Rechargeable neuromodulation system found safe, efficacious

Results from 1 year of follow-up of patients enrolled in a pivotal clinical trial show that sacral neuromodulation with a miniaturized, implanted rechargeable device (Axonics System) provides highly safe and durably effective treatment for urinary urgency incontinence (UUI), said Howard B. Goldman, MD. He presented the findings at the 2020 American Urological Association Virtual Experience.

“The reduction in UUI episodes was quite significant in the study cohort,” said Goldman. He reported that reduction in UUI episodes observed at the study’s primary end point at 6 months were sustained through 1 year.

For the full article, please turn to page 32
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From the publishers of Urology Times
HERO data impress as FDA grants relugolix priority review

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

This new therapy could change the landscape for the treatment of advanced prostate cancer.

“This treatment has the potential to become a new standard for ADT in men with advanced prostate cancer.”

“This study provides an exciting, new option for patients with recurrent or advanced prostate cancer, with the potential to change a long-established standard of care.

These comments, from J. Brantley Thrasher, MD; Neal D. Shore, MD; and Badar M. Mian, MD, respectively, all refer to relugolix, an investigational gonadotropin-releasing hormone agonist for the treatment of advanced prostate cancer. The FDA recently granted a priority review designation to a new drug application (NDA) for the agent.

The NDA is based on results from the phase 3 HERO study, which compared oral relugolix to standard leuprolide acetate injection in men with advanced prostate cancer. You’ll find plenty of coverage and commentary on these data in this month’s issue of Urology Times®, including a report on the findings, commentary from Thrasher, and an analysis of the HERO study, which was published in the New England Journal of Medicine, from Mian. Be sure to visit our newly relaunched website (www.urologytimes.com) in order to stay current on this and all urology-related pipeline updates.

Another highlight from this month’s prostate cancer coverage is an in-depth interview with Samuel J. Peretsman, MD, in which Peretsman discusses his extensive experience with high-intensity focused ultrasound (HIFU) The wide-ranging discussion encompasses how Peretsman first began utilizing HIFU and how clinicians can start to incorporate the modality into their own practice.

Moving on to benign prostatic hyperplasia, look for reports on photosensitive vaporization of the prostate with a proprietary laser system (GreenLight XP5); an investigational, minimally invasive system for transurethral anterior commissurotomy of the prostate with localized transfer of paclitaxel (Optilume BPH Catheter System); and the UroLift prostatic urethral lift.

In kidney stones, we cover a recent American Urological Association Virtual Experience study on use on study using ureteroscopy, while in sexual dysfunction, you will find articles on marketing practices of men’s health clinicians, the effect of exceeding exercise guidelines on testosterone levels, and data suggesting a steady decrease in testosterone levels among US men.

In bladder cancer, be sure to read our report on a phase 3 trial investigating intravesical nedaplatin firdavenoc (recombinant adenovirus interferon alfa with Syn3 [rAD-IFNα/Syn3], FerGene) for patients who have bacillus Calmette-Guérin-unresponsive high-grade non-muscle-invasive bladder cancer.

Finally, in overactive bladder/incontinence, we cover results from 1-year follow-up of patients enrolled in a pivotal clinical trial evaluating sacral neuromodulation with a miniaturized, implanted rechargeable device (Axonics System).

This issue of Urology Times® includes the usual columns from Jonathan Rubenstein, MD, and Mark Painter; Robert A. Dowling, MD; and Jeff Witz, CFP. This month’s “Coding and Reimbursement” column is a must-read primer of what to expect from anticipated changes to evaluation/management coding for 2021. Although 2020 has been an inordinately difficult year (and it’s not over yet), Rubenstein and Painter’s article is a pertinent reminder to keep an eye on the path forward. Thanks for reading.

REFERENCE

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Chairman's Letter
Are phase 3 HERO results a game-changer for urologists?

A ndrogen deprivation therapy (ADT) has been a mainstay of treatment for advanced prostate cancer for decades and has been shown to provide long-term disease control and improve symptoms. However, there is evidence that ADT increases cardiovascular (CV) risk, especially in men with preexisting CV disease. Additional concerns for gonadotropin-releasing hormone (GnRH) agonists are delayed castrate levels of testosterone and the need for intermittent injections, among many others.

The recent results of a phase 3 randomized controlled trial investigating relugolix, an oral GnRH antagonist, vs leuprolide may change the landscape in the treatment of advanced prostate cancer (see article, page 8). HERO (NCT03085095) was a multinational, open-label trial that randomized 934 men 2:1 to treatment with relugolix (360 mg on day 1, then 120 mg po qd) or subcutaneous leuprolide injection 22.5 mg (11.25 mg in Japan and Taiwan) every 3 months. Eligible men had confirmed advanced prostate cancer defined as biochemical or clinical relapse, metastatic disease, or advanced localized disease. Additionally, the men had to have serum testosterone levels of 150 ng/dL or greater, serum prostate-specific antigen above 2 ng/mL, and require at least 1 year of ADT. Men with a history of ADT for more than 18 months, active liver disease, or significant CV risk were excluded. The primary end point for the study was sustained castrate levels of testosterone (< 50 ng/dL) for the entire study period and found a 54% risk reduction in the relugolix group. If further studies confirm the efficacy and lower CV adverse effects with this new oral GnRH antagonist, this could make a substantial impact on most urologists’ practices. Patients could avoid an injection, initial testosterone surge would be alleviated, and a significant reduction in CV events would be realized. However, several questions remain to be answered, among them the following: 1. What will be the cost of this new therapy? 2. Will third-party payers reimburse this drug is given in conjunction with nonsteroidal antiandrogens such as bicalutamide?

Although there remain several unanswered questions about this new drug, the initial report is very promising. This new therapy could change the landscape for the treatment of advanced prostate cancer.

REFERENCE

J. BRANTLEY THRASHER, MD
Thrasher, a Urology Times® Editorial Consultant, is executive director of the American Board of Urology, Charlottesville, Virginia.
Oral gonadotropin-releasing hormone receptor antagonist shows benefits

Cheryl Guttman Krader, BSPharm
Urology Times® Contributing Editor

Oral GnRH receptor antagonist has “potential to become a new standard for ADT,” investigator says.

The HERO trial, the phase 3 clinical trial investigating relugolix for the treatment of advanced prostate cancer, met its primary endpoint showing that the oral gonadotropin-releasing hormone (GnRH) antagonist provided sustained testosterone suppression to castrate levels through 48 weeks of follow-up.

The FDA recently granted a priority review designation to a new drug application for relugolix for the treatment of patients with advanced prostate cancer, according to Myovant Sciences, the manufacturer of the oral GnRH receptor antagonist. Additional findings from the randomized, controlled study (NCT04352946) showed that men treated with relugolix achieved faster and more sustained testosterone suppression than the control group treated with subcutaneous leuprolide and had a markedly lower risk of having a major adverse cardiovascular event (MACE), said Neal D. Shore, MD.

Shore presented data from HERO as a late-breaking abstract for the 2020 American Urological Association virtual meeting. He is the lead author of an article reporting the study’s findings that was published online in the New England Journal of Medicine on May 29, 2020.

“Prostate cancer is the most common cancer diagnosis in the United States, and cardiovascular mortality is the leading cause of death among patients with prostate cancer. Luteinizing hormone-releasing hormone receptor agonists, such as leuprolide, that are used for androgen deprivation therapy [ADT] in advanced prostate cancer have several drawbacks. They are associated with an early testosterone surge, do not fully suppress follicle-stimulating hormone [FSH], which may be a mitogen for cancer cells, and since 2011 have had several drawbacks. They are associated with an early testosterone surge, do not fully suppress follicle-stimulating hormone [FSH], which may be a mitogen for cancer cells, and since 2011 have carried an FDA mandated label warning about an increased risk of myocardial infarction, sudden cardiac death, and stroke,” said Shore, the medical director at Carolina Urologic Research Center in Myrtle Beach, South Carolina.

“Through a direct inhibitory effect on pituitary GnRH receptors, relugolix more completely suppresses both luteinizing hormone and FSH compared with leuprolide, and relugolix avoids an early testosterone surge. Based on the results of HERO, relugolix has the potential to become a new standard for ADT in men with advanced prostate cancer.”

HERO is a multinational, open-label trial that randomized 934 men 2:1 to treatment with relugolix (360 mg on day 1, then 120 mg once daily) or subcutaneous leuprolide 22.5 mg (11.25 mg in Japan and Taiwan) every 3 months. Eligible men had confirmed advanced prostate cancer with a biochemical or clinical relapse, newly diagnosed metastatic disease, or advanced localized disease and were deemed as candidates for at least 1 year of ADT. Men with a history of MACE within the prior 6 months were excluded.

The relugolix and leuprolide patient groups were well-balanced at entry in their demographic and clinical characteristics. Approximately 90% of men in both arms completed the 48-week trial, and the treatment compliance rate was 99% in both groups.

More than 90% of men in each treatment arm had at least 1 cardiovascular risk factor, and approximately 14% had a history of MACE.

“Approximately 30% of men with advanced prostate cancer would be expected to have a history of a MACE. The lower rate in HERO reflects the study’s exclusion criteria,” Shore noted.

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“Based on the results of HERO, relugolix has the potential to become a new standard for ADT in men with advanced prostate cancer.”

NEAL D. SHORE, MD

The primary end point analysis showed that 96.7% of men treated with relugolix and 88.8% of the control group achieved sustained suppression of testosterone to castrate levels (< 50 ng/dL) from day 29 through week 48. In statistical analyses, relugolix demonstrated both noninferiority and superiority to leuprolide.

