Severe Complications of Pelvic Radiotherapy and Urinary Diversion

Since the inception of the National Cancer Act and “War on Cancer” in 1971, there have been significant advances in the multimodality treatment for pelvic malignancies. Because of this the numbers of men and women living for long periods after their life-saving treatment is rapidly increasing. In fact, 14.5 million Americans with prior cancer were alive in 2014 and this number of cancer survivors will exceed 19 million in 2024.1

Over the last 4 decades there have been striking improvements in life-saving cancer therapies. While originally the focus was cancer cure, now as so many patients are living longer after treatment the emphasis is evolving to long-term quality of life for cancer survivors.

Primary pelvic malignancies make up almost 20% of all cancer. The improvement in outcomes is due to multimodal therapy including surgery, chemotherapy and radiation therapy (RT). Radiation therapy has played a significantly larger role in the treatment of these patients with greater than 50% of patients suffering from prostate, cervical, colorectal and bladder cancer receiving radiation as part of their therapy.

Radiation’s therapeutic effect is primarily through cellular DNA damage. Toxicity from RT has 2 time components: acute—arising during active treatment—and late—ones that present and persist for long periods of time after primary treatment. While the acute side effects often resolve within 1 to 2 months, it is the late ones that urologists are saddled with caring for because of the improvements in survival. These may include incontinence, urinary retention, bladder overactivity, pain, fistula, hemorrhagic cystitis and urethral and ureteral strictures leading to significant morbidity. In many cases, patients have the unsavory situation of experiencing more than one of these for many years after their life-saving therapy.2

While the true incidence of side effects after RT is unknown, Elliott and his group outlined estimates of these rates based on the review of SEER data and Medicare data (see table).3

A vexing component of this problem for the clinician is that many of these late side effects may arise years and even decades later. This is particularly relevant to prostate cancer survivors who develop end-stage bladders, pubic symphysis fistula and pubic bone osteomyelitis an average of 8 to 10 years after therapy.4

Although it would be ideal to offer reconstructive options for all cases of pelvic radiation injury, in many cases these necessitate

Is a 24-Hour Urine Study Necessary to Initiate Metabolic Stone Prevention?

The goal of metabolic management for kidney stones is to prevent recurrent stone episodes, which occur in up to 50% of individuals within 5 years of a first stone event. This high recurrence rate is a significant source of morbidity and cost in urological care. The 24-hour urine study is central to the metabolic evaluation of nephrolithiasis patients, and its goal is to allow the physician to document a metabolic abnormality that can be addressed by a dietary or pharmacological intervention, with the ultimate goal of reducing stone recurrence rate. But does it actually work?

\[Continued\text{ on page 3}\]
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Pelvic Radiotherapy and Urinary Diversion

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Urinary diversion with or without cystectomy. Situations where the bladder is not salvageable are those with large fistula to the rectum or fistula in women, which often involve the bladder, vagina and rectum, especially when associated with extensive necrosis (fig. 1). Other devastating examples of unsalvageable high grade RT injury include symphysis fistula (fig. 2) and the predictable osteomyelitis of the pubic bone, which are often associated with severe necrosis of the prostac fossa and bladder floor with very little viable tissue to repair.

A key element in evaluating these injuries is the condition of the bladder. Even if a fistula can be repaired, if the bladder has severe radiation cystitis and contraction patients may remain crippled by their urinary symptoms even if the fistula is successfully closed. Often in these situations patients will have multiple side effects from the RT including fistula, concomitant ureteral stricture and incontinence. We have found that when multiple complications are present patients are often best served by urinary diversion. Another situation where upfront urinary diversion should be presented to patients as an option is when an artificial urinary sphincter will be needed after lower urinary tract reconstruction. A common problem would be a recalcitrant bladder neck contraction after radical prostatectomy followed by adjuvant pelvic radiotherapy. If this is not amenable to robotic repair from the pelvis and perineal repair is performed with bulbar mobilization, patients often will end with total incontinence. In this circumstance patients are at very high risk for artificial urinary sphincter (AUS) erosion, even if the AUS is placed in a transcorporeal fashion and staged 3 to 12 months after the initial repair. It is important to explain the unhappy scenario of successful repair followed by a period of total incontinence followed by AUS placement followed by AUS explantation for erosion and ending up with a suprapubic tube and eventually urinary diversion. Some patients when confronting this long path often elect for upfront urinary diversion.

Many of these patients have suffered for years with these chronic illnesses, and when planning for urinary diversion due to severe side effects of RT it is paramount to optimize all of the modifiable surgical risk factors before surgery. Diabetes should be well-controlled and patients should not be in a catabolic state with low albumin with optimized comorbidities for surgery. In men undergoing urinary diversion after prostate cancer pelvic RT we found that the patients were often older (mean age 71 years), presented 8 years after radiotherapy and had a rate of death and major complications (Clavien–Dindo complication 3 or greater) of 5% and 36%, respectively. A similar death rate and major complication rate were noted in women undergoing urinary diversion after pelvic RT for gynecological malignancy. Some patients are so ill on presentation that they may require outside-the-box strategies such as concomitant placement of colostomy and colon conduit or switching an existing conduit to a urinary conduit and creating a new colostomy more proximally. These strategies have the advantage of eliminating a bowel anastomosis, which may not heal in a severely debilitated patient, leading to disaster.

There are significant gaps in our knowledge about high grade RT complications. It is unclear if genetics, environment or patient factors predispose patients to high grade complications, and it can be at times perplexing to understand why some patients develop these complications and others with the same radiation dose barely have any visible tissue effect. One could imagine a future when genetic or epigenetic milieu may be combined with tumor and patient factors to predict the optimal treatment for the tumor and the risk of high grade RT complications in the individual patient.

### Table. Incidence of complications stemming from common cancers and radiotherapy.

<table>
<thead>
<tr>
<th>Common Cancer Types by Disease Group</th>
<th>% Rate of RT Delivered</th>
<th>% Incidence of Side Effects</th>
<th>Time Course in Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urological: Prostate Bladder</td>
<td>37</td>
<td>1–41</td>
<td>6–27</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>6–12</td>
<td>8–10</td>
</tr>
<tr>
<td>Gynecological: Cervical Endometrial</td>
<td>53</td>
<td>1–15</td>
<td>6–16</td>
</tr>
<tr>
<td>Vulvar</td>
<td>23</td>
<td>5–20</td>
<td></td>
</tr>
<tr>
<td>Colorectal: Rectal/anal</td>
<td>70</td>
<td>12–70</td>
<td>2–12</td>
</tr>
</tbody>
</table>


24-Hour Urine Study for Metabolic Stone Prevention

Continued from page 1

### Updated Evidence: What Do We Know?

A large body of research has assessed the impact of 24-hour urine studies on the risk of stone recurrence, but only one prospective study has documented a significant reduction in stone recurrence rate (7% vs 23%) when adopting a tailored dietary regimen based on the 24-hour urine evaluation compared to generalized, nonselective preventive dietary measures. While these results appeared to favor the tailored approach, the lack of improvement in urinary calcium and oxalate parameters at the end of the study in the tailored approach arm suggests that the reduction in stone recurrence risk is more likely due to the stone clinic effect rather than metabolic assessment. The stone clinic effect proposes that closer medical followup and attention to stone symptoms by patients can lead to improved clinical outcomes, and the diagnostics and tailored treatment plans used have a smaller impact comparatively.

Furthermore, the benefits of thiazides and citrate supplementation to prevent kidney stones in patients who do not have hypercalciuria or hypocitraturia are well recognized.
Both have shown benefit for calcium stone formers treated empirically who were not given medication based on 24-hour urine calcium or citrate excretion. In other words, empirical treatment with these therapies based on stone composition and clinical profile alone appeared to have a positive impact on stone recurrence rate without affecting an underlying metabolic abnormality. These data further strengthen the argument that the 24-hour urine study in directing medical management for stone prevention may not be as useful as once thought.

What Are the Limitations of 24-Hour Urine Study?

Although a detailed metabolic evaluation including a 24-hour urine study is endorsed by multiple national and international society guidelines, it is crucial to understand the limitations of this commonly used tool. First, the interpretation of urine collection results can be challenging to clinicians, especially since more than a single abnormality is often present on initial workup and other borderline values may be present that might also have clinical importance, challenging the physician to choose which abnormality to address and in what order.

Second, 24-hour urine studies may not account for diurnal and nocturnal variations in urine constituents related to diet and physiological metabolism, and are strongly affected by a patient’s behavior. A collection done during a weekday is different than one done over a weekend day, as the patient’s diet and hydration are different. Although some societies recommend 2 separate collections to overcome this issue, a patient undergoing a repeat collection tends to modify their diet to improve results and may unintentionally further limit the interpretability of the test.

The fact that stone formers can have a normal 24-hour urine study and nonstone formers can have abnormal urine parameters raises the question of the accuracy of the laboratory cutoffs used for these collections. This highlights their somewhat arbitrary nature. These measured values likely do not represent dichotomous measurements distinguishing normal from abnormal values, but rather a reflection of the stone formation risk: a higher concentration of urinary calcium, for example, carries a higher risk of calcium stone formation, and that is true even within the “normal range.”

Lastly, one cannot overlook the cost associated with these collections. It can be a real burden for recurrent stone patients who are usually asked to do this test repetitively. For example, out-of-pocket costs for a Litholink collection kit (Itasca, Illinois) are more than $400 per test at the full rate and less than $200 if discounted. This can be a serious limitation for uninsured patients and those with a limited income.

Future Directions for 24-Hour Urine Studies

Despite the aforementioned drawbacks, 24-hour urine studies still play a central role in the metabolic evaluation of urolithiasis patients. It is the only risk assessment tool that is currently available for practicing urologists for the prevention of urinary stone disease. In addition to being essential for the diagnosis of rare metabolic anomalies like primary hyperoxaluria or cystinuria, it is an efficient way to assess the extent of dietary sodium ingestion and hydration, which provides an opportunity for the clinician to enforce the importance of these 2 dietary factors both in stone prevention and for general health. Nonetheless, it is clear that more data on 24-hour urine studies driven by clinical outcomes are needed in order to increase the clinical value for this diagnostic tool and to develop more accurate risk assessment algorithms. It may be that in the age of rapidly developing biomarkers, new technologies will open the way for augmenting 24-hour urine studies with new tools to risk stratifying kidney stone patients.

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Monitoring Kidney Function in Children with Spina Bifida: Challenges and Opportunities

Spina bifida (SB) is a congenital birth defect that causes a wide spectrum of neuromuscular complications related to a neurogenic bladder. Since the bladder is inherently connected to the kidneys, individuals with SB experience a lifelong risk of developing kidney dysfunction. As improved care has extended life expectancy and kidney dysfunction increases with age, it is not surprising that admissions for chronic renal insufficiency in SB patients is increasing. Management of individuals with SB therefore prioritizes protecting kidney health. This prioritization is reflected in myriad international, national and societal guidelines and serves as the basis for the Centers for Disease Control and Prevention (CDC)-sponsored Urologic Management and Control and Prevention (CDC)-sponsored Urologic Management to Preserve Initial Renal Function Protocol for Young Children with Spina Bifida (UMPIRE) study. However, recent research demonstrates that monitoring kidney function in individuals with SB is a greater challenge than in other urological patients, for reasons we will highlight here.

First, determining kidney function in children often relies on common equations to calculate an estimated glomerular filtration rate (eGFR). Unlike adults, where a creatinine value alone often suffices as a surrogate for kidney function, creatinine values in children change inherently during growth. Hence, eGFR equations were created to “normalize” kidney function, adjusting laboratory values, such as creatinine, to growth parameters, such as height. Unfortunately, the large cohorts in which these eGFR equations were developed usually excluded children with SB. Given the discrepancy in height and muscle mass in children with SB compared to children without SB, there has been increasing evidence showing that commonly used eGFR equations give highly variable results. Specifically, creatinine-based eGFR equations generally give higher eGFR values [ie better estimates of kidney function] than cystatin C-based eGFR equations. Additionally, over time, creatinine-based eGFR equations give increasing values for eGFR with age, although it is extremely unlikely that kidney function improves with time. Cystatin C-based eGFR equations meanwhile report declining eGFR values as children age, which seems more realistic. These results question the reliability and accuracy of current eGFR equations in children with SB.

A second challenge reflects artefactual changes in eGFR through application of adult vs pediatric eGFR equations. In populations excluding children with SB, eGFR equations were developed separately for children and adults, often using a cutoff age of 18 years to determine which set of equations to apply to calculate eGFR. However, in a single institutional study of patients 18 to 28 years old with SB, when corresponding adult eGFR equations were applied using the same creatinine or cystatin C values as a pediatric eGFR equation, there was an artefactual increase in eGFR by 20% to 25%. In other words, application of an adult eGFR equation automatically “improves” the eGFR, even if cystatin C is used. This artifact may downgrade the severity of kidney function, which further complicates the recognized difficulties of successfully transitioning an individual with SB from pediatric to adult medical care.

A third challenge is that studies of practice patterns suggest that adherence to routine kidney function surveillance is suboptimal. Despite the limitations of creatinine, as aforementioned, there is still value inherent in the data, eg an abnormally low creatinine-based eGFR is likely to reflect true kidney dysfunction. Additionally, several SB guidelines include a role in checking serum creatinine. However, within a large cohort of 5,445 patients with SB who participate in the CDC-sponsored National Spina Bifida Patient Registry (NSBPR) at clinics committed to SB research and care, wide variability was found across clinics in terms of their adherence to kidney function surveillance, which was defined as at least 1 renal ultrasound and at least 1 serum creatinine within a 2-year window. The average adherence to this combined surveillance definition was only 62%, ranging from 6% to 100% across 23 clinics participating in NSBPR. Notably, more clinics checked routine ultrasound (93%) than routine serum creatinine (69%) to assess kidney health.

However, this practice pattern segues to a fourth challenge to monitoring kidney function in individuals with SB, which is that ultrasound-based hydronephrosis is a poor screening test for low eGFR. In a single center retrospective series of 247 patients with SB, using cystatin C eGFR as the gold standard, hydronephrosis as determined by ultrasound had 23% to 48% sensitivity in children for eGFR <90 mL/min/1.73 m². High grade hydronephrosis was even worse, with 4% to 15% sensitivity. Results were unchanged after excluding patients with small kidneys or scarring. In other words, many children with SB can have low eGFR and kidney dysfunction without hydronephrosis. Coupled with the prior results showing a bias toward surveillance ultrasounds rather than creatinine testing, many patients with SB may not be having their kidney function monitored accurately with current, commonly used tools.

It is important to put these challenges in monitoring kidney function into the global context of the overall care of children with SB. The lifelong health risks of this population are not limited to kidney health, but also apply to other key issues including bladder and bowel continence, skin care, prevention of obesity and obesity-related health problems, loss of mobility and neuropsychosocial concerns. In this context, several opportunities arise for additional kidney health-related research. For example we do not know how individuals with SB perceive kidney health relative to their other health risks, nor how these perceptions change during their lifetime. Patient reported outcomes followed longitudinally may shed light on this knowledge gap. Additionally, as shown in the prior work within NSBPR, dissemination and implementation of clinical guidelines remain suboptimal. Efforts are needed to enhance uptake of ideally evidence-based protocols, or consensus protocols if high quality definitive evidence is unavailable. Better laboratory or imaging based methods or tools must be developed to accurately and reliably assess kidney health in the SB population. Hopefully, within multi-institutional infrastructures such as those offered by the UMPIRE and NSBPR studies, these and other important research and clinical questions can be adequately answered.◆

What to do with Prostatic Urethral Carcinoma?

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Urethral carcinoma of the prostate (UCP) represents a rare entity, arising from the prostatic urethra or from direct invasion into the prostate via the bladder, with a crude incidence of 0.06/100,000 per year. However, in isolation UCP may be underreported given that the incidence of UCP is observed in up to nearly 50% in cystectomy series where detailed pathologic evaluation of the prostate was undertaken, with stromal invasion in 8% to 17%. In patients with a history of nonmuscle invasive urothelial carcinoma, tumor recurrences may be identified in the prostatic urethra in 24% to 39% of cases. Common presenting symptoms and signs include microscopic or gross hematuria and obstructive voiding symptoms. Risk factors for UCP include carcinoma in situ (CIS) of the bladder neck or trigone and prior intravesical therapy, and involvement of the prostate by CIS is almost always associated with CIS within the bladder.

The histologic subtype of UCP is urothelial carcinoma in 90% and squamous cell origin in 10%. The TNM Staging system for the prostatic urethra is presented in the Appendix. Of note, both primary papillary tumors of and CIS limited to the prostatic urethra are relatively rare, occurring in 2.7% and less than 4% of patients with primary bladder cancer, respectively. Urothelial carcinomas are risk stratified into low vs high grade disease according to the current WHO/ISUP grading system. For squamous cell and adenocarcinoma of the prostatic urethra, tumor grade is recommended to be described as well differentiated (G1), moderately differentiated (G2), poorly differentiated (G3) or indeterminate (Gx).

Diagnostic Evaluation
In patients with a clinical suspicion for prostatic urethral carcinoma or undergoing evaluation for obstructive voiding, initial evaluation includes a digital rectal exam and serum prostatic specific antigen (PSA). Flexible cystoscopy in the clinic may demonstrate a mass within the prostatic urethra, which may be papillary or sessile in nature. The bladder should be carefully evaluated to rule out multifocality. Urine cytology may be obtained. However, the sensitivity of urine cytology in urethral carcinoma is somewhat limited (80% in urothelial carcinoma vs 50% in squamous cell carcinoma).

