Multiparametric-MRI in prostate cancer

An expert’s view

BLADDER CANCER
UGN-102 shows promise in low-grade NMIBC

BENIGN PROSTATIC HYPERPLASIA
Previsit BPH decision aid provides valuable insights and optimizes care

SEXUAL DYSFUNCTION
Proinflammatory diet is associated with testosterone deficiency

KIDNEY STONES
Trilogy, ShockPulse-SE lithotripters demonstrate efficacy

KIDNEY CANCER
Study supports routine brain imaging at baseline in metastatic kidney cancer
TABLETS ARE AVAILABLE

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Chairman’s Letter

Hoping for a return to in-person meetings soon

This issue of Urology Times® was just going into production when the news broke that the 2021 American Urological Association (AUA) annual meeting was going to convert to an all-virtual format. It is unfortunate that this yearly highlight will not be held in person for the second year in a row, and we can only hope that better circumstances will prevail in 2022 for the meeting to go ahead as planned in New Orleans, Louisiana.

In the meantime, we press forward and will still deliver our usual robust coverage of the AUA annual meeting, beginning with next month’s issue. This month, among our highlights is a Q&A discussion with Marc A. Bjurlin, DO, MSc, FACOS, who discusses MRI of the prostate and its role in cancer detection.

Also in prostate cancer, for Journal Article of the Month, Badar M. Mian, MD, analyzes 2 recent studies that “examined the outcomes of early vs delayed [radiation therapy (RT)] and of RT dose escalation on health-related quality of life and functional outcomes.”

In bladder cancer, read our interview with Thomas Powles, MD, MBBS, MRCP, who discusses findings from the EV-301 trial (NCT03474107) of enfortumab vedotin-epatol (Pdme).

In benign prostatic hyperplasia, look for coverage of studies evaluating a previsit decision aid, the UroLift treatment, and racial disparities in surgical management of the condition. In sexual dysfunction, we report on a study examining the association between a proinflammatory diet and testosterone deficiency, and in kidney stones, you’ll find an article on a recent study comparing 2 lithotripter devices.

We lead off our columns this issue with a collection of coding questions submitted by readers to columnists Jonathan Rubenstien, MD, and Mark Painter. In this installment, they tackle questions regarding biofeedback after robotic radical prostatectomy, cystoscopy with bilateral ureteral stent removal, and a situation in which a patient comes in to have a ureteral stone removed only to find the stone has already passed. In Practice Matters, Robert A. Dowling, MD, analyzes urologists’ performance in the Quality Payment Program’s Merit-based Incentive Payment System in 2019 and looks at how that performance stacks up against that of other specialties. Dowling also briefly discusses the Physician Compare website to explain how these data are presented to patients. In Money Matters, Jeff Witz, CFP, explains the effects of increased inflation on the economy.

For this month’s installment of Speak Out, Karen Nash asked 3 urologists how their treatment of prostate cancer has changed in recent years, eliciting fascinating replies.

“New and different drugs indicated at different points in the treatment cycle have been the biggest change. Enzalutamide, for example, was approved, initially for a very specific indication, but indications keep broadening, so we keep being able to use those drugs earlier in the advanced prostate cancer process. So I think medicines are the biggest things that are different,” says urologist Robbie Hurtt, MD.

Finally, in Malpractice Consult, Amanda Wager, Esq, filing in for regular Malpractice Consult columnist Kenton H. Steele, Esq, walks the reader through the process of taking depositions in a case. Stay safe, and thanks for reading.

Chairman and Founder
Mike Hennessy Sr.
IN

advanced prostate cancer,

ARE YOU SEEING

the risks, such as cardiovascular?

Patients with advanced prostate cancer are at risk for other serious conditions, such as cardiovascular disease, diabetes, and osteoporosis—risks that may increase with androgen deprivation therapy.1-5


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FDA approves dostarlimab companion diagnostic for use across dMMR solid tumors

The FDA has approved the Ventana MMR RxRx Panel test as a companion diagnostic to help identify patients with advanced solid tumors that are mismatch repair deficient (dMMR) in order to determine eligibility for the newly approved immunotherapy dostarlimab-gxly (jemperli).1

Ventana MMR RxRx Panel is a qualitative immunohistochemistry test that assesses a panel of MMR proteins to help guide clinicians in their treatment decisions.

The FDA approved the PD-1 inhibitor dostarlimab-gxly (jemperli) on August 17, 2021, for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test.2

The approval provides urologists with another tool in the armamentarium for the treatment of patients with genitourinary cancers. It also underscores the rapidly growing significance of genetic testing in the field of urology.

REFERENCES

FDA approves adjuvant nivolumab in bladder cancer

The FDA has approved opdivo (nivolumab) for the adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection, regardless of prior neoadjuvant chemotherapy, nodal involvement, or PD-L1 status, Bristol Myers Squibb announced in a news release.1

The approval’s basis comes from the randomized, double-blind phase 3 CheckMate 274 trial (NCT02632409), which evaluated nivolumab, 240 mg, in 353 patients vs 356 patients receiving placebo.2 Patients who received nivolumab had median disease-free survival of 20.8 months (95% CI, 16.5-27.6) vs 10.8 months (95% CI, 8.3-13.9) in the placebo arm.

REFERENCES

Prostate cancer trial starts treatment with novel PSMA theranostic 64/67Cu SAR-bisPSMA

The first US patient has been treated in the phase 1/2 SECuRE trial (NCT04868604) examining the novel PSMA theranostic 64/67Cu SAR-bisPSMA and the PSMA targeted therapy 67Cu-SAR-bisPSMA. The patient received the novel radiopharmaceutical therapy at the Urology Center and GU Research Network in Omaha, Nebraska.

The theranostic 64/67Cu SAR-bisPSMA combines the PSMA PET imaging product 64Cu-SAR-bisPSMA and the PSMA targeted therapy 67Cu-SAR-bisPSMA.

The study aims to enroll 44 patients at multiple locations in the United States. To enroll in the trial, patients must have mCRPC that has progressed despite being treated with androgen-deprivation therapy and at least 1 second-generation androgen receptor pathway inhibitor, such as abiraterone acetate (Zytiga) or enzalutamide (Xtandi).2 Patients are required to have an ECOG performance status of 0 to 2 and a castrate level of serum/plasma testosterone (< 50 ng/dL or < 1.7 nmol/L). Individuals with brain metastases are not eligible to enroll.

The estimated study completion date for the SECuRE trial is September 2026.

REFERENCES

FDA grants clearance to soft-tissue 3D printing technology for genitourinary conditions

The FDA has granted 510(k) clearance to Lazarus 3D for its PRE-SURE 3D printing technology for use across all genitourinary conditions.1

The technology produces synthetic, soft-tissue models with a lifelike quality—including bleeding—that allows clinicians to map out and simulate surgeries in preparation for operating on their actual patients. The PRE-SURE system creates the realistic models directly from patient MRI/CT data. Urology areas covered for this FDA clearance include conditions of the prostate, bladder, kidneys, and genitalia.

The FDA’s 510(k) clearance designation allows a company to market a medical device in the United States if the company can prove to the regulatory authorities that its device is “substantially equivalent” to a device that is already legally marketed in the country.2

According to the company, medical billing codes have been issued by the American Medical Association to reimburse for PRE-SURE.

REFERENCES
onsurgical primary chemoablation with the mitomycin-containing reverse thermal gel UGN-102 showed promise as an alternative to repetitive surgery for patients with low-grade non–muscle-invasive bladder cancer (NMIBC), according to findings from the phase 2b OPTIMA II trial published in the *Journal of Urology*.

The study, from K. Kent Chevli, MD, FACS, and co–authors, focused on patients with intermediate-risk NMIBC. At 3 months after treatment initiation, the complete response (CR) rate with UGN-102 was 65%. An estimated 73% of these patients with CRs maintained their response 12 months after starting therapy. The median duration of response had not been reached.

Transurethral resection of bladder tumor (TURBT) is the standard of care for patients with low-grade, intermediate NMIBC. However, recurrence is common, requiring repeated TURBT, which is associated with several risks, including failure to cure, bladder perforation, bleeding that necessitates a hospital stay, and repeated anesthe sia in older patients that is linked to cognitive decline.

Explaining the rationale for evaluating UGN-102 in this population, the authors wrote, “Studies of aqueous preparations of mitomycin suggest that chemoablation with mitomycin may obviate the need for surgery in some patients or reduce the perioperative morbidity associated with surgery secondary to lower volume disease and may be associated with fewer clinically significant adverse effects [AEs].”

In the multicenter prospective, open-label, single-arm OPTIMA II trial (NCT03558503), 63 patients with biopsy-proven, low-grade, intermediate-risk NMIBC were treated with up to 6 once-weekly UGN-102 instillations. The median age was 63 years (range, 33–96), and there were 38 male and 25 female patients. Twenty-seven patients were younger than 65 years of age, 11 were aged 65 to less than 75 years, and 25 were 75 years or older. Most patients were Caucasian (n=55).

Overall, 72.1% of patients had tumors <3 cm or smaller, 98.4% had noninvasive papillary sarcoma, and 98.4% had low-grade papillary urothelial carcinoma. Prior low-grade NMIBC episodes occurred in 77.8% of patients, and 44.4% had a low-grade NMIBC episode 1 year or sooner from their current diagnosis. The median number of prior TURBTs in recurrent patients was 3 (range, 0–13), including 37 and 28 patients who received 2 or more and 3 or more prior TURBTs, respectively.

All 63 patients received at least 1 UGN-102 instillation, and 57 patients (90%) received all 6. The primary end point of the study was CR, which the trial design defined as “the proportion of patients with negative endoscopic examination, negative cytology, and negative for-cause biopsy 3 months after treatment initiation.” The investigators conducted a quarterly follow-up of the complete responders for up to 1 year to evaluate the durability UGN-102’s impact.

Overall, 41 of the 63 patients achieved a CR. In this group, 39 patients remained disease free at 6 months following the start of treatment, 30 were disease free 9 months after, and 12 were disease free 12 months after.

Most AEs were considered mild to moderate. Overall, 63% of patients (n=40) had treatment-emergent AEs (TEAEs) that investigators categorized as related to UGN-102 itself or procedure. All-grade TEAEs occurring in 10% or more of patients included dysuria, urinary frequency, hematuria, micturition urgency, urinary tract infection, and fatigue.

**REFERENCE**

**EV-301 investigator discusses enfortumab vedotin**

“Significant survival advantage” vs chemotherapy was observed

**NICHOLE TUCKER**
Senior Editor, Targeted Oncology™

In July 2021, the FDA granted a standard approval to enfortumab vedotin-ejfv (Padcev) for the treatment of patients with bladder cancer, based on findings from the EV-301 (NCT03474107) and EV-201 (NCT03219333) trials.

The antibody-drug conjugate is specifically approved for use in patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy or in patients who are ineligible for cisplatin-containing chemotherapy and previously received 1 or more prior lines of therapy.

In an interview with Urology Times® sister brand Targeted Oncology™, lead EV-301 trial author Thomas Powles, MD, MBBS, MRCP, professor of genitourinary oncology, lead for solid tumor research at Barts Cancer Institute, and director of Barts Cancer Centre, in London, United Kingdom, discussed findings from the pivotal study and where enfortumab vedotin fits in the bladder cancer treatment paradigm.

**TARGETED ONCOLOGY™: Can you describe what outcomes look like currently for patients with locally advanced or metastatic urothelial carcinoma who progress after platinum-containing chemotherapy and on PD-1/PD-L1 regimens?**

**POWLES:** The standard treatment for metastatic urothelial cancer is to give platinum-based therapy predominantly as a first-line treatment. And then in sequence with immune checkpoint inhibitors, maintenance avelumab [Bavencio] is a standard of care. Some individuals get second-line immunotherapy instead. So we’re sequencing chemotherapy and immunotherapy together. After progression occurs on those 2, there’s a lot of uncertainty around treatment options, so we tend to rechallenge with chemotherapy, then test some patients for FGF alterations. Overall, the data are limited for this patient group, and so it’s an area where we need to develop new drugs.

**Q. What had been observed previously with enfortumab vedotin that led you to evaluate its use in this patient population?**

**A.** Enfortumab vedotin is an antibody-drug conjugate targeting Nectin-4, which is expressed on the vast majority of urothelial cancers. The payload is called MMAE [monomethyl auristatin E], which is a microtubule disrupting agent. The drug is being tested in patients who have cancers that have progressed on chemotherapy and immune checkpoint inhibitors, and it has a response rate of about 40%, leading to accelerated FDA approval in 2019. The purpose of the randomized phase 3 EV-301 study was to test enfortumab vedotin against standard chemotherapy in a randomized phase 3 manner.

**Q. Can you discuss the results of this study?**

**A.** This is a 650-patient study, which is robust, and it showed a significant survival advantage for enfortumab vedotin vs chemotherapy. The chemotherapy choice was docetaxel, which is [sic] standard. The hazard ratio was 0.70, which was statistically significant, suggesting or showing a 30% reduction in the risk of death. The overall survival in the enfortumab vedotin arm was approximately 13 months, which is long in this setting.

The response rate was 40% vs 18%, respectively. The percent and the hazard ratio for [progression-free survival] also favored enfortumab vedotin significantly, so that the efficacy signal was consistent, which is really important. When I give this drug to my patients, this is reinforced. We see great responses and we see patients’ pain reducing with therapy. So it’s a very active therapy in urothelial cancer.