Relugolix also demonstrated statistically significant superiority compared with leuprolide in all key secondary end points, which included measures of onset of prostate specific antigen response and testosterone suppression, FSH reduction, and sustained castration rates (P < .0001 for all end points), Shore said.

“By day 4, 56% of men treated with relugolix achieved testosterone suppression to castrate levels. In the leuprolide arm, the testosterone level showed the expected initial surge, reaching a mean of 625 ng/mL, and the mean did not fall to castrate levels until day 29,” he reported. A substudy investigating testosterone recovery showed that by day 90 after treatment was stopped, serum testosterone returned to the normal range in the relugolix group (mean, 288 ng/dL), but the mean testosterone level was just 58.6 ng/dL in the leuprolide group.

At day 90, 54% of relugolix-treated patients versus just 3% of leuprolide-treated ones achieved testosterone recovery, Shore reported.

In both study groups, > 90% of men experienced at least 1 adverse event (AE). The rate of a grade 3 or higher AE was 18% in the relugolix group and 20.5% in the leuprolide group. The fatal AE rate in the relugolix and leuprolide groups was 1.1% and 2.9%, respectively.

“The known consequences of ADT, including hot flashes, were the most common adverse events in both groups. The rate of diarrhea was higher in the relugolix group, but these events were mild or moderate and did not lead to treatment discontinuation,” Shore said.

The HERO protocol included a prespecified analysis of MACE, which included nonfatal myocardial infarction, nonfatal stroke, and death from any cause. At 48 weeks, MACE rates were 2.9% in the relugolix group and 6.2% in the leuprolide group. A Kaplan-Meier analysis of cumulative MACE incidence over the 48-week treatment period showed a 54% risk reduction in the relugolix group relative to the leuprolide group.

“The MACE event rate was almost 6-fold higher in the leuprolide group compared with the relugolix group among men with a history of MACE (17.8% vs 3.6%) and was 50% higher in the leuprolide group compared with the relugolix group in men without a history of MACE (4.2% vs 2.8%),” Shore said.

Disclosure: Myovant Sciences provided funding for the study. Dr Shore does research for and is a consultant to AbbVie, Ferring Pharmaceuticals, Myovant Sciences, and Telmar.

REFERENCE

Apalutamide + ADT improves survival for men with nonmetastatic CRPC

Combination treatment also delayed time to cytotoxic chemo vs androgen deprivation plus placebo

Lisette Hilton
UT Correspondent

Apalutamide (Erleada) combined with androgen deprivation therapy (ADT) improves overall survival more than androgen deprivation therapy alone in men with nonmetastatic castration-resistant prostate cancer (nmCRPC) at high risk of metastases, according to results from investigators’ final analysis of the phase 3 Study of Apalutamide (ARN-509) in Men With Non-Metastatic Castration-Resistant Prostate Cancer (SPARTAN) trial.

Apalutamide, an androgen receptor inhibitor, became the first FDA-approved therapy for nmCRPC in February 2018. In September 2019, the FDA approved apalutamide for the treatment of patients with metastatic castration-sensitive prostate cancer.

Investigators enrolled 1207 patients in the SPARTAN study (NCT01946204), who were randomized 2:1 to receive either 240 mg apalutamide orally once daily in combination with ADT or placebo once daily in combination with ADT.

“The answer is yes.”

At their final survival analysis with a median follow-up of 52 months, Small and coauthors found that apalutamide significantly increased overall survival (OS) from 59.9 months to 73.9 months. This represents an increase of 14 months in median survival, with a hazard ratio for death of 0.78 (P = .0161).

“If you correct for the benefits in survival from crossing over from placebo to apalutamide, the increase in survival goes up to 21 months,” Small said.

The combination decreased the risk of death by 22%. And treatment with apalutamide and androgen deprivation therapy significantly delayed patients’ time to cytotoxic chemotherapy compared with placebo in combination with ADT (HR, 0.63; P < .0002).

“A fair question that is always raised about studies like this where an active agent is used early, is if overall survival is improved not because earlier is better than later, but because the placebo group ends up not getting any active therapy at all. The study ends up being a study of early treatment versus no treatment,” Small said.

That wasn’t the case in SPARTAN, according to Small.

“Over 80% of placebo patients went on to receive active, life-prolonging, FDA-approved therapy. Around 70% of placebo patients went on to receive abiraterone or other life-prolonging therapy at the time of metastases. All 19% of placebo patients who hadn’t yet progressed at the time of study unblinding went on to receive open-label apalutamide. Parenthetically, in addition to prolonging life, apalutamide also significantly delayed the time to chemotherapy use, a secondary end point of the trial,” he said.

Small said that in his estimation, the data are really important to the practicing clinician and an absolute game-changer for patients with prostate cancer.

“We already knew that apalutamide would delay time to metastases. But there was always this gnawing worry that maybe we were burning that bridge, and that it would ultimately disadvantage the patient to use this therapy early. In fact, the results in SPARTAN were exactly the opposite. Early use prolongs life, even when compared to later use. This means that we can use apalutamide in nonmetastatic castration-resistant prostate cancer patients with the full confidence that we are prolonging life and not ‘burning a bridge’ that we will later regret,” Small said.

Apalutamide’s safety and tolerability were consistent across studies. Median treatment duration was nearly 3 times longer, at 33 months, for patients treated with apalutamide plus ADT compared with 12 months in the placebo group. The most common adverse events in the SPARTAN study, occurring in 10% or less of patients were fatigue, hypertension, rash, diarrhea, nausea, weight decrease, arthralgia, falls, hot flush, decreased appetite, fracture, and peripheral edema.

References:
Enzalutamide and ADT found efficacious for nonmetastatic CRPC

Treatment reduces risk of death by 27% compared with placebo

Lisette Hilton
Urology Times® Correspondent

Enzalutamide (Xandi®) treatment reduced risk of death in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC) and rapidly rising prostate-specific antigen (PSA) by 27% compared with placebo, according to research presented at the 2020 American Society of Clinical Oncology Virtual Scientific Program.1

Enzalutamide, an androgen receptor inhibitor, is indicated for the treatment of men with castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer. This final analysis of the phase 3 PROSPER study (NCT02003924) supports enzalutamide and androgen deprivation therapy as the standard of care to improve overall survival in prostate cancer patients before the onset of detectable metastasis.

“This is great news for urologists who see patients with this type of disease. The data are reassuring that patients with nonmetastatic castration-resistant prostate cancer and a rapidly rising PSA have a safe and effective option that improves overall survival by almost 1 year,” according to the study’s lead author Cora N. Sternberg, MD, of Weill Cornell Medicine, New York Presbyterian in New York City, New York.

PROSPER is a randomized, double-blind, placebo-controlled, multinational trial of about 1400 men with nmCRPC. Patients had no evidence of metastatic disease, but their prostate cancer had progressed based on a rising PSA. Investigators evaluated treating patients with once-daily 160 mg oral enzalutamide and androgen deprivation therapy vs placebo and androgen deprivation therapy.

PROSPER had previously shown that, compared with placebo, enzalutamide resulted in a significant and clinically meaningful lower risk of radiographic progression or death and improvement in metastasis-free survival of 71%. Overall survival (OS) data were immature when the investigators first reported their findings.

In this final OS analysis, median OS was 67.0 months among men who received enzalutamide compared with 56.3 months among those who received placebo. Sternberg and colleagues reported a median follow-up of 48 months. Of 466 deaths, 288, or 30.9%, were in the enzalutamide arm vs 178, or 38.0%, in the placebo arm. 11 months of additional survival benefited patients

Enzalutamide treatment resulted in 11 months of additional survival benefit for patients, according to Sternberg.

“The safety profile was consistent with the established safety profile of enzalutamide. These data should be reassuring to colleagues who are interested in overall survival data and this is a confirmation of metastasis-free survival results,” Sternberg said.1

Disclosures: Pfizer and Astellas Pharma funded the trial. Dr Sternberg has been a consultant to Astellas Pharma, AstraZeneca, Bayer, Incyte, Merck, MSD, Pfizer, Roche, Roche-Genentech, Celio Oncology, and Sanofi Genzyme. For full disclosures, visit bit.ly/prosper-disclosures.

REFERENCE

Ipatasertib plus abiraterone and prednisone improves radiographic PFS

No new safety signals emerged with combination regimen in phase 3 study

Jason M. Broderick
Associate Editorial Director, Urology Times®

Adding the AKT inhibitor ipatasertib to abiraterone acetate (Zytiga) and prednisone improved radiographic progression-free survival (rPFS) in patients with metastatic castration-resistant prostate cancer (mCRPC) whose tumors had PTEN loss, meeting a coprimary end point of the phase 3 IPATential150 study.1

The triplet, however, did not meet the other coprimary end point of rPFS in the overall study population (ITT). Roche (Genentech), the developer of ipatasertib, also noted in a press release that, “While initial data are encouraging, overall survival (OS) benefit and additional secondary end points are not yet mature.” The company also noted in the press release that no new safety signals emerged with the combination regimen in the phase 3 study. No data were made available at this time, with Roche

See IPATASERTIB page 11

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ADT-free option shows potential in advanced prostate cancer

Strong activity seen in castration-sensitive disease, investigators report

Jason M. Broderick
Associate Editorial Director, Urology Times®

The androgen deprivation therapy (ADT)-free regimen of apalutamide (APA; Erleada) combined with abiraterone acetate (Zytiga) and prednisone (AAP) showed strong activity in advanced castration-sensitive prostate cancer (CSPC), according to findings from the phase 2 LACOG 0415 study shared during the 2020 American Society of Clinical Oncology Virtual Scientific Program.