The patient is then taken to the operative room for exam under anesthesia and transurethral resection of the prostatic urethra, including the prostatic stroma to establish the diagnosis. Enhanced cystoscopy, with either blue light cystoscopy or narrow-band imaging, is recommended if available for the evaluation of bladder cancer; however, there are no specific data available to date regarding its utility in the setting of UCP. Needle biopsy of the prostate (eg transurethral or transperineal ultrasound-guided biopsy of the prostate) may be undertaken if the digital rectal exam is abnormal. In addition to debulking any visualized tumor, transurethral resection of the prostate is generally obtained in the 5 and 7 o’clock positions in the prostatic urethra to ensure sampling of the prostatic ducts. These resections should extend from the bladder neck to just proximal to the verumontanum. A separate resection of the prostatic urethral floor may also be obtained. Of note, in the setting of a positive cytology with a visually normal cystoscopy, the prostatic urethrium should be sampled in the manner described above.

If not already undertaken, in patients with urothelial carcinoma of the prostatic urethra, upper tract imaging should be performed with a computerized tomography (CT) urogram, retrograde pyelogram or magnetic resonance (MR) urogram to complete evaluation of the remainder of the urethrium. Patients with urothelial carcinoma invading the prostatic ducts and acini or the prostatic stroma (pT1 or greater) should also undergo imaging of the chest (chest x-ray [CXR] vs CT chest) and cross-sectional imaging of the abdomen/pelvis if not already undertaken to rule out metastatic disease. Contrast-enhanced pelvic magnetic resonance imaging (MRI) provides the best resolution to delineate the local extent of the tumor and also evaluated regional lymph node involvement. Position emission tomography (PET)/CT is utilized to identify systemic and nodal metastases in urothelial tumors, although data regarding its use in UCP are sparse.

Treatment
The management of UCP is determined based on tumor histology, stage and grade. For patients with CIS (see figure) or noninvasive urothelial UCP, transurethral resection is followed by induction Bacillus Calmette-Guerin (BCG), and patients are followed according to guideline-based surveillance recommendations. This conservative and organ-sparing approach is appropriate only if the tumor can be completely resected. The resection should include resection of the bladder neck to permit reflux of the intravesical BCG into the prostatic urethra. These patients are followed carefully with surveillance cystoscopy and imaging because recurrence in the prostate is associated with poor prognosis. Frequent random biopsies of the prostatic urethra are recommended during subsequent cystoscopies to detect local recurrence accurately. Patients with recurrence of high grade pTa or pTis are generally recommended to undergo radical cystoprostatectomy with or without urethrectomy, bilateral pelvic lymphadenopathy and urinary diversion. Patients who are unwilling to consider radical surgery or who are poor candidates for radical cystoprostatectomy may be offered resection and reinduction with BCG and subsequent management according to principles of management of BCG unresponsive urothelial carcinoma but should be counseled that there are limited data regarding outcomes in this space.

Patients with urothelial carcinoma of the prostate involving the prostatic ducts and acini but without stromal invasion (pT1) may be managed with radical cystoprostatectomy with or without urethrectomy, bilateral pelvic lymphadenopathy and urinary diversion vs transurethral resection of the prostate (TURP) and induction BCG, with local recurrence prompting radical cystoprostatectomy with or without urethrectomy and bilateral pelvic lymphadenopathy. In the event of stromal invasion (pT2) or locally advanced nonmetastatic urothelial carcinoma of the prostate (pT3/4N0/XM0), neoadjuvant cisplatin-based chemotherapy followed by radical cystoprostatectomy with or without urethrectomy and pelvic lymphadenectomy is the treatment of choice. Patients who underwent frontline radical surgery should be considered for adjuvant systemic therapy. Patients with localized invasive nonurothelial tumors of the prostatic urethra (eg squamous cell carcinoma or adenocarcinoma) proceed to upfront radical cystoprostatectomy with or without urethrectomy.

In the event of metastatic UCP, patients proceed to systemic therapy appropriate for the histologic subtype. In patients with metastatic urothelial carcinoma who are cisplatin eligible, patients generally receive either gemcitabine or...
Prostatic Urethral Carcinoma

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dose-dense MVAC with growth factor support. For patients who are cisplatin ineligible, preferred regimens currently include gemcitabine and carboplatin followed by avelumab, atezolizumab or pembrolizumab in patients with tumors expressing PD-L1 or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression.

Prognosis
Treatment of CIS of prostatic urethra associated with nonmuscle invasive bladder cancer (NMIBC) with TURP and BCG is associated with complete response rates of 70% to 100% in the prostatic urethra, as reviewed by Palou et al.7 Stomal invasion of the prostate by urothelial carcinoma is associated with an increased risk of nodal metastases and poor prognosis overall. The 5-year cancer specific survival for patients with UCP with stomal invasion is estimated at 74% compared with 26% in those without stomal invasion.3

Summary
UCP is a rare and often unrecognized entity, frequently associated with synchronous bladder cancer, that requires a high index of suspicion to accurately diagnose and identify its presence and extent both endoscopically and in patients who have undergone radical cystoprostatectomy. Management is risk stratified by histology, grade and stage. Correct staging and close followup in the setting of coexistent NMIBC is imperative to avoid progression secondary to undiagnosed stomal invasion2 and accurately identify recurrences that should prompt consideration of radical extirpation.◆


- T Primary tumor
- Tx Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Ta Noninvasive papillary carcinoma
- Tis CIS involving the prostatic urethra or periurethral or prostatic ducts without stromal invasion
- T1 Tumor invades urethral subepithelial connective tissue immediately underlying the urothelium
- T2 Tumor invades the prostatic stroma surrounding ducts either by direct extension from the urothelial surface or by invasion from prostatic ducts, invasion of the corpus spongiosum, periurethral muscle
- T3 Tumor invades the periprostatic fat, corpus cavernosum, bladder neck
- T4 Tumor invades other adjacent organs (eg, extraprostatic invasion of the bladder wall, rectal wall)

The CONTACT•02 study is designed to explore the safety and efficacy of an investigational drug combination—cabozantinib with atezolizumab—for patients with metastatic castration-resistant prostate cancer (mCRPC).

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- Progressive disease as defined by prostate-specific antigen progression or soft tissue progression
- No prior systemic antancer therapy for mCRPC; prior chemotherapy for mCSPC allowed
- ECOG performance status of 0 or 1

*Patients must meet additional eligibility criteria to enroll.

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Schwannoma and Testis Cancer—What’s the Link?

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Background

We present the first reported case of transformation of a germ cell tumor (GCT) into a retroperitoneal schwannoma.

Case Presentation

A 48-year-old man who had undergone a left orchiectomy and adjuvant chemotherapy in 2017 for a mixed GCT was referred for consideration of robot-assisted laparoscopic retroperitoneal lymph node dissection (RPLND) for a slowly enlarging para-aortic node. Three years after initial treatment his tumor markers remained normal. Histology from orchiectomy demonstrated a mixed GCT consisting of 70% embryonal carcinoma, with possible elements of seminoma, trophoblastic giant cells and yolk sac tumor.

The para-aortic node had increased from 7 mm to 17 mm in a year. 18F-Fluorodeoxyglucose positron emission tomography (18F-FDG-PET) showed low avidity within the enlarged node with a maximum standardized uptake value (mSUV) of 2.1, and no other sites of disease (fig. 1).

A left template supine robot-assisted laparoscopic RPLND was performed with successful dissection of preaortic, para-aortic and interaortocaval lymph nodes and left gonadal vein. Macroscopic examination of the excised nodes revealed a 17 mm solid spherical nodule (fig. 2) consistent with that seen on PET and computerized tomography (CT). Histological analysis confirmed a schwannoma entirely replacing the node and 33 other normal nodes. Fluorescence in situ hybridization (FISH) analysis of the schwannoma was positive for the presence of isochromosome 12p (fig. 3), strongly supporting a GCT origin rather than an incidental de novo finding. The patient recovered well postoperatively and was discharged back to his oncology team to resume surveillance.

Discussion

Enlarged retroperitoneal nodes with normal tumor markers in the context of testis cancer present a diagnostic challenge. There may be a role for FDG-PET in the evaluation of equivocal nodal findings seen on CT. However, this requires further study because a negative node on PET may still harbor small volume viable cancer, and furthermore PET avidity cannot distinguish between viable cancer, teratoma and a reactive node. Minimally invasive RPLND offers a diagnostic and potentially therapeutic option for resolving uncertainty in this situation with relatively little morbidity.

In this case the final histology was surprising and did not conform to any of the conventional pathology seen in this context such as seminomatous GCT or nonseminomatous GCT (NSGCT) including yolk sac, embryonal, choriocarcinoma and teratoma. As the schwannoma had entirely replaced the node, it was unclear if this was an incidental tumor or a transformed teratoma. Teratoma can range from benign, well-differentiated (mature) cystic lesions to those that are solid and malignant (immature). Furthermore, teratomas may be monodermal, instead of tridermal, and highly specialized with 1 cell type. Somatic transformation occurs in 3% to 6% of teratomas and is one of the reasons for recommending surgical excision if teratoma is suspected, with the other reason being growing teratoma syndrome. Somatic transformation is characterized by differentiation of pluripotent teratoma cells into somatic tumor cells. The most frequent histological types seen in transformation are rhabdomyosarcoma, adenocarcinoma and primitive neuroectodermal tumors. A range of other histological transformations have been described, but not schwannoma.

When unusual histology is encountered, distinguishing between GCT-associated tumor and nonGCT is not straightforward. Sometimes this distinction is critical to deciding further management.

Figure 1. Left panel, CT shows enlarged para-aortic node. Right panel, 18F-FDG-PET scan shows low avidity (mSUV 2.1) within same node.

Figure 2. Left panel, 17 mm schwannoma excised with clear margin. Right panel, spindle-shaped cells with nuclear palisading arranged in interlacing bundles characteristic of schwannoma. H&E, reduced from x100.

Figure 3. Interphase FISH shows presence of two 12p isochromosomes (arrows) identified by 1 red (represents centromeric region of chromosome 12) and 2 green (represents p-arm of chromosome 12) signals.
Case Report

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This is where molecular genetic analysis can help.4

Gain of the short arm of chromosome 12, most commonly as an isochromosome 12p (i12p), is a highly nonrandom chromosomal marker seen in >80% of GCTs.5 During transition from germ cell neoplasia in situ to invasive tumor, neoplastic cells acquire additional genetic material on the p-arm of chromosome 12, usually in the form of i12p or the amplification of specific areas of chromosome 12 (i12p gain).5

While i12p is not 100% specific for GCT, the literature indicates it has diagnostic and possible therapeutic relevance for these tumors.4 i12p can be identified on interphase nuclei by FISH, simultaneously using a probe specific for the centromeric region and the short (p) arm of chromosome 12. i12p can also be detected using quantitative polymerase chain reaction (PCR). i12p is not seen in de novo schwannomas.

The presence of i12p in this case effectively confirms the diagnosis of teratoma transformation in the retroperitoneum to schwannoma, which has not previously been described.


ETHICAL DECISION MAKING in Urology

Background and Case Presentation

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Medical ethics play a role in all specialties. However, the medical ethics literature specific to the field of urology is underdeveloped. We present the case of an elderly man with dementia who needs consideration for transurethral prostatectomy (TURP) because of urinary retention. The goal of this case presentation and literature review is to analyze the complexities of ethical decision making and how it applies to a clinical case that a general urologist will see on a regular basis. Just in this brief and common case, the topics of advance directives (ADs), decisional capacity, surrogate decision making, best interest, substitut ed judgment and informed consent can arise. There exist complicated ethical scenarios, some of which are unique to urology, that need to be presented and discussed as part of the larger ethical discourse.

Introduction and Literature Review

Urologists are faced with ethical dilemmas on a daily basis, but the essential textbooks of urology have little to no significant discussion of ethics in multivolume sets.2,4 One of the few such statements surrounds the issue of postmortem sperm retrieval and states that “the ethical appropriateness of such retrieval is the most important issue surrounding its use” without any specific guidance as to what is ethically appropriate.1 The Accreditation Council for Graduate Medical Education (ACGME) has identified 6 general ethical competencies for residents in training, which include respect for patients, responsiveness to patients’ needs, accountability, commitment to furthering one’s own education, confidentiality and cultural competency. It is unclear from published studies and sources to what extent urology residency programs are providing training or education in these areas.

There are few published articles addressing ethical issues in clinical urology. One article highlights the great variability in how medical professionals of different ages and levels of training respond to different ethical dilemmas.3 In the paper, a group of urologists, medical students, residents and risk managers were presented with 10 ethical dilemmas in urology. The authors found that younger practitioners were less likely to hold a paternalistic view of shared decision making. This study also identified a lack of understanding of mandatory reporting, the laws surrounding sexually transmitted infections testing disclosure in adolescents and the need to disclose a cancer diagnosis. There is little concordance among the different groups on how to handle ethically challenging scenarios.

In another paper, Mohan discusses several areas of ethical interests to urologists.4 One discussion relates to whether true informed consent is obtained when a surgeon workshop utilizes a visiting surgeon. A second discussion includes the conflict of interest that exists between conducting clinical trials with new pharmaceuticals or surgical products and what is in our patients’ best interests. Lastly, there are issues with surgical innovation when new technology that does not have to meet institutional review board approval has outcomes that are unknown and untested. Thomas explored ethical and legal issues in urology practice, encouraging physicians to remain knowledgeable about local and federal laws that regulate them as well as the increasing litigation of physicians practicing in good faith.5 Despite this acknowledgment, guidance on how to address each dilemma from an ethics standpoint is lacking.1

We present and analyze a typical urological case to highlight the numerous ethical concepts inherent in the case, reviewing each of them in turn. We hope that this case analysis will help urologists to think about how they make the decisions they make every day during clinical care of their patients.

Case Presentation

Mr. Jones is a 75-year-old male with mild dementia who presents with immediate urinary retention following an emergent cholecystectomy for acute cholecystitis. He otherwise did well postoperatively and recovered well from the anesthetic. During his hospitalization, he experiences delirium with waxing and waning decisional capacity. During an episode of delirium, he experiences urethral trauma when he pulls out his catheter while confused. He has a history of mild dementia and resides in a memory care unit of a nursing home. His daughter is his closest relative, and he also has 2 sons. The daughter and patient present to the office to discuss management of his urinary retention. He has tolerated the catheter better at the nursing home but he clearly has periods of agitation related to its presence. He has been on tamsulosin and finasteride for management of his benign prostatic hyperplasia for 3 years prior to this episode. A voiding trial is attempted in the office, where he is only able to void 80 ml, with a post-void bladder volume of 400 ml. The indwelling catheter is replaced because he cannot cognitively master the ability to perform in-and-out catheterization.

The urologist begins the discussion about TURP with the patient and daughter.

Does the Patient Have Written Advance Directives?

Written ADs are designed to provide guidance for care and treatment at a future time when patients lose the capacity to make their own decisions. The goals of ADs are to designate surrogate decision makers, stimulate discussions around end of life choices and remove some of the burden on the family to make difficult choices when they arise. Unfortunately, only 20% to 30% of adults have some type of advance directive.8 ADs provide a starting point of discussion between the patient and their caregivers as well as a framework within which to understand patients’ authentic preferences. This allows the clinician to consider the risks and benefits of a given treatment option within the framework of the patient’s values and preferences as understood by a knowledgeable surrogate in a more data-rich way. Advance directives have disadvantages, including...
Ethical Decision Making in Urology

Continued from page 9

Their lack of specificity, difficulty in interpreting expressed wishes in the context of complex medical circumstances and the lack of updates to the documents as frailty and prognosis change. The “desirability of interventions often changes in the face of this new reality.” The Patient Self Determination Act of 1990 requires hospitals to ask for an advance directive on hospital admission but does not specify assistance in facilitating its completion. Examples of ADs include durable power of attorney for health care documents, living wills and physician orders for life-sustaining treatment (POLST).

The living will is a written document specifying preferences for life prolonging treatments at the end of life. A living will can be drawn up at any time in someone’s life with the knowledge that a trauma or life-threatening condition can happen at any time. An attorney is not needed to create a living will, but it does require a witness and/or a notary. The living will can specify comfort measures only or instruct a withdrawal of life prolonging treatments once a terminal diagnosis is made and the physician believes that death is likely. It also specifies the desire for and/or refusal of artificial nutrition and hydration in the setting of a terminal illness. These documents are encouraged to be updated at least once per decade and are revocable at any time. The limitations of living wills surround the inability to apply them to specific situations, the interpretation by the care providers, the varying ability of patients to cope with new disability and patients’ preferences, which may evolve over time.

The POLST form is the “physician orders for life-sustaining treatment.” It is a standardized, actionable medical order set that transfers end-of-life care orders between care settings. POLST forms specify that the order set can only be created once a patient has a life expectancy of less than 1 year. The orders address code status, goals of care, antibiotic use and artificial nutrition. The form applies even in an emergency situation and acts as an order for emergency responders. Section A addresses code status. Section B determines if the goal of care is for comfort measures, limited interventions without the use of intubation or intensive care unit services, or full interventions. Section C describes the reason for antibiotic use, such as for therapeutic vs comfort measures only. Section D states whether a patient would desire no artificial nutrition, a time-limited trial or long-term artificial nutrition. For the document to be valid, the POLST requires a physician signature and the patient’s or legal guardian’s signature (appointed guardian, health care power of attorney or health care representative). The document cannot be signed by a default surrogate decision maker. The goal of the POLST form is to promote patient autonomy, clarify treatment intentions and facilitate appropriate treatment by emergency medical services. As of August 2017, there were 23 developing states and 21 endorsed states with POLST forms available. One important part of the legislation is that there is legal protection for physicians who comply with the orders on a POLST form.

