AUA advanced prostate cancer guideline

Highlights include addition of PARP inhibitors for metastatic CRPC

Jason M. Broderick
Associate Editorial Director, Urology Times®

The 2020 American Urological Association (AUA) Virtual Experience included expert insight on the new AUA Guideline for Advanced Prostate Cancer from William Lowrance, MD, MPH, and Michael S. Cookson, MD, MMHC, 2 of the experts on the panel that created the guideline.

“The primary aim of this guideline is to assist clinicians with decision-making. The evidence-based guideline recommendations are furnished according to disease state across the entire continuum of advanced prostate cancer,” said Lowrance, associate professor of urology at the University of Utah School of Medicine, Salt Lake City. Lowrance was chair of the panel.

“This guideline was produced by a multidisciplinary panel with representation from AUA, the American Society of...

For the full article, please turn to page 11
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 fall risk.

Seizure — In 2 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.

Advises 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 (8.7, 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® 7% (0.4%), placebo 1% (0.6%). In the SPARTAN study: anemia ERLEADA® 7% (0.4%), placebo 6% (0.5%); leukopenia ERLEADA® 47% (3.1%), placebo 29% (0%); 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 40% (0%); hyperglycemia ERLEADA® 70% (2%), placebo 59% (7%); hypertriglyceridemia ERLEADA® 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA® 32% (2%), placebo 22% (0.5%).
In the TITAN study\(^1\):  
**33% reduction in the risk of death**  
(ERLEADA® + ADT vs placebo + ADT; median overall survival was not estimable in either arm; HR = 0.67; 95% CI: 0.51, 0.89; \(P = 0.0053\))

In the SPARTAN study\(^5\):  
**2-YEAR improvement in median MFS**  
(ERLEADA® + ADT vs placebo + ADT; 40.5 months vs 16.2 months; HR = 0.28; 95% CI: 0.23, 0.35; \(P < 0.0001\))

**Start Early with Erleada®**  
To Push Back on Progression

Rash — In 2 randomized studies, 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 (8%) 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, hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% 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 Other Drugs on ERLEADA® —  
Co-administration of a strong CYP2C9 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 Dosing and Administration).  

Effect of ERLEADA® on Other Drugs — ERLEADA® is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP3A4/CYP2C19 could result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is concomitant. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

P-gp, BCRP, or OATP1B1 Substrates — Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1)/OATP1B3 clinically. 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.

**References:**  
1. Erleada® (Apalutamide) [Prescribing Information]. Horizon, PA: Janssen Biotech, Inc.  

**Visit erleadahcp.com**

**Please see Brief Summary of Full Prescribing Information for ERLEADA® on subsequent pages.**

**Investigators:**  
Janssen Research & Development, LLC; 849034

**Address:**  
Janssen Research & Development, LLC

**Contact:**  
Investigator Support  
1-800-223-1889  
Investigator.Support@Janssen.com
adverse reactions occurred in 20% of ERLEADA-treated patients and 28% in patients receiving placebo. Table 3 shows adverse events occurring in ≥10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows adverse events occurring in ≥15% of patients treated with ERLEADA compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ERLEADA (N=803)</th>
<th>Placebo (N=806)</th>
</tr>
</thead>
<tbody>
<tr>
<td>System/Organ Class</td>
<td>%</td>
<td>%</td>
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<tr>
<td>Adverse reaction</td>
<td></td>
<td></td>
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<tr>
<td>Infection</td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>47</td>
<td>39</td>
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<tr>
<td>Hematologic</td>
<td>22</td>
<td>18</td>
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<td>Injury, poisoning, and procedural</td>
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<tr>
<td>Neoplasm and anatomical administration site</td>
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<tr>
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<td>Skin and subcutaneous</td>
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<td>Grade 3</td>
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<td>Includes fatigue and anemia</td>
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</tbody>
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Table 2: Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence Than Placebo (Between Arm Difference ≥ 5% All Grades) in TITAN (n=803)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA (n=803)</th>
<th>Placebo (n=806)</th>
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</thead>
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<tr>
<td>Hypothyroidia</td>
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<td>1</td>
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<tr>
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<td>Includes fatigue and anemia</td>
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<tr>
<td>Diabetes</td>
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<td></td>
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<td></td>
<td>Includes fatigue and anemia</td>
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Table 3: Adverse Reactions in TITAN (n=803)

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<td>System/Organ Class</td>
<td>%</td>
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<tr>
<td>Adverse reaction</td>
<td></td>
<td></td>
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<tr>
<td>Infection</td>
<td>43</td>
<td>32</td>
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<tr>
<td>Gastrointestinal</td>
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Table 4: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence Than Placebo (Between Arm Difference ≥ 5% All Grades) in SPARTAN (n=2348)

<table>
<thead>
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<tr>
<td>Hypercalcemia</td>
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Table 5: Adverse Reactions in SPARTAN (n=2348)

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<td>System/Organ Class</td>
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<tr>
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<td>Infection</td>
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<tr>
<td>Skin and subcutaneous</td>
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<tr>
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Table 6: Antibiotic Use in SPARTAN (n=2348)

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<tr>
<td>Vascular disorders</td>
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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.

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 1337 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 reactions 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).

Ischemic Cardiovascular Events
• Inform patients that ERLEADA has been associated with ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular 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].

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.

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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].

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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**From the publishers of Urology Times**
Putting new clinical guidelines in the spotlight

MIKE HENNESSY SR
Mike Hennessy Sr is chairman and founder of Urology Times® parent company, MJH Life Sciences®

One of the highlights of each year’s American Urological Association annual meeting is the unveiling of new clinical guidelines and updates to existing guidelines. This year’s meeting, despite being held virtually, was no exception in this regard, as you’ll see in this issue of Urology Times®.

For this month, we break down this year’s guidelines, beginning on the cover with an in-depth look at the new guideline for advanced prostate cancer.

Also covered are new guidelines for microhematuria and ejaculatory disorders, as well as updates to the guideline for surgical management of benign prostate hyperplasia (BPH). Each article includes insightful commentary from guideline panel members, and we hope you will find them helpful for quickly getting up to speed on these important updates. In addition, for his “Practice Matters” column, Robert A. Dowling, MD, explains how data can be used to measure adherence to clinical guidelines.

Moreover, our clinical coverage leads off with “Journal Article of the Month.” In this issue, Badar M. Mian, MD, casts an analytical eye at a recent study evaluating quality performance indicators for transurethral resection of the bladder tumor.1

Also in bladder cancer, look for coverage of a multi-institutional retrospective study examining sequential intravesical instillations of gemcitabine and docetaxel for preventing recurrence of non–muscle-invasive bladder cancer in patients with disease recurrence after BCG failure. The article is also the subject of this month’s “From the Board” editorial, written by Urology Times® Editorial Council member Leonard G. Gomez, MD.

In prostate cancer, look for coverage of imaging agents 18F-DCPyL-PET/CT and 18F-rPSMA-73, along with coverage of an American Society of Clinical Oncology Virtual Scientific Program presentation regarding a novel PSMA-targeted radioligand therapy. Also included are reports on recent research on cancer-related pain and prognosis for metastatic castration-sensitive prostate cancer, genomic treatment targets in African American men, and outcomes for delayed radical prostatectomy (RP) vs immediate RP in men with intermediate- and high-risk prostate cancer.

Continuing on to benign conditions, technology is spotlighted with reports on the Solvite SuperPulse Laser System for stone lithotripsy and soft tissue applications, as well as FemPulse, an investigational wearable neuromodulation device for overactive bladder. Finally, in BPH, we recap a wide-ranging discussion among key opinion leaders on topics including the coronavirus disease 2019 (COVID-19) pandemic and how their management of BPH has evolved over time.

This issue’s columns kick off with the latest installment of “Coding Q&A,” which includes a very timely question regarding reimbursement for virtual visits. For “Money Matters,” Jeff Witz, CFP, gives advice for reducing required minimum distributions in retirement accounts.

Meanwhile, for “Speak Out,” Karen Nash interviews 3 urologists regarding how they choose between partial and radical nephrectomy.

We close this edition with “Malpractice Con.” In the column, Acacia Brush Perko, Esq, examines a case in which a man died following a lithotripsy procedure. Perko’s customarily sharp analysis makes this installment a must-read.

For next month, look for highlights from the 2020 European Association of Urology Virtual Congress. Thanks for reading.

REFERENCE
Quality performance initiative may improve TURBT outcomes

Increased usage of bladder diagrams observed following implementation

Transurethral resection of bladder tumor (TURBT) is probably the most technically challenging procedure among all the endoscopic urological procedures of the upper and lower urinary tract. Often viewed as a basic urological procedure, TURBT has long been associated with incomplete resection of tumor, incomplete staging, and early recurrence, especially for non–muscle invasive bladder cancer (NMIBC). Many experts have suggested TURBT quality performance indicators over the past 20 years, but there have been no specifically implemented quality improvement programs.

In a recently published study, Mariappan et al present the outcomes of prospectively developed quality performance indicators (QPIs) for TURBT that were implemented nationally in Scotland in 2014 to improve compliance with guidelines and improve outcomes.

Of the 4246 newly diagnosed bladder cancers (from April 2014 to March 2017) in Scotland, 2689 were diagnosed at the collaborative hospitals, of which 1925 (69%) were diagnosed as NMIBC on TURBT. Multiple and larger (≥ 3 cm) tumors were noted in 32% and 33% of cases, respectively. Low-grade Ta and high-grade Ta or T1 tumors were identified in a near-equal number of patients.

The 3 quality performance indicators specifically related to initial TURBT included use of a bladder diagram showing tumor location, presence of detrusor muscle on initial TURBT specimen, and use of a single instillation of mitomycin C (MMC) after TURBT. The outcome measures after implementation of QPIs for initial TURBT for low-risk NMIBC included recurrence rate at first surveillance cystoscopy. For high-risk NMIBC (HR-NMIBC), outcomes of interest included either the presence of any residual tumor or T2 (muscle-invasive) cancer on the required re-TURBT.

Re-TURBT was not performed in 30% because patients were deemed medically unfit or unlikely to benefit from further surveillance or lost to follow-up.

Annual compliance rate with 3 QPI measures was similar between all of Scotland and the collaborative study centers during the 3-year study period. The most significant increase in QPI compliance was noted in use of bladder diagrams increasing from 33% to 77%. The overall rate of detrusor muscle presence in the TUR specimen and the use of post-TUR MMC did not change during the 3-year study period. The detrusor muscle in the specimen was noted in 80% of cases at the high-volume centers (>90 TURBT/year), which was significantly higher than the 66% from the low-volume centers (<60 TURBT/year).

Regarding oncological outcomes as a result of these QPIs, the recurrence rate at first surveillance cystoscopy for the low-grade group improved steadily from 24% to 14% to 12%. Importantl, there was 3-fold reduction in early recurrence in the group with low-grade small tumors after postoperative single-dose MMC. There was a higher (but not statistically significant) rate of early recurrence for cases with multiple tumors and at low-volume centers. In the T1 and/or high-grade cancer group, re-TURBT showed presence of any residual tumor in 33% of the entire cohort and 35%, 31%, and 31% over the 3-year study period. Muscle-invasive tumor on re-TURBT was noted in 2.9% of cases. On multivariable analysis, tumor size (≥ 3 cm), stage T1, surgeon experience (trainee vs attending), and postop MMC instillation were significantly associated with finding residual tumors, including muscle invasive, on re-TURBT. However, it’s not clear how a single postop MMC instillation would affect the incidence of muscle invasive residual cancer.

Although a bladder diagram with tumor location was used increasingly during the study period, it’s probably the least impactful of the QPIs in this study, as noted by lack of association with any of the oncological outcomes on multivariable analysis. Still, capturing the location and foci of the tumor using either a diagram or a digital image obtained during TURBT is quite easy and can be helpful during surveillance and re-TURBT.

The authors report quite a low and acceptable rate of understaging of muscle invasive bladder cancer (2.9%), which was almost entirely in the group with T1 disease. Overall, residual tumor on re-TURBT of the high-grade, T1 group showed residual cancer in 33% of cases, but the details of the grade/stage or size of residual tumors are not provided. It would be informative to know the rate of high-grade or T1 residual tumors.

It’s likely that some of the increased compliance and resultant improvement in some of the outcomes in this study are due to the Hawthorne effect. It is a well-established phenomenon that there can be significant alteration in behavior (TURBT) of the study subjects (urologists) when they are aware of being observed. Yet, there was no improvement in the residual cancer rate from year 1 to year 3 after implementing...
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Dave Amerson
President, Interventional Urology

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Treatment alternatives to radical cystectomy for bladder cancer continue to evolve

LEONARD G. GOMELLA, MD

Gomella, a member of the Urology Times® Editorial Council, is professor and chair of urology at Thomas Jefferson University, Philadelphia, Pennsylvania.

Non–muscle invasive bladder cancer (NMIBC) often responds to induction and maintenance BCG when doctors are treating intermediate- and high-risk disease. The NMIBC guidelines issued by the American Urological Association (AUA) favor radical cystectomy in patients with high-risk disease who have failed induction or maintenance courses of BCG. For low- and intermediate-risk disease, further therapies are indicated before radical cystectomy should be used. Although the initial response to BCG can be as high as 70%, the lack of benefit after 2 induction courses of BCG increases the risk of disease progression. In these cases, alternatives to radical cystectomy are desirable.

Brooks et al reported on a multi-institution intravesical chemotherapy trial at the 2020 AUA Virtual Experience in June (see article, page 11). In high-risk patients who failed BCG, Brooks and colleagues used sequential intravesical instillations of gemcitabine (Gemzar) and docetaxel (Taxotere). The recurrence-free survival in the primary analysis was 60% at 1 year and 46% at 2 years. Nearly two-thirds of the patients enrolled were cystectomy candidates on the basis of current guidelines.

Numerous intravesical monotherapy chemotherapies have been published with limited data on combining intravesical chemotherapies. Intravesical mitomycin (Mitosol) is well established as a single intravesical administration following resection of low-risk NMIBC and as an alternative to BCG induction and maintenance. Epirubicin (Ellence) has been used but is inferior to BCG. Valrubicin and thiopeta (Tepadina) are the only officially FDA-approved intravesical chemotherapy agents for bladder cancer, with toxicity often limiting their use. Monotherapy studies on the use of docetaxel are limited.

There are robust data on the use of intravesical gemcitabine. The SWOG S0337 (NCT00445601) trial randomized immediate posttransurethral resection of the bladder tumor with intravesical instillation of gemcitabine vs saline in patients with NMIBC. When used post resection, gemcitabine significantly reduced the risk of recurrence over a median of 4 years with an excellent safety profile. Another study, however, failed to confirm the recurrence benefit, but both indicated a good safety profile.

Combination and sequential immunotherapies have been used previously, such as BCG with interferon, with mixed results. This 2020 study sequencing 2 chemotherapies (gemcitabine and docetaxel) is 1 of the first to report a benefit for the combination of intravesical agents. These medications are normally administered systemically and require specific monitoring. The intravesical route, with limited absorption compared with other intravesical chemotherapy agents, minimizes systemic toxicity.

Another area of interest in NMIBC that is based on the legacy of the effectiveness of BCG continues to be immunotherapy. Systemic pembrolizumab (Keytruda) is approved for patients who are ineligible for cystectomy. Many other intravesical and systemic immune modulatory agents are in the late stages of development, such as the novel gene-mediated therapy nadofaragene firadenovec, for intravesical administration.

Not all patients respond to or can tolerate BCG immunotherapy. Therapeutic strategies are needed in the management of NMIBC that recurs after gold-standard intravesical BCG. The worldwide BCG shortage is also a reason to investigate alternative bladder cancer therapies. Although immunotherapy approaches to NMIBC are rapidly moving ahead, new approaches to intravesical chemotherapy, such as the combination of agents, are also proving to be useful in fighting this disease.

TURBT

continued from page 8

QPIs. So, is the nearly 30% residual cancer rate on TURBT the best we can expect, and is that an inherent limitation of TURBT procedure? Could enhanced visualization techniques (blue light cystoscopy, narrow-band imaging) reduce the residual cancer rate? There were no data provided on the preimplementation compliance or outcomes, so it’s not clear whether there was an early improvement in this quality indicator. Even a retrospective review of pre-QPIs implementation data could be instructive about the potential impact on compliance and early outcomes.

