsy but without any ionizing radiation. MRI/US fusion technology holds significant potential and will continue to be used for new applications in the future.


Results

Of the 409 patients, 207 (51%) underwent surgery before ERAS and 202 (49%) after ERAS protocol implementation. Robot-assisted laparoscopic approach was used in 285 cases, with 158/285 (55%) before ERAS. Patient characteristics are outlined in table 1. There was a significant difference in the type of opioid medications prescribed after ERAS implementation, as tramadol was prescribed at a significantly higher rate than hydrocodone or oxycodone (p < 0.001).

There was a significant decline in the mean opioid tablets prescribed at discharge after initiating ERAS (fig. 1). After ERAS, opioid tablets decreased by 38.2% [mean±SD 49.7±15.4 vs 30.7±18.5 tablets, p <0.001] following open radical and open partial renal procedures, and by 34.6% (37.6±14.6 vs 24.6±14.3, p <0.001) following robotic renal procedures. In robotic prostatectomy and open cystectomy patients, there was a reduction in opioid

Thus, the impetus to use all available measures to reduce dissemination of prescription opioids remains essential. With emphasis on nonopioid analgesics, enhanced recovery after surgery (ERAS) protocols have demonstrated successful reduction in the use of opioids during hospital stay to facilitate early discharge. We studied the impact of initiating ERAS protocols on the opioid prescriptions given at discharge after major urological cancer surgery.

Materials and Methods

We reviewed the medical records of 409 patients undergoing robotic radical prostatectomy, open or robotic nephrectomy (radical or partial), or radical cystectomy from 2016 to 2018. Discharge instructions included use of acetaminophen and/or ibuprofen prior to using opioids for breakthrough pain. The type and amount of opioid prescriptions given were based on the discharging provider’s assessment of pain control and necessity of opioid prescriptions at discharge. We also reviewed the outpatient records of patients on ERAS protocols for 30 days after discharge to identify any additional opioid prescriptions.

Primary outcomes included the difference in the number (mean±SD) of standardized hydrocodone 5 mg tablet equivalents prescribed at discharge before and after initiating the ERAS protocols, as well as the type of opioids prescribed.

Introduction

Opioids prescribed by medical practitioners contribute significantly to opioid-related deaths due to prescription diversion and opioid abuse.1 Despite years of regulations, the opioid abuse crisis continues to remain a major public health concern, claiming more than 68,000 lives due to opioid overdose in 2018.2
Table 2. Regression analysis of difference in opioid (hydrocode 5 mg equivalent) tablets prescribed at discharge, including all procedures.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Univariable Difference (95% CI)</th>
<th>p Value</th>
<th>Multivariable Difference (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>106</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>303</td>
<td>-0.07 (-3.59, 3.45)</td>
<td>0.970</td>
<td>2.75 (-0.81, 6.32)</td>
<td>0.13</td>
</tr>
<tr>
<td>Age (for every 1yr increase)</td>
<td>62.3 (10.9)</td>
<td>-0.20 (-0.34, -0.06)</td>
<td>0.005</td>
<td>-0.17 (-0.30, -0.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>373</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
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<tr>
<td>Black</td>
<td>21</td>
<td>0.93 (-6.07, 7.93)</td>
<td>0.793</td>
<td>-0.60 (-6.95, 5.75)</td>
<td>0.85</td>
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<td>Other</td>
<td>15</td>
<td>-1.10 (-9.31, 7.12)</td>
<td>0.794</td>
<td>-1.72 (-9.25, 5.80)</td>
<td>0.65</td>
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<td>Preop narcotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>392</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17</td>
<td>9.38 (1.71, 17.05)</td>
<td>0.017</td>
<td>4.14 (-3.11, 11.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>Procedure type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open renal surgery*</td>
<td>84</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Robotic renal surgery*</td>
<td>139</td>
<td>-4.96 (-9.22, -0.71)</td>
<td>0.022</td>
<td>-6.85 (-10.86, -2.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>Robotic prostatectomy</td>
<td>146</td>
<td>-7.05 (-11.26, -2.83)</td>
<td>0.001</td>
<td>-10.98 (-15.30, -6.67)</td>
<td>&lt;0.001</td>
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<td>Open cystectomy</td>
<td>40</td>
<td>-1.07 (-6.98, 4.84)</td>
<td>0.723</td>
<td>-4.84 (-10.49, 0.80)</td>
<td>0.09</td>
</tr>
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<td>ERAS protocol</td>
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<td></td>
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<td>Pre-implementation</td>
<td>207</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Post-implementation</td>
<td>202</td>
<td>-10.99 (-13.89, -8.10)</td>
<td>&lt;0.001</td>
<td>-12.63 (-15.51, -9.75)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| * Includes radical nephrectomy, partial nephrectomy and nephroureterectomy.

Figure 2. Change in type of opioid medications prescribed at discharge from hospital after implementation of ERAS protocol.

Figure 1. Reduction in standardized opioid tablets prescribed in patients treated under ERAS protocol for various procedures.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>No. Pre-Eras (%)</th>
<th>No. Post-ERAS (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Male</td>
<td>160 (77.3)</td>
<td>143 (70.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>47 (22.7)</td>
<td>59 (29.2)</td>
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</tr>
<tr>
<td>Race</td>
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<td></td>
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</tr>
<tr>
<td>White</td>
<td>187 (90.3)</td>
<td>186 (92.1)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>12 (5.8)</td>
<td>9 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (3.9)</td>
<td>7 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Preop narcotics</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>No</td>
<td>195 (94.2)</td>
<td>195 (96.5)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (5.8)</td>
<td>7 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Opioids prescribed at discharge</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>49 (23.7)</td>
<td>6 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>140 (67.6)</td>
<td>93 (46.0)</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>18 (8.7)</td>
<td>103 (51.0)</td>
<td></td>
</tr>
</tbody>
</table>

Journal Brief

The opioids prescribed at discharge included hydrocodone with acetaminophen, oxycodone, and tramadol. Before ERAS protocol, 91% of patients received either hydrocodone (24.7%) or oxycodone (67.6%). After ERAS protocol, the use of tramadol increased from 9% to 51% (p <0.001), signifying a substantial trend away from potent opioids (fig. 2).

A review of outpatient medical records of the 202 patients on ERAS protocols identified phone calls from 38 (18.8%), primarily related to Foley catheter, gastrointestinal issues, bladder spasms, pain, and hematuria. Of these patients 27 (13.4%) required additional opioids. All 27 of these patients had undergone renal surgery (open in 8, robotic in 5), and 20 were under age 55 years.

Discussion

Opioid abuse and opioid related deaths continue largely unchecked, in part aided by prescription opioids. Two recent studies have brought overprescribing into stark relief. Theisen et al reported that for 155 patients, an average of 39 hydrocodone-equivalent tablets were prescribed at discharge, of which 60% remained unused. Raskolnikov et al reported that discharge prescription after renal surgery averaged an alarming 73 hydrocodone-equivalent tablets. Contemporary opioid prescribing habits remain quite concerning, prompting the American Urological Association to organize an opioid stewardship summit in 2018. Therefore, it is essential to identify all measures, direct or indirect, that have the potential to reduce opioid prescriptions at discharge.

In our 409 patients undergoing open or robotic surgery, there was a significant (27% to 38%) decrease in opioid prescriptions after ERAS implementation. On multivariate analysis, ERAS protocols were independently associated with the largest decrease in post-discharge opioid prescriptions (table 2).

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Continued from page 21

analysis, ERAS protocols were independently associated with decreased outpatient opioid prescriptions. The largest decrease in prescribed opioids after discharge (38%) was noted in the open renal surgery group. The smaller decrease in opioid prescription in the radical cystectomy group after ERAS (27%) was not statistically significant, likely due to the small sample size.

Concerns related to limited prescriptions of opioids include poor pain control, excessive phone calls and additional requests for refills. While pain scores were not available in our cohort, refill requests for opioids may be used as a surrogate for ongoing pain after discharge. In the ERAS group, only 6% of patients needed additional opioids. These were primarily patients younger than 55 years old who had undergone renal surgery. These data identify a subgroup of patients who could benefit from adjustments in the postoperative analgesic regimen (eg addition of cyclobenzaprine or pregabalin).

To our knowledge, this is one of only a few studies evaluating opioid prescriptions following ERAS for urological surgery. We reviewed several ERAS protocols for abdominal/pelvic surgery from other centers (including various surgical specialties) and noted that while ERAS protocols focus on reducing opioid use during hospital stay, these often do not specifically address opioid prescriptions at discharge. The mechanism of the impact of ERAS protocols on postoperative opioid prescriptions is likely multifactorial. However, it is at least partly related to an increased awareness and standardization of opioid-sparing pain management strategies, which have been brought into focus with the use of ERAS protocols. This has likely translated into fewer discharge opioid prescriptions and a trend away from more potent opioids.

Conclusions

A significant decrease in opioid prescriptions at discharge was noted following implementation of ERAS protocols for open and minimally invasive urological cancer surgery. Bringing a focus on controlling opioid use during inpatient stay was associated with a reduction in outpatient opioid prescriptions and a significant shift away from potent opioids.


**“Familiarity” Trends of Successful Urology Residency Match Applicants**

R. Corey O’Connor, MD
Milwaukee, WI

Urology remains a highly competitive and sought-after surgical subspecialty. Factors previously shown to coincide with applicant success in the residency match include United States Medical Licensing Examination scores, research experience, strong letters of recommendation and positive communication/interpersonal skills.1 2 Many believe audition rotations help students gain additional medical/surgical knowledge, set themselves apart from their peers and, ultimately, increase the likelihood of matching at a specific program.3 In fact, both candidates and program directors rank visiting rotations as one of the most important aspects of the selection process.4 4

We analyzed information from successful urology match participants between 2015 and 2020 to determine if training program familiarity played a role in a successful match process. Selected “familiarity” categories included applicants’ medical school, location of visiting subinternships, hometown, undergraduate schools and graduate/research programs (if applicable). Data were collected from the American Association Medical Colleges applications, UrologyMatch.com and SurveyMonkey.

Overall, 1,080 of 1,451 (74.4%) successful urology match candidates met one or more “familiarity” criteria (Figure). Specifically, 329 (22.7%) and 508 (35.0%) students successfully matched into their home and visiting urology training programs, respectively. Of the remaining applicants, 153 (10.5%) and 90 (6.2%) registrants matched into training programs <150 miles from their hometowns and within institutions of previous academic pursuits, respectively.

In conclusion, roughly 75% of successful urology applicants matched into either their home programs, sites of visiting subinternships, previous undergraduate/graduate institutions or training hospitals within 150 miles of their hometowns. Obviously, neither students nor program directors can change an applicant’s hometown or educational pedigree at the time of submission. However, our results provide evidence that a significant subset of candidates (35%) benefit from completing urology subinternships at programs outside of their home institution. Therefore, residency applicants should strongly consider participating in visiting rotations. Additionally, for the same reason program directors should increase the number of available subinternship positions for outside students. Finally, although the ideal number does not exist, submitting applications to a surplus of residency programs does not likely increase match success. Our findings may help urology candidates improve match outcomes by applying strategically, rather than to an ever-increasing abundance of programs.

Is the Toxicity of Salvage Prostatectomy Related to the Primary Prostate Cancer Therapy Received?

Luis Ribeiro, MBBS

Nonsurgical treatments for prostate cancer include traditional radiation (external beam radiotherapy and brachytherapy) and new minimally invasive therapies such as high intensity focused ultrasound, cryotherapy and electroporation. Salvage radical prostatectomy (SRP) in men with local recurrence after nonsurgical treatment has been traditionally associated with poor outcomes. Early studies with small sample sizes have reported a high degree of technical difficulty and complication rates due to post-radiation changes. However, recent studies with modern radiation therapies (RT) and improved surgical experience have shown reasonable outcomes in select patients.

Outcomes of salvage surgery following local recurrence after focal therapy are limited given its relative modernity. As focal therapies (FT) are designed to cause less tissue damage, the toxicity of SRP after FT could be hypothesized to be significantly less than after RT. Our goal was to compare the toxicity profile and oncological outcome of salvage radical prostatectomy following focal therapy versus salvage radical prostatectomy after radiation therapies. Data concerning all men undergoing salvage radical prostatectomy for recurrent prostate cancer after either focal therapy, external beam radiation therapy or brachytherapy were retrospectively collected from 4 high volume surgical centers: Guy’s Hospital (London, UK), Institut Mutualiste Montsouris (Paris, France), Imperial College Healthcare Trust (London, UK) and The Peter MacCallum Cancer Centre (Melbourne, Australia).

The primary outcome measure of the study was toxicity of salvage radical prostatectomy characterized by 30-day postoperative Clavien-Dindo complication rate, 12-month continence rate and 12-month potency rate. The secondary outcome was oncological outcome after salvage radical prostatectomy including positive margin rate and 12-month biochemical recurrence rate. Between April 2007 and September 2018, 185 patients underwent salvage radical prostatectomy of whom 95 had salvage radical prostatectomy after focal therapy and 90 had salvage radical prostatectomy after radiation therapy (external beam radiation therapy or brachytherapy). Median follow-up was 29.5 months.

Our results demonstrated that men undergoing SRP after FT experience lower postoperative complication rates and better urinary continence outcomes compared to men undergoing SRP after RT. SRP after RT was associated with a significantly higher 30-day Clavien-Dindo complication rate (34% vs 5%, p<0.001, see table). In the RT group, 4% of men experienced an anastomotic leak and 10% experienced an anastomotic sticture. Comparative figures in the FT group were 1% and 0% respectively. There was 1 rectal injury in the RT group and 0 in the FT group.