In order to proceed with surgery in this patient’s case, it would be appropriate to establish goals of care with the patient and his daughter. Did he determine he would want everything done, including a palliative surgery? Did he wish for comfort measures only on the previous documents? If he wished for comfort measures only, then maintaining the catheter may be the best option as it would be the least invasive method of managing his urinary retention. If he specified more aggressive measures, then consideration of a TURP is appropriate. Mr. Jones does have an advance directive in the form of a living will. It states that “I do NOT want a feeding tube if I have a terminal illness, I do WANT life-sustaining procedures used if I am in a persistent vegetative state, and I do WANT a feeding tube if I am in a persistent vegetative state.” Based on the information in the advance directive and previously giving consent for his recent cholecystectomy, it seems likely he would accept interventions in a state of advanced dementia. In his advance directive, he was willing to undergo medical procedures even when his physical state was more impaired (persistent vegetative state). This would suggest that this endoscopic surgery aligns with these values and preferences and, therefore, proceeding with the TURP would be consistent with his previously expressed wishes, which predate his dementia.

This article is part 1 of a 2-part series. In part 2, which will appear in the March issue of AUA News, we will examine whether the patient had the capacity to make the decision for surgery, as well as the informed consent process.

Registry Snapshot

Continued from page 4

BCG utilization after the release of the notice. Although this change may represent a decrease in inappropriate use of BCG (ie, for low-grade disease), this large percentage drop is quite concerning for what is considered the gold standard and first line treatment for nonmuscle invasive bladder cancer.

We hope to investigate this trend further by analyzing how it compares with the utilization of other intravesical agents.

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 www.veranahealth.com.

Figure 1. Average BCG procedures per practice per day (14-day rolling average).

Predicting Loss of Compliance in Neurogenic Bladder: Urodynamics as an Evolving Tool

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Ann Arbor, Michigan

Improvements in the general care of children with spinal cord injury and myelodysplasia led to longer survival. This advance, in turn, led to the observation that some of these survivors would later suffer from significant urological complications, including hydronephrosis, chronic urinary tract infection, stone formation, renal damage and loss of renal function. Others would fare better, and in 1981 one of the earliest insights into the physiological basis of this clinical difference came with the description by McGuire et al of the detrusor leak point pressure (DLPP). He found that in 42 myelodysplastic patients followed for a mean of 71 years, none with intravesical storage pressures under 40 cm H2O developed vesicoureteral reflux (VUR), whereas 60% of those with pressures above 40 cm H2O did. This allowed urodynamics to emerge from an academic investigative exercise to an objective clinical tool to predict renal decline, and that this deterioration was linked to a loss of bladder compliance, thus guiding treatment and helping to establish the pressure based management of neurogenic bladders.

Time Line

1893 Einthoven introduces EKG
1924 Einthoven wins Nobel Prize
1927 cystometer term introduced
1942 12-lead EKG
1950s analog to digital
1975 Am Heart Association recommendations on automated readings
1981 McGuire introduces 40 cm H2O Pressure based management
2004 Limitations of computerized readings defined: recommendations for combining computer and human readings.

Figure. Time line of EKG and urodynamics

This concept was proactive, and now, rather than waiting for upper tract deterioration to occur before intervening, urologists could monitor and act early before there was lasting damage. Persistent high pressure begets loss of compliance. High bladder pressure causes inflammation and fibrosis of the bladder wall, leading to a loss of bladder compliance, which, in turn, only makes the bladder storage pressures worse: a vicious feed-forward situation. Ultimately, if unchecked, storage pressure is sufficient to work against ureteral peristalsis, leading to urinary stasis, infections, stone formation and, in its terminal stages, direct pressure effects on the kidney. This is the underlying logic for urodynamic testing to predict the loss of compliance.

Early critics of this concept expressed concerns for overtreatment when proactively treating all children with elevated DLPP. In 1990, Klose et al reported a greater than 90% resolution rate of radiological changes (hydronephrosis and reflux) with initiation of treatment. Why not then just treat once pathology was visually evident? This reactive approach was made obsolete with the recognition that high storage pressures could be monitored, successfully identified and treated. The timely use of anticholinergic drugs and clean intermittent catheterization had immediate effects with lowered rates of VUR, hydronephrosis, renal insufficiency and failure among these patients. There was also seen a lowering of the rate of augmentation cystoplasty, and for those who still progressed to reconstruction, the lower rates of renal failure were important in decreasing overall morbidity and mortality. Today, this opposition seems as odd as if one were arguing to wait on treating vascular hypertension until there was end organ damage.

Despite the general appreciation of the concept, predicting which neurogenic bladder patients will progress to a poorly compliant neuropathic (so called “hostile”) bladder remains imperfect. One of the first challenges was to standardize terminology and definitions. It is hard to communicate and share findings if it is unclear if everyone is actually discussing the same issues and concerns. In 2015, the International Children’s Continence Society created a standardization report that helped to create some degree of uniformity and transparency, and ease the process of pooling and sharing results.

The second challenge is the current nature of urodynamics for bladder compliance. The urodynamic study (typically a multichannel cystometrogram with or without electromyography, and video fluoroscopy) is one of the urologist’s best objective tools in the management of neurogenic bladders. However, one of its great limitations is the need for contextual interpretation by well trained and experienced personnel. The term “urodynamacist” was coined to describe this role of simultaneously conducting and interpreting the study. Interpretation is nuanced, and it has been shown that when this contextual presence is removed, many urologists have difficulty consistently interpreting readings from other centers or even their own units. Pathological findings, normal physiological reactions and test artifacts can become confused. This stands in stark contrast to a test like the electrocardiogram (EKG), where a technician attaches the leads and presses a button, and voila, a fully computerized tracing is generated complete with interpretation. Despite these limitations, urodynamics remains a key decision making factor when we consider the many options now available for treating poor bladder compliance, including new anticholinergic drugs, botulinum toxin injection, neurostimulation and bladder augmentation.

The 40 cm H2O value used as a cutoff by McGuire et al was developed at a time when it was still common to use water manometer cystograms. This methodology could not provide the number of data points that later electronic systems could yield. It obscured the point that the 40 cm H2O was a useful rule of thumb but one still had to look at the urodynamic tracing and clinical history. Casual readers may have misunderstood that any value under 40 cm H2O was safe. Others have noted that while 40 cm H2O may be useful when one is trying to look at large groups of patients, individual patients may benefit from lower pressures, such as 20 to 25 cm H2O. Tarcan et al noted in their study of myelodysplastic children that a lower cutoff value of 20 cm H2O may have greater sensitivity in predicting upper tract changes. Backhaus et al noted that hydrostatic pressures less than 40 cm H2O can cause alterations in some of the molecular determinants of the bladder matrix that affect bladder compliance. In addition, other factors such as the presence of VUR and bladder trabeculations (physical manifestations of poor compliance) if present already portend a high risk of renal deterioration.

Pressure based management with urodynamics, despite its 40-some
XTANDI is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC) or metastatic castration-sensitive prostate cancer (mCSPC).1

When your patients present with mCSPC* or CRPC1...

No need to wait.
START XTANDI.

The first and only oral treatment approved by the FDA in 3 advanced prostate cancer patient types—mCSPC, nmCRPC, and mCRPC1

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LHRH, luteinizing hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

*Metastatic castration-sensitive prostate cancer is defined as metastatic disease in patients who have not yet received, or who have received and can still respond to, androgen deprivation therapy (LHRH therapy or prior bilateral orchiectomy).1

†Castration-resistant prostate cancer is defined as disease progression on androgen deprivation therapy (LHRH therapy or prior bilateral orchiectomy).1

Important Safety Information
Warnings and Precautions

Seizure occurred in 0.5% of patients receiving XTANDI in seven randomized clinical trials. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following predisposing factors: use of medications that may lower the seizure threshold, history of traumatic brain or head injury, history of cerebrovascular accident or transient ischemic attack, and Alzheimer’s disease, meningioma, or leptomeningeal disease from prostate cancer; unexplained loss of consciousness within the last 12 months, history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection. Advise patients of the risk of developing a seizure while taking XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES) There have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder that can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI in seven randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

Ischemic Heart Disease In the combined data of four randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.9% vs 1.3%). Grade 3-4 ischemic events occurred in 1.4% of patients on XTANDI versus 0.7% on placebo. Ischemic events led to death in 0.4% of patients on XTANDI compared to 0.1% on placebo. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

Falls and Fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents. In the combined data of four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo.

Embryo-Fetal Toxicity The safety and efficacy of XTANDI have not been established in females. XTANDI 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 with XTANDI and for 3 months after the last dose of XTANDI.

Adverse Reactions (ARs)

In the data from the four randomized placebo-controlled trials, the most common ARs (≥ 10%) that occurred more frequently (≥ 2% over placebo) in XTANDI-treated patients were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. In the bicalutamide-controlled
XTANDI significantly extended metastasis-free survival\(^1\) and overall survival\(^8\) in patients with nmCRPC\(^1\)

PROSPER was a multinational, randomized, double-blind, placebo-controlled phase 3 study in 1401 patients with nmCRPC who had progressed\(^6\) on LHRH therapy\(^7\). Overall survival data were updated in the final analysis\(^1,3\).

**METASTASIS-FREE SURVIVAL (PRIMARY ENDPOINT)**

\[71\% \quad \text{reduction in the risk of metastasis or death with XTANDI + LHRH therapy}\(^6\) vs placebo + LHRH therapy\(^6\) \quad (HR = 0.29 \ [95\% CI, 0.24-0.35]; \ P < 0.0001)\(^1\)

**OVERALL SURVIVAL (SECONDARY ENDPOINT)**

\[27\% \quad \text{reduction in the risk of death with XTANDI + LHRH therapy}\(^9\) vs placebo + LHRH therapy\(^9\) \quad (HR = 0.73 \ [95\% CI, 0.61-0.88]; \ P = 0.0011)\(^1\)

Permitted at baseline: Patients with prior anti-androgen therapy with a 4-week washout period to randomization. Bicalutamide treatment prior to randomization was received by 55% and 58% of patients in the XTANDI and placebo arms, respectively.\(^4\)

Key eligibility criteria included nmCRPC (central review), \(>3\) rising PSA values despite castrate testosterone levels (\(\leq 50\ ng/dL\)), \(\leq 2\) prior LHRH therapy (within 6 months), no prior chemotherapy, ECOG Performance Status of 0 or 1, and no central or clinically significant cardiovascular disease.\(^6\)

Exclusion criteria included prior abiraterone acetate use, history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, or clinically significant cardiovascular disease.\(^3\)

\(^\text{1}\) The primary endpoint of the study was metastasis-free survival, defined as the interval from randomization to whichever of the following occurred first: 1) loco-regional or distant radiographic progression per blinded independent central review; or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression.\(^1\)

\(^\text{2}\) Overall survival was measured as the interval from randomization to death from any cause.\(^3\)

\(^\text{3}\) Progression was defined as at least 3 rising PSA values (PSA1 < PSA2 < PSA3) taken at least 1 week apart despite castrate levels of testosterone (\(\leq 50\ ng/dL\)) on LHRH therapy or after bilateral orchiectomy.\(^3\)

\(^\text{4}\) Or after bilateral orchiectomy.\(^3\)

**Drug Interactions**

**Effect of Other Drugs on XTANDI**

Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI. Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

**Effect of XTANDI on Other Drugs**

Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

Please see adjacent pages for Brief Summary of Full Prescribing Information.

**References**


For more information, please visit [XtandiHCP.com](http://XtandiHCP.com)

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XTANDI® (enzalutamide) capsules for oral use
XTANDI® (enzalutamide) tablets, for oral use

Initial U.S. Approval: 2012

BRIEF SUMMARY OF PRESCRIBING INFORMATION

The following is a brief summary. Please see the package insert for full prescribing information.

INDICATIONS AND USAGE

XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with:

- Castration-resistant prostate cancer
- Metastatic castration-sensitive prostate cancer

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Seizure

Seizure occurred in 0.5% of patients receiving XTANDI in seven randomized clinical trials. In these trials, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 1776 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy, and all seizure events resolved.

In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, of 8 of 366 (2.2%) XTANDI-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with XTANDI after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (~ 54%), history of traumatic brain or head injury (~ 28%), history of cerebrovascular accident or transient ischemic attack (~ 24%), and Alzheimer’s disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all ~ 5%). Approximately 17% of patients had more than one risk factor.

Advise patients of the risk of developing a seizure while receiving XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XTANDI in patients who develop PRES.

Hypersensitivity

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in seven randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

Ischemic Heart Disease

In the combined data of four randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.9% vs 1.3%). Grade 3-4 ischemic events occurred in 1.4% of patients on the XTANDI arm compared to 0.7% on the placebo arm. Ischemic events led to death in 0.4% of patients on the XTANDI arm compared to 0.1% on the placebo arm.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

Falls and Fractures

Falls and fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In the combined data of four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo. Grade 3-4 fractures occurred in 5% of patients treated with XTANDI and in 2% of patients treated with placebo. The median time to onset of fracture was 336 days (range: 2 to 1914 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.

Embryo-Fetal Toxicity

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI 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 with XTANDI and for 3 months after the last dose of XTANDI.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in WARNINGS and PRECAUTIONS reflect seven randomized, controlled trials (AFFIRM, PREVAIL, TERRAIN, PROSPER, ARCHES, Asian PREVAIL, [NCT02294461], and STRIVE, [NCT01664923]) that were pooled to conduct safety analyses in patients with CRPC (N=3509) or mCSPC (N=572) treated with XTANDI. Patients received XTANDI 160 mg (N=4081 patients) or placebo orally once daily (N=2472 patients) or bicalutamide 50 mg orally once daily (N=387 patients). All patients continued androgen deprivation therapy (ADT). In these seven trials, the median duration of treatment was 13.8 months (range: <0.1 to 87.6) in the XTANDI group.

In four placebo-controlled trials (AFFIRM, PROSPER, PREVAIL, and ARCHES), the median duration of treatment was 14.3 months (range: <0.1 to 87.6) in the XTANDI group. In these four trials, the most common adverse reactions (~ 10%) that occurred more frequently (~ 2% over placebo) in the XTANDI-treated patients were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension.

AFFIRM (NCT00974311): XTANDI versus Placebo in Metastatic CRPC FollowingChemotherapy

AFFIRM enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids. Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in AFFIRM that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in AFFIRM

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<th>Placebo N = 399</th>
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<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
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<tr>
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<td>Dizziness²</td>
<td>9.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Spinal Cord Compression and Cauda Equina Syndrome</td>
<td>7.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Mental Impairment Disorders³</td>
<td>4.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>4.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>
PREVAIL (NCT01212991): XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in PREVAIL that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in AFFIRM (cont’d)

Table 2. Adverse Reactions in PREVAIL

Table 3. Adverse Reactions in TERRAIN

Metastatic CRPC

TERRAIN enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI and 5.8 months with bicalutamide. Discontinuations with an adverse event as the primary reason were reported for 7.6% of XTANDI-treated patients and 6.3% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and pathological fracture, which occurred in 3.8% of XTANDI-treated patients for each event and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (≥ 10%) in XTANDI-treated patients.

TERRAIN (NCT01288911): XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

PROSPER (NCT02003924): XTANDI versus Placebo in Non-metastatic CRPC Patients

PROSPER enrolled 1401 patients with non-metastatic CRPC, of whom 1395 received at least one dose of study drug. Patients were randomized 2:1 and received either XTANDI at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months (range: 0.0 to 42 months) with XTANDI and 11.1 months (range: 0.0 to 43 months) with placebo. Overall, 32 patients (3.4%) receiving XTANDI died from adverse events. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 2), and secondary malignancy (n = 5; one each of acute myeloid leukemia, brain neoplasm, mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse events of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1). Grade 3 or higher adverse reactions were reported among 31% of XTANDI-treated patients and 23% of placebo-treated patients. Discontinuations with an adverse event as the primary reason were reported for 9.4% of XTANDI-treated patients and 6.0% of placebo-treated patients. Of these, the most common adverse event leading to treatment discontinuation was fatigue, which occurred in 1.6% of the XTANDI-treated patients compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

PROSPER (NCT02003924): XTANDI versus Placebo in Non-metastatic CRPC
≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

placebo-treated patients. The most common adverse events resulting in permanent discontinuation in XTANDI-treated patients were alanine aminotransferase increased, and seizure, each in 0.3%. The most common reason for death in ≥2 patients included heart disease (n=3), sepsis (n=2) and stroke (n=2). The most common adverse events resulting in permanent discontinuation due to adverse events as reasons for death in ≥2 patients included heart disease (n=3), sepsis (n=2) and stroke (n=2).

Disabilities and Administration Site Conditions

Investigations

Weight Decreased 5.9 0.2 1.5 0.0

Injury, Poisoning and Procedural Complications

Fall 11 1.3 4.1 0.6

Fractures 9.8 2.0 4.9 1.7

Psychiatric Disorders

Anxiety 2.8 0.2 0.4 0.0

1. Includes dizziness and vertigo.

2. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.

3. Includes anxiety and fatigue.

4. Includes all osseous fractures from all sites.

ARCHES randomized 1150 patients with mCSPC, of whom 1146 received at least one dose of study drug. All patients received either a gonadotropin-releasing hormone (GnRH) analogue concurrently or had bilateral orchiectomy. Patients received either XTANDI at a dose of 160 mg once daily (N=572) or placebo (N=574).

The median duration of treatment was 12.8 months (range: 0.2 to 26.6 months) with XTANDI and 11.6 months (range: 0.2 to 24.6 months) with placebo.

Overall, 10 patients (1.7%) receiving XTANDI died from adverse events. The reasons for death in ≥2 patients included heart disease (n=3), sepsis (n=2) and pulmonary embolism (n=2). Eight patients (1.4%) receiving placebo died from adverse events. The reasons for death in ≥2 patients included heart disease (n=2), and sudden death (n=2). Grade 3 or 4 adverse events were reported in 24% of patients treated with XTANDI. Permanent discontinuation due to adverse events as the primary reason was reported in 4.9% of XTANDI-treated patients and 3.7% of placebo-treated patients. The most common adverse events resulting in permanent discontinuation in XTANDI-treated patients were alanine aminotransferase increased, aspartate aminotransferase elevation, and seizure, each in 0.3%.