High-quality TURBT remains elusive due to limitations posed by the shape of the bladder and instruments and concerns over perforation of bladder, coupled with lack of specific, continued training for this procedure. In contrast, significant strides have been made in the endoscopy for the upper tract and resection or ablation of the prostate with improvements in technology (instruments, energy sources, and imaging).

This appears to be the first endeavor of its kind in which QPI measures for TURBT were developed, implemented, and tracked for compliance to show improvement in early oncological outcomes. This QPI tracking approach may be more feasible in the context of a national health system; such a program may be quite difficult to implement in a large, heterogeneous system like that of the United States. Still, large health care systems such as Veterans Health Affairs and the ever-growing consolidated hospital systems are well suited for implementing such quality improvement initiatives. Further, at the local level, tumor registries and tumor boards can easily provide anonymized, non-punitive reports to the urologists regarding certain quality indicators (detrusor muscle in specimen or recurrence at first cystoscopy) to improve compliance and performance.

REFERENCE

Sequential gemcitabine and docetaxel proves efficacious in NMIBC

Intravesical instillations prevent recurrence of non–muscle-invasive bladder cancer

Cheryl Guttman Krader, BSPharm
Urology Times® Contributing Editor

Sequential intravesical instillations of gemcitabine and docetaxel are safe, well tolerated, and efficacious for preventing recurrence of non–muscle-invasive bladder cancer (NMIBC) in patients with disease recurrence after bacillus Calmette–Guérin (BCG) failure, according to recent findings.

Investigators in the multi-institutional retrospective study reported the results during the 2020 American Urological Association Virtual Experience.1

The study1 included 76 patients representing a heavily pretreated, high-risk population. Bladder recurrence-free survival (RFS) was analyzed as the primary endpoint; based on data collected during a median follow-up of 22.9 months after the start of induction therapy, the rate was 60% at 1 year and 46% at 2 years (Table). Findings from secondary end point analyses showed the rate of high-grade RFS was 65% at 1 year and 52% at 2 years. The progression-free survival rate was 97% at 1 year and 93% at 2 years.

59% of patients experienced no adverse events

Urgency/frequency and dysuria were the most common adverse events (AEs) of the instillations. Fifty-nine percent of patients experienced no AEs, just 3% were unable to complete full induction therapy, and there were no treatment-related deaths, reported Nathan A. Brooks, MD, urologic oncology fellow at The University of Texas MD Anderson Cancer Center in Houston.

“There is an unmet need for alternatives to radical cystectomy for patients with high-risk NMIBC that recurs after BCG,” Brooks explained.

“[Using] intravesical gemcitabine and docetaxel avoids systemic infusion and has other advantages [because] both medications are generic, are easily reconstituted, and have not been plagued by supply shortages. Based on these features and our study’s findings, we believe that prospective evaluation of intravesical gemcitabine/docetaxel is not only warranted but is pragmatically necessary for patients with BCG failure and possibly for BCG-naïve patients, given the current and recurrent supply shortages for BCG,” added Brooks, who worked on the study with Michael O’Donnell, MD, and coauthors. The nationwide study identified patients treated at 9 centers between June 2009 and May 2018 for recurrent NMIBC after prior BCG. Eligible patients also needed to have completed at least 1 surveillance follow-up visit.

The intravesical regimen involved 6 weekly instillations of gemcitabine 1 g/50 mL sterile water that was drained after 60 to 90 minutes and followed by docetaxel 37.5 mg/50 mL with a dwell time of 90 to 120 minutes. Some patients received oral sodium bicarbonate the night before and the morning of the treatment, as well as prophylactic oral ondansetron. Most patients who had no recurrence at 3 months went on to receive 12 to 24 monthly maintenance instillations, although some received 3 weekly minicourses of treatment at 3 months, at 6 months, and every 6 months from induction. At 1 institution, the chemotherapy was heated prior to instillation.

“Although there was some heterogeneity in the treatment regimens used, we observed no differences in outcomes in analyses of individual institutions,” Brooks said.

The study patients had received 1 to 8 prior courses of BCG with a median of 2 prior courses; 38% were unresponsive to BCG, and 61% were judged to be candidates for cystectomy by their treating physicians. Carcinoma in situ was present in almost two-thirds of patients, and approximately 90% had high-grade disease.

Median time to recurrence for those who recurred was 6.8 months. BCG failure category (relapsing, intolerant, unspecified, unresponsive) and pathologic subgroup were not associated with response to gemcitabine/docetaxel, Brooks reported.

Among patients without recurrence at 4 months, receipt of maintenance intravesical therapy was associated with improved bladder RFS. The bladder cancer-specific mortality rate for the cohort was 1% in the first year and 4% in the second year.

“These low mortality rates suggest there is a safe window for potential curative cystectomy,” Brooks said.

He noted that the retrospective design is a limitation of the study. “[Although] our review lacks the specific entrance criteria of prospective studies, it is strengthened by its large sample size, multi-institutional nature, and 2-year results,” Brooks said. Valid reference cited.

REFERENCES


NATHAN A. BROOKS, MD

Source: Nathan A. Brooks, MD

**TABLE. SEQUENTIAL GEMCITABINE AND DOCETAXEL FOR NMIBC**

<table>
<thead>
<tr>
<th>Bladder recurrence-free survival (RFS)</th>
<th>1 year</th>
<th>2 years</th>
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<tbody>
<tr>
<td></td>
<td>60%</td>
<td>46%</td>
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</table>

<table>
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<tr>
<th>High-grade RFS</th>
<th>65%</th>
<th>52%</th>
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<table>
<thead>
<tr>
<th>Progression-free survival</th>
<th>97%</th>
<th>93%</th>
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</table>

Source: Nathan A. Brooks, MD
A new clinical guideline for microhematuria embraces a risk-stratified approach to evaluating patients.

The guideline was presented at the 2020 American Urological Association (AUA) Virtual Experience by guideline panel cochairs Daniel A. Barocas, MD, MPH, associate professor and vice chair of urology at Vanderbilt University Medical Center, Nashville, Tennessee, and Stephen A. Boorjian, MD, professor of urology at Mayo Clinic, Rochester, Minnesota.1

The multidisciplinary panel included members of the AUA, Society of Urodynamics, Female Pelvic Medicine & Urogynecology, American College of Obstetricians and Gynecologists, as well as a patient advocate from the Bladder Cancer Advocacy Network. The panel’s evidence base consisted of 5 systematic reviews and 91 primary literature studies.

In presenting the guideline, Barocas explained that hematuria is 1 of the most common urologic diagnoses, “by some estimates accounting for 25% or more of urologic evaluations.”

“The is quite a bit of variability across current guidelines and consensus statements regarding the definition of microhematuria, criteria for evaluation, and the components for evaluation, including the optimal imaging modality.”

DANIEL A. BAROCAS, MD, MPH

Barocas also discussed the variability related to microhematuria evaluation.

“There is quite a bit of variability across current guidelines and consensus statements regarding the definition of microhematuria, criteria for evaluation, and the components for evaluation, including the optimal imaging modality,” Barocas said.

With the guideline, Barocas said the panel sought to address the following issues: conflicting guidelines, a low overall yield of evaluation, harms of evaluation in terms of risks to patients and cost to the health care system, and poor adherence to existing guidelines.

“Microhematuria guideline emphasizes risk-stratified approach

Benjamin P. Saylor
Content Managing Editor, Urology Times®

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Expiration by guideline panel cochairs Daniel A.

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• Due to this risk, use JATENZO only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies.

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August 2020
Defining microhematuria

The guideline panel defines microhematuria as “[greater than or equal to] 3 red blood cells per high-power field on microscopic evaluation of a single, properly collected urine specimen.”

The guideline further advises that clinicians do not define microhematuria solely by positive dipstick testing alone but rather proceed to formal microscopic evaluation of the urine following a positive dipstick test. “This is because a variety of factors, including myoglobinuria, dehydration, exercise, and beta dyeing, can produce false-positive dipstick results,” Barcos said.

Barcos also described statements of the guideline related to patients diagnosed with gyneco-logic or nonmalignant genitourinary sources of microhematuria. For these patients, the clinician should conduct a repeat urinalysis following the resolution of the gynecologic or nonmalignant genitourinary cause.

Following this, “If the hematuria persists or the etiology can’t be identified, clinicians See MICROHEMATURIA page 14
should perform a risk-based evaluation. By the same token, in patients with hematuria attributed to a urinary tract infection, clinicians should obtain a urinary analysis with microscopic evaluation following treatment to ensure the resolution of the hematuria,” Barcos said. During his presentation, Boorjian described the risk stratification components of the guideline. The development of a risk classification system represents a recognition on the part of the guideline panel of the heterogeneity in risk among patients presenting with microscopic hematuria for undergoing genital urinary malignancy and an effort to provide an individualized approach to evaluation,” Boorjian explained.

The guideline directs clinicians to categorize patients based on risk, with low-risk being defined as being at low, intermediate, or high risk for genitourinary malignancy. Criteria for risk stratification are outlined in the guideline and include age, smoking status, degree of microhematuria, persistence of
microhematuria, history of gross hematuria, and additional urothelial cancer risk factors.

In patients categorized as low risk, the guideline recommends a shared decision-making process to choose between repeating urinary analysis within 6 months or proceeding with cystoscopy and renal ultrason. Low-risk patients who choose not to undergo initial cystoscopy or upper tract imaging but are found to have microhematuria after repeat urine testing should be reclassified as intermediate or high risk and should then undergo cystoscopy and upper tract imaging.

Cystoscopy and renal ultrason are recommended in patients with intermediate-risk microhematuria.

“The panel wants to emphasize that the overwhelming majority of genitourinary malignancies diagnosed among patients with microscopic hematuria are bladder cancers, and therefore cystoscopy represents an absolute cornerstone to the evaluation of microhematuria patients,” Boorjian said. In patients categorized as being at high risk for malignancy, the guideline recommends that clinicians perform cystoscopy and axial trauma imaging.

“The panel wants to emphasize that the overwhelming majority of genitourinary malignancies diagnosed among patients with microscopic hematuria are bladder cancers, and therefore cystoscopy represents an absolute cornerstone to the evaluation of microhematuria patients.”

STEPHEN A. BOORJIAN, MD

GUIDELINE UPDATE / Bladder Cancer

REFERENCE
GUIDELINE
continued from page 1

Clinical Oncology, the American Society for Radiation Oncology, and the Society of Urologic Oncology, as well as a patient advocate. The systematic review spanned the dates of 1998 through January 2020. The evidence base that we compiled consisted of 192 publications from this time period. We also carried over an additional 46 publications from the prior AUA castration-resistant prostate cancer (CRPC) review and 26 additional studies,” added Lowrance.

The focus of the guideline is patients who have exhausted all local therapy options and now require systemic treatment options. These include patients with biochemical recurrence, metastatic hormone-sensitive prostate cancer (mHSPC), nonmetastatic CRPC, and metastatic CRPC. The guideline grades the strength of evidence as high (A), moderate (B), and low or very low (both under the umbrella of C).

In their discussion during the AUA virtual platform, Lowrance and Cookson highlighted the core components of the consensus guideline for urologists to follow in their daily practice.

Early evaluation and counseling

The guideline lays out principles that should be followed with the early evaluation and counseling of patients with suspicion of advanced prostate cancer who do not yet have histologic confirmation. Lowrance said a tissue diagnosis from the primary tumor or metastatic site should be obtained by the clinician.

When diagnosis is confirmed, the guideline recommends physician–patient discussions of treatment options that cover these factors: patients’ tumor characteristics, life expectancy, comorbidities, and treatment preferences. The treatment strategy should, if possible, include a multidisciplinary approach. Also, when possible, pain control and other symptom support should be optimized, explained Lowrance.

Biochemical recurrence without metastatic disease

“In the hormone-sensitive setting, prostate-specific antigen (PSA) recurrence almost always precedes clinical detection of metastases,” said Lowrance. Thus, in men with biochemical recurrence without metastases, clinicians should perform serial PSA measurements, clinical evaluations, and staging evaluations.

For these staging evaluations, the guideline recommends use of standard-of-care imaging, including bone scans and axial imaging with CT or MRI. Given the emergence of advanced PET imaging in the paradigm for advanced prostate cancer, the guideline stipulates, “Clinicians may utilize novel PET-CT scans in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging or in the setting of negative conventional imaging.”

In those patients with a rising PSA whose imaging does not reveal any metastases, the guideline recommends that the patients be offered observation or enrollment on a clinical trial. As routine practice, androgen deprivation therapy (ADT) should not be started in these patients. When ADT is used, said Lowrance, a grade B recommendation in the guideline states that clinicians may offer intermittent ADT instead of continuous ADT.

mHSPC

The guideline states that genetic counseling and germline testing should be offered to all men with mHSPC, regardless of age and family history. The germline testing in this setting focuses on genes that influence homologous recombination repair, such as BRCA1, BRCA2, and ATM.

Patients with mHSPC should be offered surgical castration or ADT combined with either LHRH agonists or antagonists (grade B). Further, grade A evidence supports the guideline recommendation that “clinicians should offer continued ADT in combination with either androgen pathway–directed therapy (eg, abiraterone acetate [Zytiga] plus predniso1one; apalutamide [Erleada]; or enzalutamide [Xandi]) or docetaxel-based chemotherapy,” said Lowrance.

“The primary aim of this guideline is to assist clinicians with decision-making. The evidence-based guideline recommendations are furnished according to disease state across the entire continuum of advanced prostate cancer.”

William Lowrance, MD, MPH

Lowrance shared some of the data supporting the use of androgen pathway–directed therapies in this setting. In the phase 3 TITAN trial (N = 1050), apalutamide plus ADT reduced the risk of death by 33% versus ADT alone in patients with mHSPC (HR, 0.67; 95% CI, 0.52-0.86; P = .002).^4^ Nonmetastatic CRPC

This population includes patients with a rising PSA but no sign of metastatic disease on standard imaging despite “the persistence of a castrate-level testosterone,” said Cookson, professor and chairman of urology, Stephenson Cancer Center, The University of Oklahoma, Norman.

In recent years, the first agents have been specifically approved by the FDA for the treatment of these patients, based on a demonstrated metastasis-free survival (MFS) benefit. All 3 therapies are androgen receptor antagonists: apalutamide, darolutamide (Nubequa), and enzalutamide.

Apalutamide, enzalutamide, and darolutamide all demonstrated an MFS benefit over placebo in the pivotal SPARTAN (HR, 0.29; P < .001),^4^ PROSPER (HR, 0.62; P < .001),^5^ and ARAMIS (HR, 0.41; P < .001) trials, respectively. Each of the 3 trials enrolled more than 1200 patients with nonmetastatic CRPC who were at high risk for developing metastatic disease (PSA doubling time of ≤10 months). Cookson noted that since the completion of the data analysis for the guideline, overall survival (OS) data from the PROSPER trial were published showing that enzalutamide led to a 27% reduced risk of death versus placebo, with a median OS of 67 versus 56.3 months, respectively (HR, 0.73; 95% CI, 0.61-0.89; P = .001).^7^ mCRPC

Docetaxel is indicated for the first-line treatment of patients with mCRPC, with several treatments approved for use before and after the chemotherapy. The immunotherapy sipuleucel-T (Provenge) is approved by the FDA for asymptomatic or minimally symptomatic mCRPC. Enzalutamide and abiraterone acetate (plus prednisone) are approved for use both in chemotherapy-naïve patients and following failure of docetaxel. The chemotherapy cabazitaxel (Jevtana) is approved as a second-line, postdocetaxel option.

The radiopharmaceutical radium-223 (Xofigo) is approved for the treatment of patients with CRPC with symptomatic bone metastases but no known visceral metastatic disease. In this setting, radium-223 has demonstrated an OS benefit over standard therapy in both chemotherapy-naïve patients and those with prior docetaxel.

Genetic testing and related treatments are a burgeoning area of the mCRPC paradigm. According to Cookson, research results indicate that "DNA damage response (DDR) alterations have been identified in 23% of patients with
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GUIDELINE 
continued from page 16

mCRPC, including both somatic and germline defects. Among the DDR alterations, *BCRA2* is the most frequently altered, and these gene alterations are expected to confer sensitivity to PARP inhibitors,” he said. Therefore, “nearly 20% of patients with mCRPC may potentially benefit from this therapy.” The AUA guideline includes the grade C recommendation that “clinicians should offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene–mutated mCRPC following prior treatment with enzalutamide or abiraterone acetate, and/or a taxane-based chemotherapy. Platinum-based chemotherapy may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor.”