**Q. Can you describe the toxicity profile of enfortumab vedotin as observed during the EV-301 study?**

**A.** The toxicity profile is manageable. In fact, the adverse event profile showed that the percentage of grade 3 or 4 adverse events was about 50% in both groups. However, the antibody-drug conjugate had a different adverse event profile compared with standard chemotherapy. We looked out for neuropathy, skin toxicity, and hyperglycemia, particularly, which require attention. And we need to look at those while we’re treating our patients. Some patients, indeed, require dose reductions or dose delays because of that. But overall, when you look at this, you say this is a new class of drug opening a new chapter in urothelial cancer…We’re showing a drug with a very consistent [safety profile] with a high efficacy signal. I think this is going to be a big change for patients with bladder cancer over the next 10 years.

**Q. How do you envision this agent changing practice?**

**A.** I think this is going to make a massive difference. I think it’s going to be a standard of care. The standard of care currently is platinum-based chemotherapy and maintenance avelumab, and if [there is] progression, I think, enfortumab vedotin is what we’ll use in the second line.

**REFERENCE**

In the OLYMPUS Study, JELMYTO demonstrated:

- **Complete Response (CR)**: 58% (95% CI: 45, 69)
- **Durability of Response**: 82% (95% CI: 66, 91)

At the 12-month assessment of durability (n=41):

- 23 patients remained in CR
- 8 patients had disease recurrence
- 10 patients were evaluable
- Median duration of response was not reached, with a range of 0-18.8+ months
- Kaplan-Meier analysis estimates probability of durable response. It does not represent an actual percentage of patients. In the OLYMPUS trial, at the time of the 12-month assessment for durability, not all patients had a recurrence (patients may have still been in CR, died, or discontinued). The KM analysis accounts for these missing data. The analysis has potential limitations: the sample size was small (n=41) and median duration of response was not reached due to the limited number of recurrences (n=8); this may be reflective of a short follow-up time (12 months)
- The most common adverse reactions in ≥20% of patients treated with JELMYTO were ureteric obstruction, urinary tract infection, hematuria, flank pain, nausea, dysuria, renal dysfunction, vomiting, fatigue, and abdominal pain

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**Indications and Usage**

JELMYTO (mitomycin) for pyelocalyceal use only and not for intravenous use, topical use, or oral administration. JELMYTO is for the treatment of adult patients with low-grade upper tract urothelial carcinoma (LG-UTUC) 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.

**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.

**Important Safety Information**

**Contraindications**

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

**Ureteral Obstruction**

Ureteral obstruction, including ureteral stenosis and hydronephrosis, 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.

**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. 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 3 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO.

**Adverse Reactions**

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

**Use in Specific Populations**

**Lactation**

JELMYTO can result in 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.

**References**

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 Urethelial 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 hydromephrosis, occurred in patients receiving JELMYTO. In the OLYMPUS study, ureteric obstruction was reported in 58% (n=49) 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: 15-482). Interventions in the 41 patients experiencing ureteric obstruction included ureteral stent placement (88%), balloon dilatation (29%), and nephroureterectomy (4.9%). In the 36 patients who required ureteral stent placement, the median duration of indwelling stents was 52 days (range: 1-292). Ureteric obstruction did not resolve or resolved with sequelae in 44% (n=18) of these patients. Of the 41 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 three patients, Grade 3 anemia in one patient, 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: 3-8). 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 39% 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 17 (24%) patients, including 11 patients who discontinued during the treatment phase and 6 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 37% 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, urinary tract infection, hematuria, flank pain, nausea, dysuria, renal dysfunction, vomiting, fatigue, and abdominal pain.
renal function. Patients who experience obstruction may require.

40% (n=17). Monitor patients for signs and symptoms of ureteric

patients who only received JELMYTO during the treatment phase

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nephroureterectomy (4.9%). In the 36 patients who required

time to first onset was 72 days (range: 15-462). Interventions

bladder or upper urinary tract.

JELMYTO is contraindicated in patients with perforation of the

CONTRAINDICATIONS

Preparation and Handling -

See the Instructions for Pharmacy

F:10”

B:20.25”

S:19.5”

T:20”

LG-UTUC. For the 71 patients treated with JELMYTO during the

Clinical Trials Experience -

Pelvi-ureteric obstruction

18 6

44 9

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>
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</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>Ureteric Obstruction†</td>
<td>58</td>
</tr>
<tr>
<td>Ureteric stenosis</td>
<td>44</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>18</td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
<td>7</td>
</tr>
<tr>
<td>Pelvi-ureteric obstruction</td>
<td>6</td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td>2.8</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>1.4</td>
</tr>
<tr>
<td>Flank pain†</td>
<td>41</td>
</tr>
<tr>
<td>Hematuria†</td>
<td>34</td>
</tr>
<tr>
<td>Urinary tract infection†</td>
<td>34</td>
</tr>
<tr>
<td>Renal dysfunction‡</td>
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<tr>
<td>Dysuria</td>
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<td>Pollakiuria</td>
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<td>Gastrointestinal disorders</td>
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<tr>
<td>Nausea</td>
<td>25</td>
</tr>
<tr>
<td>Abdominal pain‡</td>
<td>28</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue§</td>
<td>27</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
</tr>
<tr>
<td>Chills</td>
<td>11</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
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<tr>
<td>Anemia</td>
<td>14</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
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<tr>
<td>Pruritus</td>
<td>13</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
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<tr>
<td>Decreased appetite</td>
<td>10</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
</tr>
</tbody>
</table>

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>Hematology</td>
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<tr>
<td>Anemia</td>
<td>38</td>
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<tr>
<td>Lymphopenia</td>
<td>21</td>
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<tr>
<td>Thrombocytopenia</td>
<td>21</td>
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<tr>
<td>Chemistry</td>
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</tr>
<tr>
<td>Estimated Glomerular Filtration Rate (eGFR)</td>
<td>38</td>
</tr>
<tr>
<td>Creatinine Increased</td>
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</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>28</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>16</td>
</tr>
<tr>
<td>Hyperuricemia</td>
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<td>Hyperkalemia</td>
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<tr>
<td>Hypernatremia</td>
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*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5). Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available. eGFR calculated per MDRD (Modification of Diet in Renal Disease) equation

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.

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Princeton, NJ 08540

U.S. Patent Nos. 9,040,074 and 9,950,089

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The use of multiparametric-magnetic resonance imaging (MRI) to help guide prostate biopsies has been growing among urologists and was the subject of an American Urological Association (AUA) and the Society of Abdominal Radiology Prostate Disease Focused Panel standard operating procedure document. In this interview, Marc A. Bjurlin, DO, MSc, FACOS, explains the advantages of prostate MRI, in which patients it is best used, and whether it can be considered the gold standard for prostate cancer detection. Bjurlin is an associate professor of urology at the University of North Carolina at Chapel Hill.

Q. Can you describe the technology being used in prostate MRI?
A. MRI-guided biopsies can be performed in several ways. It’s most commonly performed in conjunction with a transrectal ultrasound, either with or without software assistance. When we use software assistance, this is the most common technique employed in the United States. In some situations, the software is not available; then we do MRI-guided biopsies based on what we refer to as “cognitive guidance” where, essentially, the urologist interprets the MRI and places needles free-hand into the area of interest. There is also a technique in which men can be biopsied while in the MRI scanner itself; this is referred to as “in-bore” or “in-gantry” biopsy. As you can imagine, the more we move away from the transrectal approach, the more we can also perform MRI/ultrasound fusion biopsies by way of the transperineal approach. The transperineal approach avoids biopsying via the rectal wall, significantly reducing the potential for bacterial infection. Furthermore, the transrectal approach to prostate biopsy may result in undersampling, particularly in the anterior prostate. The MRI/ultrasound-guided transperineal approach allows easy access to anterior prostate tumors.

Q. What are the advantages of using prostate MRI?
A. Using MRI as a prebiopsy risk assessment tool, then using that technology to guide biopsy, has several advantages. It’s been shown to increase the number of clinically significant cancers that are detected while simultaneously reducing the number of insignificant cancers detected. The biopsy of the region of interest reduces the number of biopsy cores taken per procedure, so ultimately, this may have a role in reducing adverse events and avoiding...

Overall, would you say that the benefits of MRI in prostate cancer justify the cost associated with it?
I think so, but with some caveats, one being that if we are going to get an MRI, we must make sure that the MRI is high quality.
some biopsy-related complications. Using this approach of getting the MRI, identifying the region of interest, and then biopsying that area has also been useful in terms of selecting men who may be candidates for focal therapy, as well as planning that focal therapy intervention.

Q. For what types of patients is prostate MRI most ideal?
A. In 2018, we published the American Urological Association [AUA] policy statement on the use of multiparametric-MRI in the diagnosis, staging, and management of prostate cancer. We updated this statement in 2019. Essentially, the take-home message from this document is that when there is a quality prostate MRI, the current evidence supports MRI and MRI-targeted biopsy in men who are at risk for harboring prostate cancer who have not yet undergone a previous biopsy, as well as men who have an increasing prostate-specific antigen [PSA] followed by an initial negative biopsy. In men with low-risk disease who are on active surveillance, there is now more evidence that MRI is also useful in this space to help risk assess men to choose who would be an appropriate candidate for active surveillance and continue to be on active surveillance in light of an elevated PSA.

Q. What are some of the drawbacks to utilizing prostate MRI?
A. Cost is a major issue, but some of the up-front costs are offset downstream, meaning that essentially by getting an MRI and doing an MRI-targeted biopsy, we have the potential to reduce the need for repeat biopsy in the future. We may reduce the number of insignificant cancers diagnosed, which may ultimately lead to a decrease in overtreatment of insignificant disease. We may also improve patient understanding and reduce anxiety when a patient has a better assessment of what their MRI looks like, and they understand the disease process.

There are some other limitations of MRI and MRI-targeted biopsy in that there is quite a bit of interobserver variability, meaning that different radiologists may interpret the MRI as having different risks. There have been several considerations in this area in terms of how to adjust interobserver variability. To reduce variability in prostate MRI interpretation, the American College of Radiology and the American Roentgen Ray Society offer a prostate MRI course with the goal of improving the interpretation of MRI of the prostate and establishing a quality assurance program for prostate imaging. Additionally, there will soon be an American College of Radiology Prostate Cancer MRI Center designation to help standardize MRI protocols and interpretation.

There are also some data that show several prostate cancers that are not visible on MRI; somewhere between 5% and 35% of MRIs may miss high-risk disease. Even though the MRI is a useful tool, it is not perfect by any means.

Q. Overall, would you say that the benefits of MRI in prostate cancer justify the cost associated with it?
A. I think so, but with some caveats, one being that if we are going to get an MRI, we must make sure that the MRI is high quality. The big picture is that not every single man with an elevated PSA needs an MRI and, subsequently, an MRI/ultrasound fusion biopsy. There are several risk stratification tools that can be employed in this shared decision-making process, including biomarkers and family history. I think a comprehensive approach really lends itself to further areas of research to determine when we should be using biomarkers, when we should be using MRI, and what the ideal combination of both is in order to help risk assess men, in terms of moving forward with a prostate biopsy.

Q. How widespread is its use currently?
A. This technology has been leading the way in the United States and Europe, but it’s not widely adopted universally. I think that’s a result of many reasons. No. 1, at least in the United States, insurance coverage is still an issue. No. 2, there are up-front costs, in terms of purchasing the MRI/ultrasound fusion platform, as well as software and access to high-quality MRIs. Not all institutions have that.

How widespread is the use of prostate MRI currently?

This technology has been leading the way in the United States and Europe, but it’s not widely adopted universally.

MARC A. BJURLIN, DO, MSC, FACOS

Q. At this point, would you say that MRI-guided biopsy is the gold standard for prostate cancer detection?
A. I think we’re heading in that direction, but again, with several caveats. In men who ultimately have had a shared decision-making experience and opted to undergo a biopsy, when a high-quality MRI can be obtained, an MRI/ultrasound fusion biopsy is the gold standard. With that being said, not every man with an elevated PSA needs this, and there are additional biomarkers and risk stratification tools that we should be incorporating into risk assessment to help guide men in terms of who needs a biopsy and who can avoid a biopsy.

REFERENCE
Treatment with enzalutamide (Xtandi) was associated with an overall survival (OS) benefit compared with abiraterone acetate (Zytiga) among US veterans with metastatic castration-resistant prostate cancer (mCRPC), according to a retrospective analysis shared during the 2021 American Society of Clinical Oncology Annual Meeting.1

In the overall population, the median OS was 24.1 months with enzalutamide vs 22.2 months with abiraterone (P = .003) (Figure); however, this modest OS benefit was more pronounced among patients who received only 1 treatment (median OS, 18.9 months vs 13.6 months, respectively; P < .001).

Among patients who received 2 or more treatments, there was no difference in median OS: 28.0 months vs 27.9 months, respectively (P = .24). Of note, patients receiving 1 treatment were generally older (mean age, 78.3 years vs 73.2 years) and had more comorbidities (median Elixhauser Comorbidity Index score, 6.4 vs 5.7) compared with patients who received 2 or more treatments.

“[In older patients with higher comorbidity burdens who are not candidates for docetaxel, consider using enzalutamide instead of abiraterone.”

MARTIN SCHOEN, MD, MPH

Among patients who received 2 or more treatments, there was no difference in median OS: 28.0 months vs 27.9 months, respectively (P = .24). Of note, patients receiving 1 treatment were generally older (mean age, 78.3 years vs 73.2 years) and had more comorbidities (median Elixhauser Comorbidity Index score, 6.4 vs 5.7) compared with patients who received 2 or more treatments.