Dose reductions due to an adverse reaction occurred in 4.4% of patients who received XTANDI. Fatigue/asthenia was the most frequent adverse reaction requiring dose reduction in 2.1% of XTANDI-treated patients and 0.7% of placebo-treated patients.

Table 5 shows adverse reactions reported in ARCHES that occurred at a ≥2% higher frequency in the XTANDI arm than in the placebo arm.

Table 5. Adverse Reactions in ARCHES

<table>
<thead>
<tr>
<th></th>
<th>XTANDI (N = 572)</th>
<th>Placebo (N = 574)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>4.9 0.2</td>
<td>2.6 0</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive and Memory Impairment</td>
<td>4.5 0.7</td>
<td>2.1 0</td>
</tr>
<tr>
<td>Restless Legs Syndrome</td>
<td>2.4 0</td>
<td>0.3 0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>27 3.3</td>
<td>22 0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8.0 3.3</td>
<td>5.6 1.7</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic conditions</td>
<td>24 1.7</td>
<td>20 1.8</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>6.3 0.2</td>
<td>4.0 0.2</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures</td>
<td>6.5 1.0</td>
<td>4.2 1.0</td>
</tr>
</tbody>
</table>

1. CTCAE v4.03.
2. Includes memory impairment, amnesia, cognitive disorder, dementia, disturbance in attention, transient global amnesia, dementia Alzheimer’s type, mental impairment, senile dementia and vascular dementia.
3. Includes asthma and fatigue.

Table 4. Adverse Reactions in PROSPER

<table>
<thead>
<tr>
<th></th>
<th>XTANDI (N = 930)</th>
<th>Placebo (N = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>9.6 0.2</td>
<td>3.9 0.2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 0.5</td>
<td>5.2 0</td>
</tr>
<tr>
<td>Headache</td>
<td>9.1 0.2</td>
<td>4.5 0</td>
</tr>
<tr>
<td>Cognitive And Attention Disorders</td>
<td>4.6 0.1</td>
<td>1.5 0</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>13 0.1</td>
<td>7.7 0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 4.6</td>
<td>5.2 2.2</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
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<tr>
<td>Nausea</td>
<td>11 0.3</td>
<td>8.6 0</td>
</tr>
<tr>
<td>Constipation</td>
<td>9.1 0.2</td>
<td>6.9 0.4</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>40 4.9</td>
<td>20 0.9</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>5.9 0.2</td>
<td>1.5 0.0</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>11 1.3</td>
<td>4.1 0.6</td>
</tr>
<tr>
<td>Fractures</td>
<td>9.8 2.0</td>
<td>4.9 1.7</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.8 0.2</td>
<td>0.4 0.0</td>
</tr>
</tbody>
</table>

Table 6 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies.

Table 6. Laboratory Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>XTANDI (N = 3173)</th>
<th>Placebo (N = 2282)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20 0.9</td>
<td>17 0.4</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>17 0.4</td>
<td>9.8 0.2</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>83 3.2</td>
<td>75 3.1</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>16 0.1</td>
<td>13 0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>13 1.4</td>
<td>8.6 1.5</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>6.8 0.1</td>
<td>4.5 0</td>
</tr>
</tbody>
</table>

Hypertension

In the combined data from four randomized placebo-controlled clinical trials, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: vomiting

Neurological Disorders: hyperesthesia (edema of the face, tongue, lip, or pharynx)

Drug Interactions

Drugs that Inhibit CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold.

Co-administration of XTANDI with a strong CYP2C8 inhibitor should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that Induce CYP3A4

Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) with XTANDI should be avoided if possible. St John’s wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI.

Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady-state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozone, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephentoin, clopidogrel) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose (see Data).
OVERDOSAGE

In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.
Predicting Loss of Compliance in Neurogenic Bladder

Continued from page 11

years of expanded use, remains a young concept, and has continued to evolve as a predictor of which neurogenic bladders will clinically deteriorate. While we have noted its limitations, it is worth recalling that Einthoven first introduced the idee of an elektrocardiogram at the Dutch Medical Association meeting in 1893, although it was not until 50 years later that the now familiar 12-lead EKG was standardized.13,15 When viewed in this historical context, the current efforts to standardize terminology, methodology, and interpretation of urodynamics portend a good future (see figure).


Outpatient Percutaneous Nephrolithotomy: Should Day Surgery be the New Gold Standard?

Garen Abedi, MD Seth Bechis, MD
San Diego, California

Traditionally, patients undergoing percutaneous nephrolithotomy (PCNL) have been admitted to the hospital for observation for a variety of reasons, including monitoring for bleeding, sepsis, administration of intravenous antibiotics and pain control. With the shift to tubeless (no nephrostomy tube) or “totally tubeless” procedures and their reduction in pain, hospital stay and recovery time, there has been a renewed interest in considering outpatient surgery.

Can Patients Safely Go Home the Same Day as Their Surgery?

In a small series, Shahrour and Andonian showed the feasibility of same-day discharge for patients undergoing PCNL (see table). The inclusion criteria were strict and consisted of generally healthy patients (American Society of Anesthesiologists® [ASA] score 2 or less), single tract access without any intraoperative complications and without any hemodynamic issues in the postoperative recovery area. Average stone size was 17 mm and body mass index (BMI) was 25.9 kg/m², and the complication rate was 20%. In larger studies, which loosened the inclusion criteria to include patients with staghorn stones and ASA scores greater than 2, outpatient PCNL patients had relatively low complication rates.12 The table summarizes findings of selected studies evaluating outcomes of outpatient PCNL.

Why Should We Consider Day Surgery for PCNL?

Outpatient surgeries offer benefits to both the hospital and patient. Postoperative narcotic use is decreased, the patient is able to sleep in the comfort of his or her own bed, and the hospital saves on patient care costs since insurance reimbursements as an outpatient procedure. In the era of COVID-19, being able to return home and avoid an overnight hospital stay is particularly attractive.

In our experience at University of California San Diego Health, patients receive intercostal nerve blocks and are placed on an opiate-sparing protocol, which we believe is part of the prerequisite for sending patients home after their procedure. Without proper pain management, outpatient PCNL becomes a challenging endeavor. In our early study comparing inpatient with outpatient PCNL cases, the 2 most common reasons for outpatient PCNL patients staying overnight at the hospital were poor pain control (41%) and social factors (35%).

Is it Possible for More Complex PCNL Patients to be Discharged Home from the Recovery Area?

Several of the studies in the table included complex patients and reported low complication rates. In our series, in which we did not apply strict selection criteria, 44% of patients had elevated ASA scores (3 and higher), 43% had a stent or nephrostomy tube in place prior to surgery for PCNL.

Table. Summary of recent studies evaluating outpatient PCNL

<table>
<thead>
<tr>
<th>References</th>
<th>No. Pts</th>
<th>BMI or ASA Requirement</th>
<th>Stone Requirement</th>
<th>Access Requirement</th>
<th>Stone Size</th>
<th>BMI</th>
<th>Readmission Rate (%)</th>
<th>Emergency Department Visit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shahrour and Andonian*</td>
<td>10</td>
<td>BMI &lt;3, ASA &lt;3</td>
<td>None</td>
<td>Single access</td>
<td>Mean±SD 17±7.4 mm</td>
<td>Mean 25.9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Beiki et al†</td>
<td>52</td>
<td>ASA ≥3</td>
<td>None</td>
<td>None</td>
<td>Mean 19.6 mm (range 7–60)</td>
<td>Mean 29.3</td>
<td>4 (range 21–52)</td>
<td>12</td>
</tr>
<tr>
<td>Fahmy et al†</td>
<td>146</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Mean±SD 50±381 mm²</td>
<td>Mean 31</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Bechis et al†</td>
<td>43</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Mean±SD 25.8±2.7 mm</td>
<td>Mean±SD 27.8±1.2</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Schoenfeld et al†</td>
<td>52</td>
<td>BMI &lt;45</td>
<td>None</td>
<td>Single access</td>
<td>Mean±SD 23±14 mm</td>
<td>Mean 30.4</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Tian et al†</td>
<td>18</td>
<td>ASA ≥2</td>
<td>S.T.O.N.E. score ≥7</td>
<td>Mini-PCNL</td>
<td>Not reported</td>
<td>5.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*S.T.O.N.E. score consists of (S)ize, (T)opography (location of stone), (O)struction, (N)umber of stones present and (E)valuation of Hounsfield units.
surgery, 45% underwent multiple punctures to achieve access and 17% had more than 1 dilated renal access tract. Despite this more complex cohort, we had acceptable complication rates. In our experience, significant renal bleeding or precursors of infectious complications are apparent perioperatively or immediately postoperatively, allowing for identification of patients needing admission before the time that they would be discharged home.

Nonetheless, patient selection—whether preoperative or postoperative—is essential for the success of outpatient PCNL. For the urologist starting out, selecting healthier patients (low BMI and low ASA) with smaller stones and simple renal anatomy requiring a single access tract likely offers a more feasible route to discharging patients on postoperative day 0. From a patient perspective, they may also be more amenable to going home early if their procedure is “tubeless” (without a nephrostomy tube). It has been shown previously that the presence of a nephrostomy tube introduces significant morbidity after PCNL. Perhaps the clearest indication of whether a patient can be safely discharged on the same day is their clinical status in the postoperative recovery area, including stable vital signs, afibrile status, good pain control and normal voiding function. Clinical factors aside, thorough patient counseling both in the office during the preoperative visit and postoperatively plays a major role in determining the ability to have a successful outpatient PCNL practice. Proper counseling and setting realistic expectations allow the patient to be comfortable with the idea of going home after a surgical procedure.

In an era when hospital beds may be scarce at times and health care costs are rising, PCNL day surgery offers a reasonable strategy to address these issues, albeit in a properly selected patient. In a Canadian cost analysis evaluation of PCNL procedures, outpatient PCNL resulted in $3,000 savings per case. Factor in the number of cases each year that could potentially be sent home on the same day and the savings overall are substantial. One new addition in recent years to a urologist’s armamentarium has been the mini-PCNL. In small studies, mini-PCNL has been shown to be amenable to same day surgery, although given the narrow inclusion criteria, it is difficult to generalize these promising early results to a wider population.

All in all, same-day discharge for PCNL patients is feasible as long as certain criteria have been met. The goal of outpatient PCNL is to minimize complication rates and maximize patient recovery.

Which patients can be safely discharged home on the day of surgery? The answer ultimately lies in surgeon comfort and clinical judgment, with patient selection criteria as an additional guide.


Lessons Learned in the Adoption of Supine Percutaneous Nephrolithotomy

Brian Eisner, MD
Boston, Massachusetts

Percutaneous nephrolithotomy (PCNL) was initially described as a procedure to be performed in the prone position in 1976, and remained a prone-only procedure for 2 decades until the description of supine PCNL in 1998.1 The most recent global study on PCNL [nearly 10 years old] reports the proportion of PCNLs worldwide by position as 80% prone and 20% supine.1 At present, PCNL position debates are a feature of many urology congresses, where debaters argue the merits of their preferred position as well as the downsides of the opposite.

As a resident and fellow, I observed and learned only prone PCNL. However, certain aspects of supine PCNL appealed to me as potentially advantageous compared to prone PCNL. These include but are not limited to 1) ease of performing endoscopic combined intrarenal surgery, 2) increased success of treatment of upper pole stones from a lower pole puncture, 3) less variation in hemodynamic parameters and 4) decreased risks of ventilation and general anesthesia, especially in overweight and obese patients.2 With these in mind, I began performing supine PCNL in 2016, starting with the most straightforward PCNL procedures. As I continued to realize the aforementioned advantages of the supine position, the proportion of supine PCNL procedures in my own practice rose gradually from around 25% in the first year of incorporation to nearly 90% at present. It is important to acknowledge that although I believe there are advantages to supine PCNL (when the position is feasible), several recent meta-analyses have failed to report that 1 position is definitively superior to the other in terms of stone-free rates or complication rates.3,4 Following are some lessons learned from the perspective of a surgeon trained in prone PCNL who has adopted supine PCNL for the majority of PCNL procedures.

Lesson 1. For patient positioning, the patient should be close to the lateral edge of the bed on the operative side, and ideal body rotation angle is <20 degrees.2 It is tempting for those inexperienced with supine PCNL to overrotate the patient, but increased rotation can make fluoroscopy images difficult to interpret. Anatomical landmarks include the ribs, the anterosuperior iliac spine (ASIS) and the posterior axillary line (PAL). Puncture posterior to the PAL minimizes the risk of intestinal injury (fig. 1).

Figure 1. Patient position for supine PCNL with landmarks noted. Note that degree of torso angulation is <20 degrees because surgeon’s fist cannot fit fully beneath patient in this example.
Lessons Learned in Adoption of Supine Percutaneous Nephrolithotomy

Lesson 2. The simplest supine PCNL puncture technique is to begin with a puncture that is parallel to the floor of the operating room. Before the procedure, review of the preoperative computerized tomogram (CT) can help determine if supine puncture is safe and will avoid injury to adjacent structures. During the procedure, ultrasound can be used to determine the skin site of puncture that enables a puncture parallel to the floor (if performing fluoroscopy guided puncture); otherwise, ultrasound can be used for the entirety of the puncture (figs. 2 and 3).

Lesson 3. Even a mild rotation of the torso will make the kidney appear closer to the spine on fluoroscopic images. This can be off-putting or anxiety-provoking for the surgeon who is accustomed to interpreting standard anteroposterior fluoroscopic images of nonrotated patients in the prone position (fig. 4).

Lesson 4. The kidney can be more mobile in the supine position and, as such, puncture technique must sometimes accommodate for this. This phenomenon seems to be greatest for patients with body mass index <25 kg/m². Application of manual abdominal pressure (by the surgeon’s or assistant’s hand) or placement of a guidewire into the bladder (or out of the urethra) are techniques that have been suggested for patients with significant renal mobility. Studies have not been successful in quantifying the relative increased mobility of the kidney in the supine vs prone position; neither have they been able to demonstrate that increased mobility leads to changes in success rates or complications of supine PCNL. Nonetheless, it is an important consideration, and this increased kidney mobility may result in the need for rapid, real-time adjustment of the needle trajectory in order to achieve the desired puncture.

Lesson 5. Upper pole puncture is feasible in the supine position in the majority of patients. A recently reported multicenter study demonstrated the safety and feasibility of supine upper pole puncture. However, the prone position enables the surgeon to achieve a puncture that is in a more medial position on the patient’s flank (ie closer to the spine) than the supine position. For a small subset of patients, those with retrorenal liver, spleen or colon, the safest window for puncture is via the upper pole and close to the spinal column, and the prone position may be the safest position for PCNL (fig. 5).

Lesson 6. My own personal journey in incorporating supine PCNL into my practice has helped me understand the following: There is no “correct” or “superior” position for PCNL. Advocates of each position can and continue to make cogent arguments and debates in support of either position. As with many topics in endourology (eg stented vs stentless ureteroscopy, standard vs mini-PCNL, use or omission of ureteral access sheath during ureteroscopy), patient characteristics, surgeon experience and surgeon preference inform the choices that are made in the operating room. The goal of any procedure is to optimize success while minimizing complications. Personally, I believe that my patients and I have realized many of the theoretical benefits of supine PCNL mentioned above, which explains the high percentage of supine PCNL procedures in my practice. I do, however, perform prone PCNL for patients such as those described in Lesson 5 above, where anatomical considerations favor the prone position.

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Urodynamic studies (UDS), with their complexity in terms of obtaining, recording and interpreting data, are ideally suited for innovative methods to take advantage of the electronic health record (EHR) for data aggregation and analytics. EHR platforms allow users to design and implement structured data entry systems (SDES), which allow data to be entered in real time based on predefi ned categories and conditions. SDES can also be tailored to specific procedures and allow for uniformity and standardization of data entry and collection, which is a must when multiple providers are performing a complex procedure such as UDS. Use of SDES has been shown to decrease research costs, increase patient-oriented research and facilitate medical advancements.1 With this in mind, we aimed to develop a SDES for UDS that would allow us to better serve our patients by standardizing the study, provide a safety function to allow us to quickly aggregate data from all UDS and analyze data to find the most hostile bladder, and allow for effi cient hypothesis generated research.

A working group of pediatric urologists, advanced practice providers and members of our hospital informatics team designed and implemented a template SDES in a flowsheet within Epic (Epic Systems Corporation, Madison, Wisconsin). Over a 3-month trial period, the template was used in the offi ce and additional parameters were added as determined by a consensus of the working group. The fi nal SDES included dropdown and fi ll-in questions on clinical history, UDS technique, UDS fi ndings and subjective assessments including safe bladder capacity and if the study led to change in management (fi g. 1).2 The SDES also included equations that automatically calculated estimated bladder capacity (EBC) and 25%, 50% and 75% of EBC to assist with timing of pressure measurements and fi luoroscopic imaging. Since the SDES flowsheet is fi lled out in real time, all data are easily incorporated into a prepopulated area of the clinical note, thus fulfilling billing requirements and improving effi cacy for the provider who does not need to repeat or retype the information. The template for the clinical note also has space for the provider to enter a history and summary impression in prose, which allows the clinician to provide a record of their thinking behind their decision making based on the urodynamic data. Another benefi t of SDES is that they help standardize how UDS are performed with multiple providers, in effect serving as a checklist.