Two PARP inhibitors were recently approved by the FDA for the treatment of patients with mCRPC. In May 2020, the FDA approvedrucaparib (Rubraca) for the treatment of adult patients with *BRCA1* mutation (germline and/or somatic)—associated mCRPC who have been treated with androgen receptor–directed therapy and a taxane-based chemotherapy. The approval was based on data from the phase 2 TRITON2 study, in which the confirmed objective response rate was 44% in a cohort of 62 patients with *BRCA1*-mutated mCRPC.8 Also in May 2020, the FDA approved olaparib (Lynparza) for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene–mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone acetate. The approval was supported by the phase 3 PROFound trial, in which the risk of disease progression or death was reduced by 66% with olaparib compared with abiraterone acetate or enzalutamide (HR, 0.34; *P* <.0001) in patients with *BRCA1/2-* or *ATM-mutant mCRPC.*9

The final option for mCRPC that Cookson covered was the immune checkpoint inhibitor pembrolizumab (Keytruda), which is available as an option for patients with microsatellite instability–high or mismatch repair–deficient tumors.

Bone health

Cookson concluded the discussion with a focus on bone health. Preventive treatments with bisphosphonates or denosumab should be recommended to patients with advanced prostate cancer whose bone loss has put them at high fracture risk, according to the guideline. It is also indicated that, when appropriate, these patients should be referred to experts in the area of osteoporosis. Among patients with mCRPC with bony metastases, the guidelines include the grade B recommendation that “clinicians should prescribe a bone protective agent—denosumab or zoledronic acid—to prevent skeletal-related events,” said Cookson.

REFERENCES


AI PROGRAM RECOGNIZES, CHARACTERIZES PROSTATE CANCER

A study published in *The Lancet Digital Health* by researchers from the University of Pittsburgh Medical Center (UPMC) and University of Pittsburgh in Pennsylvania demonstrated the highest accuracy to date in recognizing and characterizing prostate cancer using an artificial intelligence (AI) program.1

To train the AI to recognize prostate cancer, Rajiv Dhir, MD, MBA, chief pathologist and vice chair of pathology at UPMC Shadyside and professor of biomedical informatics at Pitt, and colleagues provided images from more than a million parts of stained tissue slides taken from patient biopsies. Each image was labeled by expert pathologists to teach the AI how to discriminate between healthy and abnormal tissue.

The algorithm was then tested on a separate set of 1600 slides taken from 100 consecutive patients seen at UPMC for suspected prostate cancer. During testing, the AI demonstrated 98% sensitivity and 97% specificity at detecting prostate cancer—significantly higher than previously reported for algorithms working from tissue slides.

Disclosures: Ibex Medical Analytics provided funding for the study. Several study authors have received fees from Ibex.

REFERENCE


GUIDELINE UPDATE

Prostate Cancer
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Agent shows effective diagnostic performance in recurrent prostate cancer

18F-DCFPyL-PET/CT led to change in management in most of the participants in phase 3 study

Wayne Kuznar
Urology Times® Correspondent

Imaging with 18F-DCFPyL–PET/CT is able to detect and localize disease in men with biochemically recurrent prostate cancer who had no evidence of disease on standard-of-care imaging, and it led to a change in the management of most patients who participated in the phase 3 multicenter CONDOR study.

Of 208 men with a rising prostate-specific antigen (PSA) level after definitive therapy and negative or equivocal standard-of-care imaging who were enrolled in CONDOR, the correct localization rate (CLR) with 18F-DCFPyL–PET/CT was 85% to 87% and the detection rate was 59% to 65%.

Further, 63.9% of the patients had a change in intended management after their 18F-DCFPyL–PET/CT scan.

Data from the study were presented by Michael J. Morris, MD, during the 2020 American Society of Clinical Oncology Virtual Scientific Program.1 "CONDOR met its primary end point. Indeed, it well exceeded it. It demonstrated excellent diagnostic performance of PyL–PET in men with biochemically relapsed prostate cancer, even at very low PSA values," said Morris, clinical director of the Genitourinary Medical Oncology Service, Division of Solid Tumor Oncology, at Memorial Sloan Kettering Cancer Center in New York City, New York. "It clearly showed superiority to the standard imaging these men received as part of their local work-ups. And the results demonstrated that actionable intervention was furnished to clinicians in order to make clinically significant decisions."

There is ample evidence that prostate-specific membrane antigen (PSMA)–PET is superior to current standard imaging modalities for the detection of prostate cancer, Morris said. However, PSMA–PET imaging has not yet earned regulatory approval in the United States," he stated. PyL is a PSMA-directed PET tracer under investigation.

"Men with rising PSA after definitive therapy and negative or equivocal standard-of-care imaging were eligible for CONDOR. Patients were required to have a PSA ≥0.2 if they had undergone radical prostatectomy (RP) or a PSA level ≥2.0 if they were treated with radiation therapy or cryotherapy. The primary end point was CLR, defined as percentage of patients with a 1:1 correspondence between at least 1 lesion identified by PyL–PET/CT and the composite standard of truth (pathology, correlative imaging, or PSA response). PyL scans were read by 3 blinded independent central readers.

About 85% of the 208 patients underwent RP, either alone or with radiation. Median PSA level of the cohort was 0.8 ng/mL, and 68.8% had a PSA level ≤2.0 ng/mL. Some 27.9% had received supplementation with or replacement by systemic therapy; 24% of patients had a change from observation to initiating therapy and 4.4% the converse."

Disclosures: Progenics Pharmaceuticals, Inc, provided funding for the study. Dr. Morris is a consultant/adviser for Advanced Accelerator Applications, Astellas Pharma, Bayer, Blue Earth Diagnostics, Endocyte, ORIC Pharmaceuticals, Tokai Pharmaceuticals, and Tolmar; has received institutional funding from Bayer, Concept Therapeutics, Endocyte, Progenics, Roche/Genentech, and Sanoﬁ; and has received travel, accommodations, and expenses from Bayer and Endocyte. For full disclosures, see bit.ly/31R12Wz.

REFERENCE

PET imaging agent found superior to CT for lymph node staging

Cheryl Guttman Krader, BSPharm
Urology Times® Contributing Editor

Positron emission tomography (PET) imaging with fluorine 18 (18F)–rhPSMA-7.3 is superior to morphological imaging with computerized tomography (CT) for lymph node (LN) staging in patients with primary intermediate- and high-risk prostate cancer, according to the findings of a retrospective study presented at the 2020 American Urological Association Virtual Experience.1 The data from an initial clinical evaluation of the diagnostic efficacy of the investigational radiohybrid 18F-labeled PSMA-7.3 ligand was reported by Tobias Maurer, MD, a urology specialist at the Martini-Klinik prostate cancer center at the University of Hamburg-Eppendorf in Germany.2 18F-Ga-PSMA PET imaging has become a common method for primary staging of prostate cancer in Europe," Maurer said. “Although our evaluation of 18F-rhPSMA-7.3 PET imaging is a retrospective analysis, the findings demonstrating its performance are consistent with evidence from studies reporting increased LN detection rates using 18Ga-PSMA PET imaging compared with CT.”

Radiohybrid PSMA ligands are a new class of diagnostic/therapeutic PSMA-targeting agents that can be efficiently labeled with 18F. Compared
Novel PSMA-targeted radioligand therapy shows promise in mCRPC

Hannah Slater
Assistant Editor, Oncology®

A randomized phase 2 trial presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program found that in men with metastatic castration-resistant prostate cancer (mCRPC) who progressed after being treated with docetaxel, \(^{18}\text{Lu-PSMA-617}\) (LuPSMA) was more active than cabazitaxel (Jevtana).

Further, grade 3 to 4 adverse events (AEs) were relatively fewer with the use of LuPSMA and prostate specific antigen–progression-free survival (PSA-PFS) favored LuPSMA as well.

“[Metastatic castration-resistant prostate cancer] is a lethal disease, and novel treatments are urgently needed to improve patient outcomes,” Michael S. Hofman, MBBS, of the Peter MacCallum Cancer Centre in Melbourne, Australia, said in a presentation of the results.

The trial, TheraP (NCT03992428), randomly assigned men with mCRPC, and imaging with \(^{68}\text{Ga-PSMA-11}\) and \(^{18}\text{F-FDG PET/CT}\) that confirmed high prostate-specific membrane antigen (PSMA) expression and no sites of FDG-positive/PSMA-negative disease, in a 1:1 fashion to \(^{18}\text{F-rhPSMA-7.3}\) (PSMA) expression and no sites of FDG-positive/PSMA-negative disease, in a 1:1 fashion to either LuPSMA or cabazitaxel. Men in the experimental arm of the study underwent posttherapy single-photon emission computed tomography or CT scans after each cycle of LuPSMA, and if an exceptional response was demonstrated, their treatment was paused and could resume thereafter at the time of PSA progression.

The primary end point of the study was PSA response rate, defined by a reduction of 50% or greater. Key secondary efficacy end points included PSA-PFS, AEs, and overall survival. The data cutoff for the results reported was March 31, 2020.

Overall, 200 of 291 men across 11 sites in Australia who received PET scanning were randomized to LuPSMA (n = 99) or cabazitaxel (n = 101). Importantly, 17 patients withdrew or died before receiving study treatment (1 in the LuPSMA arm vs 16 in the cabazitaxel arm).

The PSA response rate was higher in patients who received LuPSMA than in those who received cabazitaxel (66% [95% CI, 56-75] vs 37% [95% CI, 27-46]; P < .001). This represented a 29% (95% CI, 16%-42%; P < .0001) absolute greater PSA response rate in participants receiving LuPSMA compared with cabazitaxel. For sensitivity analysis per protocol, the difference observed was 23% (95% CI, 9%-37%; P = .0016). At a median follow-up of 13.3 months, LuPSMA was shown to have significantly improved PSA-PFS (HR, 0.69; 95% CI, 0.50-0.95; P = .002). These data were based on 157 of the 170 events required for primary analysis.

“Importantly, improvements in overall survival have not yet been demonstrated, and we eagerly await the results of the upcoming phase 3 VISION trial [NCT03511664],” Hofman said.

Efficacy results were similar when the analyses were restricted to per-protocol-treated men.

Grade 3 to 4 AEs occurred in 36% of men treated with LuPSMA compared with 49% of men treated with cabazitaxel. Moreover, grade 5 AEs occurred in 11 patients treated with LuPSMA and in 5 patients treated with cabazitaxel. There were no treatment-related deaths.

The investigators indicated that they await further follow-up results of other key secondary end points, including radiologic PFS (the next planned analysis after 170 events), quality of life, and PFS. Moreover, they believe that LuPSMA warrants study in earlier phases of prostate cancer, as well as in combination with other therapies.

“On the basis of these results, LuPSMA appears to represent a new class of effective therapy for men with metastatic castration-resistant prostate cancer,” said Hofman.  

REFERENCE

Analysis identifies genomic treatment targets in African American men

Findings create opportunity for precision medicine options in prostate cancer

Jason M. Broderick
Associate Editorial Director, Urology Times®

Researchers have identified genes more commonly altered in tumors from African American men with prostate cancer, opening the potential to develop precision medicine therapies for these patients.1,2

“These results reinforce the idea that there can be biological differences in prostate cancers between different ancestral groups and that samples from black Americans need to be included in future molecular studies to fully understand these differences,” co-corresponding author Joshua Campbell, PhD, assistant professor of medicine at Boston University School of Medicine (BUSM), stated in a press release.

Despite detecting these novel genomic differences, the study also found that genomic alterations in therapeutic targets related to currently available treatments occurred at similar frequencies in African American men and men of European descent, indicating the treatments should be beneficial in both groups.

“The poorer health outcomes we see in black men with prostate cancer are not easily explained by any of the distinct gene mutations we identified in prostate tumors from men of African ancestry. This highlights the need to examine the environmental and social inequities that are well known to influence health outcomes across the board,” co-corresponding author Franklin Huang, MD, PhD, an assistant professor in the University of California, San Francisco (UCSF) Division of Hematology/Oncology and member of the UCSF Helen Diller Family Comprehensive Cancer Center, stated in the press release.

“On the other hand, our tumor genomic analysis also showed that current precision medicine approaches ought to be as effective in black Americans as they have been for other groups—if we can ensure that these drugs are applied equitably going forward,” added Huang.

Investigators from BUSM, UCSF, and Northwestern University undertook the study because, despite the prostate cancer mortality rate being higher in African Americans than any other racial/ancestral group, there is a paucity of available data regarding potential differences in somatic gene alterations in tumors in African American men compared to other populations. These potential differences remain unknown because African American men have not been well represented in genomic research.

The study included data from 4 publicly available datasets that comprised 250 African American men and 611 European American men with prostate cancer, as well as data for 456 African American men and 308 European American men obtained from a targeted sequencing dataset from a commercial platform. The investigators evaluated the occurrence of somatic alterations in prostate cancer in these patient populations.

Deletions in ETV3, mutations in ZFHX3 detected

Results showed that, in tumors from African American men, focal deletions in ETV3 and mutations in ZFHX3 were more common. CCND1 amplifications and KMT2D truncations were detected more often in primary prostate cancer from African American patients. TP53 mutations were linked with an increasing Gleason score. Rearrangements in TMPRSS2-ERG and PTEN deletions were detected less frequently in tumors from African American patients. MYC amplifications occurred more commonly in tumors from African American men with metastatic prostate cancer.

“Additional studies that profile large numbers of well-matched tumors from African American and non–African American men from the same clinical setting will be needed to confirm the novel associations reported in this study and to understand the clinical significance,” the investigators wrote.

As noted, significant differences between the 2 groups were not detected; however, in genomic features related to FDA-approved treatments. These features included microsatellite instability (MSI) status, tumor mutation burden (TMB), and genomic alterations in AR, select DNA repair genes, and CDK12. Thus, approved treatments, such as the immune checkpoint inhibitor pembrolizumab (Keytruda) for patients with TMB-high tumors, and PARP inhibitors for patients with BRCA-mutated (rucaparib [Rubraca] or HRR-mutated (olaparib [Lynparza]) tumors, should equally benefit both patient populations.

“Our tumor genomic analysis also showed that current precision medicine approaches ought to be as effective in black Americans as they have been for other groups—if we can ensure that these drugs are applied equitably going forward.”

FRANKLIN HUANG, MD, PhD

Looking ahead, Campbell stated, “These types of studies will remain important to understand when certain therapies may preferentially benefit black patients, who continue to remain underrepresented in clinical trials.”

Specifically, the authors noted that the results will inform the ongoing efforts of the National Cancer Institute–supported RESPOND study. The RESPOND study is partnering with African American communities nationwide to enroll 10,000 African American men with prostate cancer to improve the overall understanding of the specific drivers of prostate cancer’s highly disproportionate burden on African American men.

REFERENCES
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Cancer-related pain indicative of poor prognosis for metastatic CSPC

Patients with metastatic castration-sensitive prostate cancer with pain had OS of 27 months

Lisette Hilton
Urology Times® Correspondent

Cancer-related pain is indicative of a poor prognosis in patients with metastatic castration-sensitive prostate cancer (mCSPC), according to a paper published in Prostate Cancer and Prostatic Diseases.1

Some distinguish mCSPC prognostic classes based on disease burden and other clinical features. Researchers have used the presence of visceral metastasis, extent of bone metastasis, and Gleason score to classify these patients prognostically.

However, without direct comparisons among therapeutic options and given the absence of a reliable molecular and clinical prognostic stratification of mCSPC, it’s difficult to optimally select treatment, according to the study results.

“Being able to distinguish different prognostic ‘classes’ of mCSPC so as to tailor the treatment for each patient is 1 of the greatest future challenges,” the investigators wrote.

A group of French researchers analyzed data from about 370 de novo metastatic patients. Pain data were included for 365 of those patients, and pain was present in about a third (34.8%) of cases. According to the paper, pain was associated primarily with high value of prostate-specific antigen, greater bone extension of disease, and lymph node involvement. Pain was not associated with visceral metastases.