In the study, 79.5% of patients with advanced CSPC treated with APA plus AAP reached a prostate-specific antigen level of 0.2 ng/mL or less at week 25. The rate was comparable to the 75.6% rate achieved in the study by a regimen of ADT plus AAP, showing the ADT-free regimen to be a potentially viable alternative in this setting.

“This is the first randomized trial that evaluated the efficacy and safety of androgen signaling inhibitors without castration in patients with advanced CSPC,” said lead study author Fernando C. Maluf, MD, Latin American Cooperative Oncology Group. “Apalutamide plus abiraterone demonstrated high efficacy in terms of PSA decline.”

The ongoing, open-label, noncomparative LACOG 0415 trial (NCT02867020) included ed 128 asymptomatic to moderately symptomatic patients with advanced CSPC and an indication to start ADT. At baseline, 17.2% of patients had biochemical recurrence (PSA ≥4 ng/mL and PSA doubling time <10 months, or PSA >20 ng/mL); 8.6% had node-positive disease and were not candidates for local therapy; and 74.2% of patients had metastatic disease. The median patient age was 70 years (range, 49-88).

The median PSA was 22.5 ng/mL (IQR, 6.9-117.4), and the median testosterone level was 405.7 ng/dL (IQR, 152.3-909.9).

In the mITT analysis for the primary end point, 79.5% (95% CI, 63.5-90.7) of patients in the APA plus AAP arm had a PSA ≤0.2 ng/mL at week 25.

Planning to share the results at a future medical conference.

“Prostate cancer remains a leading cause of death in men worldwide and patients with metastatic castration-resistant prostate cancer can be difficult to treat,” Levi Garraway, MD, PhD, Roche’s chief medical officer and head of global product development, stated in a press release. “The early results of the IPATential150 study are encouraging in our ongoing mission to develop new treatment options for people with advanced prostate cancer.”

Ipatasertib is a small molecule inhibitor of all 3 isoforms of AKT. Blocking these isoforms blocks the PI3K/AKT signaling pathway, which is hypothesized to stop the proliferation and survival of tumor cells.

The double-blind phase 3 IPATential150 trial accrued adult male patients with asymptomatic or mildly symptomatic, previously untreated mCRPC. Patients were randomized to abiraterone and prednisone/prednisolone plus either ipatasertib or placebo. Beyond the rPFS coprimary end points, secondary end points include overall survival, safety, time to pain progression, time to initiation of cytotoxic chemotherapy, and time to function deterioration.

Phase Ib/2 data for the combination of ipatasertib and abiraterone/prednisone in patients with metastatic or advanced prostate cancer were previously published in Clinical Cancer Research. The study accrued patients aged ≥8 years who had an ECOG performance status of 0 or 1. Patients had prior docetaxel and disease progression following at least 1 hormonal therapy. Patients were also required to have adequate liver, hematologic, and kidney function at baseline.

In the study, patients were randomized to 1 of 3 arms: ipatasertib (400 mg) plus abiraterone (1000 mg) and prednisone/prednisolone (n = 84); ipatasertib (200 mg) plus abiraterone (1000 mg) and prednisone/prednisolone (n = 87); or placebo plus abiraterone (1000 mg) and prednisone/prednisolone (n = 82). The coprimary end points were the same as in the phase 3 trial: rPFS in the ITT population and in the subgroup of patients whose tumors had PTEN loss.

In the mITT analysis for the primary end point, 79.5% (95% CI, 63.5-90.7) of patients in the APA plus AAP arm had a PSA ≤0.2 ng/mL at week 25.

The early results of the IPATential150 study are encouraging in our ongoing mission to develop new treatment options for people with advanced prostate cancer.

**REFERENCES**

THE FIRST AND ONLY FDA-APPROVED TREATMENT FOR LOW-GRADE UTUC

CHEMOABLATE NOW SPARE THE KIDNEY FOR TOMORROW

*JELMYTO is instilled via the pyelocalyceal system in a procedure that spares the kidney.

†Study design: The efficacy of JELMYTO was investigated in the ongoing OLYMPUS Study (N=71), a phase 3, open-label, single-arm, multicenter trial in patients with treatment-naïve or recurrent low-grade non-invasive UTUC with ≥1 measurable papillary tumor between 5-15 mm (partial resection/ debulking was permitted if >15 mm). Patients were treated with 6 instillations once a week. The dosage of JELMYTO was individualized based on volumetric measurements using pyelography with the intent to fill the renal pelvis. CR was defined as complete absence of tumor lesions at 3 months after initiation of treatment and evaluated via urine cytology, ureteroscopy, and biopsy (if warranted). The primary endpoint was CR. Secondary endpoint: durability of response at 12-month follow-up of CR evaluation.

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

Important Safety Information
Contraindications
JELMYTO is contraindicated in patients with perforation of the bladder or upper urinary tract.

Ureteric Obstruction
Ureteric obstruction, including ureteral stenosis and 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. Withhold or permanently discontinue JELMYTO based on the severity of ureteric obstruction.

Bone Marrow Suppression
The use of JELMYTO can result in bone marrow suppression, particularly thrombocytopenia and neutropenia. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin. Withhold JELMYTO for Grade 2 thrombocytopenia or neutropenia. Permanently discontinue for Grade 3 or greater thrombocytopenia or neutropenia.

Please see Important Safety Information on the adjacent page for JELMYTO.
IN THE OLYMPUS STUDY,†
JELMYTO treatment in patients with low-grade UTUC achieved:

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

of patients treated with JELMYTO achieved a Complete Response (CR)†

The OLYMPUS Study is ongoing. At the time of data cutoff†:
• 19 patients remained in CR
• 7 patients had disease recurrence
• 9 patients continued to be followed for 12-month duration of response

• Median duration of response was not reached, with a range of 0-18.8+ months†

The most common adverse reactions (≥20%) reported were ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting†

Learn more at JELMYTO.com/hcp

Important Safety Information (cont’d)

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.

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

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

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

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

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

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

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

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

**BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION**
Please refer to the JELMYTO Package Insert for Full Prescribing Information, including instructions for preparation and administration.

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

**DOSEAGE 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 Project12 Lever, a Luer lock syringe, and a ureteral catheter with molded Luer lock connector. Once chilled at -3°C to 5°C (27°F to 41°F), JELMYTO will convert to a viscous liquid for instillation and is stable for up to 1 additional hour. Reconstituted JELMYTO must be instilled within 1 hour after it is converted to a viscous liquid.

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

**WARNINGS AND PRECAUTIONS**
**Ureteric Obstruction**
Ureteric obstruction, including ureteral stenosis and hydronephrosis, occurred in patients receiving JELMYTO. In the OLYMPUS study, ureteric obstruction was reported in 58% (n=41) of patients receiving JELMYTO, including 17% (n=12) of patients who experienced Grade 3 obstruction. The median time to first onset was 72 days (range: 15-462). Interventions in the 41 patients experiencing ureteric obstruction included ureteral stent placement (88%), balloon dilatation (32%), and nephroureterectomy (4.9%). In the 36 patients who required ureteral stent placement, the median duration of indwelling stents was 5 days (range: 1-292). Ureteric obstruction did not resolve or resolved with sequelae in 51% (n=20) 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 two patients and Grade 3 neutropenia in one patient. Gross extravasation of JELMYTO via urinary tract perforation or impaired mucosa was not observed in these patients. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin. Withhold JELMYTO for Grade 2 thrombocytopenia or neutropenia. Permanently discontinue for Grade 3 or greater thrombocytopenia or neutropenia.

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

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

**Clinical Trials Experience**

<table>
<thead>
<tr>
<th>Clinical Trials Experience</th>
<th>Adverse Reactions</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone Marrow Suppression</strong></td>
<td>Thrombocytopenia</td>
<td>Grade 3: 2 patients</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Grade 3: 1 patient</td>
<td></td>
</tr>
<tr>
<td><strong>Embryo-Fetal Toxicity</strong></td>
<td>Fetal harm</td>
<td>Pregnant women</td>
</tr>
<tr>
<td><strong>Adverse Reactions</strong></td>
<td>Clinical Trials Experience</td>
<td>71 patients</td>
</tr>
<tr>
<td><strong>Clinical Trials Experience</strong></td>
<td>Serious adverse reactions</td>
<td>37% of patients</td>
</tr>
<tr>
<td><strong>Clinical Trials Experience</strong></td>
<td>Discontinuation</td>
<td>16 patients (23%)</td>
</tr>
<tr>
<td><strong>Clinical Trials Experience</strong></td>
<td>Dosage interruptions</td>
<td>34% of patients</td>
</tr>
<tr>
<td><strong>Clinical Trials Experience</strong></td>
<td>Most common adverse reactions</td>
<td>20% of patients</td>
</tr>
</tbody>
</table>

**Laboratory Abnormalities**
Table 2 summarizes the laboratory abnormalities in OLYMPUS. Based on content from JEL-PI-001 Package Insert.
Table 1: Adverse Reactions (≥ 10% All Grades) in Patients Who Received JELMYTO in OLYMPUS

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

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

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

Table 2 summarizes the laboratory abnormalities in OLYMPUS.