“In older patients with higher comorbidity burdens who are not candidates for docetaxel, consider using enzalutamide instead of abiraterone,” said lead study author Martin Schoen, MD, MPH, an assistant professor of medicine at Saint Louis University and a staff physician at the St Louis Veterans Affairs Medical Center in Missouri.

Explaining the investigators’ rationale for conducting the study, Schoen said, “Both abiraterone and enzalutamide are used to treat mCRPC, but no head-to-head trials have been performed, and these agents are commonly used in older patients with medical comorbidities. So we wanted to identify differences in survival in veterans across the country.”

The study included 5895 men with mCRPC treated with abiraterone or enzalutamide in the Veterans Health Administration between September 10, 2014, and June 3, 2017. Follow-up went to April 2020.

Overall, 43.5% (n = 2562) of patients initially received enzalutamide and 56.5% (n = 3333) initially received abiraterone. The mean age in the enzalutamide arm was 75.9 years compared with 75.0 years in the abiraterone arm. The mean comorbidity scores on the Elixhauser Comorbidity Index were 6.2 vs 5.9, respectively.

Patients initially treated with abiraterone were more likely to have received docetaxel (28.4% vs 24.1%) and both abiraterone and enzalutamide (51% vs 45.2%). Overall, 2578 patients received only 1 treatment and 3317 patients received 2 or more treatments.

When using statistical models to adjust for age and comorbidity, there was a 13% (HR, 0.87; P < .001) reduced risk of death with enzalutamide vs abiraterone. This reduction in risk went up to 27% (HR, 0.73; P < .001) in patients who received only enzalutamide or abiraterone and no docetaxel. The risk of death was the same among patients receiving 2 or more treatments.

Regarding next steps with this research, Schoen said, “In the future, we would like to prospectively define patients with mCRPC who benefit from enzalutamide based on comorbidities and concomitant medications and would also like to determine if this association is also present in patients with metastatic hormone-sensitive prostate cancer.”

REFERENCE
MRI-guided screening limits prostate cancer overdiagnosis

Technique shows noninferiority for detecting clinically significant cancer

JASON M. BRODERICK
Associate Editorial Director, Urology Times®

Prostate cancer screening with MRI-guided biopsy reduced the detection of clinically insignificant prostate cancer vs use of standard biopsy alone, while also demonstrating noninferiority for detecting clinically significant disease, according to findings from the STHLM3-MRI trial presented at the 2021 European Association of Urology Annual Congress and simultaneously published in the New England Journal of Medicine.1

“Our results from a large, randomized study show that modern methods for prostate cancer screening maintain the benefits of screening while decreasing the harms substantially. This addresses the greatest barrier to the introduction of nationwide screening,” study investigator Tobias Nordström, MD, PhD, associate professor of urology in the Department of Clinical Sciences, Danderyd Hospital at Karolinska Institutet, Solna, Sweden, said in a news release.2

The STHLM3-MRI study was a prospective, randomized trial in men aged 50 to 74 years from the general population who were invited by mail to participate. Blood samples from enrolled patients were then submitted for prostate-specific antigen (PSA) analysis as well as an assessment by the Stockholm3 blood test, which was developed by investigators at Karolinska Institutet. Men with PSA levels of 3 ng/mL or higher were then randomized in a 2:3 ratio to receive standard biopsy or undergo MRI, with targeted and standard biopsy if the MRI results indicated prostate cancer.

Overall, 1532 of 12,750 men who enrolled had a PSA of 3 ng/mL or higher and were randomized to the standard group (n = 603) or the MRI group (n=929). The primary end point of the trial was the proportion of patients in the intention-to-treat population who received a diagnosis of clinically significant prostate cancer, defined as Gleason score of at least 7. The results showed that only 4% (n = 41) of the MRI group were diagnosed with clinically insignificant cancers compared with 12% (n = 73) of the standard group. Further, 21% (n = 192) of the MRI group and 18% (n = 106) of the standard group were diagnosed with clinically significant cancer, demonstrating noninferiority for the MRI approach (P < .001) (Table1).

“Refined screening methods are required to reduce overdiagnosis and overtreatment of low-risk tumors and prevent unnecessary biopsies and biopsy-related [adverse] effects,” study investigator Martin Eklund, PhD, associate professor in the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, said in the news release.

Regarding next steps, Nordström said, “We will soon present the second of the 2 main reports from the STHLM3-MRI trial where we assess the role of a novel blood test as adjunct to MRI in prostate cancer screening. The future of prostate cancer diagnostics probably includes both improved blood tests and MRI. Nationwide screening for breast and cervical cancer among women has been available in the Western world for some time. We are finally able to show that men can also reduce their risk of malignant cancer through nationwide prostate-cancer screening that utilizes modern methods.” •

REFERENCES

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SEPTEmBRE 2021 | 15
Each episode of our podcast, “Speaking of Urology”, features timely and informative insights from leaders in the specialty, helping practitioners stay up to date with expert clinical analysis, practice advice, and policy perspectives.
Adding abiraterone to ADT and docetaxel improves rPFS

Approximate 2.5-year absolute benefit in median rPFS seen in men with de novo mCSPC

BENJAMIN P. SAYLOR
Content Managing Editor, Urology Times®

The addition of abiraterone acetate (Zytiga) and prednisone to androgen-deprivation therapy (ADT) and docetaxel improved radiographic progression-free survival (rPFS) in men with de novo metastatic castration-sensitive prostate cancer (mCSPC), according to initial results from the phase 3 PEACE-1 study (NCT01957436).1

The findings, which were presented at the 2021 American Society of Clinical Oncology Annual Meeting, showed that adding abiraterone/prednisone to standard docetaxel/ADT was associated with an approximately 2.5-year absolute benefit in median rPFS in this patient population.

The PEACE-1 study randomized men with de novo mCSPC in a 1:1:1:1 ratio to standard docetaxel/ADT associated with an approximately 2.5-year absolute benefit in median rPFS in this patient population. The PEACE-1 study randomized men with de novo mCSPC in a 1:1:1:1 ratio to standard docetaxel/ADT and was associated with an approximately 2.5-year absolute benefit in median rPFS in this patient population. The PEACE-1 study randomized men with de novo mCSPC in a 1:1:1:1 ratio to standard docetaxel/ADT and was associated with an approximately 2.5-year absolute benefit in median rPFS in this patient population. The PEACE-1 study randomized men with de novo mCSPC in a 1:1:1:1 ratio to standard docetaxel/ADT and was associated with an approximately 2.5-year absolute benefit in median rPFS in this patient population.

The investigators reported a median rPFS of 4.5 years in the abiraterone arm in the overall population vs 2.2 years for SOC (P < .0001). Similarly, better rPFS was observed in the abiraterone arm vs the SOC arm in the ADT plus docetaxel population (4.5 years vs 2.0 years; P < .0001). In addition, PFS including PSA progression as an event was also improved with abiraterone in both the overall population (3.8 years vs 1.5 years; P < .0001) and the ADT plus docetaxel population (3.2 years vs 1.4 years; P < .0001).

“It was very reassuring to see that abiraterone, even used concomitantly with docetaxel, did not increase the risk of febrile neutropenia... or other hematological toxicities related to docetaxel,” Fizazi said.

Grade 3 to 5 gastrointestinal toxicity and fatigue, which are typically associated with docetaxel, had a lower incidence in the group of patients receiving abiraterone (2% vs 4%, respectively), which Fizazi said may be due to the abiraterone cohort also receiving prednisone.

“In conclusion, adding abiraterone and prednisone to ADT plus docetaxel clearly improves radiographic PFS in men with de novo metastatic prostate cancer,” Fizazi said.

REFERENCE

“Adding abiraterone and prednisone to ADT plus docetaxel clearly improves radiographic PFS in men with de novo metastatic prostate cancer.”

KARIM FIZAZI, MD, PHD

much seemed to benefit from the addition of abiraterone,” said lead study author Karim Fizazi, MD, PhD, head of the Department of Cancer Medicine at the Institut Gustave Roussy, Villejuif, France, and a professor of oncology at the University of Paris-Sud.

In the docetaxel population, grade 3 to 5 toxicities that were higher in patients receiving abiraterone and docetaxel vs patients receiving docetaxel but not abiraterone included liver toxicities (6% vs 0%, respectively) and hypertension (12% vs 8%).

Dr Zhang on risk stratification and treatment selection in mCSPC

Risk factors highlighted by Jingsong Zhang, MD, PhD, an assistant professor of oncology and internal medicine at the University of South Florida College of Medicine, Tampa, include site of metastases, PSA response, and metastases burden.

Using your phone’s camera, hover over the QR code and scan to read more.
Postprostatectomy radiation dose and timing affect quality of life

Postprostatectomy radiation dose and timing affect quality of life

The oncologic benefits of radiotherapy (RT) dose escalation for treating primary prostate cancer have been well established over the last 20 years. However, the optimal dose and timing of post radical prostatectomy (RP) RT have remained controversial. To address these questions, 2 recent studies examined the outcomes of early vs delayed RT and of RT dose escalation, on health-related quality of life (HRQOL) and functional outcomes.

Ghadjar et al1 conducted a prospective, randomized phase 3 trial with the aim to demonstrate the superiority of dose-escalated sRT (study group) over the standard-dose sRT (control group) in terms of biochemical (PSA) progression. Men in the control group received 64 Gy and those in the study group received 70 Gy, with 175 patients in each group. The median prostate-specific antigen (PSA) at randomization was 0.3 ng/mL and median follow-up was 6.2 years.

The median PSA progression-free survival was similar in the control and study arms, at 8.2 years and 7.6 years, respectively (log-rank P = .4). Other outcomes such as clinical progression, time to hormonal treatment, and overall survival also did not differ between the 2 arms.

Similar rates of late grade 2 and 3 genitourinary (GU) toxicity were observed between the 2 arms. However, late grade 2 gastrointestinal (GI) toxicity was observed at a higher rate in the dose-escalation group: 20% vs 7.3% (P = .009). Grade 3 erectile dysfunction did not differ significantly between the 2 arms (27% vs 30%; P: NS).

DOES EARLY SALVAGE RT AFFECT QUALITY OF LIFE?
To assess the effect of timing of post-RP RT, Westhofen et al2 conducted a propensity score-matched retrospective analysis of a large contemporary cohort. Men were divided in 2 study groups: those receiving early RT (eRT; within 6 months after RP) vs those receiving deferred RT (dRT).

The investigators evaluated HRQOL using the validated EORTC QLQ-C30 questionnaire, as well as on functional outcomes following RT.

Patient-reported outcomes were obtained through mailed-in questionnaires to 1599 eligible patients at 6 weeks, and 12, 24, 36, and 48 months after surgery. The inclusion criteria for post-RP RT included stage pT3 or higher or grade group 4 or higher, or positive surgical margins. A total of 307 patients received eRT and 1292 patients were treated with dRT.

In the eRT group, all 307 patients received RT within 6 months, whereas in the dRT group, 27.0% received dRT by 12 months after RP, 44.4% at 24 months, and 51.4% at 48 months. Median PSA prior to RT was 0.13 ng/mL in the eRT group and 0.18 ng/mL in the dRT group.

Erectile function scores were significantly better in the dRT group at 12 and 24 months, but were similar at 36 and 48 months. Similarly, the mean incontinence scores were significantly better for the dRT group at 12 and 24 months. Good general HRQOL was reported by 35.5% (eRT) vs 52.7% (dRT) after 12 months and 37.3% (eRT) vs 45.8% (dRT) after 24 months (P > .02).

Multivariate regression analysis identified dRT as an independent predictor of good general HRQOL. It is apparent from the results of these 2 studies that neither the higher-dose RT nor eRT after RP provide sufficient oncological benefits to justify the adverse impact on functional outcomes and HRQOL. Dose-intensified sRT was not superior to conventional-dose sRT, but it was associated with higher rates of late grade 2 GI toxicity.

A limitation of the higher-dose sRT study is the relatively small proportion of patients with Gleason score of 8 or higher and/or pT3b disease. To improve the outcomes for patients at risk of progression after RP, improved risk stratification is needed to identify patients who are potentially more likely to benefit from intensified RT dose or schedule. The anticipated wider availability of prostate-specific membrane antigen (PSMA) PET scans will improve risk stratification and patient selection for postoperative RT by rendering visible the disease foci that are currently invisible on conventional imaging. However, the impact of the inevitable stage-shift related to PSMA scans and any potential oncologic and functional benefits will remain unclear for years to come.

At present, an initial period of observation, and deferred RT, appears to be a safe and effective approach for most post-RP patients with high-risk pathology features to avoid the adverse effects on HRQOL, without compromising cancer control.

REFERENCES
What have been the biggest changes in the way you treat prostate cancer?

In terms of localized disease, it’s not that we have different treatment options but that we do those things differently. For example, we still do surgery, but now we do it robotically. We do brachytherapy; we’ve just changed how we do it.

With active surveillance, patients now are aware of why we’re doing it. They understand the rationale, so they are on board. They don’t feel that urge to cut out any sign of cancer immediately because they know we can keep track of the cancer’s progression without endangering them. We don’t have to convince them, as we used to do, that watchful waiting is a viable alternative. That makes it a lot easier to put men on active surveillance.

As for advanced disease, medical oncologists now handle a lot of that, but we are still involved too.