The real benefi t of using an SDES flowsheet for UDS in the offi ce come from the fact that the information obtained and data recorded are searchable. Each week our hospital information systems team aggregates data from all UDS performed that week and sends the data to us via email in a CSV delimited format for easy use in common data analysis programs such as Excel®, Stata® and R (R Project for Statistical Computing, Vienna, Austria). Weekly data can be added to previously collected studies to form a prospective database, which can be used for monitoring patients for safety, quality improvement initiatives and for research projects. Data can also be entered and uploaded into REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee) for sharing across all urodynamic studies performed that week and sends the data to us via email in a CSV delimited format for easy use in common data analysis programs such as Excel®, Stata® and R (R Project for Statistical Computing, Vienna, Austria). Weekly data can be added to previously collected studies to form a prospective database, which can be used for monitoring patients for safety, quality improvement initiatives and for research projects. Data can also be entered and uploaded into REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee) for sharing across

![Figure 1](image1.png)

Figure 1. UDS structured data entry system utilized in our department. SDES are easy to use fi lowsheets that can be opened up in patient EHR and allow for prompted entry of data in real time. UTI, urinary tract infection. DESD, detrusor-external sphincter dyssynergia.

![Figure 2](image2.png)

Figure 2. Example of using SDES data to quickly assess patients above safe end storage bladder pressure. Graph shows end storage detrusor pressure for all UDS obtained at our institution in last 6 months. Red line set at 25 cm H2O as cutoff for safe end storage bladder pressure (this value can be set to whatever level is appropriate for patient population and determined by provider). All patients above this threshold can be reviewed and checked for adherence to followup plan. Patients with missed appointments can be called and rescheduled.
Data Analytics and Urodynamics in Children

Continued from page 22

multiple institutions if needed for a multicenter study or trial.

Since implementing the UDS SDES flowsheet in June 2015, we have now aggregated data from 2,210 UDS at our institution. Overall, review of data consistently shows that less than 5% of all cells or data entry points are missing. This high data accrual rate is achieved by the physician performing the UDS without the need for research assistants or any manual copying of the data, which could lead to errors.

Quality improvement is one way to harness the power of SDES in the care of complex patients and can be implemented via the “plan-do-study-act” (PDSA) approach. An example of the ease with which collected data can be used for patient safety review or quality improvement is illustrated in figure 2, which shows the end storage pressures obtained from each study over the last 6 months. By organizing the studies in this way, a cutoff can be determined above which all patient charts can be reviewed to see if followup has been consistent and management changes implemented. Patients with missed followup visits can be reached out to and called so that these high risk patients are not lost for months or years.

While our pilot use of SDES in the EHR focused on UDS, SDES flowsheets can also be implemented for other office or operating room procedures. Our colleagues have designed flowsheets and are using them in our division for hypospadias diagnoses both in clinic notes to standardize measurements and preoperative and postoperative findings. Additionally, SDES flowsheets can be used within operative notes to standardize data collection and facilitate recording of information for patient safety and research purposes. The near universal use of the EHR allows for the possibility of multi-institutional sharing of SDES flowsheets and aggregation of data across centers for quality improvement and research purposes. While SDES flowsheets take buy-in from providers, minimization of provider resistance can be accomplished by creating SDES that are easy to use without increasing time burden or interrupting clinical workflow.


Revisiting Autologous Fascial Pubovaginal Slings

Victor W. Nitti, MD
Los Angeles, California

The surgical treatment of female stress urinary incontinence (SUI) has evolved over the last 3 decades. In recent years, higher quality outcomes research has shown that 3 procedures are superior to others based on level 1 evidence. Mid-urethral synthetic slings (MUS), autologous fascia pubovaginal slings (PVS) and Burch colposuspension are the procedures that are supported by the American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine and Urogynecology (SUFU) guideline on the surgical treatment of female stress urinary incontinence in the index patient as first line surgical therapy to treat SUI. After being introduced in the late 1990s, MUS overwhelmingly became the most popular surgical procedure to treat SUI due to the excellent outcomes, low complication rates and short recovery time. However, since 2008, international regulatory agencies have increased regulation and issued warnings on vaginal mesh, and this has led to increased scrutiny of MUS by patients, surgeons and health care advocates. As such, the AUA/SUFU guideline recommends that all patients be counseled regarding the risks and benefits of the use of synthetic mesh to treat SUI, as well as understand alternatives to MUS. Increased concerns about synthetic mesh plus an increasing number of patients who have failed or suffered a complication from MUS have created and increased the need for surgical expertise in alternative procedures such as PVS. In our own Female Pelvic Medicine and Reconstructive Surgery specialty practice, we found that in women undergoing surgical treatment of SUI, the use of PVS went from 0% in 2010–2011 (before the 2011 FDA notification) to 6% to 20% per year from 2012 through 2017. This included index patients with uncomplicated SUI who chose PVS over MUS.

The popularity and almost exclusive use of MUS to treat female SUI have left a large gap in the performance and surgical teaching of PVS. In 2012, urologists submitting surgical logs for certification or recertification reported that 86% of surgical and minimally invasive treatments for female SUI were MUS, and less than 1% were PVS. On the urogynecology side, a recent Internet based survey of members of the International Urogynecological Association found that 72% of members did not even offer PVS to their patients. Clearly, as we move into 2021, there will continue to be an increased demand for PVS to treat both simple and complex SUI in women. Thus, it is important that urologists and urogynecologists are adequately trained in the performance of these procedures. Appendix 1 lists the common indications for PVS.

Rectus Fascia vs Fascia Lata

The majority of level 1 evidence on PVS is for autologous fascia. Other biologics such as allographic fascia and various xenographs have been used, although the results are generally inferior. The sentinel study...
INDICATIONS
ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
• Metastatic castration-sensitive prostate cancer (mCSPC)
• Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Cerebrovascular and Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies. In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA® compared with 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from a cerebrovascular event. Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures — In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA®, and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Falls — In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for falls.

Seizure — In two randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® 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 3 months after the last dose of ERLEADA®. See Use in Specific Populations (8.1, 8.3).

ADVERSE REACTIONS
Adverse Reactions — The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)
• Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (3%), placebo 10% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0.7%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%)
• Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (3%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 76% (0.1%), placebo 45% (0%); hyperglycemia ERLEADA® 79% (2%), placebo 59% (1%); hypertriglyceridemia ERLEADA® 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.5%)

Janssen Biotech, Inc.
Rash — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%).

The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

**DRUG INTERACTIONS**


effect of ERLEADA® on Other Drugs — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability [see Dosage and Administration (2.2)].


effect of ERLEADA® on Other Drugs — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability [see Dosage and Administration (2.2)].

**Study Design:** TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had newly diagnosed mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. Patients with severe (≥ 4ever or lung metastases) or the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchiectomy. The dual primary endpoints were overall survival (OS) and rPFS. All patients who enrolled in the TITAN study started ADT for mCSPC 6 months prior to randomization.

**Study Design:** SPARTAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (N=1207). Patients had a PSA doubling time <10 months and serum testosterone levels <50 ng/dL. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review. Patients with a history of severe, predisposing factors for severe, or receiving drugs known to decrease the serum threshold or to reduce severity were excluded. Patients were randomized 2:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchietomy. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic chemotherapy.

**References:**

Brief Summary of Prescribing Information for ERLEADA® (apalutamide) tablets

ERLEADA® (apalutamide) tablets

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

TITAN, a randomized (1:1), double-blind, placebo-controlled, multi-center, phase III clinical trial, enrolled patients who had known or developing distant metastases. The median duration of exposure was 24 months (range: 0.1 to 127 months) in patients who received ERLEADA and 18 months (range: 0.1% to 127 months) in patients who received placebo. Grade 3-4 fractures occurred in 3% of patients treated with ERLEADA and in 7% of patients treated with placebo. The median onset was at 10 months (range: 0.1 to 59 months) in patients treated with ERLEADA and at 9 months (range: 0.1 to 59 months) in patients treated with placebo. ADVERSE REACTIONS

Table 1: Adverse Reactions in TITAN (mCSPC)

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, rash associated with ERLEADA was most commonly reported as grade 1 (76%) versus placebo (71%). Seizure occurred from 159 to 650 days after last dose of ERLEADA and in 0.1% of patients treated with placebo. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA.

Embryo-Fetal Toxicity

The safety and efficacy of ERLEADA have been established in females. Based on animal data, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female (see Clinical Pharmacology: Nonclinical Toxicology). Advise females with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA (see Use in Specific Populations).

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

Carcinogenicity and Herbicide Carcinogenicity Events (see Warnings and Precautions). Fractures (see Warnings and Precautions). Falls (see Warnings and Precautions).

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reaction (≥ 10%) that occurred more frequently in the ERLEADA (apalutamide) and placebo arms of the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, anemia, rash, decreased appetite, fall, weight decreased, hyper tension, hot flush, diarrhea, and fracture.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ERLEADA (N=803)</th>
<th>Placebo (N=803)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Rash</td>
<td>25 (3.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>2 (0.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>7 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rash confluent</td>
<td>2 (0.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rash generalized</td>
<td>5 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rash urticarial</td>
<td>2 (0.2)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Additional clinically significant adverse reactions occurring in ≥5% of patients treated with ERLEADA included hypothyroidism (5% versus 2% on placebo), peripheral neuropathy (3% versus 2% on placebo), hyponatremia (4% versus 1% on placebo), and postural hypotension (1% versus 1% on placebo).
ERLEADA® (apalutamide) tablets

(2.2) in Full Prescribing Information]. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

Effect of ERLEADA on Other Drugs

CYP4A4, CYP2C9, CYP2C19, and UGT Substrates

ERLEADA is a strong inducer of CYP4A4 and CYP2C19, and a weak inducer of CYP2C8 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP4A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyltransferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity [see Clinical Pharmacology (12.3) in Full Prescribing Information].

P-gp, BCRP, or OATP1B1 Substrates

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The safety and efficacy of ERLEADA have not been established in females. Based on its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy [see Clinical Pharmacology (12.1) in Full Prescribing Information]. There are no human data on the use of ERLEADA in pregnant women. ERLEADA is not indicated for use in females, so animal embryo-fetal developmental toxicology studies were not conducted with apalutamide.

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA, [see Use in Specific Populations].

Infertility

Males

Based on animal studies, ERLEADA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) in Full Prescribing Information].

Pediatric Use

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

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and over. No overall differences in effectiveness were observed between older and younger patients.

Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse events occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

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

Cerebrovascular and Ischemic Cardiovascular Events

Inform patients that ERLEADA has been associated with cerebrovascular and ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cerebrovascular or a cerebrovascular event occur [see Warnings and Precautions].

Falls and Fractures

Inform patients that ERLEADA is associated with an increased incidence of falls and fractures [see Warnings and Precautions].

Seizures

Inform patients that ERLEADA has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they experience a seizure [see Warnings and Precautions].

Rash

Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash [see Adverse Reactions].

Dosage and Administration

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

Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see Dosage and Administration (2.1) in Full Prescribing Information].

Instruct patients who have difficulty swallowing tablets whole to mix the recommended dose of ERLEADA tablets with applesauce. Do not crush tablets [see Dosage and Administration (2.2) in Full Prescribing Information].

Embryo-Fetal Toxicity

Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman [see Warnings and Precautions].

Infertility

Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA [see Use in Specific Populations].

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Revisiting Autologous Fascial Pubovaginal Slings

on PVS was the randomized controlled SISTEr (Stress Incontinence Surgical Treatment Efficacy) Trial, which compared autologous rectus fascia sling to Burch procedure in a large population. The majority of other series have also reported the use of autologous rectus fascia for PVS. However, in some women, the use of rectus fascia can be challenging, for example in those with extensive prior abdominal surgery, synthetic mesh in the abdominal wall, poor quality abdominal fascia or significant central obesity. In such cases, autologous fascia lata can be used as an alternative to rectus fascia with similar results. It has been our experience that in such patients, fascia lata harvest has a lower morbidity and a quicker recovery time than rectus fascia harvest. In a recent nonrandomized cohort study, we found overall complications were comparable between fascia lata and rectus fascia groups, although the proportion of Clavien grade 2 or greater complications was higher in the rectus fascia group (4.8% vs 20.2%). It has become our practice to offer both rectus fascia and fascia lata (when appropriate) to all women undergoing PVS, and to discuss the pros and cons of each. The relative indications for fascia lata are summarized in Appendix 2.

Summary
In 2021, PVS should be a valued option for the treatment of SUI in women. It is applicable to the index patient as well as women with more complicated SUI. One must, however, keep in mind that total complications of PVS in general are higher than for MUS. While the risks of mesh-specific complications (erosion, exposure, pain related to synthetic material) are eliminated, there is an approximately threefold higher risk of voiding dysfunction requiring a second procedure (eg sling revision or urethropaxy) and a higher incidence of wound complications (hernia, seroma, wound infection). Thus, thorough counseling and shared decision making are critical. With that said, it is vital that we continue to train the current and next generation of urologists in this time-honored procedure.

Vaginal Lasers for Use in Genitourinary Symptoms: Ready for Prime Time?

The genitourinary syndrome of menopause (GSM) is a common condition affecting more than half of postmenopausal women. Symptoms include vaginal dryness, dysuria, urinary urgency/frequency and recurrent urinary tract infections. The mainstay of treatment for GSM is local hormone replacement, most commonly with estradiol creams or inserts. Vaginal laser therapies (VLTs) provide an additional option for women to treat these bothersome symptoms that can severely affect quality of life and overall health. They are thought to act by inducing microtrauma to encourage collagen formation, angiogenesis and thickening of the vaginal epithelium. Treatments are typically performed in the office, with 3 short procedures separated by 4 to 6 weeks each.

Common types of lasers used for the treatment of GSM are the fractional CO₂ (ablative) laser and the Er:YAG (nonablative) laser. Although these technologies have received U.S. Food and Drug Administration (FDA) approval for use in incision, ablation and coagulation of soft tissues, including in the genitourinary system, their initial marketing and use were targeted at consumers as a treatment for “vaginal rejuvenation.” In addition, manufacturers encouraged their use in many genitourinary conditions, including vaginal laxity and stress urinary incontinence, without evidence to show their efficacy. “Vaginal rejuvenation” is an unfortunate term used to describe treatment of GSM, giving VLTs a reputation akin to cosmetic surgery. With their increased use over the last 5 years, and as a result of some reported adverse effects, the FDA subsequently issued a safety communication in 2018 alerting consumers and health care providers that the use of VLTs for the purpose of “vaginal rejuvenation” has not been thoroughly evaluated.

In response to the 2018 FDA safety communication, several national and international associations have published committee opinions and statements regarding the use of VLTs in genitourinary conditions. A committee opinion from the International Urogynecological Association in 2018 suggested that VLTs have promise in the treatment of GSM but require more robust clinical trials to recommend their routine use. A best practice statement by the International Society for the Study of Vulvovaginal Disease and the International Continence Society in 2018 noted a lack of evidence to support the routine use of VLTs in the treatment of GSM. More recently, a clinical consensus statement was published by the American Urogynecologic Society in May 2020. Perhaps in consideration of studies published in the last several years, this group found that VLTs have promise in the treatment of GSM, with benefits lasting up to 1 year. In regard to safety, it was noted that VLTs have a favorable profile but that the long-term sequelae of treatment are unknown.

Although the intention of the FDA safety communication was to protect consumers from predatory marketing, the actual effect may have been to limit treatment choices for women with GSM by creating an unwarranted fear regarding the safety of VLTs. A
Artificial Urinary Sphincter Erosion: Which Patients Are at Risk?

As urologists, the treatment of GSM is a standard part of our practice, and clinicians should be knowledgeable regarding the use of VLTIs. Although there is a general consensus that more robust clinical data are needed to support the long-term efficacy and safety of VLTIs in the treatment of GSM, the 2018 FDA safety communication should not be interpreted to mean that the treatments are highly likely to cause harm. To the contrary, the evidence for their use in GSM shows good short-term safety and efficacy without strong evidence of serious adverse events. The questions regarding which patients represent the best candidates for treatment, the ideal number of treatments and treatment intervals and the long-term safety and efficacy have yet to be answered. Therefore, the routine use of VLTIs should not be recommended for GSM, but their use in clinical trials as well as use by qualified and knowledgeable physicians has the potential to help many women experiencing GSM.

The technology is currently being used by many different clinicians, ranging from plastic surgeons to aesthetic based nurse practitioners, with little knowledge of the female genitourinary tract. As urologists, we should continue to stay at the forefront of research in the use of VLTIs for GSM.


Risk Factors for AUS Erosion

Patient comorbidities including peripheral vascular disease, diabetes mellitus and smoking, all of which decrease microvascular supply to the urethra, have been identified as risk factors for erosion in retrospective studies. Unfortunately, the effect size has been poorly defined and is generally a secondary consideration in the literature to patient surgical and radiation histories.

Prior open urethral surgery has been identified as a risk factor for erosion. Specifically, prior AUS erosion or infection and a history of urethroplasty are predictors of erosion.1 Cuff size, particularly the smallest (3.5 cm) cuff, has also been linked with urethral cuff erosion, and small cuffs are largely avoided in patients with a history of radiation. Results are mixed in nonradiated patients, but there is evidence a 3.5 cm cuff increases the risk of erosion in patients who have been treated with pelvic radiation.1,3

A history of pelvic radiation, independent of cuff size or placement, is associated with a shorter overall device survival and increased risk of erosion for both an initial and second AUS. In a retrospective review of AUS erosion events, it was shown that the time to erosion was significantly shorter in patients who had been treated with pelvic radiation than those who had not (1.00 vs 3.15 years).4 This was corroborated by a recent study, in which it was found that the time to explant of an initial AUS and second AUS was shorter in patients who had undergone pelvic radiation than those who had not. AUS explantation secondary to infection or erosion (vs device malfunction) was higher in patients who had received prior radiation.3

Risk Factors for AUS Erosion Are Cumulative

In a multi-institutional study, it was hypothesized that a history of pelvic radiation, recalcitrant bladder neck contracture requiring repeat transurethral interventions, prior urethroplasty, UroLume® stent placement and prior AUS erosion or infection were all risk factors for erosion.1 The investigators found that when patients had an increasing number of these risk factors, erosion was more likely. Specifically, patients with zero risk factors had a 2.61% likelihood of AUS explant over the study period, while patients with 3 risk factors had a 25% likelihood.