They found that while patients without pain had an overall survival (OS) of 56 months, patients with pain had an OS of only 27 months. Patients with pain in the study also had significantly lower progression-free survival at 10.1 months versus 17.4 months among patients who did not report cancer-related pain.

When it does metastasize, prostate cancer most often spreads to bone, which often results in debilitating pain and limited function. Many consider cancer-related pain to be a key prognostic indicator that men with castration-resistant prostate cancer have a poorer prognosis than patients without pain. But more work is needed to determine cancer pain’s true prognostic value in mCSPC.

“External prospective validation of CSPC patient cohorts is required to establish if cancer-related pain can help in guiding the treatment decision process,” the investigators concluded.

Urologists should consider 2 important takeaways from this paper, according to urologist and urologic oncologist Christopher Filson, MD, MS, assistant professor of urology at Emory University School of Medicine in Atlanta, Georgia.

“One is understanding the importance of being thorough and assessing the degree of pain that patients should be pain present, to consider addressing their needs,” Filson said. “The second point is ensuring symptoms like pain,” he said. “For me, reading the article reinforced my belief that, first of all, assessing patients’ cancer pain is critical, and should there be pain present, to consider addressing their needs with palliative care whether they have weeks, months, or even years to live.”

REFERENCE


Patient dosing begins for phase 3 trial of PET imaging agent

Agent to be examined in men with suspected prostate cancer recurrence

Jason M. Broderick
Associate Editorial Director, Urology Times®

The first patients have been dosed in the phase 3 SPOTLIGHT trial, which is examining the investigational PSMA-targeted radiolabeled PET imaging agent rhPSMA-7.3 (18F) in men with suspected prostate cancer recurrence.1

The single-arm SPOTLIGHT study (NCT04186843) is specifically assessing the safety and diagnostic capability of rhPSMA-7.3 (18F) PET in men whose elevated PSA following prior therapy has made them clinically suspicious for biochemically recurrent disease. The primary end points of the phase 3 trial are the positive predictive value (PPV) and correct detection rate (CDR) of rhPSMA-7.3 (18F) PET.

“At Emory, we scanned our first patient in the SPOTLIGHT study in late June, and we are rapidly recruiting more patients in this exciting trial.”

DAVID M. SCHUSTER, MD

“At Emory, we scanned our first patient in the SPOTLIGHT study in late June, and we are rapidly recruiting more patients in this exciting trial.”

David M. Schuster, MD, the coordinating investigator for the SPOTLIGHT study, stated in a press release.

“There’s a presumption that palliative care is reserved for patients who have end-of-life issues or are within the last 30 days of their lives. But the data suggest that palliative care has a role for any patient with advanced cancer who may be experiencing symptoms like pain,” he said. “For me, reading the article reinforced my belief that, first of all, assessing patients’ cancer pain is critical, and should there be pain present, to consider addressing their needs with palliative care whether they have weeks, months, or even years to live.”

REFERENCE

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Delayed RP does not increase adverse outcomes risk vs immediate surgery

Radical prostatectomy 4 to 12 months after diagnosis did not increase odds of adverse pathology

Jason M. Broderick
Associate Editorial Director, Urology Times®

Delayed radical prostatectomy (RP) does not increase the risk of early adverse oncological outcomes compared with immediate RP in men with intermediate- and high-risk prostate cancer, according to a retrospective analysis published in the Journal of Urology.1,2

Compared with patients receiving RP within 3 months of diagnosis, patients undergoing surgery 4 to 12 months after diagnosis did not have increased odds of adverse pathology, upgrading on RP, or node-positive disease. The investigators hope their findings offer some reassurance to urologists and patients trying to balance medical decisions with safety precautions during the coronavirus disease 2019 (COVID-19) pandemic.

“In men who had radical prostatectomies for intermediate- and high-risk disease, we found that a delay of up to 12 months did not result in any worse outcomes compared to immediate surgery within 3 months of diagnosis. The men who had delay had equivalent final pathology reports, and they did not undergo additional secondary treatments at a higher rate compared with men who had immediate surgery,” senior study author Michael Cher, MD, professor and chair of urology, Wayne State University School of Medicine, Detroit, Michigan, said in a press release.

The investigators accrued data from the National Cancer Database for men with intermediate- and high-risk prostate cancer who received RP between 2010 and 2016. Surgery 3 months from diagnosis was defined as immediate RP, with delayed RP being evaluated in 3-month intervals up to 12 months (4-6 months, 7-9 months, 10-12 months).

Overall, the analysis included 128,062 patients with a median age of 63 years (IQR, 58-67) and a median PSA at diagnosis of 6.3 ng/mL. Just over half (50.1%) of the patients had GG2 disease. The median interval between diagnosis and treatment was 3 months (IQR, 2-4). Overall, 73.2% (n=93,764) of patients underwent RP within 0 to 3 months of diagnosis, 23.7% (n=30,337) within 4 to 6 months, 2.5% (n=3,213) within 7 to 9 months, and 0.6% (n=748) within 10 to 12 months.

Compared with the immediate RP group, the odds of adverse pathology were not higher with the delays of 4 to 6 months (odds ratio [OR], 0.98; 95% CI, 0.94-1.02; P=0.310), 7 to 9 months (OR, 1.02; 95% CI, 0.99-1.04; P=0.521), and 10 to 12 months (OR, 1.00; 95% CI, 0.80-1.26; P=0.98). Separate subgroup analyses of men with GG2/3 and GG 4/5 disease also did not show a significant difference in adverse pathology between any of the 3 delay intervals compared with immediate RP.

No link between delayed RP, pathologic upgrading

There was also no link between delayed RP and pathologic upgrading. The odds of pathologic upgrading at RP were similar between the delayed RP cohorts compared with the immediate RP cohort: 4 to 6 months (OR, 1.0; 95% CI, 0.95-1.05; P=0.922), 7 to 9 months (OR, 1.09; 95% CI, 0.95-1.24, P=0.288), and 10 to 12 months (OR, 1.06; 95% CI, 0.82-1.37; P=0.649). The odds of nodal metastases were similarly not higher for the delayed RP cohorts compared with the immediate RP cohort.

In an accompanying editorial, Geoffrey H. Rosen, MD, and coauthors wrote, “In this work, Ginsburg and colleagues present a timely, important analysis of a large nationwide database, where they do not find correlation between time to treatment and adverse outcomes. This practice-informing study could be furthered with more details about the sample, outcomes, and models. This work is an excellent addition to the literature on timing of intervention for prostate cancer that has taken on new relevance in the setting of COVID-19.”

REFERENCES
Thulium fiber laser system for urinary stones launched in United States

System dusts stones in half the time of standard holmium yttrium aluminium garnet laser

**Jason M. Broderick**
Associate Editorial Director, Urology Times®

The Soltive SuperPulsed Laser System (Soltive Laser System) has been launched in the United States as an option for urologists to use for stone lithotripsy and soft tissue applications.1

The Soltive Laser System, which uses thulium fiber laser technology, has US FDA 510(k) clearance. In a clinical trial, the Soltive system generated finer particulate and dusted stones in half the time as a standard holmium yttrium aluminium garnet (Ho:YAG) laser.2 Among other benefits, Soltive has also demonstrated an infinitesimal level of retropulsion.

“The SuperPulsed thulium fiber laser is a game changer. Besides being faster, this laser dusts stones into very fine particles that more easily wash out during the procedure, which is a significant benefit for patients,” Bodo Knudsen, MD, director of the Comprehensive Kidney Stone Program at Ohio State University, Columbus, who was the first clinical user of the Soltive Laser System, stated in a press release.

In a pivotal trial, Soltive was assessed in 268 patients with stone disease, including 173 kidney, 80 ureteral, and 15 bladder.2 The average stone size was 11.4 mm (range, 7-25) for kidney, 7.6 mm (range, 3-18) for ureteral, and 22.2 mm (range, 9-36) for bladder. The average stone density was 987 HU (range, 330-1960), 995 HU (range, 460-1700), and 980 HU (range, 860-1050), respectively.

Regarding the time to complete stone fragmentation (to dust or small fragments), the average time was 27.2 minutes for renal stones, 17.1 minutes for ureteral stones, and 19 minutes for bladder stones. The investigators observed that the retropulsion was insignificant in all cases with energy level less than 0.5 J. In most cases, surgeons estimated visibility as optimal.

There were no major safety issues with Soltive. The investigators did not observe any optic or working channel damages, or urinary tract injuries. Further, no grade ≥IIIa complications (Clavien-Dindo) were reported.

The investigators wrote in their conclusion, “Based on the analysis of data on 268 subjects available today, the SuperPulse fiber laser is safe and efficacious for all types of urinary stones in all relevant anatomic locations.”

In a separate trial, Soltive with an emission wavelength of 1.94 μm was compared to a Ho:YAG laser (P120H; Lumenis, Yokneam, Israel) with Moses technology using BegoStone, a stone phantom for shock wave lithotripsy research.3 The findings
Wearable neuromodulation device shows promise for overactive bladder

Feasibility study results indicate nonimplanted, intravaginal device is safe and comfortable

Cheryl Guttmann Krader, BSPharm
Urology Times® Contributing Editor

A nonimplanted, intravaginal neuromodulation device (FemPulse) for treating overactive bladder (OAB) symptoms demonstrated favorable results in a feasibility study assessing wearability, safety, and clinical utility, reported Suzette E. Sutherland, MD, MS, FPMRS, at the 2020 American Urological Association Virtual Experience.1

“This device aims to provide a simple, convenient, and affordable form of continuous neuromodulation to ameliorate bothersome symptoms of OAB. The collective findings of the feasibility study justify its further investigation,” said Sutherland, the primary study investigator and director of Female Urology at the University of Washington School of Medicine in Seattle.

Sutherland’s coinvestigators were Steven W. Siegel, MD, FPMRS, Minnesota Urology in St. Paul, Minnesota, and Michael J. Kennelly, MD, FACS, FPMRS, McKay Urology, in Charlotte, North Carolina.

The FemPulse device is a pessarylike ring that is placed against the cervix for delivering electrical stimulation to the inferior hypogastric plexus, known as the pelvic plexus. The final iteration of the device will be a self-contained unit. However, the device investigated in this feasibility study was an initial prototype that was connected via wires exiting the vagina to an FDA-cleared transcutaneous electrical nerve stimulator (TENS).

The multicenter feasibility study randomized 21 women 2:1 to treatment versus sham groups. The treatment subjects received a conductive connector and stimulation at around 70% of the subject’s sensation threshold. The system used for sham patients had a nonconductive connector, but all other aspects of the set-up were identical. At the initial study visit, patients completed pretherapy (or sham) quality-of-life (QOL) questionnaires; underwent preliminary stimulation testing and mapping, after which the device was removed. The participants then completed a 3-day bladder diary and returned the following week for randomization, device placement, and configuration. They completed another 3-day bladder diary and then returned for a final visit on the following day to undergo device removal, a final vaginal examination, and complete posttherapy (or sham) QOL questionnaires.

In an intent-to-treat (ITT) cohort that included all 19 women who completed the study, the device was fit easily and was reported to be comfortable. In addition, it exhibited good self-maneuverability, as 86% of subjects could place and orient the device and 79% were able to remove it without assistance. “A few patients had difficulty reaching the device to remove it either because of the length of their vaginal canal or their body habitus. A future iteration of the device will include a feature for assisting with self-placement and removal,” Sutherland said.

Safety of the device was demonstrated, as there were no clinically important direct or reflexive effects on heart rate, rhythm, or blood pressure during stimulation, nor any untoward issues in the vagina due to the device. One woman reported mild lower abdominal ache or cramping that resolved when the device was removed. She also noted scant pink-tinged blood on the device following final removal.

“This patient had no sense of discomfort or irritation on [the] vaginal exam that was attributable to the device. It was concluded that the blood was related to postmenopausal atrophic tissues,” Sutherland said.

Clinical utility was evaluated by analyses of changes in voids per 24 hours, urgent voids per 24 hours, changes in urinary urge, and incontinence-related QOL questions from 3 validated questionnaires. In the ITT cohort, similar improvements in these variables were seen in both the treatment and control groups. However, signals of treatment benefit were observed in an efficacy-analysis (EA) subgroup comprised of 11 women (7 treatment subjects, 4 controls).

“The EA subgroup excluded 6 treatment subjects and 2 controls who reported feeling the stimulation and who were therefore thought to be biased,” said Sutherland.

“It was in this EA subgroup that a trend toward OAB improvement in the stimulation group compared to controls was seen, which in turn provides the justification to pursue larger-scale investigations into the efficacy of the FemPulse device for the treatment of OAB,” Sutherland said.

Disclosure: FemPulse provided funding for the study. Dr. Sutherland is a study investigator and consultant for FemPulse and other companies that market or are developing treatments for OAB.

REFERENCE

LASER SYSTEM
continued from page 27
showed that retropulsion for the HoYAG laser was higher than for Soltive (P<.02). The super-pulse thulium fiber laser also led to a 2-fold higher ablation compared with the HoYAG laser.

“The regulatory approval and launch of the Solitive Laser System introduce thulium fiber laser technology into the medical world globally. In doing so, Solitive ushered in a new era in endourology,” Olivier Traxer, MD, professor of urology at the University Sorbonne, Paris, France, and director of the Minimally Invasive Surgery Department at Tenon Hospital, stated in the press release."[1]

REFERENCES
Guidelines for disorders of ejaculation aim to address knowledge gaps

Document is “most scientifically rigorous guidance on the subject to date,” committee chair says

Jason M. Broderick
Associate Editorial Director, Urology Times®

During the 2020 American Urological Association Virtual Experience, Alan W. Shindel, MD, provided an expert summary and analysis of the 2020 AUA Guidelines for Disorders of Ejaculation.

“Disorders of the timing of ejaculation/organism are poorly understood, but pharmacotherapy options do exist for both premature and delayed ejaculation,” explained Shindel, the chair of AUA Ejaculation Disorders Committee and associate professor, male reproductive health, University of California, San Francisco, department of urology.

The AUA Guidelines for Disorders of Ejaculation are intended to address these knowledge gaps.

“The 2020 AUA Guidelines are the newest and most scientifically rigorous guidance on the subject to date,” said Shindel.

Shindel explained that the evidence level associated with statements in the guidelines is classified as high (A), moderate (B), or low (C), and that recommendations without a sufficient evidence basis are labeled as a clinical principle or expert opinion.

In his presentation, which covered premature ejaculation and delayed ejaculation, Shindel stressed that beyond pharmacotherapy, “education, mental health evaluation, and attention to the relationship are critical considerations in management” of disorders of ejaculation.

The AUA guidelines define lifelong premature ejaculation (LPE) as “consistently poor ejaculatory control, associated bother, and ejaculation within about 2 minutes of initiation of penetrative sex that has been present since sexual debut.”

This definition extends the ejaculatory latency time (ELT) to 2 minutes, when it had previously been 1 minute with some standard definitions. Shindel explained the adjustment was made because men with an ELT of 1 to 2 minutes are more similar in terms of symptoms/experience with men who have an ELT of less than 1 minute than those with an ELT of 2 to 5 minutes.

The guidelines define acquired PE as “consistently poor ejaculatory control, associated bother, and ejaculation latency that is markedly reduced from prior sexual experience during penetrative sex.”

There is no evidence-based consensus on ELT in patients with acquired PE. Clinical experience suggests these patients have an ELT of under 2 to 3 minutes and/or substantial reduction (ie, ≥50%) in ELT from previous experiences of partnered sex.

Regarding circumcision, a grade C recommendation in the guidelines suggests that “clinicians should advise patients that ejaculatory latency is not affected by circumcision status.”

According to Shindel, “There are certainly patients who may experience difficulties or problems relating to their foreskins, and in those men, circumcision may be considered an option, but circumcision itself is not thought to intrinsically modify ejaculation latency during partnered sex.”

The guidelines also issue a grade C recommendation in the area of mental health, stating that “Clinicians should consider referring men with premature ejaculation to a mental health professional with expertise in sexual health.”

**Pharmacotherapy for premature ejaculation**

The first-line pharmacotherapy options for PE, also supported with grade B evidence, include selective serotonin reuptake inhibitors (SSRIs), on-demand clomipramine or dapoxetine (where available), and topical penile anesthetics.