<table>
<thead>
<tr>
<th>Laboratory Abnormality*</th>
<th>JELMYTO (All Grades (%))</th>
<th>Grade ≥ 3 (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>37 (%)</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>21 (%)</td>
<td>2.9 (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21 (%)</td>
<td>2.8 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated Glomerular Filtration Rate</td>
<td>37 (%)</td>
<td>10 (%)</td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>32 (%)</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>30 (%)</td>
<td>2.8 (%)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>17 (%)</td>
<td>0 (%)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16 (%)</td>
<td>16 (%)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>13 (%)</td>
<td>1.4 (%)</td>
</tr>
</tbody>
</table>

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

Lactation

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

Females and Males of Reproductive Potential

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

Geriatric Use

Of the total number of patients in the OLYMPUS trial, 75% (53 patients) were 65 years of age and over and 37% (26 patients) were 75 year 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

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Based on content from JEL-PI-001 Package Insert
409.2 ng/mL (IQR, 319.3-500.5). Gleason score at diagnosis was ≤6 (7.8%), ≤7 (35.2%), or ≥8 (57%). All patients except 1 had an ECOG performance status of 0 or 1. Overall, 46.2% of patients had de novo metastatic status at diagnosis. Prior treatments included radiotherapy (36.7%), prostatectomy (43%), and neo-adjuvant ADT (10.9%). Prior ADT could not have occurred within 12 months of study enrollment.

Patients were randomized in a 1:1:1 ratio to ADT plus AAP (n = 42), APA alone (n = 42), or APA plus AAP (n = 44). Abiraterone was administered at 1000 mg orally daily and apalutamide was administered orally at 240 mg daily.

The primary end point was the rate of patients achieving a PSA level ≤0.2 ng/mL at week 25. This was measured in the modified intention-to-treat (mITT) population and in a sensitivity analysis. The mITT population included only patients with an evaluable PSA at week 25; this included 41 patients in the APA plus AAP arm, 40 patients in the APA alone arm, and 39 patients in the APA plus AAP arm. The sensitivity analysis included all randomized patients, categorizing missing PSA data at week 25 as failures.

**Combination reaches threshold for success**

In the mITT analysis for the primary end point, 79.5% (95% CI, 63.5-90.7) of patients in the APA plus AAP arm and 60% (95% CI, 43.3-75.1) of the patients in the APA arm had a PSA ≤0.2 ng/mL at week 25. The rate was 75.6% (95% CI, 59.7-87.6) in the ADT plus AAP arm. The APA arm did not meet the study’s primary end point, as the trial design established the threshold for success as 65% of patients in a cohort having a PSA ≤0.2 ng/mL at week 25.

In the sensitivity analysis, 70.5% (95% CI, 54.8-83.2) in the APA plus AAP arm and 57.1% (95% CI, 41-72.3) of patients in the APA arm had a PSA ≤0.2 ng/mL at week 25. The rate per the sensitivity analysis was 73.8% (95% CI, 58-86.1) in the ADT plus AAP arm.

Several secondary outcomes were only measured in the mITT population. The rate of patients with a PSA decline ≥50% at week 25 was 100% in the ADT plus AAP arm, 92.5% in the APA alone arm, and 100% in the APA plus AAP arm. The rates of patients with a PSA decline ≥80% at week 25 were 100%, 90%, and 97.4%, respectively, and the rates of patients with PSA progression at week 25 were 0, 7.5%, and 0, respectively.

“Testosterone levels from baseline up to week 25 varied significantly among the 3 arms. In patients treated with apalutamide alone, there was a 134.3% increase in testosterone level, while in patients treated with abiraterone plus abiraterone there was a 73.8% decrease up to week 25. And, as expected, in patients who received ADT plus abiraterone, the [testosterone level] decreased by 97.4%,” said Maluf.

The safety analysis included all 128 patients. In the ADT plus AAP arm, all-grade treatment-related adverse events (TRAEs) occurred in 71.4% of patients, with grade 3/4 TRAEs occurring in 19%. One patient discontinued treatment and it was due to toxicity.

In the APA monotherapy arm, all-grade TRAEs occurred in 81% of patients, with 16.7% being grade 3/4. One patient discontinued treatment due to toxicity, and 1 patient discontinued due to gliona. In the APA plus AAP cohort, TRAEs of any grade occurred in 81.8% of patients, with grade 3/4 TRAEs occurring in 22.7%. Four patients in this cohort discontinued treatment due to toxicity and 2 patients withdrew from the trial. Maluf highlighted a few specific AEs. All-grade gynecomastia occurred in 55% of the APA arm, compared with 20% of the APA plus AAP arm, and 7% of the ADT plus AAP arm. Breast pain across all grades occurred in 14%, 5%, and 0% of the 3 arms, respectively.

Hot flashes, hypertension, and hyperglycemia, Maluf noted, were more common in the 2 abiraterone combination arms compared with the APA alone arm. Rash and pruritus were more prevalent in the APA arms, either alone or combined with AAP.

“Quality of life (FACT-P) from baseline up to week 25 remained consistent among the 3 arms,” said Maluf.

Regarding next steps for this research, Maluf said, “The substitution of castration by androgen signaling inhibitors is still an open field and further research is necessary not only to answer this question but also to determine which subgroup of patients may benefit from this new strategy.”

**REFERENCE**


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**TEST PREDICTS OUTCOMES FOR UNFAVORABLE INTERMEDIATE-RISK PROSTATE CANCER**

Exact Sciences Corp. recently announced the publication of results highlighting the performance of the Oncotype DX Genomic Prostate Score (GPS) result in patients with unfavorable intermediate (UFI)-risk prostate cancer.1 Published in *Urology*, the new results demonstrate the GPS test is a strong independent predictor of critical outcomes in patients with UFI-risk prostate cancer.2

“These new findings, which demonstrate for the first time the GPS test as a strong predictor of critical end points in UFI-risk disease, indicate that Oncotype DX testing can aid physicians and UFI-risk prostate cancer patients in their decision-making process,” said Jennifer Cullen, PhD, MPH, of Case Comprehensive Cancer Center in Cleveland, Ohio.

For the study, additional statistical analyses were conducted of GPS results from 2 previously published cohort studies in men treated with radical prostatectomy. The study included 299 intermediate-risk patients, 175 of whom were classified as UFI-risk. Results showed that UFI-risk patients with a GPS test result greater than 40 had outcomes consistent with high-risk disease and a poor prognosis, indicating they may benefit from more aggressive therapies. In contrast, patients with UFI-risk prostate cancer with a GPS value less than 40 had outcomes similar to patients with favorable intermediate-risk disease, suggesting less aggressive therapy may be needed.

**REFERENCES**


Oral GnRH antagonist is highly effective and safe

Higher rate and early recovery of testosterone observed with agent

Injectable luteinizing hormone-releasing hormone (LHRH) agonists have been the mainstay of androgen-deprivation therapy (ADT) for nearly 3 decades. The slow pace of innovation in this class of drugs has been limited mostly to the development of sustained-release injections or implants to reduce serum testosterone levels from 3 to 12 months. One exception was the approval of an injectable gonadotropin-releasing hormone (GnRH) antagonist roughly 10 years ago. Now we have the results of a phase 3 randomized trial demonstrating the efficacy and safety of relugolix, an oral GnRH antagonist, used for ADT.

The HERO trial (NCT03085095) was an international, multicenter study conducted at 155 centers comparing relugolix (120 mg orally, once daily) to leuprolide (22.5 mg injection, every 3 months) for 48 weeks. Men in need of ADT to treat prostate cancer for at least 1 year were included in the study. The indications for ADT included either biochemical (prostate-specific antigen) or clinical recurrence after primary treatment, or newly diagnosed, hormone-sensitive metastatic disease, or advanced localized disease regardless of primary treatment. Men with recent (within 6 months) cardiovascular events were excluded due to the known cardiovascular outcomes in this cohort.

The primary end point of the study was the sustained suppression of testosterone to castrate levels, defined as testosterone less than 50 ng/dL for up to 48 weeks. Secondary end points included early suppression of testosterone at days 4, 15, and 28, and the rate of achieving very low testosterone levels of less than 20 ng/dL while on treatment. From April 2017 to October 2018, 934 patients underwent randomization in 2:1 fashion. 622 patients were assigned to receive relugolix and 308 were assigned to the leuprolide group. Treatment adherence was 99% in both groups, and 90.2% and 89.0% of the patients completed 48 weeks of treatment in the relugolix and leuprolide groups, respectively. Sustained testosterone suppression to castrate levels through 48 weeks was achieved in 96.7% of men on relugolix and in 88.8% of men on leuprolide. The results met the predefined criteria for both noninferiority and superiority of testosterone suppression with relugolix over leuprolide (P < .001). Further, rapid testosterone suppression to less than 50 ng/dL at day 4 (56% vs 0%; P < .001) and day 15 (98.7% vs 12%; P < .001) was significantly more likely with relugolix than with leuprolide. Similarly, profound suppression of testosterone to less than 20 ng/dL was seen with relugolix (78.4% vs 1%; P < .001).

In a subgroup analysis, at 90 days after discontinuation of treatment, the mean testosterone level was significantly higher in the relugolix group compared with the leuprolide (288.4 ng/dL vs 58.6 ng/dL). Fifty-four percent of men who received relugolix recovered testosterone levels compared with only 3% of men who received leuprolide (P < .001).