At 12 months following surgery, patients undergoing SRP after FT had significantly better continence (83% pad-free vs 49%) while potency outcomes were similar (14% vs 11%). Presalvage potency rates were similar between the two groups (FT: 67% vs RT: 65%), 74% of men in the FT group had some form of nerve sparing compared to 10% in the RT group. The similarly low potency rates in both groups are likely due to short follow up times and longer follow up may reveal further differences between the two groups.

Men undergoing SRP after RT had a significantly higher stage and grade of disease together with a higher positive surgical margin rate (37% vs 13%, p<0.001). The 3-year biochemical recurrence rates after FT were 35% compared to 32% after RT (p=0.76). Kaplan-Meier curves were also not significantly different (figure, log-rank test: p=0.67). In multivariable analysis, men undergoing SRP after FT experienced a higher risk of biochemical recurrence (HR 0.36, 95% CI 0.16-0.82, p=0.02) despite lower stage, grade, and positive margin rates compared to the RT group.

The reasoning for this is unclear however it suggests that all men considering SRP after FT should undergo cross-sectional imaging, such as prostate specific membrane antigen positron emission tomography, to exclude micrometastatic disease.

To our knowledge only 1 other study has compared the toxicity and outcomes of SRP after RT versus FT. Onol and colleagues in their single institution study report similar functional and oncological outcomes to our study.

Traditionally SRP has been associated with significant functional toxicity. However, in our multicenter study, we demonstrate that the functional outcome of SRP is not universally poor and is dependent on primary prostate cancer treatment. Patients receiving focal therapy prior to SRP have lower rates of perioperative complications and better long-term urinary continence outcomes.

Therefore, we would encourage urologists reviewing men with recurrent prostate cancer after FT to consider salvage surgery as an alternative to salvage radiotherapy or whole gland ablation. Furthermore, by performing SRP on men with recurrent prostate cancer after FT, these men still have radiation to the prostate bed in reserve if the SRP is not curative.


Table. Summary and comparison of toxicity in focal therapy (FT) versus radiotherapy (RT) salvage prostatectomies (SRP)

<table>
<thead>
<tr>
<th></th>
<th>SRP after FT (n=95)</th>
<th>SRP after RT (n=90)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative complications, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteric injury</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Rectal injury</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Postoperative complications, no. (%)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>31 (34%)</td>
<td>5 (5%)</td>
<td></td>
</tr>
<tr>
<td>Anastomotic stricture</td>
<td>11 (12%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Hernia requiring operation</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Postoperative ileus</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Intraabdominal infection</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Prolonged catheter</td>
<td>7 (8%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure. Kaplan-Meier curves of progression-free survival by biochemical recurrence after focal therapy (FT) and radiotherapy (RT) salvage prostatectomies (n=164). Log-rank test: p=0.67.
**ORGOVYX** achieved sustained testosterone suppression¹

- 97% of men achieved and maintained testosterone suppression to <50 ng/dL from Day 29 through Week 48 with ORGOVYX

**MAJOR EFFICACY OUTCOME MEASURE: SUSTAINED TESTOSTERONE SUPPRESSION RATE (TESTOSTERONE LEVELS <50 ng/dL FROM DAY 29 THROUGH WEEK 48)¹**

![Sustained testosterone suppression rate diagram](image)

Results from the HERO study, a multinational, randomized, open-label, phase 3 trial in 934 men with advanced prostate cancer. Patients were randomized 2:1 to receive ORGOVYX (360 mg on the first day followed by daily doses of 120 mg orally) or leuprolide acetate (22.5 mg injection or 11.25 mg in Japan and Taiwan per local guidelines) subcutaneously every 3 months (n=310) for 48 weeks.²

CI=confidence interval.

²Kaplan-Meier estimates within each group.

¹11.25 mg is a dosage regimen that is not recommended for this indication in the United States.

²The testosterone suppression rate of the subgroup of patients receiving 22.5 mg leuprolide (n=264) was 88.0% (95% CI: 83.4%, 91.4%).

²Two patients in each arm did not receive the study treatment and were not included.

**INDICATION**

ORGOVYX is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the treatment of adult patients with advanced prostate cancer.

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

**QT/QTc Interval Prolongation:** Androgen deprivation therapy, such as ORGOVYX may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, or frequent electrolyte abnormalities and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

**Embryo-Fetal Toxicity:** The safety and efficacy of ORGOVYX have not been established in females. Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

**Laboratory Testing:** Therapy with ORGOVYX results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropin and gonadal functions conducted during and after ORGOVYX may be affected. The therapeutic effect of ORGOVYX should be monitored by measuring serum concentrations of prostate-specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.

**Adverse Reactions**

**Serious adverse reactions** occurred in 12% of patients receiving ORGOVYX. Serious adverse reactions in ≥0.5% of patients included myocardial infarction (0.8%), acute kidney injury (0.6%), arrhythmia (0.6%), hemorrhage (0.6%), and urinary tract infection (0.5%). Fatal adverse reactions occurred in 0.8% of patients receiving ORGOVYX including metastatic lung cancer (0.3%), myocardial infarction (0.3%), and acute kidney injury (0.2%). Fatal and non-fatal myocardial infarction and stroke were reported in 2.7% of patients receiving ORGOVYX.
Introducing ORGOVYX, the only once-a-day* oral androgen deprivation therapy for advanced prostate deprivation cancer1,2

*One pill, once a day, after initial loading dose of 3 pills.

ORGOVYX offers a new option for testosterone control1-3

- **RAPID TESTOSTERONE SUPPRESSION WITHOUT A SURGE:** 56% of men treated with ORGOVYX achieved testosterone suppression to <50 ng/dL on Day 4
  - 0% of men treated with leuprolide had testosterone levels <50 ng/dL on Day 4
- **PROFOUND TESTOSTERONE SUPPRESSION:** 95% of men treated with ORGOVYX achieved profound testosterone suppression to <20 ng/dL on Day 29
  - 57% of men treated with leuprolide had testosterone levels <20 ng/dL on Day 29
- **90-DAY TESTOSTERONE RECOVERY:** in a sub-study, 55% of the 137 men treated with ORGOVYX had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after treatment discontinuation
  - 3% of 47 men treated with leuprolide had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after discontinuation

*Kaplan-Meier estimates within each group.
*This endpoint was analyzed for exploratory purposes without formal testing. The data from the leuprolide arm were not included in the US Prescribing Information for ORGOVYX.

**IMPORTANT SAFETY INFORMATION (cont’d)**

Most common adverse reactions (≥10%) and laboratory abnormalities (≥15%) in patients receiving ORGOVYX were hot flush (54%), glucose increased (44%), triglycerides increased (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), alanine aminotransferase increased (27%), fatigue (26%), aspartate aminotransferase increased (18%), constipation (12%), and diarrhea (12%).

**Drug Interactions**

Co-administration of ORGOVYX with a P-gp inhibitor increases the area under the curve (AUC) and maximum concentration (C_max) of ORGOVYX, which may increase the risk of adverse reactions associated with ORGOVYX. Avoid co-administration of ORGOVYX with oral P-gp inhibitors. If co-administration is unavoidable, take ORGOVYX first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions. Treatment with ORGOVYX may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors. If treatment with ORGOVYX is interrupted for more than 7 days, resume administration of ORGOVYX with a 360 mg loading dose on the first day, followed by 120 mg once daily.

Co-administration of ORGOVYX with a combined P-gp and strong CYP3A inducer decreases the AUC and C_max of ORGOVYX, which may reduce the effects of ORGOVYX. Avoid co-administration of ORGOVYX with combined P-gp and strong CYP3A inducers. If co-administration is unavoidable, increase the ORGOVYX dose to 240 mg once daily. After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended ORGOVYX dose of 120 mg once daily.

**References:**
The most common adverse reactions (>10%) and laboratory abnormalities (>15%), were hot flush (54%), glucose increased (44%), triglycerides increased (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), alanine aminotransferase increased (ALT) (27%), fatigue (26%), aspartate aminotransferase increased (AST) (18%), constipation (12%), and diarrhea (12%).

Table 1 summarizes the adverse reactions in HERO.

Table 1: Adverse Reactions (≥10%) of Patients with Advanced Prostate Cancer Who Received ORGOVYX in HERO

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ORGOVYX N = 622</th>
<th>Leuprolide Acetate N = 308</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>54.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>30.0</td>
<td>1.1</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>26.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>12.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>12.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* includes arthralgia, back pain, pain in extremity, musculoskeletal pain, myalgia, bone pain, neck pain, arthritis, musculoskeletal stiffness, non-cardiac chest pain, musculoskeletal chest pain, spinal pain, and musculoskeletal discomfort.

Clinically relevant adverse reactions in <10% of patients who received ORGOVYX included increased weight, insomnia, gynecomastia, hyperhidrosis, depression, and decreased libido.

Table 2 summarizes the laboratory abnormalities in HERO.

Table 2: Select Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with Advanced Prostate Cancer Who Received ORGOVYX in HERO

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>ORGOVYX N = 622</th>
<th>Leuprolide Acetate N = 308</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>44.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Triglycerides increased</td>
<td>35.0</td>
<td>2.0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>27.0</td>
<td>0.3</td>
</tr>
<tr>
<td>AST increased</td>
<td>18.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>28.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* The denominator used to calculate the rate varied from 611 to 619 in the ORGOVYX arm and from 301 to 306 in the leuprolide arm based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ORGOVYX

P-gp Inhibitors

Co-administration of ORGOVYX with a P-gp inhibitor increases the AUC and the maximum concentration (C_{max}) of relugolix, which may increase the risk of adverse reactions associated with ORGOVYX. Avoid co-administration of ORGOVYX with oral P-gp inhibitors.

If co-administration is unavoidable, take ORGOVYX first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions.

Treatment with ORGOVYX may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors.

If treatment with ORGOVYX is interrupted for more than 7 days, resume administration of ORGOVYX with a 360 mg loading dose on the first day, followed by 120 mg once daily.

Combined P-gp and Strong CYP3A4 Inducers

Co-administration of ORGOVYX with a combined P-gp and a strong CYP3A4 inducer decreases the AUC and C_{max} of relugolix, which may reduce the effects of ORGOVYX. Avoid co-administration of ORGOVYX with combined P-gp and strong CYP3A4 inducers.

If co-administration is unavoidable, increase the ORGOVYX dose. After discontinuation of the combined P-gp and strong CYP3A4 inducer, resume the recommended dose of ORGOVYX once daily.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of ORGOVYX have not been established in females. Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. There are no human data on the use of ORGOVYX in pregnant females to inform the drug-associated risk. In an animal reproduction study, oral administration of relugolix to pregnant rabbits during organogenesis caused embryo-fetal lethality at maternal exposures that were 0.3 times the human exposure at the recommended dose of 120 mg daily based on AUC (see Data). Advise patients of the potential risk to the fetus.

Data

Animal Data

In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (approximately 0.3 times the human exposure at the recommended dose of 120 mg daily based on AUC).

8.2 Lactation

Risk Summary

The safety and efficacy of ORGOVYX at the recommended dose of 120 mg daily have not been established in females. There are no data on the presence of relugolix in human milk, the effects on the breastfed child, or the effects on milk production. Relugolix and/or its metabolites were present in milk of lactating rats (see Data).

Data

Animal Data

In lactating rats administered a single oral dose of 30 mg/kg radiolabeled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animals and mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

Infertility

Males

Based on findings in animals and mechanism of action, ORGOVYX may impair fertility in males of reproductive potential.

8.4 Pediatric Use

The safety and efficacy of ORGOVYX in pediatric patients have not been established.

8.5 Geriatric Use

Of the 622 patients who received ORGOVYX in the HERO study, 81% were 65 years of age or older, while 35% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. There was no clinically relevant impact of age on the pharmacokinetics of ORGOVYX or testosterone response based on population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses in men 45 to 91 years of age.

12.3 Pharmacokinetics

Specific Populations

No clinically meaningful differences in the pharmacokinetics of relugolix were observed based on age (45 to 91 years), race/ethnicity (Asian [19%], White [71%], Black/African-American [6%]), body weight (41 to 193 kg), mild to severe renal impairment (creatinine clearance [Clcr] 15 to 89 mL/min, as estimated by the Cockcroft-Gault equation), or mild to moderate hepatic impairment (Child-Pugh A or B). The effect of end-stage renal disease with or without hemodialysis or severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of relugolix has not been evaluated.

Drug Interactions Studies

Clinical Studies

Combined P-gp and Moderate CYP3A Inhibitor: Co-administration with erythromycin (P-gp and moderate CYP3A inhibitor) increased the AUC and Cmax of relugolix by 6.2-fold.

Combined P-gp and Strong CYP3A Inducer: Co-administration with rifampin (P-gp and strong CYP3A inducer) decreased the AUC and Cmax of relugolix by 55% and 23%, respectively.

Other Drugs: No clinically significant differences in the pharmacokinetics of relugolix were observed when co-administered with voriconazole (strong CYP3A inhibitor), atorvastatin, enalapril, or acid-reducing agents. No clinically significant differences in the pharmacokinetics of midazolam (sensitive CYP3A substrate) or rosvastatin (CYP3A substrate) were observed upon co-administration with relugolix.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Relugolix is a substrate of CYP3A and CYP2C8. Relugolix is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Relugolix is an inducer of CYP3A and CYP2B6, but not an inducer of CYP1A2.

Transporter Systems: Relugolix is a substrate of P-gp, but not a substrate of BCRP. Relugolix is an inhibitor of BCRP and P-gp, but not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, or BSEP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in mice at oral relugolix doses up to 100 mg/kg/day and in rats at doses up to 600 mg/kg/day. Relugolix was not carcinogenic in mice or rats at exposures up to approximately 75 or 224 times, respectively, the human exposure at the recommended dose of 120 mg daily based on AUC.