We’re not starting androgen deprivation as early. We don’t necessarily start androgen deprivation until symptoms start to occur, unless there is a major event or huge spike in PSA [prostate-specific antigen] level. When we do treat, we aren’t starting hormones like LHRH [luteinizing hormone-releasing hormone] agonist and receptor antagonists until later. That’s something patients obviously prefer.

It has definitely made a difference in the patients’ quality of life. Patients can go on surveillance for years before we start androgen suppression.”

Stephen Strup, MD
Lexington, Kentucky

It seems to be working. Some patients on observation have fallen out and needed treatment because something changed, their [prostate-specific antigen] or rebiopsies. Multiparametric MRIs have changed the way we manage these men.

My partner has found several people on observation that due to multiparametric MRI, followed by fusion biopsy, had more aggressive tumors. We considered them reasonable candidates for observation at the time, but things changed. They have more aggressive disease, more lesions.

A lot of 77- to 79-year-old men have numerous high-grade tumors. Otherwise, they’re healthy and happy, so what do you offer them? Operating isn’t the first choice.

Radiation is an option; even kinder is cryoablation. It’s actually well tolerated and highly underused. It can control the disease. These guys are alive well into their 80s, when they might not have been.

Alternatively, we’re also finding low-grade tumors we’re comfortable watching. Confirmatory tests, like Prolaris, can indicate a patient is safe to observe, with good data behind them.

That’s been a big change. Multiparametric MRIs and fusion biopsies have become standard. We used to repeat biopsies every 1½ to 2 years to monitor people on observation. I’ll tell you, talking a patient into a second or third biopsy, he says, ‘Forget it. I’m good!’ With MRI, we can actually see lesions—if there are none, we leave it alone. If they’re high risk, we do accurate, targeted biopsies, which patients appreciate. That’s changed things a lot.”

Clifford Johnson, MD
Hendersonville, North Carolina

“With some low-grade tumors, sophisticated tests, like Prolaris, can identify specific markers in specific tumors to determine, based on molecular markers, if patients are acceptable candidates for observation.”

Clifford Johnson, MD

“New and different drugs indicated at different points in the treatment cycle have been the biggest change. Enzalutamide [Xtandi], for example, was approved, initially for a very specific indication, but indications keep broadening, so we keep being able to use those drugs earlier in the advanced prostate cancer process. So I think medicines are the biggest things that are different.

Another thing that’s changed in my practice is the Axumin PET scan and being able to localize the recurrence much more accurately. It’s much more sensitive in identifying the recurrence in the bone scan than the traditional CT.

That made a huge leap in the past 10 years. It’s the fastest change in that part of what we do. I don’t think there’s any more research, any more exciting things going on than in prostate cancer or in urology overall right now.

It’s made a definite difference in the results we’re getting. It’s well established in these drug studies that people are living much longer with the progression of their cancer and they’re living with fewer symptoms from the cancer, so it’s improving quality of life and survival.

The foundation of care is still the hormone shots we’ve been doing for decades, and adverse effects are the same. These medications are added on top of injections, so a lot of time you have similar adverse effects, but patients are getting better control of their tumor burden and feeling better overall, and they’re healthier.”

Robbie Hurtt, MD
Conway, Arkansas
Previsit BPH decision aid provides valuable insights and optimizes care

Tool reliably identifies patients referred without ever trying medical therapy

A study investigating the impact of an online patient decision aid on management decisions for benign prostatic hyperplasia (BPH) among men scheduled for a urology consultation at the University of California Los Angeles (UCLA) Medical Center demonstrated feasibility of the previsit “virtual care” approach as a method for providing patient education, assessing patient goals, and preparing men for a shared decision-making visit with their physician.

The research also showed that the decision aid was well received by patients as both satisfaction and willingness to recommend their physician were very high. In addition, the decision aid was found to reliably identify patients who had been referred to a urologist by their primary care provider without ever having tried medical therapy for BPH. Through responses to items designed to characterize patients’ values and goals for clinical risks and benefits, the decision aid also identified men for whom medication therapy would be avoidably referred to a urologist by their primary care provider without ever having tried medical therapy for BPH. The project and its findings were reported in a recently published article.1 Saigal and colleagues have done similar work investigating the impact of a decision aid in men with prostate cancer and presented the findings at the 2021 American Urological Association Annual Meeting. •

“The larger message from this study is that the future of urology practice will involve leveraging software-based approaches, including decision aids, to improve our ability to manage our large practices in a variety of ways.”

CHRISTOPHER S. SAIGAL, MD, MPH

English-speaking men aged 18 to 85 years, who were scheduled for a new patient visit with a urologist because of BPH, were invited to complete the decision aid prior to their appointment. A total of 155 patients with a mean age of approximately 66 years participated in the project.

After their clinic visit, men were asked via telephone survey whether their preferred treatment was with pills/oral medication, procedures (including anesthesia and office based), other, or if they were unsure. Only 10 men (6%) self-reported a preference for a BPH procedure, and that rate was significantly lower than in a “usual care” comparator group who did not complete the decision aid.

Analysis of the responses on the completed decision aids also identified 2 distinct groups of men based on their preferences for clinical outcomes, such as “importance of symptom improvement” and “importance of avoiding retrograde ejaculation.” Relative to 1 group, the other group of men placed greater emphasis on avoiding sexual dysfunction, dizziness/weakness, and retrograde ejaculation, and more importance on BPH symptom improvement.

“Most urologists realize that the constellation of BPH outcomes represents a series of ‘trade-offs’ for patients. We were able to cluster the trade-offs and identify a group that would seem more likely to have a ‘preference match’ for surgery ahead of time,” Saigal said.

“This latter group was small, including only 5 men, but 4 of the 5 men with this preference profile had identified a procedure as their preferred treatment, whereas all men who chose medication fell into the other preference profile group. Thus, our study shows that segmentation of patients by preference profile is possible and represents a possible avenue to establish treatment appropriateness.”

Saigal and colleagues have done similar work investigating the impact of a decision aid in men with prostate cancer and presented the findings at the 2021 American Urological Association Annual Meeting.

REFERENCE

transient ischemic attack within 6 months of randomization were an ischemic cardiovascular event. Patients with history of unstable ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Grade 3 16% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median OS: NR vs 52.2 months; HR=0.65; 95% CI: 0.51, 0.89; P=0.0053.1

INDICATIONS
ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
• Metastatic castration-sensitive prostate cancer (mCSPC)
• Non-metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS
Cerebrovascular and Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA®, and 3% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, cerebrovascular events 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 two randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA®. Advise patients of the risk of developing a seizure while receiving ERLEADA® and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to 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.

Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 76% (0.1%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%).

Laboratory Abnormalities — All Grades (Grade 3-4)
• Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%).

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.

TITAN final analysis data are not currently reported in the ERLEADA® Prescribing Information. The following TITAN primary analysis results are included in the ERLEADA® Prescribing Information:
Median OS: NE vs NE; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053.1
START EARLY WITH ERLEADA®

TO PUSH BACK ON PROGRESSION

UPDATED RESULTS: OVERALL SURVIVAL FOR TITAN FINAL ANALYSIS

TITAN study*: FIRST AND ONLY therapy to achieve a 35% reduction in the risk of death in a registration trial in mCSPC (ERLEADA® + ADT vs placebo + ADT; median OS: NR vs 52.2 months; HR=0.65; 95% CI: 0.53, 0.79; P<0.0001).†

SPARTAN study*: FIRST AND ONLY AR inhibitor to improve median MFS by 2 YEARS in nmCRPC (ERLEADA® + ADT vs placebo + ADT 40.5 months vs 16.3 months; HR=0.28; 95% CI: 0.23, 0.35; P<0.0001).‡

SPARTAN study*: FIRST AND ONLY therapy to improve median OS by 14 MONTHS in nmCRPC (ERLEADA® + ADT vs placebo + ADT 73.9 months [6.2 years] vs 59.9 months [5 years]; HR=0.78; 95% CI: 0.64, 0.96; P=0.0169).†

Rash — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 26% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%). The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with topical antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo 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 CYP2C8 or CYP3A4 inhibitor is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of CYP3A4, CYP2C19, or CYP2C9 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 inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1). Concomitant use of ERLEADA® with medications that are substrates of P-gp, vBCRP, 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.

ADT = androgen deprivation therapy; NP = prostate-specific antigen; rPFS = radiographic progression-free survival; SARPACN = Selective Prostate Androgen Receptor Targeting with Abiraterone; TITAN = Targeted Investigational Treatment Analysis of Novel Androgens.

Study Design: TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (N=163). Patients had newly diagnosed mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. Patients with visceral (i.e., liver or lung) metastases as the only sites of metastases were excluded. Patients were randomly assigned 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchidectomy. The primary endpoints were overall survival and rPFS. All patients who enrolled in the TITAN study started ADT for mCSPC 6 months prior to randomization.

Study Design: SPARTAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (N=1,052). Patients had a PSA doubling time ≤10 months and serum testosterone levels <50 ng/dL. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review. All patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. Patients were randomly assigned 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the SPARTAN trial received a concomitant GnRH analog or had a bilateral orchidectomy. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review confirmed distant metastases, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcations, or death due to any cause, whichever occurred first.

Secondary endpoints were time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic or chemohormone therapy.

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References:
ADVERSE REACTIONS

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

- Cerebrovascular and Ischemic Cardiovascular Events [see Warnings and Precautions].
- Fractures [see Warnings and Precautions].
- Falls [see Warnings and Precautions].
- Seizure [see Warnings and Precautions].

Clinical Trial Experience

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

The most common adverse reactions (≥ 10%) that occurred more frequently in the ERLEADA-treated patients were:

- Headache
- Fatigue
- Myalgia
- Seizure

More frequent than placebo (≥ 1% on ERLEADA and <2% on placebo) were:

- Dyspepsia
- Anorexia
- Nausea
- Diarrhea
- Abdominal pain
- Constipation

Table 1 shows adverse reactions occurring in ≥10% on the ERLEADA arm in the combined data of the two randomized placebo-controlled clinical trials with TITAN and SPARTAN. In the TITAN study, patients experienced a seizure. In the SPARTAN study, seizures occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with metastatic castration-resistant prostate cancer (mCSPC), fractures occurred in 8% of patients treated with ERLEADA and 6% of patients treated with placebo. Grade 3 or 4 fractures occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo with a median time of onset of fracture of 31 days (range: 20 to 153 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

In a randomized study with metastatic castration-sensitive prostate cancer, fractures occurred in 5% of patients treated with ERLEADA and 2% of patients treated with placebo. The median time to onset of fracture was 49 days (range: 20 to 153 days) for patients treated with ERLEADA.

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 [mCSPC])

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
<th>Between Arm Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
<td>19.6</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia*</td>
<td>17</td>
<td>3</td>
<td>14</td>
</tr>
</tbody>
</table>

*Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3.

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with ERLEADA included diarrhea (6% versus 6% on placebo), muscle spasm (3% versus 2% on placebo), dysgeusia (3% versus 1% on placebo), and hypothyroidism (4% versus 1% on placebo).

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 (mCSPC))

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
<th>Between Arm Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
<td>19.6</td>
</tr>
</tbody>
</table>

*Does not reflect fasting values
ERLEADA® (apalutamide) tablets

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchectomy. The median duration of exposure was 33 months (range: 0.1 to 78 months) in patients who received ERLEADA and 11 months (range: 0.1 to 37 months) in patients who received placebo.

Twenty-four patients (3%) who were treated with ERLEADA died from adverse reactions. The reasons for death with ≥2 patients included infection (n=7), myocardial infarction (n=3), cerebrovascular event (n=2), and unknown reason (n=3). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematura. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (13%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>All Grades</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>0.1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Fracture</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Hot flush</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

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 (nmCRPC))

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>76</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>67</td>
<td>2</td>
</tr>
</tbody>
</table>

Notes: 
- a Does not reflect fasting values
- Includes fatigue and asthenia
- Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3
- Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular
- Includes appetite disorder, decreased appetite, early satiety, and hypophagia
- Includes peripheral edema, generalized edema, edema, edema genital, penile edema, peripheral swelling, scrotal edema, lymphedema, swelling, and localized edema
- Additional clinically significant adverse reactions occurring in ≥2% or more of patients treated with ERLEADA included hypothyroidism (<0.01% versus 0% on placebo), pruritus (<0.01% versus 2% on placebo), and heart failure (<0.01% versus 1% on placebo).

Additional clinically significant adverse reactions occurring in ≥2% or more of patients treated with ERLEADA included hypothyroidism (0% versus 2% on placebo), pruritus (<0.01% versus 2% on placebo), and heart failure (<0.01% versus 1% on placebo).
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P-gp, BCRP or OATP1B1 Substrates
Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/ OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued [see Clinical Pharmacology (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Clinical Pharmacology (12.1) in Full Prescribing Information]. There are no available data on ERLEADA use in pregnant women to inform a drug-associated risk. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥2 times the human clinical exposure (AUC) at the recommended dose [see Data].

Data
Animal Data
In a pilot embryo-fetal developmental toxicity study in rats, apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout and after the period of organogenesis (gestational days 6-20). Findings included embryo-fetal lethality (resorptions) at doses >50 mg/kg/day, decreased fetal anogenital distance, misshapen pituitary gland, and skeletal variations (unossified phalanges, supernumerary short thoracolumbar ribs) and small, incomplete ossification, and/or misshapen hyoid bone) at 25 mg/kg/day. A dose of 100 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 2, 4 and 6 times, respectively, the AUC in patients.

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 1,327 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 medical attention if any symptoms suggestive of a cardiovascular or a cerebrovascular event occur [see Warnings and Precautions].