Similar results were found in a single institution study.2 When patients had a single risk factor for erosion (history of pelvic radiation, urethroplasty or prior AUS), there was a 34% chance of failure vs a 75% chance when all 3 risk factors were present.

The cumulative effect of risk factors also holds true for a second AUS after initial device complication. The 5- and 10-year revision-free survival of a second AUS falls off precipitously from 83.1% and 73.9% when patients have no risk factors to 63.9% and 44.9% when patients have both a history of pelvic radiation and prior urethroplasty.3

The Role of Transcorporal Placement

Men who have had a cuff erode have permanent damage to the urethra that affects the safety and durability of a second device. Transcorporal placement of an AUS, where the tunica albuginea of the corpora cavernosum is interposed between the cuff and thin dorsal urethra, is the most widely adopted approach to mitigate the risk of repeat AUS erosion. This technique is often reserved for the most challenging AUS placements and is used in men with concurrent severe erectile dysfunction. This is particularly advantageous when the urethra is fixed and/or there is a significant concern for compromised blood supply.

A recent study evaluated data from a large single-surgeon series where the transcorporal technique was used for vulnerable urethras, where vulnerable was defined as a history of anti-incontinence procedure or prior urethral reconstruction.5 The study noted that the majority of erosions using both the standard and transcorporal technique occur ventrally. This could be interpreted in 2 ways, ie the transcorporal technique was successful at protecting the dorsal urethra in at-risk patients, or the transcorporal technique is superfluous as most erosions occur...
Artificial Urinary Sphincter Erosion

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ventrally, in contrast to the notion that the dorsal urethra is thinnest and thus most vulnerable. The authors concluded that the benefit of a transcorporal approach for at-risk patients was not convincingly shown in their retrospective cohort. When preexisting erectile dysfunction is present, there is little morbidity to a transcorporal approach, and the technique certainly has not been observed to increase risks or compromise continence rates.

Summary of Recommendations

Convincing risk factors for AUS erosion include a history of AUS erosion, prior urethroplasty and pelvic radiation. Small (3.5 cm) cuffs should be used with caution and avoided in patients with a history of radiation therapy. It is unclear if a transcorporal technique mitigates the risk of device erosion as it is often reserved for the highest risk patients and only studied retrospectively. Randomized prospective studies are needed in this space to confirm these retrospectively defined risk factors, direct our use of the transcorporal approach and confirm best practice and counsel of our patients.


The Use of Magnetic Resonance Imaging for Evaluation of Male Pelvic Fracture Urethral Injury

Pelvic fractures are usually caused by high energy injuries, such as traffic accidents or falls from a height. They place patients at risk for associated urethral injury, known as pelvic fracture urethral injury (PFUI), which is caused by avulsion of the membranous urethra from the bulb urethra. Most patients with PFUI eventually develop urethral stenosis, regardless of initial treatment. Delayed anastomotic urethroplasty with the sequential use of ancillary techniques has become the standard treatment for PFUI and remains a challenging urological surgery. This is because pelvic anatomy is markedly changed by the injury, and surgeons are forced to make a precise anastomosis in a deep and small operative field.

Accurate preoperative assessment is crucial for the proper selection of surgical approach and for a successful outcome. A combined antegrade and retrograde urethrography is the cornerstone of preoperative evaluation. However, it has several drawbacks. First, the measurement of urethral gap length on urethrography is operator dependent, and accurate estimation is difficult in the case of poor filling of the posterior urethra by contrast material. The bladder neck sometimes does not open on antegrade urethrography, especially in patients with prolonged suprapubic catheterization or decreased bladder capacity. Second, the proximal end of the displaced urethra can be displaced in a horizontal as well as vertical direction, and urethrography cannot accurately determine the degree of displacement 3-dimensionally. Third, the anatomical relationship of the urethra with its surrounding structures (such as the rectum and dorsal venous complex) or periurethral problems (such as minor fistulae or cavitation) cannot be well detected by urethrography. To overcome the limitations of urethrography, magnetic resonance imaging (MRI) has emerged as a noninvasive, multiplanar and high resolution modality for the evaluation of PFUI. Important information, such as the bulbar urethral length, the site of the ends of the disrupted urethra and the urethral gap length, can be accurately measured in the sagittal view of an MRI. These results show better correlation with intraoperative findings than urethrography. The degree of lateral urethral displacement, which cannot be assessed by urethrography, is easily estimated in the coronal view (fig. 1, A). The greatest advantage of MRI over urethrography is its ability to evaluate periurethral anatomy. In patients with complete urethral disruption, the rectum can protrude into the space between the displaced urethral ends. This can be clearly seen on MRI but is not visible on urethrography (fig. 1, B). Without this information, surgeons may encounter unexpected rectal

Figure 1. Representative preoperative MRI findings (dashed arrows) and corresponding urethrogram in patients with urethral gap after PFUI. Solid arrows indicate location of distal urethral end (DE) and proximal urethral end (PE). A, lateral displacement of disrupted urethral ends (coronal T2-weighted fat-suppressed image). B, bulging of rectum into urethral gap (sagittal T2-weighted image). C, close proximity of dorsal venous complex (dashed line) to urethral ends (sagittal T1-weighted, contrast enhanced image). D, false passage from DE to bladder neck created during failed endoscopic primary realignment (sagittal T1-weighted, contrast enhanced image). Note that none of findings seen on MRI were visible in urethrogram.
injuries during urethroplasty. The disrupted proximal end of the urethra can also be in close proximity to an intact dorsal venous complex ventrally. If this association is not known preoperatively, rough handling may lead to increased blood loss (fig. 1, C). Furthermore, MRI can clearly demonstrate minor periurethral fistulae that may be missed on urethrography (fig. 1, D).

MRI findings may have an impact on the decision about the type of urethroplasty. The most challenging aspects of delayed anastomotic urethroplasty are determining the location of the proximal urethral end and creating an anastomosis in the limited operative space of the pelvis. If the proximal urethral end is not found after mobilizing the bulbar urethra, or anastomotic tension is present due to a long urethral gap, surgeons should consider using ancillary techniques. These include techniques such as corporal separation, partial pubectomy and urethral rerouting, done to increase the exposure and to straighten the bulbar urethra and reduce anastomotic tension. These methods are often necessary when the proximal urethral end is displaced upward and is hidden behind the inferior pubic arch. Therefore, we believe that identifying the location of the proximal urethral end in reference to the pubis is the key to determining the need for ancillary techniques.

We have proposed the use of a novel MRI parameter to pubourethral stump angle (PUA, fig. 2), defined as the angle between the long axis of the pubis and the line joining the proximal urethral end to the lower border of the inferior pubic ramus (measured in the sagittal plane in T2-weighted MRI). In our single-surgeon series of 74 PFUI patients, PUA was an independent predictor of the need for more complex ancillary techniques. Although a long-held belief has been that the need for ancillary techniques can cause artifacts and prevent accurate assessment. Although MRI is not necessary for the preoperative evaluation of every case, information obtained from it can be beneficial for an inexperienced surgeon. It is also useful in the management of complex PFUIs, such as after a failed previous urethroplasty, rectourethral fistula or a long gap. The appropriate use of MRI and its cost-effectiveness require confirmation from future studies.

Transurethral Resection of Bladder Tumor—How Can We Teach it Better?

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Columbus, Ohio

Transurethral resection of a bladder tumor (TURBT) is the first step in bladder cancer management for new and recurrent tumors. For urologists, it is a highly rewarding procedure as it cures most patients of the disease and provides valuable prognostic information. However, incomplete initial resection is not uncommon, particularly for high risk nonmuscle invasive bladder cancer (NMIBC), resulting in persistent disease at future surveillance cystoscopy despite the administration of adjuvant intravesical therapies. These observations are then wrongfully characterized as recurrences, undermining the patient’s therapeutic response. A complete TURBT is imperative. An enlightening study including more than 2,500 patients from phase III European trials with Ta and T1 bladder cancer determined that the high variability in tumor recurrence rates at the first surveillance cystoscopy was most influenced by the quality of the TURBT performed by the individual surgeon and not other tumor factors that were studied.1

TURBT is a technically challenging procedure influenced by patient and tumor characteristics. Patients who are obese, a high riding bladder neck, and larger tumors that are multifocal and located on the lateral or anterior wall or the dome of the bladder pose greater challenges to accomplishing a “high quality” TURBT. In addition to these factors, recent studies suggest surgeon education, experience and surgical resection technique also influence TURBT quality. Therefore, there is an important need to develop and implement tools that teach and measure TURBT quality beyond the conventional mentor–mentee (apprentice–expert) relationship. An early effort in this area was a multi-institutional collaborative that developed and implemented a 10-item surgical checklist (Appendix 1) of factors that could influence and demonstrate the quality of the TURBT and perhaps patient prognosis.2 In this study, the implementation of a prospective surgical checklist significantly improved the 10-item reporting and likely resulted in a higher quality TURBT, although it did not significantly increase the presence of muscularis propria in the surgical specimen. As sampling of detrusor muscle is considered a requisite goal in bladder cancer management, it is commonly evaluated as a surrogate of the quality of TURBT. Bos et al retrospectively reviewed 463 TURBTs and determined that urology resident involvement was associated with less likelihood of detrusor muscle in the surgical specimen of high risk patients.3 The finding was similar to previous studies that also suggested less surgical experience was associated with higher operative times, and higher readmission rates and predicted for higher rates of recurrence of Ta and T1 bladder cancer.4 However, other studies have reported that surgeon experience and tumor location had no correlation with likelihood of detrusor muscle in the specimen, suggesting there is an opportunity to improve TURBT quality for all surgeons.

Surgical education is the fine balance between maximizing procedure efficiency, treatment efficacy, patient safety and the need to train the next generation of urologists. Surgical simulation provides the opportunity to develop requisite procedural skills before engaging in patient care. Certainly, surgical simulation is a growing area of study.

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Primary Retroperitoneal Lymph Node Dissection for Stage I Nonseminomatous Germ Cell Tumors: Who Really Needs This?

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Indianapolis, Indiana

Men who present with clinical stage 1 nonseminomatous germ cell tumors (NSGCTs) have excellent cure rates approaching 99% to 100%. This excellent cure rate is regardless of the initial management option chosen, which includes active surveillance, 1 cycle of bleomycin, etoposide and cisplatin (BEP), or primary retroperitoneal lymph node dissection (RPLND). Retroperitoneal lymph node dissection has been a foundation in the treatment of NSGCT patients for numerous decades. However, its utilization has steadily trended downward as surveillance has become more recognized as an acceptable and safe alternative. This trend in management was highlighted recently by Weiner et al in 4,080 men with clinical stage (CS) IA and 2,580 men with CS IB NSGCT diagnosed from 2004-2013 using the National Cancer Database.4 Over this 10-year period, the use of RPLND decreased from 22% in 2004–2005 to 14% in 2012–2013 (p <0.001). This was largely due to the increased utilization of surveillance during this time period. During the last 30 years at Indiana University, we have performed primary RPLND for clinical stage I disease for fewer and fewer patients (fig. 1). Likewise, while we performed 46 primary RPLNDs in 2019, only 7 of these were for clinical stage I disease.

The recent American Urological Association (AUA) guidelines for early stage testicular cancer advocate for patients with CS IA to preferably be managed with surveillance, and those with CS IB can be managed with any of the previously stated treatment options.5 This discrepancy in management recommendations by stage is due to the differences in relapse rates between CS IA and IB patients. It is well established that lymphovascular invasion in the orchiectomy specimen portends a higher risk of relapse. Additionally, cases with embryonal dominant tumors are also more likely to recur while on surveillance. Nayan et al recently demonstrated the conditional risk of relapse between patients with CS IA and IB with or without pure embryonal carcinoma in the orchiectomy specimen.6 For example CS IA without pure embryonal carcinoma had only a 17% risk of relapse, while patients with CS IA with pure embryonal or CS IB had risks of relapse as high as 40% to

Continued on page 34
for many surgical procedures including TURBT when one considers advancements in virtual simulation and the potential benefits that artificial intelligence may present. The first step in the development of procedural skills curricula is to define the intended and desired outcomes of training. Learning objectives, including procedural steps and pitfalls, are identified by a training needs analysis (TNA), where the objectives close the gap between the actual needs of the learners and the desired outcomes of training. Once the TNA is established, a suitable surgical simulator is required and validated to ensure trainees acquire the intended operative skills. Individual feedback and interventions can then lead to improved performance.

A group in the Netherlands recently developed a TNA focused on all procedural steps and technical and non-technical pitfalls of TURBT: Test Objectivity Competency (TOCO)-TURBT tool.\(^5\) The Simbla TURBT simulator (SAMED GmbH, Dresden, Germany) was used to conduct the prospective, observational, and comparative study in 7 teaching hospitals. Participants were recruited equally into 3 groups based on TURBT experience: novice, intermediate, and expert. The participants performed 2 standardized TURBTs on the simulator with bladder substrates depicting anatomic details of the bladder and tumors in different locations with real-life continuous flow resectoscopes and biopolar diathermy. The simulator was judged to be most useful in learning eye-hand coordination and least useful in learning to avoid complications. Overall, all aspects of the simulator were rated above the acceptability threshold and demonstrated face and content validity. Importantly, the simulator also reliably demonstrated construct validity, assessing the simulator’s ability to differentiate between different levels of surgical experience.\(^4\) During the validation phase of the study, participants were blinded to the items measured on the TOCO-TURBT tool by independent expert urologists during the preparatory, procedural, and completion phases of the simulated TURBT. The procedural phase focused on 3 areas: 1) applies systematic and prioritizing strategy in tumor approach 2) resects strokes of adequate depth and length 3) has adequate speed/progression of tumor resection. The study clearly established the feasibility, content, and construct validity of the TOCO-TURBT tool.\(^5\) The authors suggested the tool has the potential for high stakes assessment such as certification of residents and relicensing of urologists but needs clinical validation.

At our center, we have adopted the 3 procedural areas of focus as part of our resident assessment strategy. We have recently developed and piloted a skills assessment tool that uses a 5-point Likert scale to assess 11 features of the TURBT procedure (Appendix 2) in addition to denoting the case complexity (low, medium, high) and whether preoperative technical preparation (video, simulation, other) was undertaken in anticipation of the procedure. We use a Qualtrics based survey that is accessible via web or mobile phone using a smartphone link that is stored on one’s phone and essentially appears as any other application. It is generally completed in 1 minute and serves as a tool to direct specific resident feedback. We believe that the iterative combination of evidence-based curricula, effective simulation and tools to assess and provide feedback will provide an outstanding foundation to teach this important operation.\(\blacktriangleup\)

### Appendix 1. TURBT quality components

<table>
<thead>
<tr>
<th>TURBT Quality Audit</th>
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<tbody>
<tr>
<td>A high quality TURBT includes:</td>
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<tr>
<td>1. Obtaining the information necessary for accurate classification of clinical stage and cancer risk.</td>
</tr>
<tr>
<td>2. Complete resection of all visible tumors and suspicious areas when safe, feasible and bladder preservation is planned.</td>
</tr>
</tbody>
</table>

#### Procedure Checklist

- **Assessment of prognostic factors**
  - Acceptable responses
  - 1. Describe number of tumors 1, 2–5, >5, diffuse
  - 2. Describe size of largest tumor For reference: end of cutting loop is approximately 1 cm wide
  - 3. Describe characteristics of tumors Sessile, nodular, papillary, flat
  - 4. Describe recurrent versus primary tumors Recurrent, primary
  - 5. Assess for presence of carcinoma in situ Suspicious, not suspicious
  - 6. Report 2010 AJCC clinical tumor stage cTis, cTa, cT1, cT2, cT3, cT4
  - 7. Intraoperative processes
  - a. Bimanual exam under anesthesia Yes, no
  - b. Visually complete resection Yes, no
  - 8. Bladder filling and emptying base Yes, no
  - 9. Visual inspection of the dome Yes, no
  - 10. Prostate inspection after resection Yes, no
  - 11. Use of a transrectal ultrasound probe Yes, no
  - 12. Use of a transabdominal ultrasound probe Yes, no
  - 13. Use of a transperineal ultrasound probe Yes, no

#### Areas of assessment

- **Procedural focus**
  - 1. Procedural set-up
  - 2. Strategic approach to the resection
  - 3. Resection strokes
  - 4. Timing of resection
  - 5. Depth of resection
  - 6. Resection of bladder neck tumor
  - 7. Resection of dome tumor
  - 8. Resection of anterior wall tumor
  - 9. Fulguration / achieve hemostasis
  - 10. Use of equipment
  - 11. Use of enhanced diagnostic technology

### Appendix 2. Areas of assessment

- **1. Descriptive scales**
  - 1. Describe number of tumors 1, 2–5, >5, diffuse
  - 2. Describe size of largest tumor For reference: end of cutting loop is approximately 1 cm wide
  - 3. Describe characteristics of tumors Sessile, nodular, papillary, flat
  - 4. Describe recurrent versus primary tumors Recurrent, primary
  - 5. Assess for presence of carcinoma in situ Suspicious, not suspicious
  - 6. Report 2010 AJCC clinical tumor stage cTis, cTa, cT1, cT2, cT3, cT4

- **2. Numerical scales**
  - 7. Bladder filling and emptying base Yes, no
  - 8. Visually complete resection Yes, no
  - 9. Prostate inspection after resection Yes, no
  - 10. Use of a transrectal ultrasound probe Yes, no
  - 11. Use of a transabdominal ultrasound probe Yes, no
  - 12. Use of a transperineal ultrasound probe Yes, no

- **3. Comparative scales**
  - 13. Separate deep biopsy sent from resection bed Yes, no

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Primary RPLND for Stage I NSGCT

Continued from page 32

50%. However, it must be acknowledged that even though the risk of relapse on surveillance is higher with pure embryonal carcinoma and/or lymphovascular invasion, the ability to cure these patients is similar compared to those without these higher risk features. Thus, surveillance remains an option for patients with CS IB or pure embryonal carcinoma as well.