Relugolix was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells or the in vivo rat bone marrow micronucleus assay.

In human GnRH-receptor knock-in male mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses ≥ 3 mg/kg twice daily for 28 days. The effects of relugolix were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal. In a 38-week repeat-dose toxicity study in monkeys, there were no significant effects on male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human exposure at the recommended dose of 120 mg daily based on AUC).

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) was observed in multiple organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, gastrointestinal tract or testes) after repeated oral administration of relugolix in rats and monkeys. In a rat 26-week toxicity study, phospholipidosis was observed at doses ≥ 100 mg/kg (approximately 18 times the human exposure at the recommended dose based on AUC). In a monkey 39-week toxicity study, this effect was observed at doses ≥ 1.5 mg/kg (approximately 0.6 times the human exposure at the recommended dose based on AUC) and demonstrated evidence of reversibility after cessation of treatment. The significance of this finding in humans is unknown.

17 PATIENT COUNSELING INFORMATION

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

QT/QTc Interval Prolongation

• Advise patients that androgen deprivation therapy treatment with ORGOVYX may prolong the QT interval. Inform patients of the signs and symptoms of QT prolongation. Advise patients to contact their healthcare provider immediately for signs or symptoms of QT prolongation.

Androgen Deprivation

• Inform patients about adverse reactions related to androgen deprivation therapy with ORGOVYX, including hot flashes, flushing of the skin, increased weight, decreased sex drive, and difficulties with erectile function.

Embryo-Fetal Toxicity

• Inform patients that ORGOVYX can be harmful to a developing fetus and can cause loss of pregnancy.

• Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

Infertility

• Inform patients that ORGOVYX may cause infertility.

Manufactured by Bushu Pharmaceuticals, Ltd, Kawagoe, Saitama, Japan
Manufactured for Myovant Sciences, Inc., Brisbane, CA 94005
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Retzius-Sparing vs Standard Robot-Assisted Radical Prostatectomy: A Comparative Prospective Study of Nearly 500 Patients

There are 2 main approaches to perform robot-assisted radical prostatectomy (RARP), the standard “anterior” approach and the Retzius-sparing (RS) “posterior” approach. RS-RARP was first described by Galfano et al and allows the prostate gland to be removed from under the overlying detrusor apron, entirely avoiding the pubovesical ligaments.¹ This technique can also be performed in challenging surgical scenarios such as very large prostates, prostates with median lobes, post-transurethral prostatectomy (TURP) cases, kidney transplant recipients and for salvage prostatectomies.² An international survey on worldwide diffusion of RS-RARP showed that an increasing number of institutions have explored the feasibility and reproducibility of this approach with controversial results.³

Urinary incontinence has a massive impact on quality of life and treatment satisfaction after radical prostatectomy. The highest rates of urinary incontinence and associated bother are noted during the first 12 months after surgery. There is a wide variability of results reported in the literature, partly due to the lack of uniformity in defining, assessing and reporting continence outcomes after radical prostatectomy. Furthermore, capturing patient-reported outcome measures (PROMs) using validated questionnaires is far preferable to using physician reports with their inherent biases to evaluate functional outcomes after surgery.

The end points of our study were pentafecta outcomes (continence, potency, biochemical recurrence, complications and positive surgical margins), patient-reported outcome measures of functional recovery, quality of life and perioperative outcomes of RS-RARP and RARP. Patient- and physician-reported data on 483 patients were prospectively collected by the patient management software Carebit (Carebit Health Ltd, Brighton, United Kingdom), which was used to fully automate the generation, sending and recording of completed questionnaires by patients at each time interval.

All patients underwent surgery with the da Vinci® Surgical System using the 4-arm configuration by 3 experienced robotic surgeons (>500 prior minimally invasive radical prostatectomies). A 30-degree Trendelenburg position was used in all cases and pneumoperitoneum was induced by an open Hasson technique. Six trocars were placed in a fan array configuration, and low pressure surgery was possible with the use of the AirSeal® insufflation system.

In the RARP group, the transperitoneal anterior approach was performed as described by Menon et al⁴ or the Montsouris group.⁵ When indicated, a nerve-sparing procedure was performed with a posterolateral release of the neurovascular bundles. In the RS-RARP group, the posterior Retzius-sparing technique described by Galfano et al⁶ was used with some modifications—not always using a peritoneal hitch stitch, but sometimes using a Pansadoro stitch to retract the bowel, and using a barbed suture for the anastomosis. When indicated, the nerve-sparing was performed using either an intrafascial or interfascial dissection, based on preoperative magnetic resonance imaging planning. The vesicourethral anastomosis was performed with a van Velthoven technique using 3-zero barbed sutures in both groups.

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Figure 1. Immediate functional outcomes (continence and potency) between groups.

Figure 2. PROMS outcomes between groups at various time points. IEF-5, International Index of Erectile Function 5-Item Questionnaire. ICIQ-MLUTS, International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms Module.
Retzius-Sparing vs Standard Robot-Assisted Radical Prostatectomy

Continued from page 28

The immediate urinary continence at catheter removal was better in the RS-RARP group (p=0.02), and there was no statistically significant difference in the immediate potency rate between the 2 groups (p=0.069, fig. 1). No significant differences in overall urinary symptoms (prevalence and bother) or erectile function were recorded at baseline and 1, 3, 6, 9 and 12 months after surgery between the 2 groups (fig. 2). A better quality of life was recorded in the RS-RARP group during the immediate postoperative course (p=0.004), while there was no difference at 3, 6, 9 and 12 months after surgery (fig. 3). However, after a detailed subscale analysis, we found less nocturnal urinary symptom prevalence (p=0.011) and bother (p=0.009) at 1 month after RS-RARP (fig. 4). The study also showed no differences in overall positive surgical margin (PSM) rates between the 2 groups (13.9% vs 15.6%, p=0.6), as well as no differences in T2, T3 and apical PSM rates. No significant differences in other functional or quality of life outcomes, perioperative parameters, complications or margin rates were found.

The main strengths of our study are the large series of patients, the uniformity of the 2 groups with regard to the preoperative general, oncologic and functional features, including the proportions of high risk patients, the completeness of the data, including followup, the use of validated questionnaires providing high quality PROMs data, and no learning curve bias with the comparison of multiple high volume surgeons. These strengths make this study unique in the present literature.

RS-RARP showed better immediate continence rate and quality of life compared to standard RARP but with no differences recorded in other clinically relevant parameters at any other time point. The similarity in outcomes between groups lends support to the view that patients should choose their surgeon wisely rather than the specific technique used.


Is Toxicity of Salvage Prostatectomy Related to Primary Prostate Cancer Therapy?

Continued from page 23

Update on Innovative Ultrasound Technologies to Treat Kidney Stones

Burst wave lithotripsy (BWL) and ultrasonic propulsion are promising ultrasound technologies being developed as rapidly as possible with funding from NIH NIDDK Program Project grant DK043881 and NASA. The goal is to create an instrument, similar to an ultrasound imager, with a hand-held probe to image, break and reposition stones in awake subjects in the office or clinic to facilitate clearance of the stones and fragments. This is an update on status.

Over 30 participants have been treated with BWL in a number of trials at various sites despite the necessary interruptions caused by the pandemic. Those studies are ongoing; however, the results of the very first 2 cases of BWL have been recently published. The first participant was treated during ureteroscopy under anesthesia as part of a trial designed to directly observe fragmentation and any papillary injury. The stone was fragmented under 2 mm in 9 minutes. Fragmentation was observed visibly and with real-time ultrasound monitoring, and ultrasonic propulsion was used to clear some of the debris from the calyx. Mild hematuria was observed. The second participant had a 7 mm ureteroscalical junction (UVJ) stone and was treated awake without anesthesia in the clinic. He tolerated the procedure without pain from BWL and later passed the stone. We look to complete these trials in 2021, and are working on a new transducer design to expand the beam width to fragment larger stones (fig. 1). Ultrasound propulsion alone has been used safely in over 70 human volunteers to reposition small stones. In our most recent study, a 3 mm stone was pushed from the UVJ into the bladder and the patient felt immediate relief. Ultrasonic propulsion has been used in vitro to disperse fragments to assess if a stone has been comminuted by BWL. Lastly both BWL and ultrasonic propulsion can enhance the twinkling artifact making stones and fragments more conspicuous for locating and targeting during treatment.

The research group continues to expand research of these technologies to treat pediatric stone formers and individuals with spinal cord injury. We are pursuing efforts to expand research of these technologies to treat pediatric stone formers and fragile populations such as individuals with spinal cord injury as we feel they could potentially be quite valuable.

We have completed our work with NASA. Stones have long been a top risk of long duration space flight as over 30 stone events have occurred within 2 years of space flight and one cosmonaut reported passing a stone in space. As such, NASA has helped fund our research, and our technology has now been implemented into the NASA 1 Flexible Ultrasound Unit. The results of our research have contributed to a recommendation from NASA leadership to its Human System Risk Board to reduce the risk level of the renal stone risk in space flight.

Both BWL and ultrasonic propulsion were exclusively licensed from the University of Washington to SonoMotion, Inc., for commercialization. SonoMotion is working towards regulatory approval of a single platform that will provide ultrasonic propulsion and BWL capabilities, which will be called Stone Clear and Break Wave, respectively.

We appreciate all the support we have received from the urology community and continue to work to get these innovative technologies into the hands of practicing urologists.

What’s New in Intraoperative Imaging: A 2021 Update

Kidney

At last year’s annual meeting of the American Urological Association, Samiei et al described an innovative imaging technique for intraoperative renal tumor detection with the capability of predicting pathological type. They developed a noninvasive intraoperative molecular chemical imaging (MCI) device that utilizes molecular spectroscopy and digital imaging. This device uses machine learning and computer vision strategies, and is able to differentiate malignant from surrounding benign tissue. In this study of 22 patients, the MCI device had 93.5% accuracy in identifying tumor from non-tumor tissue.

Additionally, Sentell et al studied the role of indocyanine green (ICG) dye with near-infrared fluorescence (NIRF) imaging in differentiating renal tumors from normal surrounding renal parenchyma during robot-assisted partial nephrectomy. The authors evaluated a total of 330 tumors, and the overall rate of successful differential fluorescence (fluorescence of normal parenchyma in the absence of tumor fluorescence) was 87.3%. However, the differential fluorescence varied significantly by tumor histology; it was 100% for cystic and benign lesions, 90% for renal cell carcinomas and 72% for oncocytomas.

Prostate

The main goal of radical prostatectomy (RP) is to offer complete treatment outside the operating room. Exciting advances with intraoperative imaging will similarly guide surgeons to improve their surgical care in the future. We briefly highlight key advances in intraoperative imaging with prostate, kidney and bladder cancer.

Bladder

In the past few years, there has been growing interest in using deep learning for nonmuscle invasive bladder cancer (NMIBC). NMIBC accounts for 75% of newly diagnosed bladder cancer and is characterized by high recurrence rates that require frequent endoscopic procedures. The frequent recurrence of NMIBC has been associated with incomplete resection of the previously diagnosed lesion(s). Shkolyar et al utilized deep learning and constructed an image analysis platform that detects bladder tumor during white light cystoscopy. This technique of “augmented” cystoscopy demonstrated a 91% sensitivity for bladder tumor identification. While deep learning is not yet being used in daily clinical practice, similar techniques have the potential to improve bladder resection practices among providers and facilitate diagnostic decision-making. Thus, this could lead to better resections and decrease the rate of NMIBC recurrence.

A different approach to improving bladder tumor resection is endoscopic molecular imaging (EMI). The goal of EMI is to provide real-time dynamic imaging during bladder resections and help urologists identify the tumor boundaries accurately. A variety of molecular tracers, including antibodies, protein scaffolds, peptides and small molecules, have been assessed in preclinical studies with promising results. The sensitivity and specificity of bladder cancer detection were 85% to 90%, and clear surgical margins were provided in xenograft studies. The major limitation of molecular imaging is the need to administer the cancer-specific tracer and be equipped with a paired detection medical device. Thus, this new imaging technology could serve as a supporting tool that enhances the surgeon’s visualization of the tumor during white light cystoscopy, although clinical trials are still lacking.

The intraoperative imaging armamentarium of surgeons continues to evolve rapidly. We have briefly discussed the most recent and promising imaging advances that will likely infiltrate daily practice in the coming years.


How many calls in the middle of the night do we get for asymptomatic patients with a spike in blood pressure (BP)? How many acute doses of medications do we order to treat the call rather than treating the patient? How often do we raise the dose of an existing antihypertensive based on 1 call? I was skeptical about this decades ago as an intern, and now finally we have a proper study.

The authors wanted to characterize clinician response to BP in the hospital and at discharge and to compare short-term and long-term outcomes associated with antihypertensive treatment intensification. All adults admitted to a medicine service in 2017 were evaluated for inclusion. Patients with cardiovascular diagnoses were excluded. Demographic and BP characteristics were used for propensity matching. The association between acute hypertension treatment and subsequent patient acute kidney injury, myocardial injury and stroke was measured. Postdischarge outcomes included stroke and myocardial infarction within 30 days and BP control up to 1 year.