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

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

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

Dosage and Administration
• Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.
• Instruct patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.
• Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see Dosage and Administration (2.1) in Full Prescribing Information].
• Instruct patients who have difficulty swallowing tablets whole to mix the recommended dose of ERLEADA tablets with applesauce. Do not crush tablets [see Dosage and Administration (2.3) 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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Janssen Ortho LLC
Gurabo, PR 00778

Manufactured for:
Janssen Products, LP
Horsham, PA 19044

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Urologists are rapidly adopting prostatic urethral lift in treating BPH

Modality is associated with favorable readmission rates but a higher risk of retreatment

LISETTE HILTON
Correspondent, Urology Times®

Urologists are embracing prostatic urethral lift (UroLift®) as a minimally invasive treatment option for treating benign prostatic enlargement and lower urinary tract symptoms. Compared with transurethral resection of the prostate (TURP) and photo-vaporization of the prostate, prostatic urethral lift has favorable readmission rates but a higher risk of retreatment, according to a study published in the Journal of Urology.1

Investigators analyzed a database of men in the United States who were treated with endoscopic procedures for benign prostate enlargement and lower urinary tract symptoms between 2000 and 2018.

“Urologists tend to be early adopters of new technology. That said, how fast adoption of prostatic urethral lift has been in the urologic community was really impressive.”

JONATHAN SHOAG, MD

More than half of the 175,150 men were treated with TURP; nearly 27% with photo-vaporization of the prostate; and more than 10%, with prostatic urethral lift. Although only 10.8% of men had prostatic urethral lift to treat their symptoms in 2018, use of the treatment was up from less than 0.4% in 2014. TURP use was stable at 50.2% to 52.6% during the same period, whereas prostate photo-vaporization use fell from 36.5% in 2014 to 25.6% in 2018.

Urologists’ rapid adoption of the prostatic urethral lift surprised the study investigators. “Urologists tend to be early adopters of new technology. That said, how fast adoption of prostatic urethral lift has been in the urologic community was really impressive,” said study investigator Jonathan Shoag, MD, assistant professor, Urology Institute at University Hospitals Cleveland Medical Center, Case Western Reserve University, in Cleveland, Ohio.

TURP has well-established safety and efficacy profiles, and laser photo-vaporization of the prostate has been widely used to treat benign prostatic enlargement and lower urinary tract symptoms. But adverse consequences associated with these procedures, including retrograde ejaculation, bleeding, need for general or regional anesthesia, and the potential for an overnight hospital stay, led to growing interest in less invasive therapy options, including the FDA-approved UroLift, according to the investigators.

Limiting their study to the 3 most common benign prostatic enlargement treatments, the investigators found that that overall readmission rates were 2.09% at 30 days and 5.81% at 90 days.

Readmission rates at 30 days were 2.2% for TURP, 2.1% for prostate photo-vaporization, and 1.2% for prostatic urethral lift. The 90-day comparison of readmissions was 5.7% for TURP, 6.0% for prostate photo-vaporization, and 2.9% for prostatic urethral lift.

“The principal concern regarding the efficacy for [prostatic urethral lift] is treatment durability,” the investigators wrote.

They found the retreatment rate overall was 3%. But patients treated with prostatic urethral lift were almost twice as likely as those treated with TURP to be re-treated by the 2-year follow-up. Retreatment at the 2-year follow-up was 5.2% for prostatic urethral lift, 3.2% for prostate photo-vaporization, and 2.9% post TURP.

“This reinforces that counseling men appropriately on prostatic urethral lift is important. It can minimize some of the [adverse] effects of other treatments, like ejaculatory dysfunction, and decrease the need for catheterization. That said, its durability is probably lower, and it does have higher retreatment rates,” said investigator Irina Jaeger, MD, assistant professor, Urology Institute at University Hospitals Cleveland Medical Center, Case Western Reserve University.

“[The prostatic urethral lift] is a great option for patients that want to get back to normal life quickly and preserve ejaculatory function. We’ve seen that [adverse] effects tend to be minimal.”

IRINA JAEGER, MD

Jaeger offers prostatic urethral lift to appropriate patients. “It is a great option for patients that want to get back to normal life quickly and preserve ejaculatory function. We’ve seen that [adverse] effects tend to be minimal,” she said.

Prostatic urethral lift, however, is not appropriate in all benign prostatic enlargement cases, and patients need to be counseled appropriately, Jaeger said.

REFERENCE
Proinflammatory diet is associated with testosterone deficiency

Study findings suggest diet may play an important role in male reproductive health

LISETTE HILTON
Correspondent, Urology Times®

Men who consume diets high in proinflammatory foods appear to be at higher risk of testosterone deficiency. This suggests diet may play an important role in male reproductive health, according to a study published in the *Journal of Urology.*

Proinflammatory diets are high in saturated fats and refined carbohydrates and low in fruits and vegetables.

The Dietary Inflammatory Index was developed as a standardized scoring system to evaluate the effects of diet on inflammation, according to an email to *Urology Times®* from study authors Chichen Zhang, MD, and Shi Qiu, MD, of the Department of Urology, Institute of Urology and National Clinical Research Center for Geriatrics, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China.

“Proinflammatory status of individual dietary intakes has been shown to link high Dietary Inflammatory Index scores with adverse health outcomes, such as general obesity, cancer, cardiovascular disease,” the authors wrote. “Although several studies had studied the association between dietary patterns and sex hormones, literature about the relationship among the inflammatory potential of diet, testosterone level, and testosterone deficiency is scarce.”

Chinese investigators studied the potential impact of the Dietary Inflammatory Index on testosterone deficiency among US males with data from the 2013-2014 and 2015-2016 National Health and Nutrition Examination Survey (NHANES). They analyzed data from 4151 men 20 years or older who had provided a 24-hour dietary intake history and underwent serum sex hormone testing.

The investigators calculated the Dietary Inflammatory Index using 27 of the 45 food parameters from the NHANES database. They labeled each included food parameter with an inflammatory effect score. Higher numerical Dietary Inflammatory Index scores indicate a greater proinflammatory state of the diet, whereas lower numerical scores are consistent with anti-inflammatory diets.

Twenty of the 27 food parameters are anti-inflammatory, including alcohol, beta-carotene, caffeine, fiber, folic acid, magnesium, iron, riboflavin, niacin, omega-3 and omega-6 polyunsaturated fatty acids, monounsaturated fatty acid, polyunsaturated fatty acid, selenium, and thiamin, as well as vitamins A, B6, C, D, and E. The other 7 food parameters are proinflammatory, including vitamin B12, carbohydrate, cholesterol, fat, iron, protein, and saturated fat acid, according to Zhang and Qiu.

“We found that men who eat a proinflammatory diet, particularly those who are obese, have a higher risk of testosterone deficiency,” Zhang and Qiu wrote. “Our findings suggested that a more anti-inflammatory diet could be a feasible method to reduce the accumulated inflammatory burden; hence, leading to an increased testosterone level.”

The investigators found the Dietary Inflammatory Index ranged from -5.05, or the most anti-inflammatory, to the most proinflammatory +5.48, with an average index of 0.71. Average total testosterone for men in the study was 419.80 ng/dL. Testosterone was lower among men in the highest tertile for proinflammatory consumption at an average 422.71 ng/dL compared with an average 410.42 ng/dL for men in the lowest tertile.

And overall, men in the most proinflammatory Dietary Inflammatory Index tertile 3 had a 30% higher testosterone deficiency risk compared with men in tertile 1.

The authors suggest urologists should talk with male patients at reproductive ages about diet, offering tips such as limiting saturated fat and carbohydrates, both of which have a positive inflammatory effect score. Men should eat more fresh fruit and vegetables and less red meat.

Ranjith Ramasamy, MD, associate professor and director of the Reproductive Urology Program at the University of Miami Miller School of Medicine, Florida, wrote in an email to *Urology Times®* that this study reaffirms his thinking that men should be encouraged to reduce the amounts of proinflammatory foods in their diets. But overall, it remains difficult to draw any conclusions about whether making these dietary changes should be expected to improve reproductive health specifically, he said.

“We don’t yet have a lot of evidence to tell us how much of a role a proinflammatory diet directly plays in male reproductive health, but we do know that metabolic disorders that can be attributed to inflammatory diets, such as obesity or diabetes, negatively impact male fertility,” said Ramasamy, who was not involved with the research.

The use of 24-hour consumption is one of the main limitations of this study, as it cannot encompass the entirety of a participant’s diet, according to Ramasamy.

“As baseline testosterone levels are likely to change over the course of weeks to months, dietary data from a single day is unlikely to be the best method to evaluate this association,” Ramasamy said.

For now, Ramasamy said he counsels patients that the same kinds of diets that would be recommended to prevent obesity, high cholesterol, diabetes, or high blood pressure also help with overall reproductive health.

“That means reducing red meat, incorporating something green with every meal, opting for the grill over the deep fryer, cutting out soda (and alcohol), and saving sweets for special occasions,” Ramasamy said.

REFERENCE
Now recruiting for the following studies:

**Sabizabulin**

**PHASE 3 VERACITY CLINICAL STUDY:**
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Trilogy, ShockPulse-SE lithotripters demonstrate efficacy

Fewer device malfunctions are observed with Trilogy device, data indicate.

**JANELLE HART**
Assistant Editor, Urology Times®

Trilogy and ShockPulse-SE lithotripters used in percutaneous nephrolithotomy (PCNL) are highly efficient and serve as notable advancements in stone-removal technologies, according to recent study findings. However, fewer device malfunctions were reported when the Trilogy device was used.1

In 2017, Olympus America introduced the ShockPulse-SE as a unique lithotripter that produces 300 Hz of ballistic force. The following year, the ultrasonic-ballistic, single-probe lithotripter, Trilogy, was invented by EMS and Boston Scientific. Trilogy has not been measured against its competitors, so investigators study tested Trilogy’s efficacy against ShockPulse-SE.

The prospective multi-institutional randomized control trial was conducted over the course of 16 months. One hundred standard PCNLs were performed using either a Trilogy (n = 51) or ShockPulse-SE (n = 49) lithotripter on patients who were 18 years or older with stones greater than or equal to 20 mm in diameter or lower pole stones greater than 15 mm. All procedures were performed in 3 high-volume tertiary stone institutions where ShockPulse-SE was the favored lithotripter for greater than 24 months.

Between February 2019 and June 2020, the investigators compared the stone clearance time, stone clearance rate, device malfunction, stone-free rates, and complications between the Trilogy and ShockPulse-SE lithotripters. Assessments were provided via immediate postoperative REDCap survey by 7 primary surgeons, all of whom were required to perform at least 10 PCNLs with both lithotripters to ensure proficiency.

Quantitative Stone Analysis Software determined the mean stone value at 4.18 ± 4.79 and 3.86 ± 3.43 cm³ for the Trilogy and ShockPulse-SE groups, respectively. Stone clearance rates were found to be 101.3 ± 92.5 and 83.7 ± 69.3 mm²/min (1.22 ± 1.67 and 0.77 ± 0.68 mm²/min) for Trilogy and ShockPulse-SE (P = 0.0542), respectively.

In an interview with *Urology Times*, lead study investigator Amy E. Krambeck, MD, discussed how the study results would affect her clinical practice. “For harder, more aggressive stones, I’m more likely to use the Trilogy based on the results of the study,” said Krambeck, a professor of urology at Northwestern University Feinberg School of Medicine in Chicago, Illinois. “If I have a softer, easier stone, I prefer the lightness of the ShockPulse. So I’m probably going to use the ShockPulse for something that doesn’t require all the power that’s necessary behind the Trilogy.”

At a 6- to 12-week follow-up rate, no complications were reported as a direct result of the lithotripters. Compared with Trilogy, however, the investigators observed higher rates of secondary procedures for residual stones after ShockPulse-SE lithotripsy (17.7% vs 34.7%, respectively; *P* = 0.005).

“Overall surgeon satisfaction with both lithotripters was high (8.69 ± 0.87 and 8.42 ± 1.77; *P* = 0.340; Trilogy vs ShockPulse-SE),” the investigators wrote. “However, the Trilogy probe has previously been criticized as being heavy, leading to decreased surgeon satisfaction.”

**REFERENCE**


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**For harder, more aggressive stones, I’m more likely to use the Trilogy based on the results of the study. If I have a softer, easier stone, I prefer the lightness of the ShockPulse.**

**AMY E. KRAMBECK, MD**

In addition, a multivariate analysis estimated the total OR times at 104.4 ± 48.2 minutes and 121.1 ± 59.2 minutes for Trilogy and ShockPulse-SE (P = 0.126), respectively. Also measured were rates of secondary procedures (17.65% vs 40.81%; *P* = 0.005), and device malfunctions (1.96% vs 34.69%; *P* < 0.001). There was no difference in final stone-free rates among the lithotripters.

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**Krambeck discusses study comparing lithotripters for stone removal**

In this video, Amy E. Krambeck, MD, discusses her recent trial comparing the efficacy of Trilogy and ShockPulse-SE lithotripters used in percutaneous nephrolithotomy.

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**Using your phone’s camera, hover over the QR code and scan to watch the video.**
**Emerging Treatment Options for the Management of Metastatic Castration-Resistant Prostate Cancer**

**PROSTATE CANCER** is the most common solid organ malignancy diagnosed in men in the United States, accounting for 13% of new cancer cases annually. Although localized disease is associated with high survival rates, advanced or metastatic disease has proved more challenging to treat, with 5-year survival rates found to be approximately 30%.