Lower rate of major adverse CV events with relugolix group

Of note, after 48 weeks of treatment, the incidence of major adverse cardiovascular events was 54% lower in the relugolix group than in the leuprolide group (2.9% vs 6.2%). More significantly, in men with a known medical history of cardiovascular events, the risk of major cardiovascular events during treatment was 4.8 times higher with leuprolide (17.8%) than with relugolix (3.6%). Diarrhea (grade 1-2) was more common in the relugolix group than in the leuprolide (12.2% vs 6.8%).

This study provides clear evidence of the superiority of the oral GnRH antagonist relugolix over the LHRH agonist leuprolide in providing rapid, safe and sustained suppression of testosterone in men requiring ADT. Although the authors, and others, have pointed out the avoidance of testosterone surge with relugolix, it is not clear whether that surge or “flare” noted with LHRH agonists is clinically relevant in the contemporary patient with prostate cancer. More important is the higher rate and early recovery of testosterone at the end of therapy in men treated with relugolix. This is of particular relevance in terms of quality of life, especially for men on short-term ADT or those being considered for intermittent ADT. As many as 25% of men treated with LHRH agonists for 3 years may have permanent suppression of testosterone despite the discontinuation of ADT. It remains to be determined whether long-term relugolix therapy will have similar adverse effects on testosterone recovery. Significantly fewer major adverse cardiovascular events with relugolix are clearly important to men with prostate cancer who frequently have cardiac disease or cardiac risk factors. The advantages of GnRH antagonists over LHRH agonists (such as leuprolide) have also been observed with the injectable formulation, degarelix. The use of degarelix, despite its advantages over LHRH agonists, has not increased significantly as specialists had initially expected. Some of the cited reasons for this include the need for monthly injection, and skin reaction (typically mild) at injection site. It will be interesting to observe whether the oral GnRH antagonists are more readily embraced by the urologic community. Regardless, this study provides an exciting, new option for patients with recurrent or advanced prostate cancer, with the potential to change a long-established standard of care.

REFERENCE

HIFU

continued from page 1

were referring patients to Washington, DC if they were interested. That trial never expanded, so none of the men in my part of the country were able to participate locally.

Within a few years I began seeing patients who would make appointments for their HIFU follow-up. They weren’t patients I was treating primarily; they were returning to the area. Their urologists were not comfortable taking care of them after they were treated in Europe. In 2004, when I encountered the first of these men, I decided that if people from my part of the country were going to Europe to get treated, I needed to understand HIFU so I could care for them. Secondly, I should consider the technology’s advantages because men were opting out of robotic prostatectomies, brachytherapies, cryotherapies, and intensity-modulated radiation therapy. What weren’t we offering our patients that they would get on a jet and fly to another country to pursue an alternative treatment?

Q: What actually is prostate HIFU energy, and how is it delivered?
A: The “U” in HIFU stands for ultrasound, meaning therapeutic sound waves, which are basically higher-power diagnostic sound waves. The energy wave must pass through a medium, which is the human tissue. Most of the HIFU machines use a piezoelectric crystal to create amplified sound waves that are then targeted at a focal point. The focused sound energy creates thermal coagulation—coagulative necrosis. Our target tissue temperature runs in the low 90s centigrade. There are also secondary effects including mechanical disruption and immunologic responses. Similar to cryotherapy, the actual response is multimodal, but primarily thermal—created coagulative necrosis.

Q: Are your patients asleep during the procedure?
A: Yes, they need to be asleep and motionless. We did do the procedures under continuous spinal anesthesia about 15 years ago. Most importantly, you need to target well so patients can’t be moving. With cryotherapy and brachytherapy, the prostate shifting is lessened somewhat by the needles. With HIFU, patient movement is an issue.

Q: How many different HIFU devices are currently available? Is one more commonly used?
A: In the United States, there are currently 4 ultrasound-based devices. Over 90% of cases are done with the Sonablate 500. That’s the device that came along in the 1980s in this country and was also sold in Asia and Europe. EDAP TMS, a French company, markets the Ablath-

erm and, more recently, the Focal One. There’s the INSIGHTEC ExAblate, which is approved in the past for conditions such as bone metastasis and fibroids. The most recent addition is the Profound Medical TULSA-PRO, which is an in-gantry MRI-guided device that delivers thermal ultrasound from a device within the urethra. It is radically directed from a urethral transducer, so not technically focused.

Q: What are some contraindications to HIFU?
A: The first contraindication is a target that’s too far away. If, on MRI, your patient has a 15-mm lesion in a 70-g prostate and the lesion is up by the anterior capsule, you’re not going to reach it. Now you can do things to bring it toward the energy source such as transurethral resection of the prostate or any type of hormonal downsizing. Another contraindication would be a sound path issue. If the cancer on MRI is on the anterior side of a cluster of brachytherapy seeds along the rectal wall, you can’t effectively pass sound through all that metal.

There could be rectal wall calcification, and if you heat the rectal wall, you could create a fistula. The next would be a large, distal apical lesion where you don’t want to heat the backside of the pubis and create osteitis pubis. Those are the therapeutic, geometric, and safety issues.

Q: What are some contraindications to HIFU?
A: Not absolutely, but it is on the manufacturers’ list of relative contraindications. What I do is assess the rectal wall by ultrasound. If it’s not overly thickened from radiation and there is not calcium or a very low anterior resection compromising vascularity, then HIFU is not necessarily contraindicated.

Q: Talk to me about the expectations of the patients. What do you tell them to expect postoperatively?
A: The procedure is done on an outpatient basis, it’s painless, and patients are not prescribed pain medicine. Patients have some urgency from the heat for a couple of hours after the procedure.

Q: What do you tell [patients] to expect postoperatively?
A: There are technical limitations, safety limitations, prostate limitations, and cancer limitations. In terms of technical limitations, you have to be able to get the sound to target. For example, the Ablatherm and Sonablate devices, have AP height limitations due to focal length. For the commonly used Sonablate, you’re able to treat about 3.4 to 4.0 cm away.

There can’t be interference such as rectal wall calcification, large prostate calculi, or many closely approximated brachytherapy seeds. Things that impede diagnostic sound are going to impede therapeutic sound. These factors are part of the evaluation. The issue is not the total prostate size; it’s whether you are able to reach the target from the plane of the transducer. In most cases with the Sonablate 500, we’re looking for 34 mm or less to give us some wiggle room above the lesion such as an anterior lesion.

From a cancer perspective, whether you’re referring to cryotherapy or HIFU, nobody has ever shown that there’s a grade-dependent response to thermal ablation. The important question is, is all the cancer you want to treat reachable? By default, you’re not going to treat much beyond 4 cm away, so that’s the prostate and the base of the seminal vesicles. You’re certainly not going to treat lymph nodes. At the University of Southern California (USC), they’ve done robotic outpatient lymphadenectomy before they’ve taken on prostate HIFU for high-grade disease.

Q: Would you say HIFU is contraindicated in patients who have had rectal surgeries or a previous ulcer?
A: No absolutely, but it is on the manufacturers’ list of relative contraindications. What I do is assess the rectal wall by ultrasound. If it’s not overly thickened from radiation and there is not calcium or a very low anterior resection compromising vascularity, then HIFU is not necessarily contraindicated.

Q: What do you tell [patients] to expect postoperatively?
A: The procedure is done on an outpatient basis, it’s painless, and patients are not prescribed pain medicine. Patients have some urgency from the heat for a couple of hours after the procedure. The postoperative management depends on whether you are performing whole-gland or targeted HIFU. I recently had a HIFU patient whose Foley catheter was removed in just a few days, but that was a hemia-

blistion in a young man. His prostate was only 23 cc, and we treated one side. If you take on a 40-gm prostate, you can see swelling in the course of the procedure. In some men, I might leave a suprapubic tube and not even have a voiding trial for 10 to 12 days. It takes time for that edema to go away.

I try to give modest expectations. I really want patients to understand that they’re choosing HIFU in lieu of something else: including radical prostatectomy, brachytherapy, or cryotherapy—approaches with which I have decades of experience. They need to understand what they’re gaining and what they’re giving up.

There are 2 things about HIFU unequivocally demonstrated in the literature for over 20 years. When you choose HIFU, you are going to have some obstructive symptoms potentially, and you
can experience an infield recurrence (as you could with radiation or cryotherapy). You can’t have an infield recurrence with a robotic prostatectomy. So you need to understand that’s what you’re inheriting.

What you’re gaining is the lack of morbidity. Our group, along with the USC group, had an abstract presented at the 2020 International Symposium on Focal Therapy and Imaging in Prostate and Kidney Cancer, reporting on our first hundred hemicir- 

ulations. The rate of incontinence—measured as anything greater than zero pads—was zero in 100 consecutive patients. International Index of Erectile Function (IIEF-5) scores dropped 1 point. Patients are seeking diminished morbidity. I personally don’t view obstructive problems as a complication to the therapy; I build it into the expectation.

If a patient seeks to reduce the need for an inflatable penile prosthesises, artificial sphincter, or postoperative sling following surgery/radiation, he’s got to get through the short-term recovery of HIFU. I think I’m known in the community as an aggressive HIFU surgeon as far as how much tissue I treat and how much swelling I’m willing to create, because I just consider it a short-term nuisance. That’s how I counsel the patients. Other HIFU surgeons will choose to treat less surrounding tissue.

Q: Do you generally prescribe patients α-blockers and anticholinergics postoperatively?
A: They all get α-blockers. They only get an anticholinergic or mirabegron (Myrbetriq) if they have prolonged irritative symptoms, which is uncommon. If there are 10 problems postoperatively, 9 are going to be mechanical weakening of the stream.