None of these treatments have obtained FDA approval in this setting, but they have been “utilized for a great deal of time with good clinical efficacy,” said Shindel.

He explained that SSRIs, which enhance serotonergic activity in the brain, have been used off-label for PE management for years. The SSRIs used include paroxetine, sertraline, citalopram, and fluoxetine. The most commonly used with the greatest evidence of efficacy is paroxetine.

Adverse events (AEs) associated with SSRIs include fatigue, yawning, nausea, and diarrhea, and they are contraindicated in young men with suicidal ideation and/or bipolar disorder.Clinicians should also carefully consider other drugs the patient is using to protect against drug interactions that could cause serotonin syndrome.

Also in the frontline PE paradigm, topical anesthetics are widely available and are generally tolerable but can be “cumbersome to apply and can lead to irritating AEs, such as numbness and sometimes tingling sensations in both the patient and his or her partner,” said Shindel.

Efficacy in the frontline PE setting has also been shown with the tricyclic antidepressant clomipramine. The most recent evidence came from a double-blind, randomized, placebo-controlled, fixed-dose phase 3 study of clomipramine (15 mg on demand). The study included 159 patients with PE who were randomized to clomipramine (n = 106; 15 mg for 12 weeks) or placebo (n = 53).

The investigators assessed efficacy through scores on the IELT (Intravaginal Ejaculation Latency Time) and the PEDT (Premature Ejaculation Diagnostic Tool). The mean IELT increased 192 seconds with clomipramine compared with 87 seconds with placebo. The mean fold increase in IELT was 4.4 versus 2.7, respectively, and the mean PEDT decrease was 4.7 versus 1.3, respectively.

The investigators concluded that the overall severity of AEs was mild to moderate. However, Shindel noted that the rates of nausea (15.7%) and dizziness (49%) with clomipramine were unfavorable compared with those reported with SSRIs in other studies.

As far as second-line pharmacotherapy options for PE, the guidelines include on-demand dosing of tramadol (grade C) and alpha blockers (expert opinion).

Shindel said that tramadol, which is an opioid analgesic agonist and analogue, “Has a number of effects that may be relevant to ejaculation-delaying properties; however, as it is an opioid drug, there is some concern that it could lead to potential for addiction and/or interactions with SSRI and should therefore be used only cautiously in men with premature ejaculation.”

Regarding alpha-blockers, Shindel said, “There is a weak body of evidence suggesting they may have some efficacy in men with premature ejaculation. But this evidence is limited enough that we do not recommend this as a first-line agent of choice.”

He also noted that expert opinions in the guidelines recommend against using alternative therapies in treating patients with PE, and that surgical management for PE, such as injecting bulking agents, should only be offered as part of a clinical trial.

The guidelines define lifelong delayed ejaculation (DE) as “lifelong, consistent, bothersome inability to achieve ejaculation, or excessive latency of ejaculation, despite adequate sexual stimulation and the desire to ejaculate.”

Acquired DE comprises the same symptoms, with the condition being acquired and not a lifelong complication.

Treatment advice in the guidelines for patients with DE includes referral to a mental health professional with expertise in sexual health, as well as suggesting patients modify their sexual practices, including sexual positions, which may increase arousal and lead to ejaculation.

A clinical principle recommendation also suggests See GUIDELINE page 32
THE LATEST IN TESTOSTERONE REPLACEMENT THERAPY (TRT):
JATENZO® (testosterone undecanoate) Capsules CIII, an Oral Option for Patients with Hypogonadism

Introduction

There has been an explosion in treatment options for men with hypogonadism in the last 2 decades. The latest innovation in Testosterone Replacement Therapy (TRT) is JATENZO®, an oral softgel formulation of testosterone undecanoate (TU)1. Prior to the availability of JATENZO, treatment options in the United States (U.S.) included TRT injections, implantable pellets and several topical formulations.2,3 Even with so many dosing options available, many patients abandoned these kinds of treatments due to administration challenges (e.g., skin irritation for topicals, injection site pain for injectables)2,4.

JATENZO is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired) due to structural or genetic etiologies.

What took so long to develop an oral TRT?

After the discovery of testosterone and its synthesis in the 1930s, it was quickly realized that oral testosterone does not have sufficient bioavailability to be effective as a replacement therapy due to rapid metabolism in the liver.2 A number of strategies have been explored to overcome this, including chemical modification of testosterone, which eventually led to the FDA-approval of 17 α-methyl-testosterone.3 However, long-term use of 17 α-methyl-testosterone, especially at higher doses, can cause potentially serious liver toxicity, so this compound is rarely used as a TRT currently.2

Testosterone esters were also developed, both as intramuscular injections (testosterone enanthate, cypionate, and TU)15 and for oral use (TU only)15. In fact, a formulation of oral TU has been widely available and used outside the U.S. since the 1970s.2,3 It was not approved for use in the U.S. because of its pharmacokinetic profile; it is often a struggle to maintain testosterone in the eugonal range with this formulation.1 In contrast, JATENZO met the U.S. FDA regulatory standards for pharmacokinetics, and safety and efficacy, and is the first oral TU to be approved for use in the U.S.1 It became available for prescription in February 2020.1

What is different about JATENZO?

The key innovation to the formulation is the self-emulsifying drug delivery system, which allows for the formation of TU-containing lipoprotein particles in the gut as the contents of the capsules disperse.1,5,6 (Figure) This allows TU to be absorbed via the intestinal lymphatics, bypassing the liver, and avoiding hepatic first-pass metabolism of testosterone.7,8

Once in the systemic circulation, TU is released from the lipoprotein particle, and endogenous esterases cleave active testosterone (T) from TU. The fatty acid (undecanoate) is then metabolized like dietary fat.6 (Figure) The selection of the undecanoate ester is important, as other fatty acids are less lipophilic and can be diverted to the liver instead of being taken up by the intestinal lymphatic system.2

The result is consistently sustained therapeutic levels; in clinical trials of JATENZO, Cmax was reached at about 2 hours after the morning dose, with the Cmax around 12 hours. The Cavg of serum T over 24 hours was 489 ± 158 ng/dL (mean ± SD) when expressed as approximate serum T equivalents based on assay of plasma T.1,9

The most common adverse events of JATENZO (incidence ≥2%) are headache (5%), increased hematocrit (5%), hypertension (4%), decreased HDL (3%), and nausea (2%). No clinically significant changes in liver function tests have been observed in clinical trials.10

How is the formulation dosed and titrated?

JATENZO capsules are available in 3 different strengths, allowing physicians to prescribe 5 dose levels to ensure each patient achieves serum testosterone in the eugonadal range.1 JATENZO is taken twice daily (BID) with food, once in the morning and once in the evening.1 The starting dose is 237 mg TU BID, and serum T should be measured to check for response to therapy after at least 7 days on treatment, about 6 hours after the morning dose is taken.

With the addition of JATENZO to the treatment paradigm for hypogonadism, patients and physicians finally have an oral softgel option for this chronic condition. For more information, visit JATENZO.com/hcp/. Peer-reviewed publications of Phase 3 studies of JATENZO have been published and are available in Therapeutic Advances in Urology and The Journal of Clinical Endocrinology & Metabolism. Please see important safety information, including BOXED WARNING on increases in blood pressure, on the following page.

REFERENCES:


FIGURE

1. Oral TU is taken twice daily with food
2. TU is carried by lipoproteins into the intestinal lymphatics
3. Oral TU therefore bypasses the first-pass hepatic metabolism and avoids inactivation
4. Once in the systemic circulation, esterases release active testosterone from the TU prodrg

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**INDICATION**

JATENZO® (testosterone undecanoate) capsules, CII, is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.

- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

**Limitation of use**

Safety and efficacy of JATENZO in males less than 18 years old have not been established.

**IMPORTANT SAFETY INFORMATION**

**WARNING: INCREASES IN BLOOD PRESSURE**

- JATENZO can cause blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death.

- Before initiating JATENZO, consider the patient’s baseline cardiovascular risk and ensure blood pressure is adequately controlled.

- Periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension and re-evaluate whether the benefits of JATENZO outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease on treatment.

- Due to this risk, use JATENZO only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies.

**CONTRAINDICATIONS**

JATENZO is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate, in women who are pregnant, in men with a deficiency or absence of endogenous testosterone, and in women who are pregnant.

**CONTRAINDICATIONS**

- Known hypersensitivity to JATENZO or its ingredients, prostate, in women who are pregnant, in men with a deficiency or absence of endogenous testosterone, and in women who are pregnant.

- JATENZO is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate, in women who are pregnant, in men with a deficiency or absence of endogenous testosterone, and in women who are pregnant.

- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.

- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

**ADVERSE EVENTS**

The most common adverse events of JATENZO (incidence ≥2%) are headache (5%), increased hematocrit (5%), hypertension (4%), decreased HDL (3%), and nausea (2%).

**DRUG INTERACTIONS**

- JATENZO can cause changes in insulin sensitivity or glyceric control. Androgens may decrease blood glucose and may require a decrease in the dose of antidiabetic medications.

- Anticoagulant activity may be affected by androgens. More frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking warfarin, especially at initiation and termination of androgen therapy.

- Use of testosterone and corticosteroids concurrently may increase fluid retention and requires monitoring in patients with cardiac, renal, or hepatic disease.

- Some prescription and nonprescription analgesic products like JATENZO. Evaluate patients with signs or symptoms consistent with DVT or PE and, if a VTE is suspected, discontinue JATENZO and initiate appropriate workup and management.

- Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions. If abuse is suspected, check testosterone levels to ensure they are in the therapeutic range. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

- JATENZO is not indicated for use in women.

**USE IN SPECIFIC POPULATIONS**

The safety and efficacy of JATENZO in pediatric patients less than 18 years old have not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing JATENZO to determine whether efficacy or safety in those over 65 years of age differs from younger subjects. There is insufficient long-term safety data in geriatric patients utilizing JATENZO to assess the potentially increased risk of cardiovascular disease and prostate cancer.

Please visit https://www.jatenzo.com/assets/pdfs/jatenzo-pi.pdf for full Prescribing Information, including BOXED WARNING on increases in blood pressure.

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GUIDELINE
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gests that clinicians evaluate the medications the patient is taking that may contribute to DE and recommend staged cessation, dose adjustment, or replacement. Prior to taking making any changes, particularly when advising a patient to stop a therapy, there should be consultation with the prescribing physician.

Regarding medical management of DE, an expert opinion in the guidelines notes that “Clinicians should inform patients that there is insufficient evidence to assess the risk-benefit ratio of oral pharmacotherapy for the management of delayed ejaculation.”

Noting this opinion, Shindel said, “There are a number of pharmacotherapy options that may be considered in the management of DE but only after careful consideration and a discussion with the patient that none of these have FDA approval, and have a limited evidence basis.”

An expert opinion in the guidelines also indicates that physicians should counsel patients with DE that there is no clinical support for the use of invasive nonpharmacological approaches in this setting.

Shindel concluded his discussion with a review of some of the existing medical treatment options for patients with DE, starting with penile vibratory stimulation (PVS), which he said is “intended to intensify arousal.”

A small study of 36 patients with secondary anorgasmia for ≥3 months treated with intermittent PVS to frenulum showed “some evidence of utility in men with delayed ejaculation,” said Shindel. In the study, 72% (n = 26) of patients experienced at least some level of restoration of orgasm.

“This is a relatively low-risk intervention that may be incorporated into sexual interactions for the patient,” said Shindel.

Bupropion, an antidepressant agent with both central dopaminergic and noradrenergic activity, has shown potential for DE management in a small body of evidence. Studies, which have generally been conducted in young men with DE, have demonstrated some improvement versus baseline status; however, “these studies are limited in their absence of a placebo arm,” said Shindel.

Another agent with some potential is cabergoline, a D2 dopamine and 5HT2b agonist that is most commonly used to suppress prolactin-producing tumors. In a study of men with DE, 66% (n = 87) of 131 patients who received cabergoline experienced an improvement in ejaculation latency.

REFERENCES

Findings support same-day discharge after artificial urinary sphincter insertion

Jason M. Broderick
Associate Editorial Director, Urology Times®

Outpatient management after artificial urinary sphincter insertion (AUS) is a viable treatment approach, based on a retrospective analysis published in the Journal of Urology.

To determine the likelihood that outpatient management would be safe, the investigators analyzed medical records of 163 men who received inpatient AUS insertion, 99% of whom were discharged on the first day following surgery.

The data showed that only 2 patients (1.2%) had immediate postoperative complications, and 8 patients (6%) failed a voiding trial on the first day post-surgery. After leaving the postanesthesia care unit, 94% (n = 154) of patients needed oral narcotic pain medication. These patients used a median of 31.0 ± 22.9 morphine milligram equivalents.

“Immediate postoperative and peri-discharge complication rates are around 1% after artificial urinary sphincter insertion, and narcotic requirements following postanesthesia care unit stay are minimal. Outpatient artificial urinary sphincter insertion is likely to be safe, effective, and beneficial with regards to patient experience and total costs,” Benjamin M. Dropkin, MD, Department of Urology, Vanderbilt University Medical Center, Nashville, Tennessee, and coauthors wrote.

For their retrospective analysis, the investigators received approval from an institutional review board to review the electronic medical records of men who received AUS insertion (CPT code 53445) between June 2013 and September 2017 by study authors Douglas F. Milam, MD, or Melissa R. Kaufman, MD, PhD, both from the Department of Urology, Vanderbilt University Medical Center. The study had no exclusion criteria.

All 163 men included in the analysis were admitted overnight under 23-hour observational status. Of these patients, 89% (n = 146) were administered antibiostic prophylaxis prior to surgery with gentamicin and vancomycin (both weight based). For the other 17 patients, presurgical regimens were tailored according to baseline factors, such as allergies to specific medications.

The mean patient age was 69.8 years and the mean body mass index was 28.9 ± 5.1 kg/m². The mean preoperative pad use per day was 5.8 ± 3.5. Fifteen percent of patients were using chronic narcotic pain medication prior to surgery, and 31% had a history of diabetes. Seventy percent of patients had a history of hypertension, 53% were current or former smokers, 85% had prior prostatectomy, and 34% had received radiation to the prostate.

Beyond the 2 patients with postoperative complications prior to discharge, 2 other patients had to return within 48 hours to the emergency department. One of the patients had suspected aspiration pneumonia and had to be admitted to the intensive care unit (Clavien grade IVa), and the other patient had urinary retention requiring catheter placement (Clavien grade I).

REFERENCE
BPH management sees continual evolution and innovation

The management of benign prostatic hyperplasia has undergone a sea change, with several new minimally invasive treatments profoundly affecting the treatment paradigm. In a recent webinar sponsored by Teleflex, a panel of experts discussed the evolution of BPH treatment, as well as how their practices have been affected by the coronavirus disease 2019 (COVID-19) pandemic. What follows is an edited portion of their conversation. (For the full webinar, go to https://bit.ly/2PvQCV6)

The panelists were moderator Gregg Eure, MD, Urology of Virginia, Virginia Beach; Steven Gange, MD, Summit Urology Group, Salt Lake City, Utah; John Kaspar, MD, Associated Urologists of North Carolina, Raleigh; and Brian Mazzarella, MD, Urology Austin, Austin, Texas.

Edited by Benjamin P. Saylor
Content Managing Editor, Urology Times*

**EURE:** How would you say your practice has changed in the past few years, especially with the emergence of minimally invasive treatments?

**KASPAR:** It has changed dramatically. When I first started in urology in the 1990s, there was transurethral resection of the prostate (TURP). As we progressed through the 1990s, several medications emerged, including doxazosin (Cardura), terazosin (Hytrin), finasteride (Proscar), and tamsulosin (Flomax). The number of TURPs declined and medical therapy became the standard of care.

Then as things shifted in the 2000s, we went into different types of procedures. There was transurethral needle ablation (TUNA), transurethral microwave therapy, and laser procedures. We tried to find something less invasive than TURP. In 2013, the prostatic urethral lift (UroLift) was approved. That has become a mainstay of my practice.