Metastatic castration-resistant prostate cancer (mCRPC) is responsible for the majority of prostate cancer–related deaths. In recent years, newer imaging technologies have yielded additional insights about mortality risks, including the number and location of metastatic sites, whereas novel therapeutic agents have provided more options for patients.

Androgen deprivation therapy (ADT) with androgen receptor (AR)–pathway blockers are the commonly used treatments for patients with metastatic or recurrent disease and are usually associated with good initial response. However, many patients develop resistance and relapse even with castrate testosterone levels. For these patients, more aggressive treatment is needed, said Leonard Gomella, MD, the Bernard W Godwin Jr Professor of Prostate Cancer, chairman of the Department of Urology, clinical director of the Jefferson Kimmel Cancer Network, and senior director for clinical affairs at the Jefferson Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, in an interview with Urology Times. “When a man initially presents with metastatic disease or fails initial systemic therapy, our approach has to be different. We are more concerned that their disease is more aggressive,” he said.

Newer imaging technologies may affect some men with nonmetastatic CRPC (M0) based on standard imaging, according to Gomella. “A big unknown right now is in the setting of stage M0 CRPC disease and the impact of the PSMA [prostate-specific membrane antigen] scan,” Gomella observed. “Will the PSMA scan’s widespread use suddenly reduce the number of men considered to be M0 and reclassify them as stage M1? That remains to be seen and is something we’ll be watching.”

Another exciting technology that is having an immediate impact in prostate cancer management is liquid biopsy, which has become a more widely available testing option and allows identification of specific genetic alterations in tumors and evaluation of a patient’s germline, according to Gomella. “You don’t need to have a tissue biopsy of a metastatic lesion. Liquid biopsy is becoming more common [for evaluating] treatment options for metastatic disease,” he said. Liquid biopsies are not yet in broad use across the urologic specialty, but Gomella believes their convenience and reliability will increase their adoption. “Simply doing a blood draw vs biopsying a lymph node or a metastatic lesion is a much more appealing approach,” he observed. Additionally, he noted, “Having been involved with the first report using molecular techniques to detect prostate cancer cells in the blood in 1992, I am a big believer in the future of this technology in daily patient care.”

**CURRENT TREATMENT APPROACHES**

For patients with newly diagnosed hormone-sensitive, metastatic prostate cancer, ADT (luteinizing hormone–releasing hormone [LHRH] agonists or antagonists or surgical castration) combined with apalutamide, abiraterone acetate plus prednisone, enzalutamide, or docetaxel are recommended options in the 2021 treatment guidelines set forth by the American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology. After a patient has progressed on any of these initial ADT combination approaches and has developed CRPC (as defined by castrate level of testosterone and rising prostate-specific antigen [PSA] levels), next-generation agents that target the AR are the next option to consider.

For patients with negative standard imaging (CT or bone scan) and staging as M0 nonmetastatic CRPC, Gomella noted that currently approved drugs are apalutamide, darolutamide, and enzalutamide. These medications should be considered in this group of men at high risk for developing metastatic disease—for example, in those with a PSA doubling time of at least 10 months. If the patient has evidence of mCRPC, however, “continuing ADT is the mainstay, but many agents are now available as additional first line therapy, such as abiraterone, enzalutamide, chemotherapy, radionuclide therapy with radium-223, or immunotherapy using sipuleucel-T,” explained Gomella.

According to Gomella, taxane-based chemotherapy such as docetaxel, despite being beneficial in certain patients, may be underused because of the feared impact of toxicities by the patient. “When you say chemotherapy to any patient [diagnosed with] with cancer, it creates a negative impression [and is associated with things like] hair loss, nausea, and vomiting. That’s sad, because chemotherapy is administered much more safely than in the past,” said Gomella. “Today, we better understand which patients are good candidates for chemotherapy. When you have widespread, castrate-resistant metastatic disease, chemotherapy is often the best way to go based on clinical trial data,” noted Gomella. “However, you need to consider many parameters, such as patient history and laboratory values; [there are] many more considerations with chemotherapy than with some of the other agents.”
EMERGING AND LATER-LINE OPTIONS

Given the possibility of progressive disease in patients with mCRPC treated with initial first-line therapy, selection of therapeutic agents and the best sequence of agents remain unclear. Baseline resistance, acquired resistance, and cross-resistance have all been observed with the second-line use of second-generation antiandrogens such as abiraterone and enzalutamide in this setting. Along with continuing ADT and reviewing the role of chemotherapy, clinicians should consider other treatment options, according to Gomella. “We tend to focus a lot on the AR-targeting agents or chemotherapy. We have immunotherapy; radionuclide radium-223 infusions; and, over the last year, a new class of drugs, the poly (ADP-ribose) polymerase (PARP) inhibitors. This is in addition to an impressive number of investigational agents in the US and abroad,” Gomella explained. “This is an area of tremendous interest, because the concept of curing prostate cancer when it’s metastatic is still not with us. Many other cancers can be definitively ‘cured’ in advanced stages, but we are not there yet with prostate cancer, and that’s why we are seeing a continual interest in developing new agents.”

As noted, a major challenge with these new and emerging options in later lines of therapy is knowing which agent/regimen would be most beneficial for a particular patient. “One study may say that agent A may be better to use than agent B, as second line,” Gomella explained, “but these are often relatively small studies, and there are few absolutes. Most of the agents used in the first-line setting could be used again in the salvage second-line or third-line settings.”

PARP inhibitors. In 2020, olaparib (Lybraprar) was approved for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene–mutated mCRPC. Around the same time, rucaparib was granted accelerated approval for patients with a deleterious BRCA1 mutation (germline and/or somatic)–associated mCRPC who have been treated with AR-directed therapy and a taxane-based chemotherapy. To gauge optimal response to PARP inhibitors, genetic testing is recommended. According to Gomella, some clinicians are using these agents as a salvage therapy without appropriate genetic information. “The more we can define the specific patient who will have the best response, the more likely an agent will have widespread use,” he said.

Immunotherapy. Immunotherapy has demonstrated great efficacy for a variety of oncologic diseases, but, when considering its use for patients diagnosed with mCRPC, oncologists should evaluate specific histological and molecular biomarkers to predict potential response before treatment decision making. The first immunotherapy approved by the FDA for use in prostate cancer was sipuleucel-T (Provenge) in 2010; it is indicated for the treatment of asymptomatic or minimally symptomatic mCRPC. It is a good option for mCRPC patients with minimal disease and relatively low levels of [PSA],” stated Gomella. However, for patients diagnosed with disease that is more symptomatic—for instance weight loss and narcotic-dependent bone pain—other treatments are more suitable.

“It is critical for providers to look at each patient as a unique individual and decide which agent or which site of service might be best for them.”

— Leonard Gomella, MD

Pembrolizumab is another relatively new immunotherapy option for most solid tumors. It has efficacy in heavily pretreated patients who have metastatic disease harboring microsatellite instability-high (MSH-high) or mismatchrepair–deficient(MMRd) solid tumors, including prostate cancer. Notably, however, few patients who have with prostate cancer were included in the initial studies leading to FDA approval.

There is strong interest in using immunotherapy in combination with other active agents. Given the study of pembrolizumab as a component of combination therapy in the KEYNOTE-365 trial, Gomella noted that researchers have interest in identifying whether pembrolizumab may be effective in combination with abiraterone acetate (Zytiga) and enzalutamide (Xtandi).

Another immunotherapy regimen that may hold promise for patients with mCRPC is nivolumab (Opdivo) plus ipilimumab (Yervoy). The phase 2 CheckMate 650 trial evaluating nivolumab plus ipilimumab combination therapy vs ipilimumab or cabazitaxel (Jevtana) monotherapy showed positive findings, with objective response rates (ORRs) of 25% and 10% in prechemotherapy and postchemotherapy cohorts, respectively. These results suggest that larger trials would be useful and that use of this regimen in mCRPC could be expanded.

Cytoskeleton disruption. Another emerging modality of mCRPC treatment is cytoskeletal disruptors. The oral agent sabizabulin has shown enhanced antitumor activity by acting on microtubules; it inhibits division of cancer cells by disrupting AR transport to the nuclei. In combined efficacy data from phase 1b/2 trials, men with measurable disease at baseline in the intent-to-treat population (n = 29) who received sabizabulin at 63 mg per day had an ORR of 20.7% (5 partial responses, 1 complete response). In the phase 2 portion of the study, median radiographic progression-free survival (rPFS) had not been reached as of February 2021, when 10 men were still on study. No significant neutropenia or neurotoxicity was reported, and the overall safety profile appeared similar to that of AR-targeting agents.

A phase 3 trial is under way to evaluate sabizabulin 32 mg vs an AR-targeting agent (enzalutamide or abiraterone) in 245 patients diagnosed with mCRPC who have failed at least 1 AR-targeting agent. The primary efficacy end point is rPFS; secondary end points include ORR, duration of objective response, overall survival (OS) at interim analysis, time to intravenous chemotherapy, and pain progression. Investigators have the option of reducing the dose to 26 mg per day based on tolerability of the 32-mg dose until radiographic progression.

PSMA-based radioligand therapy. Prostate cancer is resistant to most forms of chemotherapy, apart from taxanes such as docetaxel and cabazitaxel. However, the fact that external-beam radiotherapy can be effective for localized disease has provided a rationale for systemic treatment using radiopharmaceuticals. In the setting of metastatic castration–resistant disease, lutetium Lu 177 (17Lu)-PSMA-617 has been studied; it combines a targeting compound, or ligand, with a therapeutic cytotoxic radioisotope that binds with prostate cancer cells that express PSMA.

UrologyTimes.com SEPTEMBER 2021
The ongoing open-label, phase 3 VISION trial is comparing $^{177}$Lu-PSMA-617 therapy with best supportive care alone in approximately 750 patients with progressive PSA-negative mCRPC. Patients have received at least 1 novel androgen axis-targeted drug (eg, enzalutamide, abiraterone) and were previously treated with 1 or 2 taxane regimens. Patients have been randomized 2:1 to $^{177}$Lu-PSMA-617 therapy or best supportive care alone, respectively. Patients were monitored for survival, disease progression, and adverse events over a treatment period of 6 to 10 months. In the first half of 2021, researchers reported that $^{177}$Lu-PSMA-617 therapy met the primary end points of OS and rPFS.

FUTURE DIRECTIONS IN CARE

Coupled with advances in imaging and genomic testing, the emergence of new therapeutic options for mCRPC suggests the potential for optimizing outcomes and survival. However, increasing patient access to these therapies remains a challenge, Gomella observed. Cost is one potential barrier, “Men are living longer and many of these newer regimens can run $8000 to $10,000 or more a month, a financial burden for most. We are going to have to deal with these practical challenges.” Also, it can be difficult to provide patients with appropriate treatment when also navigating challenges associated with insurance coverage and prior authorization. “Insurance coverage is one of those unforeseen problems [that occur] with these advances made over the last 10 years,” Gomella said. The costs of developing novel agents are very significant, as well.

Beyond the cost of these therapies, coordination of care is critical for patients with advanced prostate cancer who require the continuing care of a primary care provider. These patients can now receive many of these therapies in the large urology group practice setting in the community, often with individual providers who specialize in areas such as prostate cancer therapeutics. Increasingly, large, late-phase clinical trials are being conducted in these settings. Larger academic medical centers, particularly those that are National Cancer Institute-designated cancer centers, are where most of these new therapeutics are being developed and investigated in very early clinical trials.

Many patients with a diagnosis of complex, advanced disease may benefit from using a multidisciplinary approach commonly found at academic centers, where medical oncologists, radiation oncologists, urologic surgical oncologists, genetic counselors, interventional radiologists, oncology social workers, and others play a role in first studying these new agents and integrating all aspects of prostate cancer patient care.

“It is critical for providers to look at each patient as a unique individual and decide which agent or which site of service might be best for them at a particular point in time of their prostate cancer diagnosis and treatment,” observed Gomella. From the growing variety of standard and new options, the best treatment approach must be selected, he said: “It’s not a one-size-fits-all situation with advanced disease, and it remains a challenge today for prostate cancer—care providers.” With the wealth of standard and experimental treatment options available, it is important to optimize sequencing and combination strategies and consider how biomarkers and precision medicine may also help individualize treatment to optimize outcomes.

As urologists face these challenges, Gomella believes that the many new developments in therapeutics, investigational drug development, and precision medicine may also help individualization of standard and new options, the best treatment approach must be selected, he said: “It’s not a one-size-fits-all situation with advanced disease, and it remains a challenge today for prostate cancer—care providers.” With the wealth of standard and experimental treatment options available, it is important to optimize sequencing and combination strategies and consider how biomarkers and precision medicine may also help individualize treatment to optimize outcomes.

Whereas often challenging, having many different therapeutic options available is helping to extend the quantity and quality of [the lives of] many men with advanced prostate cancer.

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Study supports routine brain imaging at baseline in metastatic kidney cancer

Asymptomatic brain metastases showed up in 4% of patients with renal cell carcinoma

JASON M. BRODERICK
Associate Editorial Director, Urology Times®

Findings from a study of incidental brain metastases in patients with metastatic renal cell carcinoma (mRCC) suggest that baseline brain imaging should be considered in most patients with metastatic kidney cancer.1,2

The retrospective analysis, which was conducted by investigators at Gustave Roussy in Paris, France, and Memorial Sloan Kettering Cancer Center (MSK) in New York, New York, found that 4% of patients with mRCC had asymptomatic brain metastases.