Q: What do you tell patients about the risk to the bladder or bowel when you compare it to nonsurgical treatments?
A: Unlike any type of ionizing radiation, there are no delayed bladder, rectal, or urethral issues. Patients will not develop a secondary malignancy or gross hematuria years after ultrasound energy ablation. The fistula rate is about 0.7%, although most of that occurs in post radiation patients; I’ve never had one.

Compared to surgery—let’s use robot-assisted radical prostatectomy because it’s the most common in this country—there are no intraabdominal issues. There’s no ileus, and there’s never a bowel obstruction. A rectal injury without prior radiation is exceedingly rare in the literature. The main issue is prolonged obstructive symptoms based on how much tissue you ablate.

Q: What do you say about incontinence and the risk of erectile dysfunction?
A: To the best of my due diligence, there’s never been an artificial urinary sphincter placed for a HIFU patient in the United States or actually ever sold for such a patient by American Medical Systems/Boston Scientific. I am aware of 1 sling. I performed a sling procedure on a patient who was treated with HIFU outside of the country and who received a lot of apical heat and developed membranous stenosis that was cut instead of dilated. So the incontinence rate is close to zero. In our personal experience, when we looked at the first 174 patients in this country, it was zero.

Erectile dysfunction is a bit of an issue because of the variation of the delivery of the technique. If you looked at the rate of erectile dysfunction (ED) in European publications in the 1990s and 2000s, I think it is remarkably high—40% to 60% with whole-gland HIFU. Part of that is they appeared to use a non-neurovascular sparing technique. I tell patients the ED rate is 0% to 20%, and they should recover most of their function. The exception would be the case of a large lesion along the neurovascular bundle, because we can ablate a nerve and blood vessel with sufficient heat. If we target the neurovascular bundles, you’re going to lose function. But if we don’t target them, ED should be very mild and transient.

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Prostate Cancer / COVER FEATURE

HIFU continued from page 19

decisions they are. You don’t need to have it in your hand. There are online tutorials and a simulator where you can work through cases. Urologists can get so much more experience with this before they become the surgeon of record. In essence, one gets as much experience as needed to be comfortable. In my view, this is unique in terms of learning curves over my many years with other technologies.

Q: Are there courses put on by the companies, or are you proctored by experts?
A: Both are options. You can start with either a manufacturer or a service provider. There are online tutorials. You can do cases online, right on a laptop because that’s all you’re using during the case. You can go to a center where HIFU is performed and watch cases over the provider’s shoulder. You can also get as many proctors as you want when you’re doing cases; any local expert can come and help you get through the case or even by remote access to your screen.

Q: What are hospitals requiring from a credentialing standpoint? Do they require a certain number of proctored cases?
A: In my part of the country, it’s all done as an outpatient procedure, so in surgery centers and offices. You need a service provider. The device is either purchased by a facility or you use one of the national mobile providers. The largest national mobile provider, HIFU Prostate Services, has both remote and in-case proctoring, so you can do some online and then you can come watch cases. A proctor will sit next to you for as many cases as you want. The bottom line is you can get more education and experience than you could have attained with any other form of prostate cancer therapy.

Q: What are your take-homes for clinicians?
A: HIFU has been around for a few decades but has only really been in our backyard for 4 to 5 years. My take-home message is: It’s not a magic wand, it’s an ablation. It’s just controlled heat. A urologist just needs to understand how to create it, how to deliver it, how to monitor it, and then how to follow the patient. It’s not difficult; it just takes discipline and time.

REFERENCE

Nerve sparing raises positive margins risk in robot-assisted radical prostatectomy

Jason Broderick
Associate Editorial Director, Urology Times®

An analysis of a real-world cohort of patients with prostate cancer who received robot-assisted radical prostatectomy (RARP) found an association between nerve sparing and an increased risk of ipsilateral positive surgical margins.

According to the research, which was published in the *Journal of Urology,* a multivariable analysis demonstrated that nerve sparing was an independent predictor of ipsilateral positive margins (odds ratio [OR], 1.42; 95% CI, 1.14-1.82).

“The increased risk of positive margins should be considered when counseling patients who opt for nerve sparing robot-assisted radical prostatectomy,” wrote the authors in their conclusion.

The analysis assessed data from 2574 patients with prostate cancer who received RARP at Dutch teaching hospitals between 2013 and 2018. The hospitals included Martini Hospital Groningen, Hospital Group Twente, St. Antonius Hospital Nieuwegein/Utrecht, and the Canisius Wilhelmina Hospital Nijmegen.

The median patient age was 65, the median preoperative PSA level was 10.6 ng/mL, and the median PSA density was 0.26 ng/mL2. Patients’ clinical T stage was T1a/b/c (60%), T2/T2a (27%), T2b (5%), T2c (3%), T3 (5%), or unknown (1%). The Gleason sum scores for patients were ≤6 (19%), 7 (67%), 8 (7%), 9 (7%), or 10 (6 patients).

Overall, 86% of patients had preoperative MRI. The analysis was prospective. Exclusion criteria were prior treatment with salvage RARP or upfront androgen-deprivation therapy. Overall, 5148 prostate lobes were derived from these patients. The investigators assessed each prostate lobe as an individual case, and used a multilevel regression model to evaluate the relationship between nerve sparing and positive surgical margins.

The investigators reported that there were positive surgical margins in 844 (31%) of the 2574 cases. When assessed by pathological stage, the positive margin rate was 23% (n = 353) among the 1533 patients with pT2 disease, and 47% (n = 491) among the 1041 pages with pT3 disease. Sixty-eight percent (n = 1755) of patients received unilateral or bilateral interfascial nerve sparing surgery.

Beyond nerve sparing, the investigators observed several other factors that were significant predictors of positive margins, including prostate specific antigen density (OR, 3.64; 95% CI 2.16-5.90). The others were side-specific covariates, including presence of extraprostatic extension on MRI (OR, 1.42; 95% CI 1.03-1.91), percentage of positive cores on systematic biopsy (OR, 3.82; 95% CI 2.50-5.86), and highest preoperative ISUP (International Society of Urological Pathology) biopsy grade (OR, 1.58, 1.62, 2.11 and 4.49, for ISUP grades 2, 3, 4 and 5, respectively).

The investigators noted that their results are inconsistent with multiple prior studies focusing on this topic. They provided 2 potential explanations for the discrepancy.

Regarding the first, the authors wrote, “The potential confounders controlled for during analysis in previous studies were prostate specific and not prostate side specific. To determine causality between a nerve sparing approach and ipsilateral positive margins, each prostate lobe should be considered as a separate case.”

The second possible explanation the authors provided related to the design of the multivariable analysis in previous studies, specifically concerning the number and type of covariates that were adjusted for.

“In this study, the large sample size and site-specific analysis enabled inclusion of a large number of potential confounders in the multivariable analysis, including the influence of the individual surgeon (and, thus, experience) on the occurrence of positive margins. To our knowledge, none of the previous studies performed an analysis including all of the most important potential predictors, including MRI stage, for positive margins,” the authors wrote.

REFERENCE
Analyses of data from prospective follow-up of more than 3800 men show that photoselective vaporization of the prostate (PVP) with a proprietary laser system (GreenLight XPS) is a safe and durably effective procedure for treating lower urinary tract symptoms related to benign prostatic hyperplasia (BPH), said Kevin Zorn, MD.

At the 2020 American Urological Association Virtual Experience, Zorn presented findings on behalf of coinvestigators in the global GreenLight Group, which is comprised of 8 expert surgeons practicing at 7 international referral centers. He reported that the procedure was completed using just a single fiber in 92.5% of men; resulted in a prostate-specific antigen (PSA) reduction of 53.5% at 24 months, which was comparable to that achieved with other treatments for BPH; and was associated with few major complications. Furthermore, during follow-up of up to 5 years, only 1.5% of men underwent repeat surgical intervention for BPH recurrence.

“There has been accumulating evidence in the literature demonstrating the long-term durability of GreenLight PVP. To our knowledge, our multiinstitution, multiuser study is the largest collective experience with this treatment modality,” said Zorn, a professor of urology at the University of Montreal (CHUM) in Quebec, Canada.

The men included in the study were treated with the XPS 180W system between 2011 and 2019. They had a median age of 70 years and a median prostate volume of 65 mL as measured by transrectal ultrasound. Median lobe presence was observed in 36.5% of men, 35% had a Foley catheter preoperatively for urinary retention, and 34% were on anticoagulant therapy other than aspirin.

Median operative time was 62 minutes and median energy used totaled 250 kJ, corresponding to an energy density of 3.9 kJ/mL prostate volume.

“The operative characteristics in this population were typical of what we would expect with this procedure. Operating time tends to average 1 min per mL of prostate volume, and energy use typically ranges from 3 to 4 kJ per mL,” Zorn said.

The perioperative transfusion rate was only 0.8% and the median hospital stay was 2 days.

“It is important to recognize that several of these men were at higher risk of complications due to the presence of coexisting disease,” Zorn said.