**GANGE:** During my training, BPH was treated with TURP. That’s all we had. I did several hundred in my residency and then continued them after residency. Then drugs came along, and as John mentioned, became the standard of care. These drugs did give some sense of satisfaction, improved urinary symptoms, and improved quality of life. It wasn’t really until later that we realized we were essentially putting in a “placeholder” without any potential for cure, without any potential to even intercept the inevitable progression of detrusor failure. In the 2000s, we tried other procedures. In the end, all those procedures, even including TURP, had an excessive degree of morbidity. Sometimes, there’s bleeding; sometimes there’s a need to stay in the hospital. These procedures are associated with bladder neck contractures, urethral strictures, and sexual dysfunction, especially ejaculatory dysfunction. As men become more savvy, they don’t want to experience those adverse effects if avoidable.

In 2011, I was an investigator in the L.I.F.T. trial and I did the first UroLift procedure in North America. I have found it to meet the needs of these patients in terms of getting them off of medications and avoiding the morbidity of more invasive procedures. It has been the mainstay of my BPH management.

**EURE:** What has been your experience with treating larger prostates with UroLift?

**GANGE:** The FDA recently granted an expanded indication for UroLift to treat prostates between 80 cc and 100 cc. Some of us have treated prostates beyond the 100-cc level. I’ve treated a patient with a 135-cc prostate. It’s also good to know that there is no lower limit in size, and we’ve treated some really small prostates successfully.

**MAZZARELLA:** When discussing any of these minimally invasive procedures, in my own practice, as you get into more complex anatomy—things like larger prostates, elevated bladder necks, median lobes—there are 2 questions. One is, can you get an acceptable surgical outcome? The second is, have you talked to your patient and made sure you’re picking the right option for them? When I use UroLift, which I do very frequently, as I get into these upper ranges, I absolutely think I can get a good surgical outcome for that patient. I’m also very careful to talk to the patient and explain to them, “Your anatomy is a little bit more advanced, a little bit more complicated. You are probably at higher risk than a man with a 40-g prostate of this not being as successful as you want and maybe needing something else done.”

As we treat these more challenging cases with a less aggressive approach, we just want to be sure our patients understand the choice that we’re recommending.

**EURE:** I’ve been doing UroLift a little over 5 years now, and it’s very nice to have that as an option for the patient with a 20-g prostate. I do a lot of GreenLight laser procedures, but that is challenging for those smaller glands, whereas there is no lower limit with UroLift.

**MAZZARELLA:** Another point I’d like to make is that a smaller prostate makes me suspicious as to whether I’m treating true BPH or whether I’m dealing with an elevated bladder neck. That concern does potentially inform the approach I’m going to take.

Those patients are still candidates for UroLift and do well. But they are also candidates for TURP or transurethral incision of the prostate. You want to make sure that you’re picking the right approach that solves the problem the patient has. In that smaller range, I’m a little bit more diligent about considering that.

**GANGE:** Please discuss your experience treating middle lobes with UroLift.

**GANGE:** Gregg, I was inspired by the MedLift study you conducted. I was very skeptical, until I saw the data and talked to some of the investigators. I wasn’t going to do middle lobes with UroLift. However, having started that process a year or a half ago and done about 60, I think it’s a remarkable opportunity to deploy this device. I tend to do them in the OR, however, because of the risk of bleeding.

As we know from the MedLift trial, and I’ve seen this in my practice, these are our happiest patients. These patients get a 13.5- to 14-point improvement relative to the L.I.F.T. study with the bilobed prostate. It’s been a great addition to my practice.

**KASPAR:** I agree. These are men who fail medical therapy right away. When you hear a patient say that Flomax doesn’t work, either he has a real small prostate and a bladder neck problem or he’s got a middle lobe. The cystoscopy becomes very important. When you go into the OR and displace that middle lobe, the outcomes are tremendous.
Benign Prostatic Hyperplasia

BPH TREATMENT
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MAZZARELLA: One of the vexing elements of talking about and treating middle lobes is that we have no standard definition of what constitutes a middle lobe in our specialty. Some urologists will say 3% to 5% of their BPH patients have middle lobes. Another urologist will tell you that 50% of their patients have middle lobes.

I think middle lobes can be divided into 3 categories. Category 1 is just a hump of tissue. It’s not obstructing, it’s not problematic. It does not in any way inform which BPH procedure I’m going to select. The second category is more broad based and has intravesical extension and a lot of times arises from the lateral lobes. It’s fairly immobile. The third category is a pedunculated type that is fairly mobile. This is entirely my own classification that I use to help make the decisions. But I think UroLift, GreenLight, and TURP can really treat almost any of these anatomies. One of the conclusions in the MedLift trial was that UroLift outcomes were independent of what size of median lobe was being dealt with.

EURE: How has the COVID-19 pandemic affected your practice?

KASPAR: Well, it’s dramatically affected practices worldwide. We all saw a decrease in elective cases over the past couple of months. We are seeing the slow return. We have the luxury of having a big footprint in our office, but we did reduce staff, so there were only about 4 doctors and 1 PA in the office during that time. That has been increased as of late. All patients are given a questionnaire asking about things including fever symptoms, travel to high-risk areas, loss of the sense of taste or smell. They’re all getting their temperature taken. No other guests beside the patient are allowed in the office. Sometimes, we’ll allow a family member if the patient has some disposition. The other point I would make is that if you have the capability either for video cysto or to capture photos, you should do so. A patient’s understanding of what’s going on with their BPH changes dramatically the moment they see their own prostate. He was in retention before he started, passed away. That’s something that sticks with me and makes you think, how many patients do we have that are in retention? We do a TURP because we think that’s the best procedure to get them out of retention, and they’re still in retention on intermittent catheterization. To me, earlier intervention is very important to preserve bladder function.

MAZZARELLA: My pearl is that an early cystoscopy is tremendously valuable. We live in a world where our patients expect us to inform them of all the options. If you’re not doing a cystoscopy, you are allowing a patient to choose between alpha-blockers or 5-alpha-reductase inhibitors and providing them no information about what exists from a procedure-based approach.

The other point I would make is that if you have the capability either for video cysto or to capture photos, you should do so. A patient’s understanding of what’s going on with their BPH changes dramatically the moment they see their own obstruction. Very commonly, I’ll have patients who seem to want to continue on medications. I show them their lateral lobes in real time, and they know within that moment that a medication is never going to fix this problem. That dramatically changes what they choose going forward.

GANGE: I have learned so much about BPH in the past few years? For my own part, I include bladder health in the patient discussion. For a lot of patients, BPH is a confusing disease. But they understand the bladder; it’s a muscle whose job is to push urine through this obstructed prostate gland. Preserving that is important. That’s really helped to enlighten patients and get them through the workup process and think about treatments.

KASPAR: One of the big things for me has been doing a cystoscopy and an ultrasound as part of the workup. Like you, Gregg, I’ve become focused on bladder health. I use my father-in-law as an example. He had a TURP 20 years ago for a 60-g prostate. He was in retention before he started, was in retention after the TURP, and had to catheterize for 20 more years post procedure until he passed away. That’s something that sticks with you and makes you think, how many patients do we have that are in retention? We do a TURP because we think that’s the best procedure to get them out of retention, and they’re still in retention on intermittent catheterization. To me, earlier intervention is very important to preserve bladder function.

EURE: How have you changed your practice in the past few years? For my own part, I include bladder health in the patient discussion. For a lot of patients, BPH is a confusing disease. But they understand the bladder; it’s a muscle whose job is to push urine through this obstructed prostate gland. Preserving that is important. That’s really helped to enlighten patients and get them through the workup process and think about treatments.

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AUA updates guideline for surgical management of BPH/LUTS

New clinical principle discusses possibility of treatment failure, need for secondary treatments

Jason M. Broderick
Associate Editorial Director, Urology Times®

During the 2020 American Urological Association Virtual Experience, Steven A. Kaplan, MD, explained the changes incorporated into the 2020 AUA Guideline on Benign Prostatic Hyperplasia (BPH): Surgical Management of BPH/Lower Urinary Tract Symptoms (LUTS).

“[This guideline on LUTS secondary to BPH] should be used in conjunction with recent systematic literature reviews and an understanding of the patient’s treatment goals. In all cases, the patient’s preferences and personal goals should be considered when choosing therapy,” said Kaplan, a member of the AUA BPH Surgical Panel responsible for the guideline, and a professor of urology at the Icahn School of Medicine, New York City, New York.

Overall, the guideline comprises 24 statements divided into 15 categories. The broader categories are Evaluation and Preoperative Testing, Surgical Therapy, and Medically Complicated Patients.

The treatment-specific categories are Transurethral Resection of the Prostate (TURP), Simple Prostatectomy, Transurethral Incision of the Prostate (TUVP), Transurethral Vaporization of the Prostate (TUVAP), Photoselective Vaporization of the Prostate (PVP), Prostatic Urethral Lift (PUL), Transurethral Microwave Therapy (TUMT), Water Vapor Thermal Therapy, Transurethral Needle Ablation (TUNA), Laser enucleation, Aquablation, and Prostate Artery Embolization (PAE).

AUA guidelines use a 3-tiered evidence system in which the evidence level associated with a statement is classified as high (A), moderate (B), or low (C) and that recommendations without a sufficient evidence basis are labeled as a clinical principle or expert opinion.

In his presentation, Kaplan detailed the 2020 updates, which included 1 new statement and several amended statements.

New statement

The new statement, known as “statement 6,” was added to the “Evaluation and Preoperative Testing” section of the guideline. The statement, which is categorized as a clinical principle, reads:

“Clinicians should inform patients of the possibility of treatment failure and the need for additional or secondary treatments when considering surgical and minimally-invasive treatments for LUTS secondary to BPH.”

The text for this statement was taken from supporting text on retreatment and treatment failure from the treatment modality statements.

Regarding this new statement, Kaplan said, “The text for this statement was taken from the corresponding treatment modality statements.”

Some of the statements that were amended to have retreatment and/or treatment failure information moved to statement 6 included statement 15 on PUL, statement 17 on TUMT, statement 18 on water vapor thermal therapy, and statement 22 on Aquablation.

“[This guideline on LUTS secondary to BPH] should be used in conjunction with recent systematic literature reviews and an understanding of the patient’s treatment goals. In all cases, the patient’s preferences and personal goals should be considered when choosing therapy.”

STEFAN A. KAPLAN, MD

Amended statements

The first amendment was made to statement 1, which is part of the “Evaluation and Preoperative Testing” section of the guidelines. The statement now recommends that a physical examination, along with a medical history, should be conducted as part of the initial assessment of patients with “bothersome” LUTS potentially caused by BPH (clinical principle). The AUA Symptom Index should be used, and the physician should perform a urinalysis.

Additionally, supporting text added to the statement reads, “When focusing on the results of the urinalysis, clinicians should focus on the presence or absence of glucosuria, proteinuria, hematuria, and infection.”

The wording of statement 16 on PUL (grade C) was amended to now read, “PUL may be offered to eligible patients who desire preservation of erectile and ejaculatory function.”

Although the wording of statement 19 on water vapor thermal therapy (grade C) was not changed, the supportive text was amended based on the latest literature.

The statement itself reads, “Water vapor thermal therapy may be offered to eligible patients who desire preservation of erectile and ejaculatory function.”

The new supporting text states: “In the randomized controlled trial comparing water vapor thermal therapy to sham, the original 136 patients randomized to water vapor thermal therapy are expected to be followed for 5 years. Few harms occurred in the water vapor thermal therapy group between months 3 and 12. A decrease in ejaculatory volume was reported by 2% of participants. At 36 months, no de novo erectile dysfunction was reported but dysuria was reported by 1% of patients. At 48 months, there was a significant change in International Index of Erectile Function (IIEF) scores compared to baseline with a P value of .3. But there was not a significant change at the other follow-up intervals.”

Supporting text was also updated based on new literature for statement 21 on laser enucleation (grade B), and the statement itself was also changed. Specifically, the word “suitable” was removed before the word options, so it now reads: “Clinicians should consider holmium laser enucleation of the prostate (HoLEP) or thulium laser enucleation of the prostate (ThuLEP), depending on their expertise with either technique, as prostate size-independent options for the treatment of LUTS attributed to BPH.”

The wording of statement 23 on PAE (expert opinion) was also amended and now reads: “PAE for the treatment of LUTS secondary to BPH is not supported by current data and trial designs, and benefit over risk remains unclear; therefore, PAE is not recommended outside the context of clinical trials.”

The AUA BPH panel is currently working on the guideline and algorithm for the medical management of BPH, which is slated to be released next year. The literature for this guideline was pulled from the date range of 2010 through 2019, with the evidence reported included 107 randomized controlled trials and controlled clinical trials.

REFERENCES


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How do you bill for virtual visits lasting more than 30 minutes?

E/M guidelines direct code selection based on face-to-face time with patient

Q: Is there a modifier for telehealth visits when more than 30 minutes are spent with a patient? For instance, what about when time is spent explaining options to a patient with newly diagnosed prostate cancer or when a new patient has complex issues to be discussed?

A: This is a great question, and for the purposes of this answer, we are assuming that you are describing a virtual visit service provided in the outpatient setting with a patient who is located in their home or at another nonoffice and nonfacility/originating site. As of this writing, there are no specific evaluation and management (E/M) codes for those types of telehealth visits, but during this recent public health emergency (PHE) and hopefully afterward, many insurers (including Medicare) are allowing these services to be reported using the typical in-person office and other outpatient site of service (E/M) codes for those types of telehealth visits only. Implemented in January 2021, a prolonged service code for each 15 minutes of work beyond the usual service; first hour [List separately in addition to code for office or other outpatient Evaluation and Management or psychotherapy service[s] beyond the usual service].

CPT code 99354 can be added on to codes 99205 and 99215 for the first hour of additional time, and it can be used when the time exceeds the maximum time by at least 31 minutes. For example, you can bill CPT codes 99215 and 99354 for a face-to-face time of 71 minutes (40 minutes, plus a minimum of 31 minutes into the first additional hour of 99354). CPT code 99355 can be added on to the first 2 codes for each additional 30 minutes, if you reached 16 minutes past the first additional hour, which, for example, is 136 minutes for 99215 (40 plus 60 plus 16). The exact time in minutes must be documented in the note.

Of course, you will need to report appropriate place-of-service codes and modifiers to indicate that the visit was a telehealth encounter.

When the new E/M guidelines are implemented in January 2021, a prolonged service code for each 15 minutes of work above the maximum time for 99215 and 99205 has been proposed. The details of this code will likely be found in the Proposed and Final Rules for the Medicare Physicians Fee Schedule, which have not yet been released at press time.

Q: The following operative report was submitted: “A rigid cystoscope was used to intubate the meatus. The stent protruding from the left ureteral orifice was grasped with flexible grasper and brought to the meatus. A wire was inserted through the stent and the stent was removed. A flexible ureteroscope was advanced into the ureter and the 200-μm holmium laser fiber was used to fragment the ureter stone. Once this stone was treated, nephroscope was performed and the holmium laser was used to laser the 3-mm calculus in the interpolar region of the kidney and also 2 calculi of...”

Rubenstein is compliance officer and medical director of coding and reimbursement, United Urology Group and Chesapeake Urology, Towson, Maryland. Painter is CEO of PRS Urology SC in Denver, Colorado.
When reviewing this operative note, it appears that the patient presented with a ureteral calculus and also a few renal calculi, and they had been previously stented. You are correct that CPT code 52310 (cystourethroscopy, with removal of foreign body, calculus, or ureteral stent from urethra or bladder [separate procedure]; simple) is bundled to CPT code 52353 (cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy), so it cannot be billed separately. Therefore, CPT 52353 is the correct code to use for the lithotripsy of the ureteral calculus if a stent was not replaced, which it was not in this case.

It is clear from the note you provided that 52353 was performed on 2 separate locations, if one interprets the ureter being a different location from the kidney. Your comment about this insurer following Medicare MUEs seems to be the problem you are bumping up against here. We have included a screen shot from the AUACodingToday website (www.auacodingtoday.pensnetwork.com) to help explain (Figure).

You can see from the call-out box that the National Correct Coding Initiative (NCCI) lists the MUE as 1 under practitioner and with an MAI of 2. Under Medicare rules (and this insurer, according to your question), Medicare will allow only 1 unit for the code to be reported on the same date of service. Anything above 1 unit will result in a denial. The rules apply to the entire claim and therefore, you are receiving an appropriate denial per Medicare NCCI instructions. You may be asking now, “How can I report a bilateral procedure if only 1 unit is allowed per date of service?” Medicare instructs that appropriate reporting of a code with an MUE of 1 and an MAI of 2 for bilateral services would be to report the code with modifier –50 with one (1) in the units box.