Among 22,834 adults hospitalized for noncardiovascular diagnoses, 17,821 (78%) had at least 1 hypertensive BP recorded during their admission. Of these patients, 5,904 (33.1%) were treated. A total of 8,692 of 106,097 cases (8.2%) of hypertensive systolic BPs were treated. Of these, 5,747 (66%) were treated with oral medications. In a propensity matched sample controlling for patient and BP characteristics, treated patients had higher rates of subsequent acute kidney injury (466 of 4,520 [10.3%] vs 357 of 4,520 [7.9%]; p<0.001) and myocardial injury (53 of 4,520 [1.2%] vs 26 of 4,520 [0.6%; p=0.003]. There was no BP interval in which treated patients had better outcomes than untreated patients. A total of 1,645 of 17,821 patients (9%) with hypertension were discharged with an intensified antihypertensive regimen. Medication intensification at discharge was not associated with better BP control in the following year.

The authors conclude that in this cohort study, hypertension was common among medical inpatients, but antihypertensive treatment intensification was not. Intensification of therapy without signs of end-organ damage was associated with worse outcomes.


Negative clinical trials are vitally important to be published for all the obvious reasons including preventing unnecessary duplication of effort and bias towards small positive studies that might have been negative if adequately powered. Are we making progress against this bias? The authors’ goal was to assess rates of positive publications within the urological literature, comparing the years 2012 and 2017. All studies published in The Journal of Urology, Neurourology and Urodynamics, Urologic Oncology, Journal of Endourology and Urology in 2012 and 2017 were reviewed. The primary study outcome was proportion of positive studies. Additional article characteristics, including associated citations and subspecialty focus, were recorded and statistical analyses used to assess for differences in negative publication rates were based on these variables.

A total of 1,796 articles meeting inclusion criteria were analyzed. The overall proportion of positive studies decreased in comparison of 2012 and 2017 (90% to 86%, p=0.01). A statistically significant decrease was seen in 2 of 5 journals: Neurourology and Urodynamics (97% to 87%, p=0.01) and Journal of Endourology (93% to 83%, p <0.01). There were no significant differences in associated citations for positive vs negative studies in either year. Logistic regression focused on year and journal revealed that studies published in 2017 and Urology were more likely to be negative.

The authors conclude that the vast majority of studies within the urological literature are positive, with only a small increase in negative study publication comparing 2012 vs 2017. Continued efforts are needed to identify publication bias and promote dissemination of negative research findings.


Moving from content to gender, do articles in the current urological literature reflect current gender proportions among trainees and staff? The authors wished to describe the proportions of peer reviewed manuscripts authored by women in 5 high impact, widely available urology journals, and to compare these to the proportion of women in urology. About 9% of attending urologists and 25% of urology residents are women. They hypothesized that women comprised fewer than 25% of first authors and fewer than 10% of last/senior authors.

They searched peer reviewed original manuscripts in The Journal of Urology, Journal of Pediatric Urology, Neurourology and Urodynamics, Urology and Urologic Oncology from January 2014 to June 2019. First and last author gender identity was recorded. Observed and expected proportions and temporal trends were compared. Of 8,653 multiple author papers, 2,275 (26.3%) had women as first authors, paralleling the current proportion of women in training. Women were senior/last authors in 1,255 (14.5%) papers; this was higher than the current proportion of female urologists in practice (p <0.0001) for all journals but Neurourology and Urodynamics (p=0.59). Only 527 (6.1%) of multiple author papers had both female first and last authors, whereas 5,640 (65.3%) of papers had both male first and last authors. The first author was more likely female when the senior author was female (OR 2.34, 95% CI 2.06–2.65); most female first and last authored manuscripts were published in subspecialty journals and those utilizing double blind peer review.

The authors conclude that the proportion of female first and senior authored manuscripts is significantly higher than the proportion of women in urology and may reflect differential subspecialty choices and mentorship opportunities for women.
FROM THE  Urology Care Foundation

National Kidney Month and
YOUR Urology Care Foundation: Educating Patients and Supporting Research

Harris M. Nagler, MD, FACS
President, Urology Care Foundation
New York, New York

Did you know March is National Kidney Month? Many of us take our kidneys for granted. After all, they do what they should do, until they do not, or until something happens—a stone, tumor etc. This time of year, the Urology Care Foundation brings kidney health education to the top of our patients’ attention through robust patient education efforts. These include patient-focused Web articles, fact sheets, podcasts and videos.

Some of our most popular kidney health resources from the past year include:
• Living Healthy: Fight Kidney Stones with Food Cookbook (https://urologyhealth.org/educational-materials/kidney-cookbook)
• Kidney Cancer patient guide
• “What is a Renal Mass?” educational video
• Several kidney health podcasts

In addition to educating patients about their kidney health, the Foundation has funded several investigators focused on driving lasting improvements in the lives of patients facing kidney issues. I’d like to celebrate 3 of these bright investigators and share with you some highlights of their work:

Vijaya Vemulakonda, MD—Dr. Vemulakonda specializes in treating pediatric urological conditions, and one of her primary research interests is finding better ways to treat infants born with ureteropelvic junction (UPJ) obstruction. UPJ obstruction occurs when there is a blockage in the patient’s ureter where it joins the kidney, which restricts the flow of urine and can lead to swelling of the kidney.

With the combined support of a Foundation Rising Stars in Urology Research Award and an Agency for Healthcare Research and Quality (AHRQ) Career Development Award, Dr. Vemulakonda is exploring how different factors influence treatment variations in infants with suspected UPJ obstruction.

Benjamin K. Canales, MD—With support provided by a Foundation Rising Stars in Urology Research Award, Dr. Canales worked with a team at the University of Florida to create a model of enteric hyperoxaluria to better understand the development of urinary stones in humans and find a cure. Their collaborative efforts ultimately discovered that the gut bacteria Oxalobacter formigenes could bring urine oxalate back down to a normal level, thereby reducing the incidence of kidney stone formation.

Dirk Lange, PhD—Dr. Lange is a 2013 Urology Care Foundation Research Scholar and is now the Director of Basic Science Research at the Stone Centre at Vancouver General Hospital, where he has developed a research program to improve the lives of patients suffering from kidney stone disease. More than 80% of patients with indwelling stents complain of severe pain and discomfort, resulting in stents being removed too soon and putting the patient at risk for complications due to obstruction. Dr. Lange is working to address this issue by exploring how the ureter responds to indwelling stents.

Looking Forward

Despite an increasingly competitive and difficult funding environment, we know the future is bright for kidney health research, thanks to you. With strong allies supporting our research and patient education missions every step of the way, our commitment to this work simply does not waver.

Our commitments to kidney health research and urological health overall remain at the forefront of research because of you. Learn more by visiting UrologyHealth.org/Donate today. We hope you are equally committed and willing to support these efforts.

Congratulations to our 2021 AUA Award Winners!

The AUA Awards recognize top urologists and honor their service to the specialty of urology and the Association. We have the honor and privilege to recognize and celebrate physician researchers and educators for their contributions each year at the AUA Annual Meeting. This September in Las Vegas, Nevada, we will recognize a broad slate of distinguished individuals for their achievements. The following awards will be presented.

Ramon Guiteras Award: The Ramon Guiteras Award is presented annually to an individual for outstanding contributions to the art and science of urology. Ian M. Thompson, Jr., MD will receive this award for outstanding leadership and contributions in clinical trials and treatment of urological cancers.

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. Yves Fradet, MD will receive this award for outstanding mentorship, research, leadership and exemplary surgical care of patients with urological cancers.

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. Stacy Loeb, MD, PhD, MSc will receive this award for outstanding research to enhance the value of prostate cancer screening and active surveillance.

Lifetime Achievement Award: The Lifetime Achievement Award is presented annually to an individual for outstanding contributions to advance the mission and goals of the AUA. Ronald Rabinowitz, MD will receive this award for advancing the mission of the AUA by promoting education, research and advocacy.

Robert C. Flanigan Education Award: The Robert C. Flanigan Education Award is presented annually to an individual who has made exemplary contributions to the educational goals of the AUA. Tracy L. Krupski, MD will receive this award for fostering evidence-based decision making in urology and outstanding commitment to resident and medical student education.

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. Mary Ann Lynn Stothers, MD, MHSc will receive this award for excellence in advancing innovative methods for treating urinary incontinence throughout the world.

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. John L. Phillips, MD will receive this award for decades of outstanding writings, cataloging urological history and innovative use of history to educate residents.

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, for military career service or for humanitarian efforts. The following individuals will be recognized with this award:

- Michael J. Droller, MD for critical contributions to the understanding of the biology and pathogenesis of bladder cancer
- Peter A. Pinto, MD for unique and significant contributions involving novel methods for diagnosing prostate cancer
- Fred Saad, MD for numerous significant contributions to the study and understanding of advanced prostate cancer

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:

- Christopher M. Gonzalez, MD, MBA for outstanding service as AUA Public Policy Chair and launching the Annual Urology Advocacy Summit and AUAPAC
- Kevin Pranikoff, MD for dedicated service on AUA committees for 3 decades, and contributions to the Board as the Northeastern Section Representative
- Roger E. Schultz, MD for dedicated service on AUA committees for 2 decades, and contributions to the Board as the Mid-Atlantic Section Representative

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. 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. AUA continues this tradition by presenting this award to Sanford J. Siegel, MD for tireless efforts to improve urology practice and support prostate cancer research and awareness.

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 on the following individuals:

- Peter E. Clark, MD for significant contributions to the urological care of patients as Practice Guidelines Chair
- Jeffrey M. Frankel, MD for tireless support and diplomatic advocacy for high quality private practice care within organized medicine
- Marguerite C. Lippert, MD for committed contributions to the success of women in urology and the education of urologists
- Isaac J. Powell, MD for outstanding contributions regarding the biology, genetics and environmental impact of prostate cancer in Black men
- Michael L. Ritchey, MD for outstanding contributions to pediatric urological oncology, and leadership with ABU and ABMS supporting urological certification
- Norm D. Smith, MD for leadership in advocacy for fair and accurate relative value scale payments of physician services
- Celeste Alston for advancing collaborations between the Japanese Urological Association and the AUA to improve urological education
- Miguel Angel Costa for advancing collaborations between the Sociedad Argentina de Urología and the AUA to improve urological education
- Yoshihiko Tomita for advancing collaborations between the Japanese Urological Association and the AUA to improve urological education

All award winners will be recognized during the AUA Awards Dinner in September. Please join me in congratulating all of our award winners for their contributions to the specialty of urology! For more information on the upcoming meeting, visit AUA2021.org.
FROM THE
Chief Executive Officer

Build Your Network (Hint: The AUA Can Help!)

Michael T. Sheppard, CPA, CAE
Linthicum, Maryland

A strong professional network can have a vast impact on career longevity, success and new business opportunities. While professional networking can often be associated with job seeking, its benefits are numerous and include information exchange, valuable suggestions and guidance, and even lasting friendships. With a strong network, you have trusted resources and direction for professional growth at your fingertips.

Here are some tips on how to build your network:

• **Identify people with the same interests.** It is easy to connect with people when you have a common passion or goal.

• **Leverage your network’s connections.** As you build your network, take advantage of already formed contacts to expand your own.

• **Help out new connections.** When you can offer advice or guidance to help a new connection learn something new or solve a problem without expecting anything in return, they are more likely to return the favor.

• **Take advantage of networking events.** Whether they are in-person or virtual, networking events are an easy way to meet new people and collaborate to start building a network.

• **Follow up with the people you meet.** After a networking event, send a personalized message to solidify your new connection.

• **Make it a win/win partnership.** It is important when building your network to ensure both parties feel like they are gaining something and not being taken advantage of.

• **Get social.** Join conversations happening on social media to build your network and online presence.

We know how important it is to build a network, so the AUA has a variety of opportunities for our members to do so.

Here are some ways the AUA can help:

• **Attend the AUA Annual Meeting.** The AUA Annual Meeting is one of the largest gatherings of urologists in the world and the perfect opportunity to network with people from across the globe. Learn more about opportunities at AUA2021.org.

• **Participate in communities.** The AUA has many online communities for its members based on their career path. These include the Practice Managers’ Network and the Young Urologists Committee, where you can participate in discussions and connect over commonalities. Explore our communities at community.auanet.org.

• **Volunteer with the AUA.** Every year the AUA sends out a call for volunteers for its various committees and councils. Volunteer to join a committee or council you’re interested in and meet like-minded people. Browse our volunteer opportunities at AUAnet.org/volunteer.

• **Connect with attendees at other AUA events.** Start conversations when you’re at an AUA educational course or meeting to take the first steps in building your network.

Networking is about building, growing and nurturing relationships. Take advantage of the opportunities provided by the AUA to build your network and advance your urological career.

FROM THE
AUA Education Council

Final Words

Victor W. Nitti, MD
Chair, AUA Education Council
Los Angeles, California

It’s hard to believe that it has been almost 6 years since I started in the position of Chair of the AUA’s Education Council on June 1, 2015. The time has gone by so quickly, and I truly hope that during the last 6 years we were able to provide our members, urologists and urology care providers with unique and practical learning experiences. We tried hard to stay abreast of changes in learning styles and offer new programs while continuing to offer those activities that have been tried and true over the years. In the past year, the Office of Education (OE) staff did an incredible job of adapting to our virtual reality and offering almost every single planned activity in 2020.

Our YouTube channel and podcast downloads exploded as our members became more dependent on multimedia learning.

All of the things that we accomplished would not have been possible without the support of AUA leadership. I want to thank the AUA Board of Directors and AUA CEO Mike Sheppard for supporting our initiatives and placing their confidence in the OE team. I have had the opportunity to work closely with 2 AUA Secretaries, Drs. Manoj Monga and John Denstedt, in the planning of 6 annual meetings and cannot think of 2 more insightful colleagues to have shared this task with.