See PVP page 22
Benign Prostatic Hyperplasia / CLINICAL UPDATES

BPH catheter system shows encouraging outcomes in pilot trial

Significant improvements in BPH-related lower urinary tract symptoms observed

Cheryl Guttmann Krader, BSPharm
Urology Times® Contributing Editor

Results from an initial pilot trial show that an investigational, minimally invasive system for transurethral anterior commissurotomy of the prostate (TUAP) with localized transfer of paclitaxel (Optilume BPH Catheter System) is safe. Further, it provides significant objective and subjective improvements in benign prostatic hyperplasia (BPH)-related lower urinary tract symptoms that remain durable for at least 1 year, reported Steven A. Kaplan, MD, at the 2020 American Urological Association Virtual Experience.1

“The Optilume system is the first ever, minimally invasive treatment that can provide TURP [transurethral resection of the prostate]-like results without cutting, burning, steaming, laserin, or leaving a permanent implant behind, and it is designed to minimize or eliminate the common [adverse] effects associated with other surgical BPH procedures,” said Kaplan, professor of urology at the Icahn School of Medicine at Mount Sinai in New York, New York. “Follow-up of men enrolled in the pilot study is still ongoing. Based on its results, a prospective, randomized, double-blind, sham-controlled pivotal trial known as PINNACLE is now underway at 20 sites in the United States. We look forward to presenting data from longer follow-up in the pilot trial and from the larger controlled clinical trial.”

Kaplan noted that a balloon catheter dilation system was investigated as a potential treatment for BPH approximately 25 years earlier. However, although its use was associated with initial symptomatic improvement, the benefit was not sustained. “With the Optilume system, a predilation balloon catheter is passed to perform TUAP that opens and increases the size of anterior or portion of the prostatic urethra to alleviate obstruction. Then, a drug-coated balloon catheter is introduced for circumferential delivery of paclitaxel, an antiproliferative drug that is believed to maintain the opening of the newly divided tissue,” Kaplan said.

The data he presented were from the EVER-EST-1 trial (NCT03423979) that enrolled 80 men with BPH across 6 investigational sites in Latin America. The study investigated 3 sizes of the balloon, described as small, medium, and large. “Multiple sizes allow for customized treatment based on ultrasound measurement of prostate length, height, and total volume,” Kaplan said.

82.3% of patients meet efficacy end point

At the cut-off date for data analysis, 73 men had completed 1 year of follow-up. The primary end points for the study were improvement of 40% or greater on the International Prostate Symptom Score (IPSS) from baseline to 3 months and major device- or procedure-related adverse events at 3 months. Among the 79 patients evaluated at 3 months, 82.3% met the efficacy end point; 1 subject who developed stress incontinence, which resolved at the 30-day follow-up, met the primary safety end point, Kaplan reported.

Mean IPSS score was 22.3 at baseline and had improved to 8.3, 8.0, and 7.9 at 3, 6, and 12 months, respectively. Mean peak flow rate was 10.9 mL/sec at baseline and 19.6 mL/sec at 1 year. Improvements in both IPSS and Qmax were statistically significant.

Kaplan contrasted the efficacy results achieved in the pilot trial with those reported for other minimally invasive procedural treatments for BPH from studies investigating those modalities at a similar stage in their pathway.

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the participating centers were in Europe, where surgeons are obliged to keep patients in the hospital for at least 2 or 3 days because of criteria for reimbursement,” Zorn said.

Median duration of Foley catheterization was 1 day or less in approximately two-thirds of men, and 5.9% of men required recatheterization, mainly managed with anticholinergics; retention or lower.

All other major AEs occurred at a rate of 0.8% or lower.

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Functional outcomes analyses showed that median PSA was decreased by about 50% throughout follow-up to 5 years. Median Interna-
tional Prostate Symptom Score was 22 at baseline and remained at 4 or 5 between 6 months and 5 years. Median peak flow rate decreased from 6.3 mL/sec at baseline to 17 mL/sec at last follow-up, and median postvoid residual volume decreased from 122 mL at baseline to 23.5 mL at 5 years.

Discussing limitations of the global retrospective study, Zorn mentioned that because of its global nature and retrospective design, it is difficult to account for variations between surgeons in preoperative medical therapy and skill. In addition, many of the patients returned to their referring urologist after their procedure, so follow-up data needed to be obtained via phone contact.31

Disclosures: Dr Zorn is a paid consultant and proctor surgical trainer for Greenlight PVP and Rezum by BSCI (Boston Scientific), an investigator and paid consultant for Procept BioRobotics for Aquablation, and investigator for Zenflow and Urotronic BPH treatments.

REFERENCE

1. Law K, Tholomier C, Couture F et al. Global Green-

Most post-op AEs minor

Postoperative adverse events (AEs) occurring within 30 days after the procedure were categorized using the Clavien-Dindo classification system. Most were minor (grades 1-2), with the most common being lower urinary tract symp-
toms (22.3%), incontinence (10.4%), hematuria (9.9%), and retention (7.4%). The most common major AEs (grades 3-5) were retrograde ejaculation (4.4%) and postoperative transfusion (1.3%). All other major AEs occurred at a rate of 0.8% or lower.

“The lower urinary tract symptoms were mainly managed with anticholinergics; retention occurred mostly in men who were in retention preoperatively, and most cases of hematuria were managed with hydration without need for hos-
pitalization or a return to the OR,” Zorn stated.

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REFERENCE

1. Law K, Tholomier C, Couture F et al. Global Green-
Patient-reported outcomes favor urethral lift over water vapor ablation for BPH

Jason M. Broderick
Associate Editorial Director, Urology Times®

Patient experience was superior with the UroLift prostatic urethral lift (PUL) versus Rezum tissue ablation with steam injection, according to early patient reported outcomes from individuals who received one of the minimally invasive surgical therapies for benign prostatic hyperplasia (BPH).1,2

Patients completed surveys within 2 months of receiving one of the procedures. International Prostate Symptom Score (IPSS) and quality of life was significantly better with PUL versus Rezum. Treatment satisfaction was 85% with PUL versus 65% with Rezum (P = .20). There was less interference with daily activities in the PUL group versus the Rezum group, including sports interference (P = .007), entertainment interference (P = .01), and community interference (P = .04).

By day 3 following the procedure, 7% of the PUL cohort had been catheterized, compared with 55% of the Rezum arm (P = .0003). The usage rate of BPH medication post-procedure was 37% with PUL versus 91% with Rezum (P < .0001).

“The UroLift System is a game-changer for patients suffering from BPH symptoms and is supported by a robust portfolio of clinical evidence as well as a growing body of real-world evidence,” study coauthor William Schiff, MD, Urology Associates of Central California in Fresno, California, stated in a press release. “Providers should be encouraged by these findings showing the UroLift System offers a positive treatment experience and rapid recovery, allowing men to return to their daily activities with minimal downtime.”

The study included 53 patients who had received either mechanical dissociation with the UroLift PUL (n = 30) or Rezum tissue ablation (n = 23). Treatment with PUL or Rezum was the only criterion for enrollment. The study included no exclusion criteria related to prostate size, BPH medical history, symptom score at baseline, bilobar or tri-lobar prostatic obstruction, or retention history.

Baseline characteristics were similar between the 2 cohorts. Overall, the average age was 69 and the average prostate weight was 56 g. The questionnaires were filled out at an average of 30 days following the procedure.

At baseline, IPSS data were available for 19 patients in the PUL group and 12 patients in the Rezum group. There was not a significant difference in baseline IPSS data between the 2 arms at 16 ± 7 compared with 18 ± 6.0, respectively (P = .80). Among these patients with available data, the mean IPSS improvement after the procedure was 8 points with PUL versus 6 points with Rezum (P = .60). Further, the absolute IPSS scores for all evaluable patients were significantly better post-procedure, at 8.6 ± 5 with PUL compared with 15.6 ± 9.2 with Rezum (P = .001). Patients in the PUL arm also had a significantly better quality of life, with an IPSS QoL of 1.5 ± 1.5 versus 2.5 ± 1.9 with Rezum (P = .04).

The PUL cohort also had better results on the Male Sexual Health Questionnaire-ejaculatory dysfunction (MSHQ-EjD) assessment. MSHQ-EjD results were 12.2 ± 2.7 for PUL versus 9.2 ± 5.1 for Rezum (P = .04). “PUL patients reported the ability to ejaculate more often during sexual activity and trended toward better outcomes in volume of ejaculate,” the investigators wrote.

There was not a significant difference in MSHQ-EjD bother scores at 1.1 ± 1.4 versus 1.5 ± 1.6 in the PUL and Rezum arms, respectively (P = .4). However, the investigators observed a significant difference in scores on the Sexual Health Inventory for Men (SHIM) at 14.8 ± 8.6 versus 9.2 ± 7.2, respectively (P = .02).

“These data suggest the UroLift System treatment provides patients a superior experience with better preservation of sexual function, lower catheterization rates, less daily interference, and better overall satisfaction at one month following treatment compared to Rezum,” coauthor Ronald Tutrone, MD, Chesapeake Urology Research Associates in Baltimore, Maryland, stated in the press release. “The UroLift System is an accepted standard of care treatment for men with enlarged prostate and the PUL is recommended by the American Urologic Association BPH Treatment Guidelines.”

REFERENCES

DE NOVO CLASSIFICATION GRANTED FOR BPH DEVICE

Olympus recently announced the FDA de novo classification of the iTind device, a nonsurgical device for the minimally invasive treatment of benign prostatic hyperplasia (BPH). The iTind device was developed by the Israeli-based medical device manufacturer Medi-Tate. Through an investment in Medi-Tate, Olympus holds the exclusive right to distribute Medi-Tate products in the US, including the iTind device.

The flexible 3-strut nitinol device, which can be placed during an in-office procedure, gently expands over 5 days to create channels that allow urine to flow and reshape the prostate, Olympus said in a press release.