Note that if you were to review different codes, such as 52356 and 52353-XS on the same claim, it would likely process for payment. MUEs apply on to the same code and with an MAI of 2 would only apply for that date of service. As 52356 and 52353 are listed as unbundling allowed with a modifier, and –XS is an appropriate code for the circumstances listed above, you could be paid for 2 laser stone treatments on the same side. We say “likely” to process for payment because, as we noted in our February “Coding Q&A” column! CPT includes a note to this effect, which is also noted in the figure. Thus, billing for separate lasers on the same side would go against CPT rules when reported with 52353 and 52356, which a payer has the choice to enforce or ignore; this is an unfortunate rule that, in our opinion, does not allow for accurate compensation of the urologist for the work performed. This leaves only modifier –22—“unusual service or procedure with manual review and variable treatment by payers”—as the only option for those providers whose payers follow NCCI and MUEs as a hope to get paid appropriately for the work performed.

You also mention above that a stone fragment was removed, which is reflected in code 52352 (stone manipulation). This code would be unaffected by MUEs for 52353; however, this opens up a second set of problems related to the definition of global and treatment guidelines in a separate section of Medicare rules. Your listing above indicates that the 52352 was used in follow-up to code 52353 to extract leftover fragments, implying that the manipulation was a part of the global 52353 during that operative session. If, on the other hand, you indicated that the ureteral stone had been grasped and removed, this would have been considered “separate and distinct” from the laser stone treatment in the kidney and reporting with –XS would be appropriate and should be paid and supported with record review of the services.

REFERENCE
How to use data to measure adherence to clinical guidelines

Utilize your practice management, EHR systems to obtain needed metrics

Clinicians are challenged to remain up-to-date and informed... begins the new clinical guideline on advanced prostate cancer released by the American Urological Association, American Society for Radiation Oncology, and Society of Urologic Oncology in June 2020.1 However, significant burnout affecting urologists’, time pressure, bureaucratic tasks, rapidly evolving diagnostic and treatment advances, and the inherent resistance to the rationalization of skills combine to make it even harder to incorporate new guidelines into clinical practice.

Clinical guidelines are formulated and graded on scientific evidence (or expert opinion) derived from research involving populations, and clinicians treat individual patients based on personal experience in addition to the science; these competing perspectives may result in a lack of adherence to clinical guidelines, sometimes written off to “the art of medicine.” Some guidelines lead to the development of “clinical pathways” used by decision support tools, payers, and public health experts. No guideline is intended to be a rigid rule for 100% of situations, but measuring adherence can sometimes be leveraged to identify outliers for closer examination. In this article, against the backdrop of a new guideline for advanced prostate cancer, I will discuss how you might measure adherence to guidelines in your own practice using some simple examples.

Opportunities for measurement

Advanced prostate cancer is a segment of the typical urology practice that lends itself to a focus on adherence to guidelines: The disease is common in a urology practice, the diagnostic testing choices and results are discrete, the clinical status is well defined (symptom status, tumor marker status, metastatic status, castrate sensitivity status), and the therapeutic options have clear indications. Many guideline statements are unambiguous, and there is a well-developed algorithm for quick reminders. The examples below each provide an opportunity for measurement:

• “Clinicians should not offer first-generation antiandrogens (bicalutamide, flutamide, nilutamide) in combination with luteinizing hormone-releasing hormone (LHRH) agonists in patients with metastatic hormone-sensitive PC (mHSPC), except to block testosterone flare.”
• “In metastatic castrate-resistant PC (mCRPC) patients, clinicians should obtain baseline labs (eg, prostate-specific antigen [PSA], testosterone, lactate dehydrogenase [LDH], hemoglobin, alkaline phosphatase level) and review location of metastatic disease (bone, lymph node, visceral).”
• “Clinicians should prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events.”
• “Clinicians should discuss the risk of osteoporosis associated with androgen deprivation therapy (ADT) and should assess the risk of fragility fracture in patients with APC.”
• “Clinicians should prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events.”

No guideline is intended to be a rigid rule for 100% of situations, but measuring adherence can sometimes be leveraged to identify outliers for closer examination.

• “In patients with mCRPC, clinicians should offer germline and somatic tumor genetic testing to identify DNA repair deficiency mutations and microsatellite instability status that may inform prognosis and counseling regarding family risk as well as potential targeted therapies.”
• “Clinicians should discuss the risk of osteoporosis associated with androgen deprivation therapy (ADT) and should assess the risk of fragility fracture in patients with APC.”
• “Clinicians should prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events.”

How do you measure adherence to guidelines in your practice? Most urology practices have 2 sources of information: their practice management (PM) (billing) system and their electronic health record (EHR) system. The former was not designed for measuring clinical performance, but it does have the capability, when properly used, to do just that. For example, the guideline statement “Clinicians should prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events” has 3 discrete elements that could contribute to a straightforward analysis: (1) a clinical status of CRPC, (2) presence of bone metastases, and (3) administration of an injectable drug typically acquired and billed by the practice. If these discrete elements could be reliably identified in the PM data, then that system could be leveraged to measure adherence to guidelines: Find all patients with CRPC, metastatic to bone, who have received denosumab (sum A); find all patients with CRPC, metastatic to bone (sum B); calculate adherence (A divided by B).

In my experience, many urologists are not disciplined about coding for CRPC (International Classification of Diseases, Tenth Revision, code Z99.2) or bone metastases (C79.51), probably because there was never an incentive to code beyond prostate cancer (C61). However, measuring adherence to guidelines presents an excellent incentive to do so. Certified coders in your office can be trained to enter this information. Once the data are being reliably populated, measuring adherence to this guideline will be easy in the PM system using commonly available stock reports (billing records) that can be dimensioned by physician, location, time period, and even insurance payer.

Measuring adherence to other guidelines may require reporting out of your EHR system, and some EHR vendors make that easier than others. Fortunately, the data needed for this exercise are generally discrete, not dependent on physician documentation style, and easily available in many EHRs: prescriptions, lab results, x-ray results. For example, measuring adherence to “Clinicians should not offer first-generation antiandrogens (bicalutamide, flutamide, nilutamide) in combination with LHRH agonists in patients with mHSPC, except to block testosterone flare” could begin with a simple prescription utilization report for these drugs; this report could be enhanced to identify mHSPC if physicians coded for hormone status and metastatic status in the EHR (see above). While there are no reliable benchmarks for this kind of analysis, a
peer comparison in a group practice can identify outliers for further chart review. Chart review of average or above-average physicians is generally not needed.

Leveraging lab results may be slightly more complicated, but it can be simplified. The guideline statement “In mCRPC patients, clinicians should obtain baseline labs (e.g., PSA, testosterone, LDH, hemoglobin, alkaline phosphatase level)” obviously requires the ability to measure the presence or absence of these labs. All EHRs offer the ability to store, and theoretically report on, discrete lab results. One challenge, though, is that some lab results may return more discretely to the EHR than others, depending upon the performing location and interface; nondiscrete results may not be visible in the EHR unless the physician manually enters the information. The best way to avoid this common pitfall is to measure orders, not results; orders are the best reflection of the clinician’s intent and adherence to guidelines, and they do not depend on discrete results. Some smaller, niche, or older EHR systems do not offer reporting on discrete orders, but most do.

Measuring order utilization for testosterone in mCRPC patients

To simplify measuring adherence to this guideline, I recommend measuring order utilization for testosterone in mCRPC patients; you can determine a time window (testosterone order date through mCRPC first diagnosis date) to apply your own definition of “baseline,” keeping in mind that a castrate level of testosterone is technically needed to even establish a diagnosis; the order date should or may precede the mCRPC first diagnosis date. Keep it simple at first.

Leveraging radiology results is a more challenging exercise in reporting on clinical data. Only the most sophisticated EHR systems store a result discretely; most results come in as documents in different formats or are scanned with different labels. Standardization in labeling scan documents can help, but it is difficult to monitor and enforce. Again, the best answer is to leverage orders. The guideline statement “Clinicians should discuss the risk of osteoporosis associated with ADT and should assess the risk of fragility fracture in patients with APC” requires a definition of risk assessment for measuring adherence. The gold standard to assess this risk is the Fracture Risk Assessment (FRAX) tool, US version, which includes a measurement of bone mineral density using dual-energy x-ray absorptiometry (DEXA) scan (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9). So, to simplify measurement of adherence to this guideline, measure order utilization of DEXA scan in a population of patients on ADT using the time window of your choice. There is no firm consensus on when, or how often, to repeat DEXA scan in this guideline; keep it simple, measure consistently across physicians, and identify and drill down on outliers only.

Bottom line: Clinical guidelines are not rigid standards, but they draw on the available evidence to support best practices. Tools exist to simplify the measurement of adherence to clinical guidelines in your practice using your existing systems and reporting capabilities at nominal cost. Start simple, measure consistently, validate the results, leverage peer comparisons (“apples to apples”), accept that information based on data is imperfect and that adherence will rarely be 100%, focus on outliers only, and provide feedback to improve data collection. Be transparent and patient with those you are trying to educate or influence.

REFERENCES

How to reduce required minimum distributions in retirement accounts

Converting funds to Roth dollars among most effective strategies

**Q:** It looks like my required minimum distributions in the future could be substantial. Is there anything I can do to reduce them before I reach age 72?

**A:** The IRS says that you cannot keep pre-tax retirement funds in your retirement account indefinitely; it mandates that you must start taking distributions when you reach a certain age. These forced distributions are commonly known as required minimum distributions (RMDs). Many physicians worry about the impact RMDs will have on their taxes in future years.

With passage of the SECURE Act in early 2020, the IRS now mandates that RMDs begin by age 72 instead of age 70½. The RMD for any given year is calculated by taking the account balance as of December 31 of the previous year and dividing it by a certain factor; this is found in the IRS’ published tables and is based on the age of the account owner. The RMD can also be impacted if a spouse beneficiary is more than 10 years younger than the account owner.

For example, if a 74-year-old physician has $500,000 as their 2019 ending account balance in their IRA, they must take an RMD. That RMD is calculated by taking $500,000 and dividing it by 23.8 (found on the IRS Uniform Lifetime Table). The result is $21,088.40—the amount the physician must distribute from their account in calendar year 2020 to satisfy their RMD. If a physician has multiple pretax retirement accounts, they must aggregate all the account values together to determine the RMD amount across all accounts. The entire RMD can be distributed from 1 account or from multiple accounts; it doesn’t matter as long as the full RMD amount is taken.

Anytime you make a distribution from a retirement account in which pretax dollars were contributed—a 401(k), 403(b), 457, traditional IRA, or any other—you must include that distribution amount in your income and pay income taxes on it. Depending on your tax rate that year and the size of the distribution, the tax hit can be substantial.

Therefore, many physicians look for ways to reduce their RMDs before they are required to start taking them, and among the most effective methods is a Roth conversion. When a physician retires, they typically have a decline in income and thus fall into a lower tax bracket. Their income needs are often satisfied by drawing from their savings, Roth accounts, and smaller distributions from their retirement accounts if they are over age 59½. This presents an opportunity to make additional distributions from their pretax accounts in the form of Roth conversions.

A Roth conversion is when you take an amount from your pretax account, convert it to Roth dollars, pay the applicable taxes, and transfer it into a Roth account. Roth accounts do not have RMDs since the money has already been taxed. These funds can continue to grow tax-free and are distributed tax free when a need arises.

Many physicians can distribute amounts from their retirement accounts that satisfy their retirement income needs and have room left over to convert additional amounts without putting them into a higher tax bracket.

**FINANCIAL TIPS**

- With passage of the SECURE Act in early 2020, the IRS now mandates that required minimum distributions (RMDs) begin by age 72 instead of age 70½.
- A Roth conversion is when you take an amount from your pretax account, convert it to Roth dollars, pay the applicable taxes, and transfer it into a Roth account. Roth accounts do not have RMDs since the money has already been taxed.
- Many physicians can distribute amounts from their retirement accounts that satisfy their retirement income needs and have room left over to convert additional amounts without putting them into a higher tax bracket.

**Jeff Witz, CFP**

Witz is educational program director at MEDIQUS Asset Advisors, Inc. in Chicago, Illinois. He welcomes readers’ questions and can be reached at 800-883-8555 or witz@mediqus.com.
How to prepare your patient for their first telemedicine visit

Encourage patients to compile questions ahead of appointment

Teledicine visits are subject to HIPAA and are private matters, so make sure your patients are aware and have a quiet, discreet space to take the call and use headphones or earbuds if possible.

Here are 5 things you can tell your patients to do to help them prepare for their first virtual visit:

Test your tech. Patients don’t need much to get started, but virtual visits will require a basic familiarity with video conferencing on a device or smartphone. Teledicine at its core is simply a video call with a doctor and though the device they use is up to them, it’s important that they use a device they can get the same level of care by simply doing a video visit with their physician. This, in part, accounts for the meteoric rise of telehealth.

Prepared questions in advance. Teledicine visits are typically about 20% shorter than in-person appointments. As with any in-person doctor visit, patients will want to maximize their time by preparing questions they have in advance of the appointment. Encourage them to set an agenda and have questions handy during the call to ensure they get everything answered.

Check coverage and co-pays with your insurance provider. Insurance coverage for telemedicine visits vary. Medicare, for example, covers all coronavirus disease 2019–related teledicine visits, yet some private insurers may not. Efforts by insurance providers to update coverage policies amidst the surge in teledicine has created a patchwork of policies that aren’t always clear. Have your patients contact your organization before their first teledicine visit to double check what’s covered under their plan.

Get comfortable. We doctors try to make our offices and clinics as inviting as possible, but patients are likely most comfortable in their home. That said, teledicine visits are subject to HIPAA and are private matters, so make sure your patients are aware and have a quiet, discreet space to take the call and use headphones or earbuds if possible. Good lighting is also important for any visible concerns they may have. Ask them to wear clothing that is easy to move in so they are best able to participate in a physical exam.

Be prepared to talk about follow-up care. Before ending the video call, make sure that they understand clear next steps (if applicable). Patients should have a clear understanding of how to get in touch with you and understand where and how to get necessary prescriptions. They can always check in with the admin staff of your office after your telehealth visit if they are interested in written paperwork for follow-up purposes.

House calls are back and are here to stay—but they aren’t the kind our grandparents had. The first teledicine visit can seem daunting for patients, but by offering this advice and treating the virtual visit as an extension of in-person care, it can be an easy and efficient way to conduct an appointment.

PETER ALPERIN, MD

Alperin is a practicing internist and vice president at Doximity.
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**Contact**

Eric Temple-Morris • (415) 947-6231 • etemple-morris@mmhgroup.com
The Department of Surgery at the University of Vermont College of Medicine is seeking a Clinical Practice Physician in the Division of Urology to join the Champlain Valley Physicians Hospital (CVPH) in Plattsburgh, New York. CVPH is a progressive medical center with nine state-of-the-art OR's and Ambulatory Surgery Center. This position offers the unique opportunity to work in a community setting while having an active affiliation with Vermont's only Academic Medical Center, the only ACS verified Level 1 trauma center in the state providing tertiary care to patients from Vermont and Northern NY. Serving the patients from Upstate New York for decades, the local urologic surgery practice joined the faculty at the University of Vermont and is seeking an additional colleague to join the dynamic Urology faculty that span the network hospitals. Specifically, the Division seeks applications from individuals seeking a community Urology practice employment opportunity with a collegial and collaborative setting with University support.

Applicants must be board certified or board eligible and eligible for medical licensure in the state of New York. This is a full-time, 12-month, salaried position.

Plattsburgh is located on the shores of Lake Champlain, near the Adirondack Mountains, Olympic-Lake Placid region, Montreal and Burlington, VT.

The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal.

The University of Vermont is an Equal Opportunity/Affirmative Action Employer. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability, protected veteran status, or any other category legally protected by federal or state law. The University encourages applications from all individuals who will contribute to the diversity and excellence of the institution.