“With 4% overall incidence in this cohort, one might conclude that baseline brain imaging should be considered in all patients with metastatic kidney cancer, particularly those with multiorgan involvement and/or pulmonary metastases,” lead investigator Ritesh R. Kotecha, MD, of MSK, stated in a news release.

The retrospective analysis included patients with mRCC evaluated between 2001 and 2019 for clinical trial participation at Gustave Roussy and MSK who had received brain imaging during the assessment, despite no clinical suspicion of brain involvement.

Overall, the analysis included 1689 patients enrolled across 68 trials. At a median follow-up of 14.1 months, 72 (4.3%) patients were identified as harboring occult brain metastases. The risk status was favorable, intermediate, and poor in 26%, 61%, and 13% of patients, respectively, based on the International Metastatic RCC Database Consortium (IMDC) risk score. Further, 2 or more extracranial sites of disease were identified in 86% of patients; this included 92% of patients having lung metastases.

“Brain imaging is routinely obtained for kidney cancer patients with symptoms that suggest CNS [central nervous system] metastases, but none of the patients with brain metastases included here were symptomatic,” senior investigator Martin H. Voss, MD, also with MSK, said in the news release.

“In current practice, chest, abdomen, and pelvis are routinely imaged from the time that metastatic disease is first detected, yet many [clinicians] do not image the brain.”

MARTIN H. VOSS, MD

“The findings in this study are important for 2 reasons,” Jonasch added. “First, they show that the overall prognosis of patients with brain metastases is consistently worse than the broader population of patients with metastatic renal cell carcinoma. We need to develop a deeper scientific understanding of why this patient population has a worse outcome, and we need to include them in future clinical trials.

“Second, [the findings] underscore the utility for MRI imaging of all patients with metastatic renal cell carcinoma, both at initial diagnosis and at regular intervals, to detect occult brain metastases [because] specific treatment strategies are required for this patient population.”

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RITESH R. KOTECHA, MD

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RITESH R. KOTECHA, MD
Q. Is biofeedback a billable service after a robotic radical prostatectomy during the global period?
A. Payment for a procedure is based on the global surgical package, which means payment includes all the services that would typically be furnished by a surgeon prior to, during, and after a procedure. For example, included in the surgical package is the typical work the day of the procedure, all additional medical or surgical services provided in a postoperative period including hospitalization, discharge from the hospital, and routine postoperative visits within the global period. Additionally, payment includes postsurgical pain management and all medical and procedural postoperative services required because of complications that do not require additional trips to the operating room, as well as follow-up visits during the postoperative period of the surgery that are related to recovery from the surgery.

The following are not included: visits unrelated to the diagnosis for which the surgical procedure is performed, unless the visits are due to complications of the surgery; treatment for the underlying condition or an added course of treatment that is not part of normal recovery from surgery; diagnostic tests and procedures, including diagnostic radiological procedures; clearly distinct surgical procedures that occur during the postoperative period that are not reoperations or treatment for complications; procedures that are more extensive because the initial procedure failed; and treatment of complications that require a return to a qualified operating room.

In this case, 58866 is a 90-day global procedure. We could argue a couple of points within the definition of the global that may or may not support coverage of biofeedback during the global period: No. 1: Is the biofeedback a treatment for a complication of the procedure or treatment for an underlying condition? No. 2: Is the treatment an added course of treatment not a part of the recovery from surgery?

Outside the global payment concerns, we also have to consider that Medicare typically does not pay for preventive services unless they are specifically allowed. So we would also have the question “Is the treatment provided for an existing condition, or is the biofeedback provided to prevent a complication or condition that may occur in the future?”

The questions are moot for most of the postoperative period for Medicare patients, as the issue of coverage of biofeedback is the most common and biggest roadblock.

Medicare covers biofeedback for the treatment of stress and/or urge incontinence in cognitively intact patients when documentation supports a previously failed trial of pelvic muscle exercise (PME) training. A failed trial is observed when no significant clinical improvement in urinary incontinence is noted after completing 4 weeks of a physician-prescribed plan of PME. Medical record documentation of the failed PME trial must be present to justify coverage for biofeedback.

This coverage guideline has 2 requirements: (1) that the patient has or has received a diagnosis of stress or urge incontinence—this means your physician will need to provide a diagnosis for the patient appropriately after recovery from surgery; (2) according to the coverage guidance, Medicare will cover biofeedback only after 4 weeks of pelvic floor therapy has failed. After meeting these coverage guidelines, you will need to circle back and answer the questions surrounding the global inclusion to determine coverage.

Recall that these are Medicare coverage guidelines, so private payers may differ. And these are the current coverage guidelines, which can be changed, but rarely do these change rapidly, and they will not change without supporting data. In the long run, with appropriate proof, coverage may change. In the short term, you may be able to argue medical necessity and outcomes for coverage on a case-by-case basis with your Medicare carrier.

The answer to your question is that coverage is very unlikely as you will have to have the data (in peer-reviewed articles) and time to push for medical necessity (to override the coverage issue) and you will have to satisfy the global inclusion questions (either the patient had a pre-existing condition or the treatment is an added course of therapy not a part of the recovery from the surgery). If you do decide to challenge for reimbursement, please refer to our article from last year on this subject.

CPT (Common Procedural Terminology) code 90911 (biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry) was deleted on January 1, 2020. It was replaced with 2 new time-based codes: CPT codes 90912 and 90913.

CPT code 90912’s description reads, “biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; initial 15 minutes of one-on-one physician or other qualified health care professional contact with the patient.” By comparison, CPT code 90913 is an add-on code to “describe each additional 15 minutes” of one-on-one physician or other qualified health care
Q. For cystoscopy with bilateral ureteral stent removal, how many unit(s) should 52310 be billed?

A. One unit should be billed. There are 2 codes available to report removal of a stent or foreign body: CPT codes 52310 (cystourethroscopy, with removal of foreign body, calculus, or ureteral stent from urethra or bladder [separate procedure]; simple) and 52315 (cystourethroscopy, with removal of foreign body, calculus, or ureteral stent from urethra or bladder [separate procedure]; complicated).

CPT code 52310 describes the work of removing an indwelling ureteral stent by cystoscopy, when the stent is visualized and then grasped using a grasping instrument to remove the stent. This procedure can be performed in the office, ambulatory surgical, or hospital setting. The code requires and includes performing a complete cystoscopy (CPT 52000), which cannot be billed separately, and therefore documentation should include the results of an examination of the urethra (such as for strictures), the prostate (in men), and the bladder (such as for mucosal lesions, neoplasms, or stones). CPT code 52310 is also the code used for simple removal of bladder stones or a bladder foreign body. Medicare has included in its rules a Medically Unlikely Edit (MUE) of 1 for this code with an indicator of 3, meaning that Medicare will allow payment for this code with 2 units without record review. However, similar to code 52310, Medicare will not allow reporting of this code for bilateral services. The clinical description of this code would indicate that documentation should include the need to perform “twisting/torquing movement to try and dislodge some of the encrusted material from the stent.” Similarly, the provider may “regrasp the stent as often as necessary to try and remove the visible stone material, with the goal ofatraumatically removing the stent intact from the ureter.” Use fluoroscopy to monitor the progress of the stent as you slowly withdraw it from the kidney. Reintroduce the cystoscope, inspect the bladder, assure that there is efflux from that ureteral orifice, and irrigate the bladder using a Toomey syringe until all of the stone material has been removed.” This code should not be used for the removal of an encrusted stent that is easily removed, or for the removal of bilateral stents. When taking into account the various rules surrounding both codes, 52310 or 52315 should be reported with 1 unit for the removal of bilateral stents. However, if complex stent removal and complex stone removal are required for treatment of a patient, 52315 can be reported with 2 units.

Q. Could you tell me what the appropriate diagnosis would be when a patient goes in for surgery to have a ureteral stone (52351 and 52332) removed and a stent placed and the stone is no longer present, presumably it has already passed?

A. Each bill that is submitted for reimbursement must have a code for both the service performed and a reason for the service. The service performed is an HCPCS [Healthcare Common Procedure Coding System] code, either Level I or Level II. The accompanying reason is chosen from the International Classification of Diseases Tenth Revision With Clinical Modification (ICD-10-CM).

In the situation described, a patient is brought to a procedure room to perform what is scheduled as a removal of a ureteral stone and a stent placed, which encompasses 52352 (cystourethroscopy, with ureteroscopy and/or pyeloscopy; with removal or manipulation of calculus [ureteral catheterization is included]) and 52332 (cystourethroscopy; with insertion of indwelling ureteral stent [eg, Gibbons or double-J type]) or similarly for laser lithotripsy and stent placement, 52356 (cystourethroscopy, with ureteroscopy and/or pyeloscopy; with lithotripsy including insertion of indwelling ureteral stent [eg, Gibbons or double-J type]) for the indication of N20.1 stone, ureter.

However, upon performance of the case, the patient was found to have passed the stone and the patient had undergone a diagnostic ureteroscopy and stent placement (CPT codes 52351, cystourethroscopy, with ureteroscopy and/or pyeloscopy; diagnostic and 52332, respectively). Assuming there was no other pathology found and no stone found but the patient was treated with a stent, the indication for the procedure remained unchanged. Therefore, ICD-10-CM code N20.1 should still be chosen per ICD-10 guidelines, which indicate in the absence of another, more appropriate diagnosis, the intended reason for the service should be reported even if the condition no longer presents.

REFERENCES

QUESTIONS?

Send coding and reimbursement questions to Jonathan Rubenstein, MD, and Mark Painter c/o Urology Times®, at UTeditors@mjlifesciences.com.

Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.
How does urology’s 2019 MIPS performance stack up?

Urologists outscore peers in e-prescribing, providing access to health information

Eligible clinicians are halfway through the fifth performance year of the Quality Payment Program (QPP), which is the major determinant of any fee schedule adjustments for professional services paid by Medicare Part B. The same legislation that created the QPP Medicare Access and CHIP Reauthorization Act (MACRA) extended the authority of the Centers for Medicare & Medicaid Services (CMS) to publicly report performance information on doctors and clinicians on the Physician Compare website. The website is tailored to Medicare beneficiaries looking to compare individual providers in their area, but the entire data set is available for public consumption.

CMS recently published data based on the 2019 performance year—the most recent year available. In this article, I will examine urologists’ QPP Merit-based Incentive Payment System (MIPS) performance in 2019 relative to other eligible clinicians, how that information is displayed to patients on Physician Compare, and what this might mean for the future.

First, a brief refresher on the MIPS 2019 performance year. The final MIPS composite score was determined by performance in the following categories (weights): Quality (45%), Promoting Interoperability (25%), Improvement Activities (15%), and Cost (15%). Clinicians needed a final score of 30 or greater to avoid a negative fee schedule adjustment in 2021, and 75 or greater to qualify for exceptional performance. In response to the COVID-19 pandemic, CMS applied an automatic extreme and uncontrollable circumstances policy to all MIPS eligible clinicians for the 2019 performance year that resulted in a neutral adjustment for many clinicians. Before the impact of that policy, clinicians scoring below 30 would have incurred a negative fee schedule adjustment in 2021, and the “savings” from this would have been redistributed to those scoring above 30 via a positive fee schedule adjustment on a prorated basis. This redistribution scheme is among the entire pool of participating clinicians, but it is possible to examine performance by specialty by joining different CMS data sets. Finally, clinicians may report as individuals, as a group, or both. When possible, CMS will calculate the higher of the individual or group score.

How did urologists do overall, and how did our specialty perform in 2019 compared with other specialties? There were 719,244 individual clinicians in 85 specialties with a final MIPS score reported by CMS in 2019. The mean and median final MIPS composite scores for the entire pool of clinicians were 85.6 and 92.3, respectively. The data include 6672 individual clinicians identified as urologists, with a mean final score of 85.2, and a median score of 91.4. Additionally, 3651 urologists (84.6%) achieved a score of 75 or greater and qualified for the exceptional pool vs 85.3% of all clinicians. At the other end of the performance spectrum, only 0.38% of all clinicians scored below 30, including 95 clinicians with a score of 0; only 5 (0.07%) urologists had scores below 30—none with a score of 0. The performance metrics of some high-volume specialties are included in the Table.

CMS also publishes measure-level data in each of the categories. The data are reported separately for clinicians reporting individually vs as a group and contain information about which category measures—when there are several to choose from—are being reported. Remember that a urologist may report as part of a group whether they are in a single specialty, a multispecialty, or even an advanced payment model practice; most urologists reported as part of a group in 2019. In the Quality category, most groups reported electronic health record (EHR) measures, followed by registry measures and claims-based measures in 2019. In general, urologists participating in group reporting used the same generic measures as most other clinicians but, with a few exceptions, scored worse on average. This is unsurprising. First, there were only a few urology-specific measures available in 2019. Second, some urologists were/are in multispecialty groups dominated by specialties that report on primary care measures. Third, the common EHRs used in 2019 by urologists were not configured to easily calculate and/or report on urology-specific measures or certified for those measures. Urologists forced to report on primary care measures can be forgiven for not performing as well as primary care colleagues.

In the Promoting Interoperability category, urologists outperformed their peers on e-prescribing and Provide Patients Electronic Access to Their Health Information, and underperformed relative to peers on Supporting Electronic Referral Loops. In 2019, electronic referrals may have still been uncommon among urologists and/or not fully supported by their EHR. Like most clinicians, urologists performed almost perfectly on Improvement Activity
measures. CMS did not publish measure-level data in the Cost category for the 2019 performance year.