So, why the shift away from primary RPLND for patients with clinical stage I over the years? First, as mentioned previously, the safety of surveillance has become more widely recognized. Second, most historical reports of RPLND find only around 30% of patients have pathological stage II disease. Therefore, through this lens, there are 70% of patients going through an unnecessary operation. Next, like any surgery, there are procedure-related complications, which can and do occur. However, like most surgical procedures, the risk of complications when performed at high volume centers is lower. Daniel et al reported a 10% complication rate following 478 primary RPLNDs at our center in a historical series from the 1980s and 1990s. These complications do not seem to be diminished even with a robotic approach, which recently showed complications of 32% in 1 of the larger series with only 58 patients. Complications notwithstanding, our institution recently reported on the value of this surgery in pathological stage II patients, with over 80% cured with surgery alone, mitigating the need for chemotherapy and its long-term side effects.

The surgical volume of primary RPLND and its direct relation to outcomes warrant further discussion. Figure 2 emphasizes how few primary RPLND procedures are performed annually in the United States compared to other common cancer surgeries. Procedure totals for kidney, lung, prostate and colon resections represent only Medicare patients and thus underrepresent these annual totals. It is not surprising that high volume centers that perform this rare procedure might have improved surgical outcomes. Given these small numbers, there will not be many “high volume” centers to go around. The rare need for this surgery coupled with the high complexity of the procedure itself creates the perfect scenario to reduce its use when other acceptable, less morbid options exist, such as surveillance.

Finally, considering the low incidence of the disease, resulting in low surgical volumes for primary RPLND, as well as the fact that approximately 70% of patients with pathological stage I disease do not benefit from the surgery, who really needs this operation? The debate about optimal treatment for clinical stage I disease has been long and ongoing, and is tired. The problem has been a lack of good prognostic abilities, from either an imaging or a biomarker perspective. Thus, we have relied on pathological factors as mentioned previously, such as lymphovascular invasion or embryonal dominant tumors, which yield a predictive value similar to a coin flip. Some men choose primary RPLND in the hopes of limiting their need for future chemotherapy, as most with microscopic disease found during RPLND are cured with surgery alone. Lastly, some urologists might strongly suggest surgery if the patient seems unreliable to follow through with surveillance, such as someone who is underinsured or uninsured. Fortunately, this tide seems to be turning as a new biomarker continues to gain traction. miRNA 371a-3p is poised to help guide decision making, not only in clinical stage I disease, but also in other clinical scenarios of germ cell tumor management. Additionally, there are now 2 open clinical trials collecting this biomarker (Children’s Oncology Group study AGCT 1531 and SWOG 1823), and others are or will be in development in the coming years. If the prospective clinical trial data support the growing body of literature on this biomarker, gone will be the days of debates about which of the 3 treatment options, surveillance, RPLND or chemotherapy, is “best.” Patients with miRNA negative results will be placed on surveillance or maybe even discharged from clinic. Patients with positive miRNA results can be managed with primary RPLND. However, the debate will still need to be settled for clinical stage I cases with miRNA positivity regarding the role of chemotherapy vs primary RPLND. However, this topic, we are sure, will fill the gap of future panel debates until forthcoming trial data become available.

79% of AUA members think they will use more telemedicine in the future. Are you one of them?

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A dedicated research year during residency is a dwindling commodity. Given that most trainees go into private practice, do we have evidence that a single year dedicated to research during residency impacts future academic success? The authors included urologists graduating residency between 2002 and 2008 from 36 programs affiliated with a top 50 hospital for urology as ranked by the U.S. News and World Report, and collected research time during residency, fellowship training, current appointment (private practice, assistant professor, associate professor, professor, chair), National Institutes of Health (NIH) grant accrual, NIH R01 grant accrual and current H-index in Scopus database. Publication output during and after residency was identified through the PubMed database.

Of 543 urologists, 66.3% of graduating trainees pursued private practice. Increasing residency research time was associated with increased publication count (p <0.001), pursuit of professor positions (p <0.001) and NIH funding (p <0.001). A year of dedicated research increased the odds of being in the top tenth percentile of publication output during residency (OR 5.7, 95% CI 2.7–12.1), pursuing a fellowship (OR 2.0, 95% CI 1.3–3.1), promotion to professor (OR 4.9, 95% CI 2.0–12.2), obtaining a NIH grant (OR 6.2, 95% CI 2.3–16.5) and decreased the odds of pursuing private practice (OR 0.4, 95% CI 0.3–0.6). As amount of time dedicated to research in urological residency increased from 3–4 to 6–12 months, OR increased for career academic success metrics. The authors conclude that although a minority of trainees enter academic, dedicated time for research in urological residency is associated with career academic success, with more research time associated with increased publication output, academic appointments and grant funding.

Of course, residents with academic aspirations may self-select to apply to programs with more research time and resources, but it is still good to see that there is an association.


While there is a growing literature on specific needs and outcomes of gay men following prostate cancer screening, not much is known on prostate cancer screening behavior among lesbian/gay/bisexual/transgender (LGBT) individuals. The authors performed a cross-sectional study to assess patterns of prostate specific antigen (PSA) screening and decision-making in LGBT patients. The Behavioral Risk Factor Surveillance System database was queried for LGBT adults for 2014 to 2016 and 2018, when PSA questions were asked in the annual survey. Multivariable logistic regression was performed to evaluate the association of LGBT status with PSA screening and informed and shared decision making. A total of 164,370 participants were eligible for PSA screening, representing a weighted estimate of 1.2 million LGBT individuals. Compared to cisgender (CG) straight individuals, CG gay/bisexual cohorts were more likely to participate in PSA screening (CG gay OR 1.07, p<0.001; CG bisexual OR 1.06, p<0.001). CG gay participants were more likely to make informed decisions (OR 1.10, p<0.001) and engage in shared decision making (OR 2.55, p<0.001). Select gay populations were more likely to undergo PSA screening recommended by their clinicians and participate in informed and shared decision making.

The authors conclude that gay and bisexual individuals were more likely to undergo prostate cancer screening and that select gay individuals were more likely to make informed and shared decisions. However, transgender individuals were less likely to have prostate cancer screening and make informed decisions.

Certainly the risk of prostate cancer in transgender women treated with androgen deprivation is low1 but not 0, and clinical guidance for appropriate screening is needed.

The AUA has nearly 24,000 members worldwide who have been transforming and improving urological care for more than 100 years. More than 7,000 of those members live outside of the United States, and with our increased utilization of technology it has never been easier to stay connected.

Our international members support the advancement of urology and urological professionals by unifying and strengthening the specialty. The AUA remains committed to providing our members with urological education to enhance patient care around the world through the collaboration and exchange of knowledge and resources. Even with the quick pivot to virtual meetings due to COVID-19 the AUA was able to provide the same level of education to our members around the globe.

More than 100 AUA faculty participated in nearly 40 national and multinational society programs across more than 20 countries last year. These programs were stand-alone events or were held in conjunction with one of our partner’s Annual Congresses. Depending upon the type and scheduled time of the program, we provided live virtual talks or prerecorded lectures for all of these events, and most of them included a live Q&A session with the AUA faculty. AUA Assistant Secretaries, Drs. Chang, Shukla and Smith, played an integral role in providing AUA updates and scientific lectures during programs with our international partners. The AUA also participated in virtual exhibit areas in many of these international meetings to stay connected with our members despite being unable to travel to their national congresses.

Access to the AUA’s high-quality education is one of the most important benefits to our members. International members can access online urological education through the AUA University, enjoy complimentary access to The Journal of Urology®, apply for international focused research funding opportunities and participate in international academic exchange programs through partnerships with the AUA and international societies. The AUA Virtual Experience also provided a multitude of educational programming easily accessible from anywhere and was made available in Spanish through a collaboration with the Sociedad Colombiana de Urología.

In addition to the educational programs, the AUA held more than 30 virtual leadership meetings last summer to connect with our international society partners and plan for joint virtual programs for the remainder of 2020. Additionally, the AUA plans to hold more leadership meetings in January to plan for our international educational programming throughout 2021. This global exchange of information will continue to improve patient care and advance the specialty.

I would like to thank all of our AUA faculty who volunteered their time to participate in these programs, our partner societies for their flexibility in allowing the AUA’s virtual participation in their meetings and all of our members who attended these virtual programs throughout 2020. While it wasn’t the same as seeing everyone in person, continuing to learn, teach and collaborate with our colleagues around the world was certainly a bright spot during a challenging year, and we look forward to a time when we can meet in person again.
The Role Big Data Plays in Urology

Michael T. Sheppard, CPA, CAE
Linthicum, Maryland

Advances in technology have given us the opportunity to collect vast quantities of digital data. Such “big data” play a role in many aspects of health care including urology. Urologists are using big data to improve patient care and advance the specialty.

The AUA Quality Registry (AQUA) has played a significant role in the advancement of big data in urology. The AQUA Registry is a national Qualified Clinical Data Registry designed for urologists and other urological care providers to monitor and report performance at both practice and provider levels. Data on 10 major urologic conditions including prostate cancer, advanced prostate cancer, bladder cancer, benign prostatic hyperplasia, urinary stones, testosterone replacement therapy, stress urinary incontinence, cryptorchidism, hypogonadism, azoospermia and vasectomy are aggregated for quality improvement and research in the AQUA Registry.

Data available from the AQUA Registry include national benchmarks for diagnoses and treatments, urology-specific quality measures, and practice and physician performance indicators for quality improvement and accountability applications. The AQUA Registry provides a comprehensive clinical registry without the burden of manual data entry, relying upon natural language extraction from patients’ electronic records.

The real-world data (RWD) in the AQUA Registry are used for providers to document clinical outcomes of patients and the treatment journey patients took. The RWD helps build tools to support care providers with their efforts in improving quality of care and fuels comparative effectiveness research, helping advance the science of urology. These data also can be used to spur the development, refinement and validation of health care performance measures that are most important for the field.

Resolution of Disparities is Foundational to UCF’s Educational and Research Efforts

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

Inequality of access and opportunity is not consistent with the mission and vision of the Urology Care Foundation. The Foundation continues to make strides in our Diversity and Inclusion (D&I) initiatives every day. We seek and embrace new ways to ensure a future in which the principles of justice and equity are upheld and reflected within our mission.

Respecting, embracing and celebrating diversity is integral to our DNA. As the world grappled with COVID-19, several events transpired that reminded us of the stark inequalities existing within our world and intensified our efforts and commitment to achieve D&I.

Our Board of Directors is diversified in terms of race, gender, region and—yes—even specialty and industry.

We are proud to say that more than half of the 400 pieces of patient education in our library are in languages other than English and reflect, both visually and contextually, the diverse populations we serve. Additionally, we have committed to a 3-year plan to have all of our patient education materials available in Spanish.

We also strive to have our materials presented at an eighth grade proficiency level to ensure the information is easily understandable for our many patients, including their families and caregivers. It is through this library of information that we are able to reach a diverse and culturally rich audience worldwide.

Our new Public Education Council Chair, Dr. Brian Stork, shares our commitment to remove barriers of access to educational materials, which result from failure to address issues of diversity. Maintaining diversity of our public education council and committee representation is an essential element in further enabling us to actualize our commitment to reaching underserved populations.

We are proud of the diversity within our patient education governing bodies. This includes our Council being equally comprised of men and women with racially diverse backgrounds in all age groups.

Recognizing the need to grow the field of urological research and increase the universe of underrepresented investigators, the Foundation has teamed up with the AUA to expand its efforts to advance diversity initiatives across all research grant programs.

To this end, I am proud to announce the 2021 Research Scholar Award competition celebrated its first ever awards dedicated to supporting women and underrepresented minorities conducting urological research. These awards were made possible by a grant from Bristol Myers Squibb, Inc. and a new endowment from the Society of Urologic Oncology.

Additional efforts to achieve this goal include ensuring greater diversity in scientific peer review panels and increasing the representation of women and minorities on the AUA’s research program governing bodies, including the Research Council and the Research Grants and Investigator Support Committee.

The AUA and Foundation stand united in creating more opportunities for our research community to improve the diversification of our research workforce, provide higher impact research and improve patient care.

We acknowledge there is still work to be done and we pressed forward in our D&I efforts through 2021 and beyond. We encourage you to visit UrologyHealth.org to learn more. Thank you.
As part of the ongoing efforts to assist our members and improve the quality of care they provide to their patients, the AUA has renewed its focus on quality measurement to ensure that AUA Quality Registry (AQUA) measures are clinically sound, reliable, valid and effective.

During the past year, we commenced this effort by conducting a formal evaluation of the urology-specific clinical quality measures included in the AQUA Registry. We convened a 9-person Measure Evaluation Panel (MEP) to help prioritize the measures, assess the precision of the measure specifications and their alignment with the clinical evidence and propose changes to the specifications if needed. We then invited more than 30 AUA members to participate in a modified Delphi process to evaluate the importance, performance, feasibility and face validity of 7 of the measures. The results of this work informed the AUA’s ongoing measure maintenance efforts as well as our selection of measures that will be included in the 2021 Qualified Clinical Data Registries, which can be used to satisfy the Centers for Medicare & Medicaid Services’ (CMS) Measure-based Incentive Payment System (MIPS) reporting requirements.

Moving forward, the AUA, with input from its Quality Improvement Patient Safety Committee, the MEP and other members, will continue to evaluate the utility of current measures and update and clarify specifications as needed. We will also begin the important process of testing the measures empirically for feasibility, reliability and validity. We also plan to develop a conceptual measurement framework for urological conditions. This framework will serve as a blueprint for the future development of new measures. When developing this framework, we will consider including the many ways new and existing measures may be used (e.g., for quality improvement, public reporting, value-based payment etc.), what topic areas should be prioritized (e.g., appropriate use, shared decision making etc.), what type of measures are needed (e.g., clinical outcome measures, patient reported outcome and experience measures, process measures closely linked to desired patient outcomes etc.) and what data would be required to implement such new measures (e.g., survey instruments, social risk data for use in risk adjustment etc.). Once this framework is in place the AUA will begin a multiyear effort to develop new urology-specific measures.

The AUA is confident that these measurement activities will enhance members’ benchmarking and quality improvement activities. In turn, these will foster more sustainable and engaged participation in CMS quality programs such as MIPS and strengthen the value and utility of the AQUA registry. Ultimately, these efforts will help improve the quality of urological care we provide to our patients, as well as their health more broadly.

Acknowledgment: We thank Karen Johnson, PhD, AUA Director of Quality and Measurement, for her contributions to this article.

Health Policy Updates: Highlights from the American Medical Association Interim 2020 Meeting

The COVID-19 pandemic brought about unparalleled disruption to daily life throughout the global community and unprecedented strain on our national health care system. During the initial pandemic peak in Spring 2020, as ICU capacity soared and personal protective equipment (PPE) reserves dwindled, one issue became exceedingly clear: in the face of a health care crisis, the complicated yet critical link between medicine and policy cannot be understated. This year, the American Medical Association (AMA) conducted their Interim 2020 meeting via a virtual format, where delegates gathered to discuss and adopt several key policy stances.

Obviously, COVID-19 related issues remained at the forefront of policy agenda. These included resolutions to encourage more affordable insurance options such as auto-enrollment and public options that foster a competitive market for the many Americans who lost employer-linked coverage due to economic ramifications of the pandemic. To prevent the spread of the coronavirus in correctional facilities, delegates adopted policies to protect the incarcerated population and correctional workers through increased infection control and PPE measures, as well as encouraging the compassionate release of inmates with COVID-19 related illness.

The tragic deaths of George Floyd, Breonna Taylor, Ahmaud Arbery and others prompted the AMA to pass detailed policy outlining racism as a public health crisis, highlighting medicine’s role in perpetuating racial bias and inequities against vulnerable patient populations. Race was officially recognized as a social, not biological, construct. In addition to dedicating resources towards evidence-based solutions to mitigate racial bias within health care, a significant amount of discussion centered on excessive use of force by law enforcement. New policy acknowledged that police brutality disproportionately impacts people of color as a function of structural racism, stressed the importance of antibias training to avoid discrimination and racial profiling by law enforcement, and encouraged community partnerships to encourage safe practices.

Telemedicine, a major legislative priority for the AUA before COVID-19, saw rapid expansion in the wake of national lockdowns that precluded non-essential travel. In a postpandemic health care environment, the maintenance of telehealth coverage by the Centers for Medicare and Medicaid Services and private insurers was strongly supported by new AMA policy. It also advocated for equitable access to telemedicine services and required infrastructure to reduce disparities that can affect at-risk populations.

With a COVID-19 vaccine on the brink of distribution and a new incoming administration, the health policy landscape is likely to shift in 2021. President-elect Biden has committed to preserving the protections under the Patient Protection and Affordable Care Act, lowering premiums, reducing “surprise billing” and growing home health care services, of course dependent on the Congressional landscape during the first half of his term. As the health care climate is again in the midst of a transition, there continues to be a dire need for physician–namely urologist–representation in organized medicine and the federal government. For interested trainees, the AUA Advocacy and Policy Workgroup and the AUA Summit allow residents and fellows to ensure their voices are heard to advance the interests of our patients and profession.
Expert Panel Discusses Tips on Inflatable Penile Prostheses

The 2020 Sexual Medicine Society of North America (SMSNA) Fall Scientific Meeting was held virtually and featured presentations by an expert panel offering personal tips on placement of inflatable penile prostheses (IPPs). IPPs have been placed since 1973, and many approaches, management methods, and advances have been practiced. The panel presented contemporary preferred approaches, management of complex cases and billing advice for implanters.