Interested individuals should apply online at https://www.uvmjobs.com/postings/41225 (position number 00024127). Inquiries may be directed to Mark Plante, MD, FRCS(C), FACS, Division Chief, via Kristin Allard, Kristin.Allard@uvmhealth.org.
How do you decide between partial and radical nephrectomy?

**Jeffrey Ferguson, MD / Colorado Springs, Colorado**

Indications for partial versus radical depend on tumor size or location, and on a desire for nephron sparing. The goal is always to remove the tumor but save any viable kidney tissue. The first priority is cancer control, and the second is nephron sparing.

The possibility of perioperative complications, risk of recurrence, and procedure difficulty are considerations. With robotic technology and experience, we try to do a partial if we can. Cancer control is an issue, but if surgeons are experienced, the positive margin rate should be low.

I don’t think there’s much controversy now between performing radical versus partial procedures. The state-of-the-art surgery, the gold standard, is nephron-sparing surgery, preserving renal function.

If someone has a relatively small kidney cancer and the entire kidney is removed, there’s a chance of developing cancer on the other side, or renal insufficiency for other reasons. Then they’d only have 1 kidney because the other one was removed when it wasn’t necessary.

If a person has a car accident after a kidney is removed and they lose their other kidney, they’re on the transplant list and need dialysis, which is pretty horrible. If you can do partial nephrectomy and spare the noncancerous part of the kidney, you should try to do that.

The controversy has been thoroughly debated and I believe the gold standard is partial nephrectomy.

**Joseph DeOrio, MD / Long Beach, California**

Our goal is to do partial nephrectomies robotically. With urological guidelines, a partial is indicated for tumors that are 4 cm or smaller. For amenable tumors—good location, good anatomy—we may attempt a partial if we can get nice margins. Anything larger, or more technically complicated, like involvement of the renal hilum, we would probably lean toward a radical nephrectomy.

The only caveat would be someone with a solitary kidney, so you try to spare as much function as possible. We would lean toward a partial, even with soft indications.

In older patients, 75 to 80 years old, with a second normal kidney, I lean toward a radical for expediency of surgery, because blood loss may be riskier than potential recurrence or loss of another kidney. Even with an amenable tumor, at 80, I probably just remove the kidney, because the remaining kidney will probably last the rest of their life just fine.

Most problems occur when there is massive involvement of the collecting system or extensive dissection off the renal hilum. I wouldn’t consider a partial for anything with venous involvement. But with well-chosen candidates, complication rates with partials are relatively low.

We don’t do hundreds of nephrectomies, so I haven’t seen a higher risk of end-stage disease or shorter survival rates with partials. When a tumor is more technically challenging, I lean toward the radical, because risks increase.

With patients in whom a partial nephrectomy is possible but could be difficult, I refer them to the university, because I wouldn’t want to do them a disservice. Given my patient volume and technical skills, I would be more comfortable with the radical, and that might not be right for that particular patient.

**Justin Isariyawongse, MD / Monroeville, Pennsylvania**

It’s case dependent. For appropriately selected patients, partial nephrectomy is preferred. Patients tend to do equally well with either procedure. More than anything, it’s tumor characteristics that really define which we elect to do: mostly size, tumor location, and whether the tumor is primarily endophytic or exophytic.

Although we don’t have a strict size criteria, if the tumor is large enough, it’s likely to be higher-stage disease. Then I would perhaps opt for radical nephrectomy rather than a partial nephrectomy.

The potential for complications or recurrence is always in the discussion when we’re offering options to patients. It’s in the discussion, but whether I’m actually concerned about it? In our experience, recurrence rates have been low so if patients are appropriately selected, we expect recurrence rates are acceptable, if not negligible.

There’s always the potential for bleeding, and when a patient is borderline for a partial and they might be an appropriate radical nephrectomy patient, I’ve found that consideration of risks may guide the patient’s decision-making to some extent.

It’s basically a shared decision-making model for most cases. Often, when we discuss the partial nephrectomy option, we talk about other options, including cryoablation, for example, which we would have to refer out. Cryoablation may be an option for some people when otherwise they would be a candidate for partial nephrectomy.

We discuss multiple treatment modalities and all their attendant risks and benefits. To a large extent, discussing risks and benefits is just what practicing 21st-century medicine really means.
Patient dies following lithotripsy procedure

Stone embedded in bladder wall, causing slow bleed

The plaintiff’s decedent, a 67-year-old man, was admitted to the hospital through the emergency department on October 1. He had complaints of nausea, pain, and vomiting.

The admitting assessment was acute dehydration, secondary to a lithotripsy procedure he had the previous day to treat bladder stones. The complete blood count on admission was remarkable for low hemoglobin and hematocrit and elevated white blood cells. The patient was given fluids and pain medication for 18 days. He also received 2 doses of a powerful anticoagulant medication pursuant to the orders of the defendant urologist.

A change in the patient’s condition prompted a telephone order from the urologist for bed rest, to increase the IV rate to 150 cc per hour, and to contact the hospital physician on call for further orders.

The internist on call was called pursuant to the urologist’s order. The medical chart indicated that the internist gave telephone orders for an increase in the IV rate to 150 cc per hour, strict bed rest, and to apply a Posey vest (method used to restrain a patient) as needed. The internist later countersigned these orders.

At 6:45 AM the following morning, the patient’s condition deteriorated significantly. The internist was again called, and he left orders with the hospital nurses advising them to administer a diuretic and to have his partner, another internist assuming duties from him, examine the patient as soon as possible. The patient coded at 7 AM and was pronounced dead at 7:20 AM.

Patient suffered extensive hemorrhage

An autopsy revealed 2500 cc of blood in the patient’s lower abdomen caused by an extensive hemorrhage into the bladder wall, caused by an embedded bladder stone deep in the bladder wall. Apparently, the lithotripsy caused a bladder stone to become embedded into the bladder wall, commencing a slow bleed.

The patient’s wife sued the defendant urologist, the hospital, and the 2 internists for malpractice. She alleged that despite her husband’s deteriorating condition, all defendants failed to institute proper care, which caused him to bleed to death.

The plaintiff claimed the urologist should have never ordered the anticoagulant medication and doing so was below the standard of care.

The plaintiff also contended that the orders attributed to the internist, supposedly at 11 PM, were completely inadequate and below the standard of care. She contended that at the time the internist was called, it would have been possible to reverse the effects of the anticoagulant medication, perform surgery, repair the bleed, and save her husband’s life.

The internist claimed that he never gave orders to the hospital nurse when called. Instead, he argued that he was on call for the urologist, and if the urologist wanted a consultation from him, then the urologist needed to call him. Although the internist admitted he countersigned the orders, he testified that he did so in error.

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**JELMYTO™**  
(mitomycin) for pyelocalyceal solution

**BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION**

Please refer to the JELMYTO Package Insert for Full Prescribing Information, including instructions for preparation and administration.

**INDICATIONS AND USAGE**

JELMYTO™ is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

**DOSE AND ADMINISTRATION**

**Important Administration Instructions**

See the Instructions for Administration provided separately. JELMYTO is for pyelocalyceal use only. JELMYTO is not for intravenous use, topical use, or oral administration. Advise patients that JELMYTO may discolor urine to a violet to blue color following the instillation procedure. Advise patients to avoid contact with urine for at least six hours post-instillation, to void urine sitting on a toilet, and to flush the toilet several times after use.

**Preparation and Handling**

See the Instructions for Pharmacy for preparation provided separately. JELMYTO is a cytotoxic drug. Follow applicable special handling and disposal procedures. JELMYTO must be instilled as a chilled solution using a Uroject12 Lever, a Luer lock syringe, and a ureteral catheter with molded Luer lock connector. Once chilled at -3°C to 5°C (27°F to 41°F), JELMYTO will convert to a viscous liquid for instillation and is stable for up to 1 additional hour. Reconstituted JELMYTO must be instilled within 1 hour after it is converted to a viscous liquid.

**CONTRAINDICATIONS**

JELMYTO is contraindicated in patients with perforation of the bladder or upper urinary tract.

**WARNINGS AND PRECAUTIONS**

**Ureteric Obstruction**

Ureteric obstruction, including ureteral stenosis and hydronephrosis, occurred in patients receiving JELMYTO. In the OLYMPUS study, ureteric obstruction was reported in 58% (n=40) of patients receiving JELMYTO, including 17% (n=12) of patients who experienced Grade 3 obstruction. The median time to first onset was 72 days (range: 15-462). Interventions in the 40 patients experiencing ureteric obstruction included ureteral stent placement (88%), balloon dilatation (32%), and nephroureterectomy (6.9%). In the 36 patients who required ureteral stent placement, the median duration of indwelling stents was 51 days (range: 1-292). Ureteric obstruction did not resolve or resolved with sequelae in 51% (n=21) of these patients. Of the 40 patients who experienced ureteric obstruction, 17% (n=7) experienced Grades 1-2 increase in serum creatinine. In the 42 patients who only received JELMYTO during the treatment phase (no maintenance therapy), ureteric obstruction was reported in 40% (n=17). Monitor patients for signs and symptoms of ureteric obstruction, including flank pain, and fever, and for changes in renal function. Patients who experience obstruction may require transient or long-term ureteral stents or alternative procedures. Withhold or permanently discontinue JELMYTO based on the severity of ureteric obstruction.

**Bone Marrow Suppression**

The use of JELMYTO can result in bone marrow suppression, particularly thrombocytopenia and neutropenia. In the OLYMPUS study, Grade 3 thrombocytopenia occurred in two patients and Grade 3 neutropenia in one patient. Gross extravasation of JELMYTO via urinary tract perforation or impaired mucosa was not observed in these patients. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin. Withhold JELMYTO for Grade 2 thrombocytopenia or neutropenia. Permanently discontinue for Grade 3 or greater thrombocytopenia or neutropenia.

**Embryo-Fetal Toxicity**

Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with JELMYTO and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose.

**ADVERSE REACTIONS**

**Clinical Trials Experience**

The safety of JELMYTO was evaluated in OLYMPUS, an open-label, single-arm study in 71 patients with LG-UTUC. For the 71 patients treated with JELMYTO during the treatment period, the median number of instillations was 6 (range: 3-6). Following initial treatment, 29 patients were treated with up to 11 doses of maintenance instillations, with a median of 6 instillations (range: 0-11). Serious adverse reactions occurred in 37% of patients who received JELMYTO. Serious adverse reactions in > 3% of patients included ureteric obstruction (including ureteric stenosis and hydronephrosis), flank pain, and urosepsis. Two deaths occurred due to cerebrovascular accident and failure to thrive. JELMYTO was permanently discontinued due to an adverse reaction in 16 (23%) patients, including 11 patients who discontinued during the treatment phase and 5 who discontinued during the maintenance phase. Adverse reactions resulting in study drug discontinuation of JELMYTO in > 3% of patients who received JELMYTO included ureteric obstruction. Dosage interruptions due to an adverse reaction occurred in 34% of patients who received JELMYTO. Adverse reactions requiring dosage interruption in > 3% of patients who received JELMYTO included renal dysfunction, ureteric obstruction, urinary tract infection, and flank pain. The most common adverse reactions (> 20%) reported were ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting.
Table 1 summarizes the adverse reactions in OLYMPUS.

Table 1: Adverse Reactions (≥ 10% All Grades) in Patients Who Received JELMYTO in OLYMPUS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>JELMYTO* (n=71)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥ 3 (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteric Obstruction*</td>
<td>58</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Ureteric stenosis</td>
<td>44</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>18</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Pelvi-ureteric obstruction</td>
<td>16</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
<td>6</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td>2.8</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>1.4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Flank pain</td>
<td>39</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>34</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>32</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>25</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Dysuria</td>
<td>21</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Polleukuria</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>24</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5)
*Includes hydronephrosis, obstructive uropathy, pelvi-ureteric obstruction, ureteric obstruction, ureteric stenosis, and urinary tract obstruction.
*Includes flank pain and back pain.
*Includes urinary tract infection, pyelonephritis, and urinary tract infection fungal.
*Includes hematuria and hemorrhage urinary tract.
*Includes renal impairment, acute kidney injury, and renal failure.
*Includes abdominal pain and abdominal pain lower.
*Includes asthenia and fatigue.

Selected clinically relevant adverse reactions in < 10% and ≥ 2% of patients who received JELMYTO in OLYMPUS include urinary tract inflammation, bladder spasm, urosepsis, hypersensitivity, and instillation site pain.

Table 2 summarizes the laboratory abnormalities in OLYMPUS.

Table 2: Select Laboratory Abnormalities (> 10%) Worsening from Baseline in Patients Who Received JELMYTO in OLYMPUS

<table>
<thead>
<tr>
<th>Laboratory Abnormality*</th>
<th>JELMYTO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>37</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>21</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Estimated Glomerular Filtration Rate</td>
<td>37</td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>32</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>30</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>17</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>13</td>
</tr>
</tbody>
</table>

*Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**
Risk Summary - Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman. There are no available data on JELMYTO use in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise pregnant women of the potential risk to a fetus.

**Lactation**
Risk Summary - There are no data on the presence of mitomycin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with JELMYTO and for 1 week following the last dose.

**Females and Males of Reproductive Potential**

**Pregnancy Testing** - Verify pregnancy status in females of reproductive potential prior to initiating JELMYTO.

**Geriatric Use**
Of the total number of patients in the OLYMPUS trial, 75% (53 patients) were 65 years of age and over and 37% (26 patients) were 75 years of age and over. Clinical studies of JELMYTO did not include sufficient numbers of younger patients less than 65 years old to determine whether they respond differently from older patients.

**Renal Impairment**
No data are available in patients with severe renal impairment. Avoid use of JELMYTO in patients with a Glomerular Filtration Rate of < 30 mL/min.

Distributed by:
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Princeton, NJ 08540
U.S. Patent Nos. 9,040,074 and 9,950,069
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Based on content from JEL-PI-001 Package Insert
**CHEMOABLATE NOW SPARE THE KIDNEY FOR TOMORROW**

In the OLYMPUS Study, † JELMYTO treatment in patients with low-grade UTUC achieved:

- **58%** Complete Response (95% CI: 45, 69)
- **84%** Durability of Response (95% CI: 71, 97)

N=71

The OLYMPUS Study is ongoing. At the time of data cutoff:

- 19 patients remained in CR
- 7 patients had disease recurrence
- 9 patients continued to be followed for 12-month duration of response
- Median duration of response was not reached, with a range of 0-18.8+ months
- The most common adverse reactions (≥20%) reported were ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting

CI=confidence interval.

---

**Indications and Usage**

**JELMYTO** (mitomycin) for pyelocalyceal solution is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

**Important Safety Information**

Contraindications

JELMYTO is contraindicated in patients with perforation of the bladder or upper urinary tract.

Ureteric Obstruction

Ureteric obstruction, including ureteral stenosis and hydroureteronephrosis, occurred in patients receiving JELMYTO. Monitor patients for signs and symptoms of ureteric obstruction, including flank pain, and fever, and for changes in renal function. Patients who experience obstruction may require transient or long-term ureteral stents or alternative procedures.

Withhold or permanently discontinue JELMYTO based on the severity of ureteric obstruction.

Bone Marrow Suppression

The use of JELMYTO can result in bone marrow suppression, particularly thrombocytopenia and neutropenia. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin.

Embryo-Fetal Toxicity

Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose.

Common Adverse Reactions

The most common adverse reactions in ≥20% of patients treated with JELMYTO were ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting.

Additional Adverse Reactions Information

Selected clinically relevant adverse reactions in <10% and ≥2% of patients who received JELMYTO include urinary tract inflammation, bladder spasm, urosepsis, hypersensitivity, and instillation site pain.

Use in Specific Populations

Lactation

Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with JELMYTO and for 1 week following the last dose.

Preparation and Administration Information

JELMYTO is for pyelocalyceal use only and not for intravenous use, topical use, or oral administration. JELMYTO must be prepared and administered by a healthcare provider. To ensure proper dosing, it is important to follow the preparation instructions found in the JELMYTO Instructions for Pharmacy and administration instructions found in the JELMYTO Instructions for Administration.

JELMYTO may discolor urine to a violet to blue color following the instillation procedure. Advise patients to avoid contact with urine for at least six hours post-instillation, to void urine sitting on a toilet, and to flush the toilet several times after use.

JELMYTO is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Please see Brief Summary of Prescribing Information for JELMYTO on the following page.