I am extremely grateful to the entire OE team for their tremendous work during my tenure. I think it is important that you all know the people who deliver our OE products to you. The OE staff is led by its director Shelby Englert, who began in that position just after I started as Chair. She has made the OE a model of efficiency and teamwork. Patrick Kerley is the Education Manager for e-learning. He and his team are responsible for all of your e-learning on the AUA University—a daunting task that they all handle so well. Helen Scofield is the Education Manager for programs. Helen and her team of coordinators run all of our courses and webinars. Many of you have commented to me what a great job they do, Jody Donaldson is the Education Manager for Governance and Accreditation. She runs all of our Education Council Committees and Work Groups, looks after COI and makes sure that our activities meet ACCME standards for accreditation and CME credit. She is one of the most organized people I have ever worked with. Finally, Janet Skorepa, AUA’s Executive Vice President for Education, oversees the entire educational mission of the AUA and assures that we deliver what our members require. They have all become my AUA family, and I will miss working with them.

I have always believed that the AUA was made up of people who are incredibly generous with their time and resources and extremely dedicated to teaching and sharing information with their colleagues. The past 6 years has not only confirmed, but strengthened this belief. Almost everything we do at the OE is predicated on volunteerism. I am so thankful to all of you who have selflessly given your time and energy, sometimes on a moment’s notice, to ensure the success of our programs. I also want to thank the countless AUA members who have offered suggestions, encouragement and thoughtful criticism to make us better. It is because of you that our organization is as great as it is. We have outstanding leadership at the AUA, but at the end of the day an organization is only as strong as its members.

It has been an honor for me to serve as Chair of the AUA Education Council. I will always be grateful to the AUA for the opportunity that was given to me. It is my pleasure to pass the torch to Dr. Jay Raman on June 1, 2021. I am excited to see, and take advantage of, all of the programs that Jay and the team will have for us in the upcoming years.
INDICATION
LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS
Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in <1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The duration of therapy in patients who developed secondary MDS/AML varied from <6 months to >2 years. All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy, and some also had a history of more than one primary malignancy or of bone marrow dysplasia.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (<Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Occurred in <1% of patients exposed to LYNPARZA, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment.

Females
Advertise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

Males
Advertise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

Venous Thromboembolic Events: Including pulmonary embolism, occurred in 7% of patients with metastatic castration-resistant prostate cancer who received LYNPARZA plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study. Patients receiving LYNPARZA and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

ADVERSE REACTIONS—HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer
Most common adverse reactions (Grades 1-4) in ≥10% of patients in clinical trials of LYNPARZA for PROfound were: anemia (46%), fatigue (including asthenia) (41%), nausea (41%), decreased appetite (30%), diarrhea (21%), vomiting (18%), thrombocytopenia (12%), cough (11%), and dyspnea (10%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA for PROfound were: decrease in hemoglobin (98%), decrease in lymphocytes (62%), decrease in leukocytes (53%), and decrease in absolute neutrophil count (34%).

DRUG INTERACTIONS
Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

USE IN SPECIFIC POPULATIONS
Lactation: No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.
**PROfound: A PHASE 3 trial of a PARPi in mCRPC**

**TRIAL DESIGN**
- The PROfound trial was a prospective, multicenter, randomized, open-label, phase 3 trial of LYNPARZA in patients with HRm mCRPC.
- Key eligibility criteria: Metastatic castration-resistant prostate cancer; progression on prior enzalutamide or abiraterone treatment for metastatic prostate cancer and/or CRPC; a tumor mutation in at least 1 of 15 genes involved in the HRR pathway.
- Patients were divided by mutation: BRCA1/2 or ATM gene mutation (Cohort A [n=245]) and other HRR gene mutations (Cohort B [n=142]).
- Each cohort was randomized 2:1 to receive LYNPARZA (tablets, 300 mg per dose, twice daily) or an active comparator (retreatment with investigator’s choice of enzalutamide or abiraterone).

**IMPORTANT SAFETY INFORMATION (CONT’D)**

**USE IN SPECIFIC POPULATIONS (CONT’D)**

**Hepatic Impairment:** No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

**Renal Impairment:** No dosage modification is recommended in patients with mild renal impairment (CrCl 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CrCl 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CrCl ≤30 mL/min).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

- **rPFS in Cohort A was determined by BICR using RECIST version 1.1 and PCWG3 (bone) criteria.**
- **Consistent results were observed in exploratory analyses of rPFS:**
  - For patients who received or did not receive prior taxane therapy
  - For those with germline BRCA mutations identified using the Myriad BRACanalysis CDx assay compared with those with BRCA mutations identified using the Foundation Medicine FTCdx assay

The PROfound study included additional secondary endpoints not present here.

**EXPLORIE THE DATA, including secondary endpoints, and testing recommendations at LYNPARZAAprchcp.com**

**IMPROVED OS IN METASTATIC PROSTATE CANCER**

**5.7 MONTHS**


**Zejula® (niraparib) [prescribing information]. Waltham, MA: Takeda Pharmaceuticals North America, Inc.; 2020.**

**Talzenna® (talazoparib) [prescribing information]. New York, NY: Pfizer Inc.; 2020.**

**REFERENCES:**

**PRIMARY ENDPOINT: RADIOLoGICAL PROGRESSiON-FREE SURvIVAL (rPFS)**

**>2X rPFS**

**66% relative risk reduction of disease progression or death**

HR=0.34, 95% CI: 0.25–0.47, P<0.0001

**REFERENCES:**
LYNPARZA® (olaparib) tablets, for oral use

Initial U.S. Approval: 2014
Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE
LYNPARZA is indicated for the treatment of adult patients with deleterious or suspected deleterious BRCA1 or BRCA2 mutation-associated germline or somatic metastatic ovarian, fallopian tube, or peritoneal carcinoma who have failed to respond to prior platinum-based chemotherapy. LYNPARZA is also indicated for the treatment of adult patients with metastatic castration-resistant prostate cancer who have progression on or following chemo-taxane therapy. LYNPARZA is indicated for the treatment of adult patients with metastatic breast cancer who have mutations in the PI3K pathway and who have progressed following prior endocrine therapy. LYNPARZA is indicated for the treatment of adult patients with germline or somatic metastatic breast cancer with the D716_717_Del13_Fundamental_His_His_Thr_Pro_1006_Phe mutations. LYNPARZA is indicated for the treatment of adult patients with advanced solid tumors harboring deleterious or suspected deleterious BRCA1 or BRCA2 mutations. LYNPARZA is indicated for the treatment of adult patients with non-small cell lung cancer who have a germline or somatic deleterious BRCA1 or BRCA2 mutation and whose tumors harbor gBRCA1-mut, gBRCA2-m, or gPALB2-m.

CONTRAINDICATIONS
Use contraceptive during treatment and for 6 months following the last dose of LYNPARZA. Pregnant women should have a negative pregnancy test before starting LYNPARZA. Women who become pregnant while receiving LYNPARZA should discontinue therapy and undergo diagnostic evaluation. Pregnancy testing should be performed in a non-breastfeeding woman before treatment with LYNPARZA. Avoid coadministration of strong or moderate CYP3A inducers. Avoid concomitant use of strong or moderate CYP3A inhibitors with LYNPARZA. In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA. Patients with severe renal impairment or end-stage disease (CLcr ≤ 30 mL/min) are not recommended to receive LYNPARZA. LYNPARZA is contraindicated in patients with known hypersensitivity to olaparib or any component of LYNPARZA. LYNPARZA is contraindicated in patients with active lymphocytopenia (lymphocytes < 1000 cells/mm3). LYNPARZA is contraindicated in patients with active venous, arterial, or capillary thromboembolic disease. LYNPARZA is contraindicated in patients with a history of a second primary malignancy within 5 years of the diagnosis of a malignancy. LYNPARZA use is contraindicated in men who have not undergone castration.

WARNINGS AND PRECAUTIONS
Myelodysplastic Syndrome/Acute Myeloid Leukemia
In clinical studies enrolling 2351 patients with advanced solid tumors who received LYNPARZA tablets 300 mg twice daily for 300 mg twice daily, 55% of patients were aged ≥ 65 years, including 8% aged ≥ 75 years. Of the 2351 patients, 13 (0.5%) patients were aged ≥ 85 years. There were no clinically meaningful differences in the frequency of adverse reactions between patients aged ≥ 65 years and < 65 years. Of the 535 patients with advanced solid tumors who received LYNPARZA tablets 300 mg twice daily for 300 mg twice daily, 65% of patients were aged ≥ 65 years, including 11% aged ≥ 75 years. Of the 535 patients, 19 (3.5%) patients were aged ≥ 85 years. There were no clinically meaningful differences in the frequency of adverse reactions between patients aged ≥ 65 years and < 65 years. Of the 2351 patients with advanced solid tumors who received LYNPARZA tablets 300 mg twice daily for 300 mg twice daily, 55% of patients were aged ≥ 65 years, including 8% aged ≥ 75 years. There were no clinically meaningful differences in the frequency of adverse reactions between patients aged ≥ 65 years and < 65 years. Of the 535 patients with advanced solid tumors who received LYNPARZA tablets 300 mg twice daily for 300 mg twice daily, 65% of patients were aged ≥ 65 years, including 11% aged ≥ 75 years. Of the 535 patients, 19 (3.5%) patients were aged ≥ 85 years. There were no clinically meaningful differences in the frequency of adverse reactions between patients aged ≥ 65 years and < 65 years.
Pediatric Urinary Reconstruction: Lessons Learned over 25 Years

Konrad M. Szymanski, MD, MPH
Rosalia Misseri, MD

Indianapolis, Indiana

It will be soon be 25 years from the time one of us [RM] graduated from medical school. The impetus to pursue a career in urology was directly related to an interest in pediatric urinary reconstruction. It was a fascination with the ability to protect the kidneys while improving bladder dynamics and function, as well as continence and quality of life.

In addition to personal lessons, the specialty as a group has learned much about the long-term outcomes of surgeries performed in children as they grow to become adults. Many factors will affect the longevity of any reconstruction performed in childhood, including surgical technique, progression or evolution of the disease, changes in body habitus and changes in social structures that occur with aging. Independence among children with congenital urological disease varies, family structure and support systems vary, and the ability to care for oneself varies as well. The ultimate goal of any urinary tract reconstruction remains, and will always remain, protecting the kidneys from progressive injury related to bladder dysfunction. In a recent retrospective review of patients with bladder augmentation with a median followup of 11.2 years, we concluded that bladder augmentation is durable but carries long-term risks of reoperation of about 44% at 10 years.1 Interventions for bladder calculi are the most common and comprise more than half of the surgeries. The 10-year risk of perforation, a more concerning and potentially life-threatening complication, is approximately 10%, and a third of those with 1 perforation will re-perforate in the subsequent 10 years. We found the risk to be greatest in those with nondetubularized bowel segments, a technique rarely used in modern times. While we think bladder augmentation has been a reliable technique to care for the hostile bladder, we found the 10-year risk of incontinent diversion to be 3%. This has been related to recurrent perforation and, perhaps in some cases, poor patient selection. Several studies have reported the risk of developing bladder cancer after bladder augmentation, but it has also become apparent that there is an inherent risk of malignancy in the neuropathic bladder even without augmentation. We have learned of criteria for endoscopy of the augmented bladder by Higuchi et al2 and have adopted these to screen for malignancy.

Despite our best efforts, we have learned that there is no optimal technique to address persistent urethral incontinence. Regardless of the technique employed, we are certain of particular needs associated with embarking on the goal of urinary continence when poor outlet resistance is to blame. The patient undergoing bladder neck reconstruction/closure or artificial urinary sphincter placement must be carefully selected. She/he must be motivated, have a strong support structure, including a person who can help troubleshoot at home and a team of health care professionals who can troubleshoot in the clinical setting, and above all must have an excellent and reliable way to empty the bladder. Despite studies suggesting that bladder neck procedures without augmentation are safe and effective in the short term, we have learned that 50% of carefully selected patients with a seemingly adequate bladder on urodynamic evaluation will require bladder augmentation within 10 years of an isolated bladder neck reconstruction or closure.3 Up to 40% of patients developed renal scarring and/or loss of function after bladder augmentation and bladder neck reconstruction in a series of patients followed longitudinally by Husmann.4 It is sobering that 69% of patients had progression of renal disease associated with poor adherence to catheterization schedules.

In addition, introduction of clean intermittent catheterization almost 50 years ago has revolutionized the fields of reconstructive and pediatric urology. The introduction of the Mitrofanoff principle has allowed us to facilitate catheterizations in children and adults. Time has taught us many tricks to avoid the angst associated with the inability to catheterize through a continent catheterizable channel. As children grow and body habitus changes, stomas may become stenotic or hidden, while channels may kink or become traumatized. To avoid these troubles, we have learned to make channels that are as short and straight as possible, and to fix the channel to the anterior abdominal wall. In a retrospective review of more than 500 continent catheterizable channels, we found that channel continence, stomal stenosis and the overall need for stomal revisions were similar for appendicovesicostomies and Monti channels. Ten years after initial surgery, Monti-Yang channels were twice as likely to require a subfascial revision (1 in 6) compared to appendicovesicostomies (1 in 12), while spiral Monti channels to the umbilicus had the highest risk of requiring a subfascial revision (1 in 3).5

Building on the achievements of the pioneers of genitourinary reconstruction, we continue to gain more insights into the long-term results of genitourinary reconstruction. Evaluating clinically meaningful outcomes has allowed us to improve appropriate patient and family counseling and selection, as well as surgical techniques and postoperative care. This particularly includes the absolute need for long-term urological care of adults who underwent genitourinary reconstruction as children; while most complications occur early after surgery, delayed complications can and do occur even after decades in patients who have done well previously.6,7 A critical and honest approach also implies facing the prospect that some of our assumptions may be wrong (teenagers are not at higher risk for problems with catheterizable channels), and we may not be “as good as we think we are” (as many as half of children with spina bifida may be lost to followup transitioning to adulthood); adults do not irrigate their augmented bladders as repeatedly instructed8. We hope that looking at things as they really are, while keeping in mind the aspirations of patients, families and surgeons, will allow us to continue delivering ever more effective and patient-centered care.