HOW PATIENTS VIEW THE DATA
How is this performance information displayed to patients? I encourage you to go to Physician Compare and see for yourself. Search results for physicians return a page with information about EHR activities—patient view of Promoting Interoperability measures, security risk analysis, and registry reporting—and Improvement Activities. In the Quality section of the page, there are actual performance metrics for each of the Quality category measures and Promoting Interoperability measures. The measures are described in lay terms, such as "giving patients with diabetes a kidney exam" (Diabetes: Medical Attention for Nephropathy) with an explanation of the rationale: "Diabetes can cause complications, like kidney disease. Screening the kidneys of patients with diabetes can help patients receive timely treatment. To give this clinician a star rating, Medicare looked at the percentage of this clinician's patients with diabetes who had a kidney exam or received treatment for kidney disease." The performance is displayed as a "star rating," which is a value from 1 to 5 that is mapped to the actual performance score for that particular measure.

What does this mean for you and your practice? First, almost all clinicians in the 2019 performance year would have avoided a negative adjustment in 2021 because of a low bar, which means few dollars/small positive fee schedule adjustments for those who scored well. Indeed, most clinicians qualified for exceptional performance, which is a temporary benefit under MIPS that is scheduled to expire at the end of the 2022 performance year. However, the threshold to avoid a negative adjustment is rising each year and is currently proposed to be 75 points for 2022. In 2019, about 15% of eligible clinicians scored less than 75; thus, bigger fee schedule adjustments may be seen in future years. Second, these individual measure data provide a benchmark in the specialty for urologists to compare with other urologists. This may be helpful if urology-specific measures become more commonly used and data are provided more rapidly. For example, in 2019, a performance rate of 95 on the measure Prostate Cancer: Combination Androgen Deprivation Therapy for High Risk or Very High-Risk Prostate Cancer was significantly above average for all clinicians, but significantly below the mean score for urologists.

Finally, as the QPP matures, there is more information available to patients who are increasingly using tools, like Physician Compare, to evaluate their choices. When urologists start using specialty-specific measures, this information will be published and could directly influence patient choices. The trend is sure to continue as we march slowly—but relentlessly—to "value-based care." Urologists should view their own data on Physician Compare to understand the full arc of MIPS data, its current limitations, and how their patients may interpret this information.

REFERENCES

| TABLE. FINAL 2019 MIPS SCORE (MEAN) BY SPECIALTY OF INDIVIDUAL CLINICIAN |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | No. clinicians with final score | Quality category | PI category | IA category (out of 40) | Cost category | Final MIPS score |
| Internal medicine                | 51,776            | 90.8            | 69.2         | 39.3             | 70.6             | 81.8               |
| Family medicine                  | 45,716            | 93.1            | 69.4         | 39.3             | 71.6             | 86.6               |
| Obstetrics/gynecology            | 15,372            | 95.0            | 71.2         | 39.6             | 72.8             | 90.3               |
| Orthopedic surgery               | 14,622            | 88.8            | 68.2         | 39.5             | 69.7             | 80.1               |
| Cardiovascular disease (cardiology) | 13,750              | 93.5            | 72.1         | 39.6             | 71.3             | 87.3               |
| Ophthalmology                    | 12,886            | 90.7            | 70.3         | 39.1             | 74.1             | 84.3               |
| General surgery                  | 12,883            | 92.2            | 70.9         | 39.4             | 70.1             | 87.1               |
| Neurology                        | 10,008            | 92.0            | 70.3         | 39.5             | 70.3             | 85.5               |
| Gastroenterology                 | 9686              | 91.3            | 70.8         | 39.3             | 70.3             | 85.5               |
| Pulmonary disease                | 7195              | 91.9            | 71.1         | 39.3             | 69.3             | 85.5               |
| Urology                          | 6672              | 90.0            | 71.9         | 39.4             | 72.1             | 85.2               |

Source: Adapted from Doctors and Clinicians Quality Payment Program PY 2019 Clinician Public Reporting: Overall MIPS Performance file and National Downloadable file by Robert A. Dowling, MD.

40 | SEPTEMBER 2021 UrologyTimes.com
How does increased inflation affect the economy?

Inflation within healthy ranges can be advantageous for consumers.

**Q.** I think I understand the basics of inflation, but what is the greater impact of increased inflation on the economy?

**A.** Inflation is the concept that the cost of goods and services increases over time. What a dollar can purchase today is going to be more than a dollar will be able to purchase 20 years from now. The purchasing power of that dollar diminishes over time as the price of goods and services increases. Many people think of inflation as having a negative impact because they must spend more to purchase the same items. However, inflation can serve as a healthy component in an economy’s growth.

Inflation is not the increase in price of a single good or service but, rather, a broader basket of goods and services. For example, if the price of avocados increases due to a rise in popularity or lack of supply due to drought, flooding, or conflict, that is not considered inflation. The rest of the economy would carry on largely unaffected.

In the United States, the standard used to measure inflation is the consumer price index (CPI). The CPI is a measure that examines the weighted average of a “basket” of goods and services. This assortment is intended to mimic the products and services commonly purchased by US consumers and includes items such as food, energy, clothing, housing, medical care, education, communication, and recreation. The weighted average of these goods and services produces a percentage that is reported as the rate of inflation.

Although economists often disagree about the exact numbers, it is commonly believed that inflation in the range of 5% to 6%, or below is healthy for an economy, whereas inflation rates of 9% to 10% or higher are harmful to the economy.

Here are some of the common effects that inflation can have on consumers and the economy:

- **Diminishing purchasing power.** As stated earlier, when inflation raises prices, the purchasing power of a dollar diminishes. Consumers will have to spend more money to purchase the same items. Those hit hardest are the ones holding cash or who are on a fixed income that is not inflation adjusted annually. Over time, their purchasing power can be significantly affected.

- **Increased spending.** If consumers and businesses suspect inflation is on the rise, and fear that the value of their dollar will diminish, they attempt to spend that money before that occurs. In other words, they’ll likely worry that cash will only lose value due to inflation, so they’ll reason that it’s better to get any necessary shopping out of the way and stock up on things that probably won’t lose value. In turn, increased spending by consumers and businesses positively affects the economy.

- **Interest rates rise.** As consumers and businesses spend more, more money enters the money supply and inflation continues to rise. To curb run-away inflation, the Federal Reserve Board will increase interest rates. Higher interest rates mean higher payments when borrowing money. This causes consumers and businesses to reconsider taking out loans to make major purchases. The money that would have been used as a down payment or as collateral now stays in their bank accounts earning interest. Consequently, less money is spent and less money is in the money supply, which slows the rate of inflation.

- **Existing borrowers benefit.** Borrowers who already took out debt, such as a fixed-rate mortgage, will likely benefit from inflation. The value of their monthly mortgage payments will decrease over time. A fixed payment of, say, $2500 per month on a 30-year mortgage will decrease in value over the lifetime of that loan. Assuming the borrowers’ income is growing along with inflation, it will feel like they are paying less over time. However, borrowers who are in variable debt products will likely see their payments increase over time so that the value of those payments is keeping up with inflation.

- **Investors target stocks.** One way to offset rising prices is to purchase stock in the companies that are benefiting from receiving more money due to higher prices. As the companies earn more for the products they make, their stock prices will tend to increase. The value of an investor’s money will increase as the stock price increases, which will offset some of the impact of inflation.

Many consumers feel the immediate impact of inflation and interpret it as a negative. Spending more on an item you are used to buying never feels great. However, modest inflation does serve an important service to the overall economy. As long as the rate of inflation stays within a healthy range, it is something to take advantage of rather than fear.
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Investing in tech: Outside-the-box ways to earn off the digital revolution

Investing in “quasi techs” can be a lower-risk way to position for returns

Market outlooks aplenty make optimistic predictions about the near-term future of autonomous vehicles, but few investors are aware that Caterpillar has been producing the unmanned variety since the 1990s.

These vehicles work in mining, tirelessly, night and day, never stopping for lunch. As no humans are aboard, there isn’t the same hand-wringing over safety that there is with Teslas, which the company touts as being viable for autonomous fleets to carry non-owning passengers. (Don’t hold your breath waiting for this.)

Though you’ll never summon a behemoth earthmover to take you the dentist and then pick you up after chauffeuring others around, Caterpillar’s autonomous behemoths are arguably tech products. Yet, as they do industrial work, Caterpillar (CAT) is in the industrials sector.

The company also makes semi–autonomous vehicles, including human-driven earthmovers loaded with advanced technology to guide grading to specifications for boundaries, depth, and slope—sonic lasers and GPS (eliminating the lines of staked-out string once ubiquitous at construction sites). And the company’s newest tech ventures include 3D printing capabilities to eventually enable the production of parts on job sites to reduce downtime; CAT has a dedicated plant where engineers are testing this technology.

TECH WITHOUT THE CATEGORY
Caterpillar, founded in 1925, is in a growing category of companies that use technology not as an add-on, but as an integral part of products that are nevertheless viewed by the market as being anything but technical. Some of these companies are developing and/or producing autonomous vehicles and/or systems. Others are pursuing different digital endeavors.

Unlike many new tech companies, these quasi techs don’t trade at share prices hundreds of times earnings; they don’t carry this onus. Rather, these are long-established companies with real value, real profits, and real earnings that keep their price-earnings (P/E) ratios down-to-earth instead of up in the stratosphere. (CAT had a forward P/E ratio of about 20 on August 3.) Unlike many high-flying tech companies listed on NASDAQ, Caterpillar didn’t pop up a year or 3 ago with venture capital funding aimed at driving share price largely from market sentiment agog over all things tech. In 2025, CAT will celebrate its 100th birthday.

Investing in such companies, where appropriate for your portfolio and goals, can be a lower-risk way to position for returns driven broadly by the ongoing digital revolution—an economic engine that will continue to drive growth in pretty much all stock sectors, not just among tech companies per se, pushing the Dow Jones Industrial Average upward over the next few years.

The industrials sector stands to grow significantly in coming months from increasing demand in the postpandemic economy, though constricted supply chains may take a while to open up because of the Delta variant of COVID-19.

So much for tailwinds. A likely yet temporary market headwind would be a correction (a 10% drop) or a pullback of 5% to 7%. We’re long overdue for a correction, and the chances of this happening every August are increased by people going on vacation, meaning lower trading volume and potentially higher volatility.

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What you should know about the deposition process
Deposing witnesses allows for presentation of factual issues in a case

Once a medical malpractice lawsuit is filed, there are often many unknown facts and issues in the case.

What does the opposing party have to support their allegations or defenses? Who are they going to call as a witness? What is that witness going to say?

Parties have a right to investigate this information through a process called “discovery.” The purpose of discovery is to find out information about the other side’s claims and defenses, which allows parties to develop their own cases and analyze the strengths and weaknesses of their case. To do this, parties will use legal tools, such as interrogatories (written questions), subpoenaing relevant documents, and seeking admission on certain issues in the case. However, one of the other important tools used to gather information is taking a deposition.

WHAT IS A DEPOSITION?
Depositions are an essential and helpful part of our legal adversarial system. In short, a deposition is a question-and-answer process in which a witness provides an oral statement before trial, under oath.

Anyone who may have knowledge of the facts related to the lawsuit can be deposed. Therefore, it is an excellent way to determine the factual issues in the case, as well as what that witness is going to say at trial.

WHAT IS THE PURPOSE OF A DEPOSITION?
There are many reasons why a party may want to take a witness’ deposition. A primary purpose is to determine what the witness knows. Unlike what popular television shows portray, parties do not like or expect surprises at trial. Doing so is frowned upon and considered unfair. Taking depositions helps eliminate the opportunity for surprise by allowing the parties to hear what the witness will testify to at trial.

Another important purpose of a deposition is to preserve the witness’ testimony. Before answering any questions, the witness will get sworn in the same way they would before taking the stand at trial. Because the witness is speaking under oath, they are providing testimony. This makes it possible to use the witness’ testimony at trial if they are unavailable. For example, if there is a witness who has relevant testimony for a party’s case, but falls ill or passes away, that party would likely be able to use that witness’ deposition testimony at trial.

Like the other forms of discovery, depositions help parties analyze the strengths and weaknesses of their case. One of the main benefits of the deposition vs other discovery tools, such as answering written questions, is that parties can see the witness testifying in person. This means that they can examine mannerisms and appearance, and are able to make a better determination of the witness’ credibility.

WHAT HAPPENS IN A DEPOSITION?
Depositions are not generally taken in a courtroom or in front of a judge. Instead, they usually take place in law offices, hotel conference rooms, or the court reporter’s office. A court reporter will be present to transcribe the entire conversation on the record. The deposition may also be videotaped, which usually happens when a party suspects the witness will not be available at trial.

“Depositions can range from 30 minutes to 1 week, depending on the nature of the case and the witness’ knowledge.”

Once the witness is sworn in, the attorney taking the deposition will ask the witness about facts and events related to the lawsuit. Because one of the purposes of a deposition is to discover everything the witness knows about the events related to the lawsuit, questions asked during a deposition can be much broader than what is allowed at trial. Attorneys may object to certain questions asked, but the witness will most likely still be required to answer. The attorneys make objections simply to preserve them for a judge to rule on later, as the judge will not be present during the deposition to make the ruling in real time.

Depositions can range from 30 minutes to 1 week, depending on the nature of the case and the witness’ knowledge. No matter the length of the depositions, every deposition is important. The witness is testifying under oath, so providing false statements may have both civil and criminal consequences. Thus, it is critical that the witness listen to the questions carefully before answering and only provide truthful answers, even if that means answering, “I don’t know.”
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