Dr. Edward Karpman led the discussion first by highlighting his infrapubic approach to IPP in 12 steps. Intraoperatively, he administers pudendal blocks with a Marcaine® and Exparel® mixture, along with artificial erection with Marcaine to visualize deformities. He prefers the infrapubic approach due to the ability to make proximal corporotomies and the easier access to the external ring for reservoir placement. As demonstrated with surgical clips, the neurovascular bundle is easily identified and mobilized, and corporotomies are made proximal and lateral to the bundle for prosthesis placement. This approach allows the possibility of alleviating devastating reservoir complications and decreasing the need for rear tip extenders. Dr. Karpman also presented tips for accurate billing for IPP surgery. He highlighted the billing process in 3 parts: the preoperative, intraoperative and postoperative periods. He advised that all preoperative diagnostic tests and medications should be billed. The reimbursement rates were displayed, demonstrating the differences between the CPT codes, with the highest reimbursement seen with the “remove/replace infected IPP” procedure (CPT 54411). Underscoring appropriate CPT code choices such as difference in graft sizes or the use of plastic surgery codes for novel adjunct procedures allows the implantor to neither underbill nor overbill.

Dr. Faysal Yafi then presented his penoscrotal approach to penile prosthesis placement. His preference for this approach is due to better corporal exposure, lower risk of dorsal nerve injury, ease of pump placement and convenience for ventral and dorsal phalloplasty procedures. He also described his multimodal analgesia protocol including preoperative and postoperative acetaminophen, gabapentin and meloxicam, along with intraoperative pudendal and dorsal nerve blocks in an effort to decrease narcotic usage. He carefully detailed the penoscrotal approach with the aid of videos. If plication is required, he prefers preplacing Essed-Schroeder plication 2-zero Ethibond® sutures. In addition to the penoscrotal approach, Dr. Yafi also demonstrated the mini-jupette sling placement for climacturia at the time of IPP placement. Climacturia occurs in about 20% to 64% of men after radical prostatectomy and 5.2% after radiation, which likely alludes to both neuronal and anatomical etiologies of the condition. The mini-jupette sling functions by coagiting the urethra as a result of the stretched graft on IPP inflation. The corporotomy sites are made more lateral, and a Restorelle® mesh (his preferred material) is sutured to the medial edges of the corporotomies prior to the placement of the prosthesis. Due to the increasing public apprehension toward surgical mesh, he also demonstrated a technique utilizing autologous rectus fascia for the mini-jupette sling. Functional studies with retrograde urethral leak point pressure were assessed, showing pressures of 15 to 44 mm H2O with the mini-jupette sling and inflated cylinders, similar to what is observed with Virtue® slings. Although the majority of IPP procedures are relatively straightforward for the frequent implantor, difficult cases occur and present their own challenges. Dr. Dean Knoll presented advice for IPP placement in a hostile pelvis, which he defines as a pelvis that provides poor or no access to the inguinal ring for reservoir placement. He undertakes his IPP with an infrapubic approach, and reservoir placement is achieved through a horizontal incision through rectus fascia. The reservoir can then be placed in either submuscular or space of Retzius locations. In the implanted patient with concomitant Peyronie’s disease, which requires grafting, he makes an additional subcoronal incision for degloving purposes with the prosthesis inflated. The neurovascular bundle is mobilized and the most concave point is incised using cutting current of 20 W. A graft, 10% larger than the defect, is then sutured. Dr. Knoll further cautioned not to incise and graft in the setting of ventral curvatures, owing to the high risk of granular necrosis.

To conclude the panel discussion, Dr. John Mulcahy presented on the IPP salvage procedure, which he first described in 1991. By 2003, he had performed 101 IPP salvage procedures with an 86% success rate. Advances have been made in this procedure over the years with salvage rates as high as 93% with semirigid rods. Additional contemporary changes to the Mulcahy washout include the use of antibiotics solution or saline, 1:10 dilution of Betadine® and pressure washing, while omitting the more toxic hydrogen peroxide. Contraindications to the salvage procedure are sepsis, ketoacidosis, genital necrosis, immunosuppression bilateral urethral erosion, and purulent or extensive cellulitis. Predictors of salvage failure include extensive cellulitis/purulence, virulent organisms and short incubation periods. In a 2017 study of infected IPPs from 25 centers, 153 cultures were positive with 35 different organisms, which were all susceptible to vancomycin, piperacillin/tazobactam and/or fluconazole. Thus, this is the typical antibiotic cocktail he recommends, in addition to pre-salvage antibiotics for 48 to 72 hours when possible and postoperative Bactrim™ for 1 month. Dr. Mulcahy also described novel techniques for the management of cylinder aneurysm complications, which may at times require the addition of graft consolidation of the corpus cavernosum.

Sexuality and Religion in the 21st Century

Sexuality is a powerful and very human experience that influences and is in turn influenced by social and interpersonal milieus. As urologists, our focus is largely on the biological factors that contribute to sexual issues and the biomedically interventions that we apply to mitigate sexual dysfunction. Sex is fundamentally a physical act, but it occurs in a psychosocial context. The experienced urologist knows that a patient’s psychological, social and cultural milieus influence not only their perception of sexual issues, but also their willingness to address them.

Religion is an important aspect of culture that is seldom discussed in sexual medicine consultations but has enormous implications for treatment efficacy and acceptability. All religious traditions articulate rules and traditions about when, how and with whom sexual activity is appropriate for an adherent. Approximately three-quarters of Americans endorse a religious affiliation, with almost half of Americans identifying as Protestant Christian. It is a certainty that the religious affiliation (or lack thereof) of a medical provider may differ from that of...
their patient. Health care providers cannot expect to be fully versed in the nuances of the various religious traditions they may encounter in practice; even patients with whom the provider shares a religious tradition may have a different level of adherence or understanding.

While a thorough understanding of all the world’s religious traditions is not a practical goal for practicing urologists, some basic understanding of how different religious traditions view sexuality can be of great value in optimizing patient adherence and well-being. At the 2020 Annual Fall Meeting of the Sexual Medicine Society of North America (SMSNA), an expert panel of sexual medicine clinicians provided remarks on 4 major religious traditions. Each speaker was an adherent of a specific non-Protestant Christian tradition and provided information about their religious tradition, how their tradition views sexuality and the appropriate contexts for sexual expression, and in many cases how their religious belief informs their practice of sexual medicine.

Yonah Krakowsky of the University of Toronto opened the session with a discussion of his experience with Judaism and how it informs his practice and his care of patients. Sexuality as a sin that must be restricted is a pervasive theme in Jewish writing, especially in orthodox circles. This was an intensely personal story about adhering to tenets of Judaism but understanding how in some cases flexibility in interpretation is permissible. Discussion with religious leaders and delineation of intent emerged as key factors in reconciling faith with the real-world treatment of issues in sexual well-being. Dr. Krakowsky reminded us that what may be common sexual knowledge to us may be a completely foreign idea to others, and that simple recommendations we make as sexual medicine practitioners may be a life-altering request for a patient from a more orthodox background.

Amjad Alwaal of Marshall Health in Huntington, West Virginia, continued the session with information about sexuality in Islam. Intercourse is encouraged between couples and described as a “good deed.” While marriage is strongly encouraged and celibacy is condemned, premarital and extramarital sexual affairs are a punishable crime. A variety of misconceptions exist about sexuality in Islam, particularly the sexuality of women. Dr. Alwaal made clear that the central sacred text of Islam (the Koran) differs from various regional practices that are commonly associated with the religion, such as female genital cutting (FGC). FGC is not a practice that is prescribed in the Koran and most likely represents a regional custom that was integrated into Islamic practice as the religion spread in its early years. Interestingly, urology has a dedicated chapter in one of the early Islamic surgical texts written in 1233.

Brian Christine of Urology Centers of Alabama in Homewood next described in large part how his Catholic faith informs his approach to patient care. The Catholic Church is frequently in the news due to well-publicized stances on contraception, abortion and lesbian/gay/bisexual/transgender (LGBT) issues. While some may interpret these stances as not being “pro-sexual,” what is less frequently recognized by critics is the Catholic Church’s express commitment to caring for fellow humans and the intrinsic value of human life. Dr. Christine made clear how this commitment compels him to at all times to care for patients who come to him for help, sometimes bringing him into conflict with colleagues who may hold negative views and not feel compelled to meet the needs of patients.

Anand Shridharani of the University of Tennessee Urology in Chattanooga concluded the discussion with a review of sexuality in Hindu and Jain traditions. Hindu sexual practices have been a topic of great and somewhat prurient interest in Western countries for decades, if not centuries. The famed text, the “Kama Sutra,” is commonly known among the American public. Dr. Shridharani put this historical work in context; while the Kama Sutra is treated in Western countries as a catalog of exotic and sometimes dangerous sexual positions, the original intent of this work was to detail what was and was not appropriate in terms of sexual interaction between persons. The role of sex changes during the different stages of life. Sex is confined to marriage during the household stage and pleasure is encouraged. However, British colonialism influenced cultural perceptions of sex for pleasure and led to the adaptation of more puritanical views. Dr. Shridharani’s discussion of Jainism was also of import, as sexuality is seen as appropriate primarily for procreative rather than recreational purposes. One of the 5 great vows of Jainism is brahmacharya, an abstinence from self-indulgence, and sexual intercourse is included in this. Sexual passion or indulgence is thought to lead to misdeeds, and homosexuality is considered to be self-indulgent. This understanding of sexuality may be of particular importance when consulting with patients in interfaith marriages involving a Jain person who may be partnered with someone who prioritizes sexuality for pleasure.

The informative lectures by Drs. Krakowsky, Awaal, Christine and Shridharani laid out the basic practices and beliefs of these religious traditions. They elucidated the importance of considering the patient’s religious and cultural background when making a treatment plan for their sexual or reproductive function.

**Testosterone and the Brain**

![James G. Pfaus, PhD](image)

Testosterone (T) affects myriad central and peripheral physiological systems in both men and women. These include muscle growth, endocrine function, maintenance of external and internal gonadal tissues, maintenance of autonomic function, energy balance, bone, hair growth, augmentation of mood and the stimulation of brain systems for sexual arousal, desire and orgasm. The effects of T on the brain and behavior occur via binding to androgen receptors (ARs) as T or its 5α reduced metabolite, dihydrotestosterone (DHT), or by aromatization to estradiol (E2) and binding to estrogen receptors (ERs). Although aromatase exists in high quantity in granulosa cells of...
the ovaries (to convert T into E2), it exists in neurons within regions of the male brain associated with reproduction, such as the medial preoptic area (mPOA). In fact, the conversion of T to E2 is critical for sexual differentiation of the brain into a “male phenotype.”

In adult females and males, ARs and ERs exist throughout the brain, but especially in limbic and hypothalamic regions that act as processing centers for olfactory and genital stimulation, arousal, mood, reward and bonding.

Average blood plasma levels of free T range between 300 and 1,100 ng/dl for men. However, these levels fluctuate daily, being generally higher in the morning than the evening. Although overall, women have one-tenth to one-twentieth the plasma levels of T as men, these levels fluctuate monthly for women, with a steep phasic rise and fall on the day of ovulation, coming on the heels of the earlier rise and fall in E2. This can raise plasma levels of free T to those observed in the medium range of men (ie 500 ng/dl). Although hormonal replacement therapy for postmenopausal women with E2 restores and maintains gonadal tissues, bone, muscle, neuronal integrity and cardiovascular flow (all components necessary for genital sexual arousal), the addition of T over E2 augments sexual desire. Indeed, peak sexual desire occurs naturally in premenopausal women during ovulation. Periovulatory increases in sexual solicitations indicative of desire are observed in all mammalian females and appear to be driven by similar hormonal effects. In males, T is also an important regulator of sexual arousal, desire and copulatory behavior. T replacement in hypogonadal men increases the proportion who acquire and sustain erection, and restores sexual desire and orgasm.

How does T accomplish this? There are 2 modes of steroid hormone binding to receptors, “genomic” and “nongenomic.”

The genomic mechanism involves nuclear hormone receptors (fig 1). The steroid binds to these receptors and alters their shape so that they make contact with hormone response elements on different genes that stimulate transcription of those genes into functional proteins. The proteins can act as receptors for different neurotransmitters, enzymes that synthesize or metabolize different neurotransmitters or that act as substrates for second messengers (eg protein kinases), or that perform other regulatory functions in cells. Some proteins activated by steroid hormone binding are themselves neurotransmitters, such as GnRH, oxytocin, vasopressin and ß-endorphin. In the case of T, an important and ubiquitous protein it facilitates is nitric oxide (NO) synthase. NO is critical for clitoral and penile erection and for neurotransmitter release throughout the brain. One hallmark of protein synthesis is that it takes time. Thus, there is a delay of hours between peak free T levels in plasma and the constellation of proteins it makes in the brain that ultimately alter behavior. In contrast, the nongenomic mechanism is faster, working on the order of seconds to minutes. Steroids can bind to receptors on the cell membrane that are linked to second messengers, such as phosphatidyl inositol, cyclic AMP and MAP kinases (fig 2). In the case of T, these linkages lead to increased calcium mobilization within neurons, thus depolarizing them (which makes them easier to “fire”) and facilitating neurotransmitter release through the action of calcium binding proteins.

Does T work alone or in concert with its aromatized metabolite, E2? This is still an area of debate in the neuroendocrine literature, Maintenance of autonomic neurons
- Maintenance of clitoris, vagina, penis, testes, prostate tissues
- Anti-inflammatory properties
  - Nitrific oxide synthase in hypothalamus and periphery
  - D2 R (striatum), 5-HT2A Rs (raphé)
  - Serotonin transporter synthesis
  - noradrenaline, dopamine release
  - activation of mPOA, VTA, limbic regions (amygdala, hippocampus, septum)
  - MAO
What’s New in Testosterone Replacement Therapy

Jeffrey Campbell, MD
London, Ontario, Canada

Similar to most conferences in 2020, the Sexual Medicine Society of North America (SMSNA) converted its Annual Fall Meeting to a virtual platform, which ran from November 9–15, 2020. The meeting was well attended and jam-packed with a week’s worth of informative talks on novel research. One area of particular interest at this meeting was the discussion of and insight into new regimens of testosterone replacement therapy, identifying at-risk patients for testosterone deficiency and recognizing both basic science and clinical links between hypogonadism and lower urinary tract symptoms (LUTS). A total of 26 abstracts were presented and 6 plenary/podium presentations regarding testosterone replacement therapy were given over the course of the week.

One of the top basic science abstracts presented at the meeting proposed a new targetable pathway for restoring testosterone to physiological levels in patients with both sickle cell disease and hypogonadism, which may prevent stuttering priapism (see figure). Dr. Sezen Karakus and Dr. Arthur Burnett’s group from Johns Hopkins School of Medicine treated sickle cell mouse with FGIN-1-27, a drug ligand for TSPO, which is a cytosolic protein involved in cholesterol mobilization and transport. They found that treatment with FGIN-1-27 increased serum testosterone and reversed primary hypogonadism. Interestingly, correcting hypogonadism in sickle cell mice corrected prolonged detumescence, decreased nitric oxide sensitivity and downregulated phosphodiesterase type 5, thus normalizing erectile function and reducing priapic activity. This study further supports Dr. Burnett’s previous work on hypogonadism in sickle cell disease, and additional studies will hopefully confirm this novel treatment pathway that can offer a solution for sickle cell patients suffering from recurrent priapism episodes.

There was a theme of screening atypical populations for testosterone deficiency. Dr. Marisa Gray from the University of Virginia won the Sexual Tipping Point® award presented by industry and demonstrated adequate safety and efficacy at 1-year followup, although further multicenter trials are needed for generalizable outcomes.

Several new delivery methods for testosterone therapy came to fruition in 2020. Dr. Yafi and his team at the University of California, Irvine discussed the data on the new subcutaneous testosterone enantate autoinjector Xyosted®. Approved by the U.S. Food and Drug Administration in 2018, this new delivery method offers a lower post-treatment estradiol (p <0.001) and 26% lower post-treatment estradiol (p <0.001). Subcutaneous testosterone enantate autoinjector appears to be safe and a great delivery option for patients requiring testosterone replacement, although long-term studies are needed. Additionally, oral testosterone undecanoate was presented by industry and demonstrated adequate safety and efficacy at 1-year followup, although further multicenter trials are needed for generalizable outcomes.

Finally, Dr. Abdulmaged Traish from Boston University and Dr. Ranjith Ramasamy from the University of Miami provided informative discussions on the role of testosterone replacement therapy for LUTS. Preclinical data on the topic were summarized and drove home the importance of testosterone replacement
What’s New in Testosterone Replacement Therapy

Continued from page 42

therapy for smooth muscle function. Testosterone deficiency can alter the smooth muscle-to-collagen ratio, density of elastic fibers and bladder contractility, compliance and capacity. Testosterone replacement therapy can reverse all of these consequences, leading to improved bladder function. In human studies, testosterone replacement therapy has been shown to improve International Prostate Symptom Score (IPSS), reduce post-void residual volumes and improve bladder compliance in men with testosterone deficiency. Although historically a contraindication, these presentations support the use of testosterone replacement therapy in men with LUTS related to benign prostatic hyperplasia, and future clinical studies will help support this paradigm shift.

Although the meeting was held virtually, there were several interactive sessions, debates and workshops. I encourage readers to register and get access to these great talks. I’m looking forward to more innovative discussions, in person, in 2021.


Cardiovascular disease is the leading cause of death in men with prostate cancer.\(^1\)

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