It is a truism that rural communities in the United States suffer disproportionately from poor access and poor quality health care. Rural residents consistently rank lower on numerous health indicators compared to their urban counterparts, suggesting the current health system is failing this population. The divide between rural and urban health appears to be impacting prostate cancer care, specifically screening and diagnosis. Work in this area has been pioneered by researchers in Australia and New Zealand, likely due to the sizable population that resides in rural communities. Obertová et al performed a retrospective study of 34,960 patients and found that men in rural practices were 43% less likely to be screened with a prostate specific antigen (PSA) test and were more likely to be diagnosed with high risk cancer and metastatic disease. The impact of rurality on urological cancer care is being further explored in the United States. In 2018 the Centers for Disease Control and Prevention (CDC) reported that prostate cancer incidence was higher in urban areas compared to rural areas, and some hypothesize this may be secondary to reduced screening in rural communities. Using cancer registry data, Holmes et al examined the association between distance to a urologist and delayed prostate cancer diagnosis. The authors discovered that longer distances to a urologist were associated with increased rates of high risk cancer diagnoses. In light of these data, rural communities may suffer more from high risk disease given that only 2.4% of urologists practice in rural communities. Furthermore, of these urologists, half are nearing retirement age, implying that access to care will only continue to dwindle.

Not only are screening and diagnosis negatively impacted by rurality, but definitive treatment of disease appears to be as well. Several studies have recently shown that rural residents have lower rates of definitive treatment for localized urological cancer, even when controlling for clinical parameters, urologist density and sociodemographic factors. In our recent work using cancer registry data, we found that rural patients were less likely to be treated for prostate cancer, even when stratified by disease risk. This implies that patients who could benefit from treatment, such as those with intermediate or high risk disease, were still less likely to be treated if they resided in rural areas. We attempted to understand the reason for this phenomenon by controlling for access to care using urologist density and for socioeconomic factors using area deprivation index. We found that some of the reduced treatment rates were explained by these 2 factors, but not completely, implying there are additional factors inherent to rural residence that we could not account for in our model. Work by Baldwin et al using SEER (Surveillance, Epidemiology, and End Results) data similarly showed reduced rates of definitive treatment in rural patients, although the cohort was largely men with lower risk disease.

While rural residents may be less likely to receive definitive treatment, the type of treatment they receive may also differ from their urban counterparts. It has been extrapolated from the breast cancer literature that the longer the distance to treatment centers, the more rural residents may opt for surgery over radiation, which would require multiple visits to treatment facilities. Muralidhar et al showed that the greater the distance to the radiation treatment facility, the less likely a patient is to receive radiation as a treatment for localized prostate cancer. Treatment differences between urban and rural residents also exist for metastatic disease. Borno et al analyzed state cancer registry data and found that rural residents were more likely to receive surgical castration as opposed to medical castration when compared to urban residents. On the other hand, Cetrar et al used statewide cancer registry data from Wisconsin and did not find any difference in treatment based on rurality of residence or distance to a radiation facility. However, the authors noted that the majority of patients were insured and resided within 15 miles of a hospital, reflecting the state’s strategic infrastructure with easier access to care. This may suggest that with better access, the lower treatment rates found in other studies could be mitigated.

It is conceivable that these differences in diagnosis and treatment may lead to variation in survival. In fact, several systematic reviews concluded that prostate cancer patients had worse survival if they resided in rural areas when examining both international data and data from the United States. However, results of systematic reviews must be interpreted with caution, as comparison of studies of varying design and quality is difficult. These findings were corroborated by the CDC, which used the National Program of Cancer Registries and SEER data to reveal higher rates of prostate cancer mortality in rural counties compared to urban counties.

Several health determinants likely perpetuate this inequality in prostate cancer treatment between rural and urban populations. These include behavioral, socioeconomic, environmental and clinical factors (see figure). The first step to rectifying this disparity is to understand the specific barriers that exist to physicians providing care and patients receiving care. Such barriers likely vary from one region to the next. In our region, we attempted to identify these barriers by interviewing rural providers. Physicians reported that patients experience numerous hardships after being referred to a specialist, as they often have to travel long distances, lack means of transportation, are unwilling to skip work, have low health care literacy and tend to be suspicious of medical treatment. Almost all responders identified lack of access to specialists and lack of transportation as major barriers to receiving care. In fact, numerous interviewees reported patients having to travel over 2 hours to see a specialist including a urologist. Often, making an appointment with a urologist would mean forgoing a day of work, losing wages and eliciting the help of a family member to drive them over 4 hours total for their visit. Therefore, something many may deem as simple, such as keeping a doctor’s appointment, can be exceedingly challenging for others. Policy in our region will need to be directed toward rectifying these specific barriers in order

Figure.
Knowledge Gaps in Congenital Neurogenic Bladder Management

The management of congenital neurogenic bladder (CNB) must strike a balance between appropriate and timely diagnostics and therapeutics in order to prevent significant renal damage without negatively affecting caregivers’ and patients’ quality of life. The development of imaging capability and urodynamic (UDS) assessment over the last 50 years has provided insight into the pathophysiology and pathogenesis of this condition. With the advent of clean intermittent catheterization (CIC) and subsequent progress in pharmacological and surgical management, there has been a noticeable improvement in preserving renal function, continence and independence for patients with CNB. However, there remain several unknowns in the management of CNB. For the purposes of this article, we will examine knowledge gaps in CNB due to spinal dysraphism (also referred to as myelomeningocele and spina bifida), the most common etiology of CNB.

Prenatal testing for open neural tube defects and advances in fetal surgery have allowed repair of spinal cord lesions before birth. Early data from the landmark 2011 Management of Myelomeningocele Study (MOMS) demonstrated the benefits of prenatal (in utero) repair in reducing hindbrain herniation, reducing shunting for hydrocephalus and improving ambulation, although there was no decrease in the need for CIC in the first 30 months of life (52% among prenatal vs 66% among postnatal repairs; RR 0.78, 95% CI 0.57–1.07).1 In addition, parents of patients in the prenatal group reported lower rates of anticholinergic use, and parents reported that 18 children (24%) in the prenatal group were able to voluntarily void, compared to 3 (4%) in the postnatal group (p <0.001, RR 5.8, 95% CI 1.8–18.7). While these results represent subjective benefits of prenatal closure, there remains the potential for significant bias without demonstration of these benefits on UDS. Additional followup of this cohort is needed to determine the durability and efficacy of prenatal closure at decreasing the morbidity of CNB.

Beyond the prenatal setting, questions remain about the ideal management (expectant vs proactive) of patients with CNB in the early postnatal period. Historically, patients with CNB were observed until renal sequelae or other complications occurred, at which point they received urinary diversion. Expectant management, where the patient is followed with renal ultrasound, interval dimercaptosuccinic acid (DMSA) scans and voiding cystography without baseline urodynamics testing, avoids the use of CIC or pharmacotherapy as long as patients do not demonstrate adverse upper tract or clinical findings. The primary benefit of this approach is to decrease the familial/caregiver burden of CIC. The proactive approach involves scheduled CIC immediately from birth, coupled with early urodynamic assessment and continued CIC when parameters are found to be unfavorable. Early catheterization from birth appears to protect the kidneys.2 Early urodynamics allows for risk stratification and enables early intervention for patients with features that may place them at risk for progressive bladder or renal dysfunction.3 To evaluate this proactive approach, the Urologic Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida (UMPIRE), a prospective iterative quality improvement protocol, was initiated in 2016.4 This study follows a cohort of newborns with spina bifida at 9 U.S. centers and aims to demonstrate that specific scheduled imaging, urodynamics and other measured parameters can maintain normal renal function.

Historically, once patients become refractory to oral anticholinergic therapy and CIC, the only option was augmentation cystoplasty or urinary diversion. While typically successful, this operation is associated with long-term morbidity. To this end, there has been uptake of pharmacological treatments for CNB to preserve renal function and reduce urinary incontinence. Besides muscarinic receptor antagonism, activation of β3 adrenergic receptors on the bladder is the main method of bladder relaxation in humans. Mirabegron, the only β3 agonist in clinical use, is the only agent approved by the U.S. Food and Drug Administration (FDA) for nonneurogenic overactive bladder in adults. However, several recent case series of patients with CNB receiving mirabegron have shown improved urodynamic parameters (increased bladder capacity, decreased end filling detrusor pressure, attenuation of detrusor overactivity) and clinical effects (urinary incontinence resolved in more than 70% of patients).5,6 With limited side effects compared to anticholinergics, β3 agonists warrant further study in patients with CNB as an adjuvant or alternative therapy. OnabotulinumtoxinA intradetrusor injection has also proved to be an effective treatment in refractory neurogenic bladder. While widely used in the pediatric population, it has yet to obtain FDA approval in CNB. Intradetrusor botulinum toxin injection has been shown to improve compliance and capacity on urodynamic studies in patients with CNB.7 Due to its efficacy, intradetrusor botulinum toxin injection could delay or diminish indications to initiate complex reconstructive surgical treatments in some patients. There remain, however, questions regarding its long-term durability and safety in CNB.

Management decisions for patients with CNB are often based on diagnostic tests created and validated in normal people. This can result in significant inaccuracies among people with spina bifida, who may have different body mass composition and are frequently nonambulatory. Chu et al have demonstrated that traditional estimated glomerular filtration rate equations result in substantial variability and overestimation of renal function, particularly among creatinine based equations, in children with spina bifida.8 This has important implications because clinicians may limit interventions and changes in management if renal function is overestimated. These authors recommend cystatin C based equations due to their improved accuracy. Besides renal function, recent work by Dudley et al has shown substantial variability in the interpretation of UDS studies among 14 pediatric urologists interpreting the same set of urodynamic tracings.9 This 7-institution study showed that there was very poor agreement regarding detrusor external sphincter dyssynergia and neurogenic detrusor overactivity, and only moderate agreement with regard to determining the detrusor end filling pressure and if a bladder was safe. This sobering work suggests the need to improve the reliability and reproducibility of UDS studies, which will in turn improve management of children with spina bifida.

There remain several unknowns in the management of CNB throughout the natural history of the condition. With early and long-term data from prospective multicenter cohorts such as MOMS, the National Spina Bifida Patient Registry and UMPIRE, together with continued improvements in disease surveillance and diagnostic testing, we can inform progress in the care of these patients that will allow them to live longer and improve their quality of life.10


Continued on page 43
Clinical Trials: Bridging the Gap Between Knowledge and Practical Use

Unlike any other time in history, in the last year the world has gained an appreciation for well-conducted and timely clinical trials. In less than 38 weeks, shorter than the gestation period for a fetus, basic science knowledge transformed to generate COVID-19 vaccines that were distributed to patients globally. However, biopharmaceutical products are rarely brought to the market with such rapidity. According to the American Cancer Society, oncologic agents have a 1 to 1,000 ratio of success of being brought forward for evaluations in clinical trials. On average, each viable drug is studied for at least 6 years before initiation of clinical trials.

We have benefited from rigorously conducted clinical trials. For example, age-adjusted death rates in the United States have decreased by 50% from the 1980s to the 2000s because of investments in basic and clinical research. The Salk polio vaccine, which included over 600,000 school children, was the building block that led to near-eradication of the disease in the U.S.

Often, the unsung heroes in clinical trials are the study participants who take a chance and entrust their health to their providers to answer clinically significant questions, which may or may not be beneficial for generations of patients to follow.

To advance our field, the AUA Office of Research recognizes that urologists, both those in community and academic practices, need to be appropriately equipped to ask relevant questions, design appropriate studies and participate in clinical trials in order to move our field forward. Recognizing that the majority of urologists, whether in community or academic practices, may not have the knowledge or interest to initiate or participate in clinical trials, the Office of Research in collaboration with Duke University (Drs. Charles Scales and Steven Grambow) is designing a clinical trials workshop hopefully to be carried out in-person during summer of 2021. Led by Dr. Claus Roehrborn as the program chair, we are developing a robust 2.5-day workshop designed to educate our community about conducting clinical trials across the spectrum of urological diseases and conditions.

With preworkshop study material, we plan to deliver an impactful series of interactive content that will educate our urologists in different specialties with the hopes of translating the skills and knowledge to improved patient care.◆

Differences in Prostate Cancer Treatment in Rural vs Urban Settings

◆ Continued from page 40

to begin to improve care for our rural patients.

There is no doubt that the divide between rural and urban health is growing. This disparity seems to have impacted prostate cancer care, possibly resulting in reduced screening and delayed diagnosis. Even after diagnosis, rural patients likely continue to experience hardships, as they seem to receive differential treatment and sometimes no treatment at all. This may eventually lead to increased cancer mortality. As physicians, the onus remains on us to identify the hardships our patients face in receiving care, particularly for the population that resides in rural areas. Only when we identify these barriers can we begin to enact policy to remove them.◆


We Don’t Have to Defend Our Fees

Neil H. Baum, MD
New Orleans, Louisiana

“I’ve done made a deal with the devil. The devil is going to give me an air condition place when I go down there, so I won’t put all the fires out.” – Red Adair, 1991

Red Adair, the famed oil fire fighter, was called to control a massive oil well fire in the Middle East. The fire was causing the loss of several million barrels of oil each day. Red Adair was called to put out the fire, which he successfully did in just a few days. He submitted a bill for $800,012.95. The king was curious about the bill and said that the bill was certainly justified, but he asked why this strange bill including the $12.95? Red Adair said, “The $12.95 was for the cost of the chemicals used, but the $800,000 was for knowing which chemicals to select and the $800,000 was the fee submitted for knowing how to use them!”

What lesson can we learn from this perhaps apocryphal story? We spend 12-plus years after graduating high school to become a urologist. We frequently have 70-plus-hour work weeks. We frequently don’t have dinner with our families. We often are called at night to go to the emergency room. We frequently take phone calls in the evening and on weekends to answer questions from patients and provide service for which we aren’t compensated and yet we are legally responsible for the care. We are at a higher risk for drug and alcohol abuse. We have a higher rate of divorce than the rest of the population, and we have a higher rate of suicide than other professions.

Let’s put this into perspective that our patients will understand. The figure from Authentic Medicine compares the incomes of a UPS truck driver and a physician. A UPS truck driver can go to work after completing high school with an annual salary of $60,000. A pre-med/medical student/resident/fellow will often incur $300,000 of debt prior to starting a practice. The physician will often defer earning a living until age 28 to 30. As a result, it will take a doctor 17 years to earn as much as a UPS truck driver.

Now, please continue reading and hang in there with me, because the next statistic might just shock you. If the UPS truck driver were to work the 70-plus hours a week that a physician commonly does and the truck driver receives time-and-a-half for overtime after 40 hours a week, it would take a whopping 24 years for a physician to equal the salary for a UPS truck driver! Also, throw in that the UPS truck driver is usually home for dinner, doesn’t get awakened during the middle of the night to go out and deliver a package, and is highly unlikely to be named in a lawsuit by someone sending a parcel to another person!

I’m not trying to be maudlin and compare the practice of medicine to a truck driver. As urologists, we are part of the greatest profession on earth. We receive daily gratification from serving others and we hear every day from our patients how terrific we are. I doubt that the UPS truck driver receives those kinds of compliments and accolades after delivering a package.

My bottom line: We don’t have to justify our fees. Let’s be more like Red Adair. A small amount of our fee is for the cost of the medication, but the largest part of our fee is for the decision making for which medication to prescribe and the directions for using the medication. So if anyone ever questions your fees, tell them the story about Red Adair or show him the graph comparing your salary to the UPS truck driver.

Knowledge Gaps in Congenital Neurogenic Bladder Management

Continued from page 41


In part 1 of this article, which appeared in the February issue of AUANews, we reviewed the medical ethics literature and discussed advance directives (ADs). We also introduced the case of an elderly man with dementia who needs consideration for transurethral prostatectomy (TURP) because of urinary retention, representing a clinical case that a general urologist will see on a regular basis. In part 2, we discuss decisional capacity, surrogate decision making, best interest, substituted judgment and informed consent.

**Does the Patient Have the Capacity to Make the Decision for Surgery?**

Autonomous patients’ decisions are intentional, require adequate information, occur volitionally and are rational.1 But what happens if a patient lacks the capacity to make a specific medical decision, such as consenting to surgery? Capacity is the ability to make a specific decision at hand. In the hospital setting, capacity can wax and wane based on age, baseline cognition, situational stress, metabolic derangements, medication influence and delirium. Capacity can exist in a fluid state. The amount of capacity required varies with the level of complexity and risk-benefit ratio of the decision at hand. The level of capacity has to increase with the complexity of the decision that needs to be made (a complexity-risk assessment).2 Any physician can determine capacity; it is a clinical assessment, and not a legal designation.3 A physician should take into account the following factors to assess general capacity: 1) the patient’s awareness of the situation; 2) factual understanding of the issue; 3) appreciation of the consequences; 4) rational manipulation of information; 5) functionality in the environment; and 6) the extent of the demands.2 If this patient does not have the capacity to give consent for a surgical procedure, then a health care representative is necessary. Capacity assessment can be facilitated by published tools, such as the Aid to Capacity Evaluation (ACE).4 The capacity assessment includes the patient’s ability to understand the medical problem, the proposed treatment, the alternatives and the option of refusing the proposed treatment. The patient must be able to foresee the consequences of accepting treatment and the consequences of refusing treatment. Capacity assessments should take into account significant mitigating psychological factors, such as severe depression, delusions and psychosis.

Competence, on the other hand, is a legal concept. A court of law is required to determine competence. A legally incompetent patient would require a legal surrogate or legal guardian designated by the courts.1 A designated power of attorney for health care (HC-POA) is a legally named surrogate who has been chosen by the patient to make decisions when it is deemed that the patient no longer has the capacity to make the decisions for himself or herself. This designation is revocable and is applicable only during periods of incapacity. Individual states have health care representative forms where patients can designate their own representative without the need for an attorney’s involvement. If a patient has no designated health care representative, then a default surrogate decision maker is necessary. The default surrogate hierarchy varies in each state, but the individuals usually include the spouse, parent, adult child/ren and siblings. It would be appropriate to discuss the option of TURP with the power of attorney for health care or designated health care representative. If no surrogate decision makers are identified, the facility can continue to provide emergency care until the hospital can apply to the court for an appointed guardian.

Mr. Jones has a power of attorney for health care, which names his daughter as his health care representative. Mr. Jones does know he is at a physician visit and verbally expresses his dislike of the catheter. He knows the name of his daughter and the day of the week but does not know the date or the name of his facility. He is currently conversant and not agitated. He is able to make eye contact and answer simple questions. He is able to identify “the tube is needed to pee.” The nursing staff need to assist in emptying the catheter bag but he is able to dress himself and feed himself. He notes that his last surgery did not hurt too much, and he is not afraid of surgery again. He cannot remember how long his urination has been an issue other than “a long time.” His daughter states today “is a good day” for him. He does not have the capacity to consent to surgery when judged against the criteria outlined above. When a TURP is brought up, he is familiar with the “roto rooter” procedure. On discussion of the surgery with his daughter, he does reflect that he preferred his life before the catheter. Despite not being able to give consent, he is at least willing to assent to the procedure.

**What Is in the Patient’s Best Interest?**

Three hierarchical modes of decision making generally govern ethical decision making: autonomous decisions (as stated by patients or by ADs), substituted judgment (when a knowledgeable surrogate stands in for a patient) and the best interest standard, which bases decisions on what is thought to be the best thing for the patient under the current circumstances using principles of weighing the balance of risks and benefits.3 The principle of beneficence is a foundational moral imperative of doing right.4 A best interest standard is one that bases the decision for an intervention on what is thought to be the best thing for that patient.5 In order to assess what is right for this patient, an analysis of the risks and benefits of surgery vs a chronic catheter needs to be undertaken. Part of the process of consideration of the patient’s best interest includes attempting to maximize his ability to be part of the surgery discussion. For example one can discuss with involved family or surrogates whether in the past he has had any discussions with them stating his wishes and preferences about similar decisions when he did have the capacity. What does the daughter feel his hypothetical choice would be if presented with the current decision?6 What would this patient want if he could make the decision for himself? Exploring previous statements allows the use of a substituted judgment standard for decision making. Autonomous decisions and substituted judgment are preferred methods for decision making. The best interest standard is used as a type of “last resort” as studies have previously found that the hypothetical decisions of patients and surrogates around decisions correlate imperfectly, ie about two-thirds of the time.8

**What Is Involved in an Informed Consent Process?**

The informed consent process requires expression and reception and understanding of the risks, benefits and alternatives of an intervention. The patient or health care representative needs to comprehend and explain back in their own words what has been discussed with them. It is important to understand the facts presented, appreciate the possible consequences, manipulate the information provided and indicate choice.2 According to the American Urological Association’s Code of Ethics, the “information provided must include known risks and benefits, costs, reasonable expectations and possible complications, available alternative treatments and their cost, as well as the identification of other medical personnel who will be participating directly in the care delivery.”9 The “impetus for the law of informed consent was the argument that doctors could not make decisions for patients because they did not know patients’ beliefs.”10 Our society has moved away from a paternalistic approach and has shifted decision making to align with patient autonomy.

The risks of a long-term catheter include urethral trauma, recurrent urinary tract infection, sepsis, catheter malfunction, need for repetitive changes, tripping over the catheter and glans erosion. The benefit of a long-term catheter is that there is no need for a surgical procedure. The patient has failed maximal medical therapy. Transurethral procedures include UroLift®, microwave...
SPOTLIGHT on Europe, Middle East, Africa

Uncertainty and Opportunity in 2020

As for everyone, 2020 affected specific programs and planned gatherings for countries and regional societies in Europe, the Middle East and Africa. But I am happy to report that the AUA’s international relationships have remained and perhaps even strengthened during these times, underscored by the more than 1,000 new International and International Resident members who joined the AUA last year. As the Assistant Secretary, I work with the AUA International Programs team to identify new opportunities and collaborations with various national and multinational urological societies, and work to enhance relationships with partners throughout Europe, the Middle East and Africa.

International Education Programs

We were able to continue to have virtual forms of our various AUA educational programs, including Lessons in Urology (resident review courses) and Fundamentals in Urology courses (basic sciences), licensed Best of AUA programs, post-graduate courses, and joint symposia with dozens of our international society partners. Our successful Summer School program in Italy continued successfully via a virtual format with live interaction between prominent AUA faculty and selected residents from all of Italy’s programs. While this year forced an unfortunate abandonment of in-person programming, the AUA saw extraordinary participation and engagement in its online programming, both domestically and internationally. Its 2-day AUA Live event welcomed more than 300 attendees from Europe, the Middle East and African countries, and AUA University, the AUA’s online education platform, saw overall user visits increase by 71% in 2020. Visits from European, Middle Eastern and African countries more than doubled! Despite the challenges that limited us this year, these numbers speak to the global community’s continued commitment to education and the patients they serve.

Academic Exchange Programs

I’m pleased to share that we have established a new visiting scholar program with France (Association Française d’Urologie [AFU]) for 2021 and we are in our fourth year of a program with Germany [Deutsche Gesellschaft für Urologie [DGU]]. Our Academic Exchange Programs allow young academic urologists to benefit from the sharing of knowledge and experiences with colleagues around the world. The programs include a 2- to 4-week educational experience at an academic center, and attendance at an international urology meeting. During the exchange, the participants observe urological surgeries/procedures, attend clinics, present lectures and take part in staff activities. These programs foster a closer alliance between the AUA and our international partners, and assist in identifying future leaders within the global urological community.

Innovation and Involvement

We have emphasized to the international community the continued enhancements of AUA University, including online education in multiple languages and other membership benefits for use by the global urological community. In addition, we are utilizing the data we have gathered from educational needs assessments and sharing with our international partners key findings specific to their region and country. Our Office of Education and International Programs teams are continually evolving with the rapidly changing landscape to meet our international learners where they are. Importantly, under Secretary Denstedt’s leadership we have worked closely with our international partners to identify and recommend qualified international members to serve on various AUA committees and to participate in the AUA annual meeting as speakers, moderators, and abstract reviewers. The challenges of 2020 have proven that no matter the circumstances, AUA will listen closely to the needs of our international partners and will continue to provide membership and educational value for the global community.

AUA looks forward to continuing to serve as your partner and go-to resource for urological education, programs and more as we navigate 2021 and beyond. If you have not yet renewed your 2021 AUA membership, visit AUANet.org/renew to ensure uninterrupted access and another year of the most valuable benefits package in urology.

Ethical Decision Making in Urology

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therapy, laser prostatectomy and TURP (gold standard). The risks of TURP would include stress incontinence, bladder neck contracture, impact on sexual function, bleeding and need for transfusion, infection, urethral stricture and continued inability to void secondary to bladder decompensation. The anesthetic risks can include worsening of clinical dementia, and cardiac, pulmonary and thromboembolic events. Based on previously determined goals of care and what is in his best interest, the patient declares he does not want to live with the catheter and is willing to assent to the surgical procedure. His health care power of attorney is in agreement with his declarations based on previously expressed oral statements. These are consistent with his living will, suggesting that even in a persistent vegetative state, he would want life-sustaining treatments. His daughter consents on his behalf for the TURP without reservations.

Conclusion

In this case presentation and literature review, we analyzed the ethical framework that urologists need to explain the processes they are already undertaking on a daily basis. In this brief and common case, the topics of advance directives, decision capacity, surrogate decision making, best interest, substituted judgment and informed consent can arise. There is a paucity of literature addressing ethics in the field of urology. This is a call to action for the field to realize that there are complicated ethical scenarios, some of which are unique to urology, that need to be presented and discussed as part of the larger ethical discourse.

FROM THE Residence and Fellows Committee

Growth Opportunities for the Urologist in the American College of Surgeons

Over the last 4.5 years I have been honored to serve as a Liaison to the American College of Surgeons (ACS) Advisory Council for Urology. Involvement in the ACS allows the urologist or rising urological trainee the opportunity to learn, advocate, engage and network beyond the sphere of organized urology. There are also robust opportunities aimed at medical students, with many resources available to assist in pursuing a career in surgery. The American Urological Association and the American College of Surgeons have partnered together for decades in support of numerous surgical initiatives, and I am proud to be involved in both.

My path to engagement in the American College of Surgeons began, like many, with a mentor’s invitation to participate. Dr. Josh Broghammer, MD, FACS encouraged me to become involved as an intern by applying for a travel stipend to attend an ACS conference. My onboarding to the College began by attending the annual Leadership and Advocacy Summit in Washington, D.C., and I have been engaged since. If you are a trainee, there are numerous opportunities available each year to support travel to an ACS conference. My onboarding to the College began by attending the annual Leadership and Advocacy Summit in Washington, D.C., and I have been engaged since. If you are a trainee, there are numerous scholarships available each year to support travel to this excellent meeting.

If you are an early or mid-career urologist, consider getting involved to broaden your career and networking opportunities. Even if you don’t have a mentor within the ACS, you do not have to look far to find one. Fellows of the College are likely present within your department, practice or hospital, even if they aren’t urologists. Find one and ask about the path to becoming a Fellow of the College. Better yet, ask about the ways in which you can become involved in an area in which you are passionate to serve. The ACS has initiatives across the breadth and depth of surgery, including advocacy, surgical education, patient safety and quality, rural surgery, cancer care, trauma and much more. My experience has been that the perspective of a urologist is enthusiastically welcomed in these areas. Look up your local or state chapter of the ACS to find events nearby.

If you are a resident, fellow or medical student, there is specific programming available to you too. Visit the ACS Resident and Associate web page or the Medical Student member site for more information. Call in and attend one of the weekly Standing Committee Conference Calls listed at the end of this article. Apply for a scholarship, travel grant or research fellowship. Furthermore, consider submitting your scientific research to the ACS Clinical Congress, which occurs annually in October. There are urology specific poster and podium sessions moderated by leaders in urology, great networking opportunities across specialties and a relatively high abstract acceptance rate.

Finally, if you are already involved in the American College of Surgeons, great! Now take the next step, identify a mentee and encourage them to get involved in the myriad opportunities offered by the largest organized surgical organization in the world.

Resources

Becoming a Fellow of the American College of Surgeons
https://www.facs.org/member-services/join

Medical Student Resources
https://www.facs.org/member-services/join/medical-student

Resident and Associate Society
https://www.facs.org/member-services/ras

Resident and Associate Society Standing Committee Calls:
- 1-888-585-9008
- Room: 549-242-585#
- All calls begin at 9 p.m. Eastern Time

Ways to become involved in ACS at each career stage. Reprinted with permission from ACS recruiting resources.

Novel Erectile Dysfunction Treatments

Erectile dysfunction (ED) is the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance. It is a highly prevalent disorder affecting 150 million men worldwide and 30 million in the United States. ED is a harbinger of cardiovascular disease, and its management should include lifestyle counseling and treatment of underlying associated conditions. Lifestyle modifications, such as improved diet and increased physical activity, may improve the patient’s overall health and reverse the underlying pathophysiology causing ED.

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The Impact of Prostate Cancer on the Sexual Health of Partners

Daniela Wittmann, PhD, LMSW
Ann Arbor, Michigan

Attention to sexual dysfunctions in prostate cancer survivors will inevitably lead to the inclusion of partners in both clinical care and research because of the significant role partners play in the man’s sexual recovery and the recovery of sexual intimacy of the couple. Early research on men’s experience suggested that their postprostate cancer treatment sexual dysfunction made them lose confidence, fearing that they could no longer satisfy their partners. Gay and bisexual men reported feeling sexually “disqualified” after prostate cancer treatment.1 When offered pro-erectile aids, men often reject them or do not sustain their use. Dislike or lack of motivation to master pro-erectile aids by men who want to resume penetrative sex can be seen as an expression of grief about the loss of sexual function that becomes a barrier to staying sexually active.

Including partners in counseling after surgery for prostate cancer has proven to facilitate the uptake of pro-erectile aids, as was demonstrated in randomized controlled trials, most recently in Australia by Chambers et al.2 In addition, association has been found between patient and partner sexual function, suggesting that there may be a mutually influential process at work when sexual problems arise after prostate cancer treatment.

Most research has been done with female partners who have been traditionally seen as distressed supporters of the men, finding ways to adjust to the loss of sexual relationship, often privileging the men’s needs over their own. Although sexual health interventions for couples have included recommendations for mitigation of female partners’ sexual dysfunction, partners have typically not been asked about their own sexual needs either in research or in clinical care. Research on male partners is only emerging.

Recent qualitative research on couples after prostatectomy has begun to illuminate partners’ sexual concerns. Both male and female partners reported unmet sexual needs and difficulty initiating sexual activity either for fear of distressing the man who now lacked confidence or because the role of initiator was new to them and they were uncertain about adopting it. Importantly, patients were not aware of their partners’ sexual and support needs. A study of partners of Black African and West Indian patients by Bamidele et al highlighted the importance of understanding the impact of culture on partners.3 Partners reported that the role of the man as the head of the family limited the partners’ inclusion and ability to negotiate a role in the sexual recovery process.

Partners do have a point of view. In a study of patient and partner sexual health intervention priorities by Mehta et al, female partners expressed worry about being judged for pursuing sexual goals in the context of both vulnerable male partners and culturally biased expectations of sexual passivity in women. Male partners wished that providers would understand and address same sex couples’ sexual practices and concerns.4 Including cultural issues in the context of counseling couples as they work toward regaining sexual intimacy after prostate cancer was recommended by Bamidele et al.3

Loeb et al published a “Call to Arms” this year in the Journal of Sexual Medicine, urging the multi-disciplinary community engaged in prostate cancer care to take up the cause of partners’ sexual health.5 As in any system, neglecting the well-being of a critical part will endanger the health of the whole. Couple sexual well-being requires mutual needs awareness and responsiveness by both members of the couple. The urology community has always sought to maximize sexual health outcomes for prostate cancer patients. It is important that it widen its lens and include partner sexual health needs in its purview. This will primarily require that partners be involved in prostate cancer care from the first consultation, that they be educated about the sexual side-effects and rehabilitation and asked about their sexual concerns, and that both patients and partners be given the option to pursue sexual health counseling as they navigate sexual recovery after cancer treatment. If this kind of support is not already embedded in usual care, urologists can find certified sex therapists near them on the website of the American Association of Certified Sexuality Educators, Counselors and Therapists (aasect.org) and develop collaborative relationships. A holistic approach that recognizes the integral and equal role of the partner in the recovery of sexual intimacy after prostate cancer treatment will go a long way to improving patient and partner sexual well-being in survivorship.

Novel Erectile Dysfunction Treatments

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There has been increased interest by the medical community and general public in finding treatments to reverse the underlying causes for ED beyond lifestyle modifications. Low intensity shockwave treatment (LiSWT) and platelet-rich plasma (PRP) injections are promising options that have become more common with the rise of men’s health clinics. However, the American Urological Association and Sexual Medicine Society of North America have advised that LiSWT and PRP be considered investigational and experimental treatments, respectively. Both groups have recommended these agents only be pursued under research protocols in compliance with institutional review board approval.

LiSWT

LiSWT has been used to treat ED for more than 10 years. It is postulated that LiSWT produces an acoustic wave that interacts with the target tissue, inducing a cascade of biologic reactions promoting neovascularization.1 Nevertheless, high quality data investigating the effect of LiSWT is insufficient. Many questions remain due to a lack of consistency among the trials completed to date. The inability to draw conclusions arises from variation in shockwave generators, type of shockwaves used, energy use, number of pulses per session, duration of treatment, sessions per week and penile sites of application.2-4

Several meta-analyses have shown that LiSWT can increase International Index of Erectile Function (IIEF) score by mean of 2 to 6.4 points. Studies also reported an improvement in Erection Hardness Scores (EHS).2-4 This appears to be most pronounced in men with mild, vasculogenic ED. Data suggest that it could improve erectile quality or response to erectile aids, downgrading treatment needs to less invasive options. However, it must be noted that there was a significant variability in shockwave generators, treatment protocols and followup duration. The authors recommended that future trials use 18,000 shocks with a followup of at least 3 months with controls receiving sham treatment. Additionally, phosphodiesterase inhibitors must be stopped with an appropriate washout period for all patients. Given there were no significant adverse events, condensed protocols (defined as shorter than 6 weeks) may be considered. Some data suggest that applying a greater number of shocks [at least 3,000] per session and using a lower energy flux density may improve outcomes.

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Treatments
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Novel Erectile Dysfunction Treatments
◆ Continued from page 47

Our group is currently performing a prospective, randomized, single-blind, sham-controlled clinical study aimed at evaluating the safety and efficacy of LiSWT on symptomatic ED patients in 3 distinct patient populations: mild-moderate ED, patients after prostate cancer treatment and patients planning to undergo prostate cancer treatment. We are unlikely to see industry sponsored trials in the future, so investigator initiated trials need to be methodologically sound to answer some of these remaining questions.

PRP
PRP is autologous blood plasma that contains more than 4 times the normal human physiological serum platelet concentration and inherently contains growth factors that may promote tissue healing and neovascularization. Data on PRP is less mature than LiSWT, although 2 clinical studies on PRP were reported recently. Epifanova et al demonstrated an improvement in penile Doppler parameters (peak systolic flow, resistive index), IIEF and sexual encounter profile score in men receiving PRP. No adverse events were noted. In an effort to decrease washout, Matz et al used platelet-rich fibrin matrix (PRFM) instead of PRP in 17 patients with ED and/or Peyronie’s disease. They reported a 4.14 improvement IIEF-5 score and mild penile bruising in 3 patients after undergoing intracavernosal injections. These authors suggest that PRP is safe, but larger studies are needed to assess its efficacy in treating ED.

Conclusion
LiSWT and PRP may be promising treatment options for patients with ED. However, until high quality data are available, they must continue to be used in an experimental setting.


Figure 1. Average procedures per practice per day before and after announcement of BCG shortage.

Figure 2. Total procedures before and after announcement of BCG shortage.

BCG  Gemcitabine  Mitomycin C

Table 1. Number of procedures

Period 1  Period 2  Period 1  Period 2  Period 1  Period 2

Bar chart showing the number of procedures before and after the announcement of BCG shortage.

AQUA Registry Snapshot: Verana Health Analyses of AQUA Registry Data Provide Insights into Contemporary Urological Practice Patterns

Primary question: How has the utilization of BCG, and other intravesical agents, for the treatment of nonmuscle invasive bladder cancer changed since the BCG shortage?

Bacillus Calmette-Guérin (BCG) is considered the gold standard first line therapy for high grade nonmuscle invasive bladder cancer. In January 2019 Merck, the sole manufacturer of BCG, announced severe shortages in the supply of BCG that subsequently limited the availability of this therapy in practice.

In cooperation with Verana Health (San Francisco, California), we sought to evaluate the impact of the BCG shortages on the utilization of BCG within urology practices in the United States. Using the AUA Quality (AQUA) Registry data, and analyzing 72 practices from March 20, 2018, to January 20, 2020, we found a dramatic decrease in BCG utilization nationwide after the shortage happened.

As such, there was a 66.9% decrease in BCG utilization following the release of the notice from Merck. In addition, there was a 39.0% increase in the utilization of gemcitabine and a 475.2% increase in mitomycin C—alternative therapies for nonmuscle invasive bladder cancer that are typically not used as first line treatments. These findings demonstrate the value of an ongoing, prospective, longitudinal registry for characterizing trends in the delivery of urological care across the United States.

Verana Health is the data and technology partner for the AQUA Registry. Verana Health partners with leading medical associations to transform clinical data into actionable real-world evidence. These partnerships enable Verana to harness the comprehensive data found in qualified clinical data registries and other specialty data sources to accelerate medical research and enhance patient care. Learn more at veranahealth.com.
As the worldwide consequences of COVID edge toward the first anniversary, 2021 appears to be delivering further disruption and the unknown. I recall the difficulties our Board had in the decision to cancel the Sydney 2020 Urological Society of Australia and New Zealand (USANZ) Annual Scientific Meeting (ASM). This decision has been vindicated, as now in-person international scientific meetings do not exist and may never be quite the same. We are observing the second wave of COVID with shock and hope that the production and rollout of the vaccination program bring relief soon. It is a time when we need to show kindness and collaboration, and share resources and learning to help everyone get through.

Australia and New Zealand have pursued an elimination strategy in dealing with COVID that has been remarkably successful in preventing cases plus maintaining business as usual locally. It has, however, kept us internationally isolated, which is likely to continue until global COVID herd immunity is obtained.

USANZ has elected to push “pause” on in-person events and review options for virtual member education. There has been an explosion of on-line educational material, although we recognize the value of our ASM was the memories created by personal interactions and direct observations. Virtual meetings have struggled to provide this engagement. We do need to continue and provide locally relevant educational content plus a vehicle for our members and trainees to present their research. We had scheduled our 2021 ASM for March and the Urological Association of Asia (UAA) meeting for August in Sydney, along with myriad sectional and training meetings.

The Royal Australian College of Surgeons (RACS) has elected to hold their Annual Scientific Congress (ASC) May 10 to 14 as a virtual meeting and invited all surgical disciplines to join them. This meeting is based in Melbourne and will be held in-person if possible, although it is set up as a virtual format. USANZ elected to integrate our ASM in the RACS ASC to celebrate the first ASC meeting that all surgical disciplines will attend. Professor Henry Woo, as urological convener, has developed a program mixed with international speakers, cross-discipline sessions, the best of local talent and our valued trainee presentations: the Keith Kirkland and Villis Marshall awards. There is a strong focus on equity and local relevance (https://www.surgeons.org/en/conferences-events/annual-scientific-congress).

Mr. David Winkle has stepped up as the UAA President-elect, and USANZ was planning to showcase Sydney at the Congress in August this year. The UAA leadership under the guidance of Allen Chui, Secretary General, elected to postpone this event and hold a combined virtual meeting instead. This will see scientific input from all 4 major regions of the UAA, use a central Professional Congress Organizer (PCO) and cover a broad urology footprint. USANZ, with David Winkle, will open this event to be held August 19 to 21. The proposed Sydney UAA Congress is now planed for 2022.
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HRR, homologous recombination repair; NCCN, National Comprehensive Cancer Network.