REFERENCE

REFERENCE

CATHETER SYSTEM
continued from page 22

toward regulatory approval.

“ Compared with UroLift or Rezum, the benefits of the Optilume system for improving symptoms and peak flow rate occur earlier and are more pronounced, and its benefits also occur earlier than TURP,” he said.

Analyses performed with men stratified by balloon size showed that the level of symptom improvement and its durability were similar regardless of balloon size. However, maximum symptom relief was achieved by day 30 using the small balloon whereas it took 6 months to achieve maximum symptom relief with the large balloon.

Analyses of improvements in peak flow rate showed that the large balloon was associated with significant improvement within the first 30 days, but there was a slight deterioration in benefit at 1 year. Peak flow rate improvements were relatively smaller using the small and medium balloons, but peak flow still increased to about 17 mL/sec and remained stable throughout the 1-year follow-up.

“Based on these observations, only the small and medium balloons are being used in the PINACLE trial,” Kaplan said.

Safety was favorable, and there were no changes in sexual function.

Kaplan is the principal investigator for EVEREST-1.

Disclosure: Urotronic provided funding for the study.
Patients undergoing post-URS stent placement more likely to visit ED

Study results show wide variation in stent placement following ureteroscopy

Cheryl Guttman Krader, BSPharm
Urology Times® Contributing Editor

The Michigan Urological Surgery Improvement Collaborative (MUSIC) sought to provide insight on stent use following ureteroscopy and its impact on unplanned health care use.

The recent analysis included ureteroscopic procedures for urinary stone disease from the MUSIC Reducing Operative Complications from Kidney Stones (ROCKS) clinical registry. It found that stent placement after ureteroscopy was common, varied substantially across urologists as well as practices, was associated with certain demographic and clinical characteristics, and increased the likelihood of a postoperative emergency department (ED) visit.

Spencer C. Hiller, MD, Endourology Fellow at the University of Michigan in Ann Arbor, presented the findings on behalf of his MUSIC colleagues. Hiller said, “It is common practice to place a ureteral stent after ureteroscopy for urinary stone disease.

"Because of our finding that patients with a stent are more likely to have an ED visit, we recommend that efforts should be made to identify patients suitable for stent omission in order to decrease these unplanned health encounters."

Spencer C. Hiller, MD

“Several studies have demonstrated that stents are associated with patient discomfort, but the impact of stent placement on unplanned health care utilization is less clear,” added Hiller, working with Casey Dauw, MD, and colleagues.

The study, presented at the 2020 American Urological Association Virtual Experience included all patients who underwent primary ureteroscopy for urolithiasis from June 2016 to May 2019 in the MUSIC ROCKS clinical registry. After excluding urologists and practices with fewer than 10 ureteroscopies during the study period and patients having a second-look ureteroscopy, bilateral procedure, or with stones measuring greater than 2 cm, investigators identified 9662 procedures performed by 137 urologists representing 24 separate practices across the state of Michigan. Both academic and private practices, including group and solo practices, were represented.

Overall, a stent was placed following ureteroscopy in 73% of procedures, but the utilization rate ranged from 11% to 100% among providers and from 34% to 100% among practices. Investigators saw profound variation in stent use irrespective of case volume, even among urologists within individual group practices.

Bivariate and multivariate analyses were carried out to identify demographic and clinical characteristics associated with stent placement. Findings of the logistic regression analysis showed that the likelihood of stent placement decreased by 75% when a ureteral stent was present prior to ureteroscopy and by 31% in cases with a renal stone location. The likelihood of stent use increased by 5.43-fold in cases with ureteral access sheath use.

Increasing age was also a risk factor for stent placement. Relative to cases with a stone measuring 5 mm or less, stones larger than 5 mm to 10 mm were associated with a 1.89-fold increased risk of stent placement, and 4.68-fold in cases with stones larger than 10 mm.

In a bivariate analysis, the use of a stent after ureteroscopy was associated with a statistically significant increase in the rate of both ED visits and hospitalizations. The ED visit rate was 8.5% in cases where a stent was placed versus 7.1% where a stent was not used (P = .018), and the hospitalization rate was 3.8% for cases with a stent versus 2.9% for cases without a stent (P = .03).

Clinical characteristics associated with stent placement were measured as follows:

<table>
<thead>
<tr>
<th>Stent placed</th>
<th>No stent placed</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency department visit rate</td>
<td>8.5%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Hospitalization rate</td>
<td>3.8%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

Source: Spencer C. Hiller, MD

Hiller concluded, “Because of our finding that patients with a stent are more likely to have an ED visit, we recommend that efforts should be made to identify patients suitable for stent omission in order to decrease these unplanned health encounters.”

REFERENCE

Positive phase 3 results for hyperoxaluria agent

Alnylam Pharmaceuticals Inc recently announced positive phase 3 results from the ILLUMINATE-A study of lumasiran, an investigational RNAi therapeutic targeting hydroxyacid oxidase 1 in development for the treatment of primary hyperoxaluria type 1. The clinical data were presented at the European Renal Association-European Dialysis and Transplant Association International Congress virtual event on June 6-9. Lumasiran achieved the ILLUMINATE-A primary end point with a 53.5% mean reduction in urinary oxalate relative to placebo (P = 1.7x10^-14) and showed a 65.4% mean reduction in urinary oxalate relative to baseline. All tested study secondary endpoints were met, including the proportion of patients achieving near-normalization (84%) or normalization (52%) of urinary oxalate, compared with 0% in the placebo group. Lumasiran administration was associated with an encouraging safety and tolerability profile, with no serious or severe adverse events and with mild injection site reactions as the most common drug-related adverse event. Based on the ILLUMINATE-A results, Alnylam filed a new drug application (NDA) with the FDA. The FDA has granted a priority review for the NDA and has set an action date of December 3, 2020, under the Prescription Drug User Fee Act.

REFERENCE
Men’s health clinics marketing campaigns prompt concerns
Clincis giving “significant misinformation” about erectile dysfunction, hypogonadism treatments

Cheryl Guttman Krader, BSPharm
Urology Times® Contributing Editor

Findings from a study characterizing the providers and services offered by stand-alone commercialized men’s health clinics should be eye-opening and alarming for urologists, said Jagan K. Kansal, MD, MBA, at the 2020 American Urological Association Virtual Experience.

“Our review shows that these clinics are providing significant misinformation about treatment of erectile dysfunction and hypogonadism. Furthermore, they are often offering treatments that are not supported by evidence or have no therapeutic benefit but that may carry large out-of-pocket costs,” Kansal said.

“We believe that urologists should be aware of what is happening in the men’s health mainstream landscape because patients we see may have questions related to information they have gotten from these clinics or their websites or even have complications after being treated at one of them.”

Kansal conducted the study as a fellow in Men’s Sexual and Reproductive Health at the Medical College of Wisconsin, Milwaukee, working with Peter Dietrich, MD, Amy Guise, and colleagues. After completing the fellowship in June, he will be leading the Men’s Health Clinic at the DuPage Medical Group, DuPage County, Illinois.

The research analyzed content found on the web-sites for men’s health clinics identified through a Medical Group, DuPage County, Illinois. After completing the fellowship in June, he will be leading the Men’s Health Clinic at the DuPage Medical Group, DuPage County, Illinois.

The research analyzed content found on the web-sites for men’s health clinics identified through an internet search using the terms “men’s health clinic.”

KANSAL

REFERENCE

Exceeding exercise guidelines may reduce likelihood of low T in men
Link between lower activity level, low testosterone significant in obese men

Kristie L. Kahl
Editorial Director, Urology Times®

Men whose activity exceeded guideline-based exercise levels experienced a decreased likelihood of lower serum testosterone, according to study results presented at the 2020 American Urological Association Virtual Experience.

Richard J. Fantus, MD, from the University of Chicago, explained during a press briefing that the AUA republished guidelines in 2018 stating that all men with testosterone deficiency should be counseled regarding weight loss programs as an initial treatment strategy.

“(Weight loss programs) are relatively inexpensive and safe and reversible,” he added, saying that losing weight can improve a man’s testosterone and improve the signs and symptoms associated with testosterone deficiency.

In 2018, the Physical Activity Guidelines Advisory Committee (PAGAC) set a target activity goal of 500-1000 metabolic equivalent of task (MET) minutes per week.

See LOW T page 26
Testosterone levels show steady decrease among young US men

Decline in total testosterone observed even among men with normal body mass index

Kristie L. Kahl
Editorial Director, Urology Times®

From 1999 to 2016, testosterone levels have declined in adolescent and young adult men (AYA), according to results presented at the 2020 American Urological Association Virtual Experience. “Overall male testosterone decline can be attributed to multiple etiologies. The United States has an aging population with older males exhibiting lower testosterone levels. Furthermore, overall population has an increase in comorbidities, including diabetes, which may have cause this testosterone decrease nationally,” Soum Lokeshwar, MD, MBA, incoming urology resident at Yale School of Medicine, New Haven, Connecticut, said during a press briefing.

“However, most of these explanations for testosterone deficiency may be attributed to age. This time-dependent decline in testosterone has not been investigated in adolescent and young adult males,” added Lokeshwar, who was at the University of Miami Miller School of Medicine, Miami, Florida, at the time of the study.

Testosterone deficiency has a prevalence of 10%-40% among adult males, and 20%-30% among AYA men aged 15-39 years, he added. Therefore, Lokeshwar and colleagues hypothesized that serum total testosterone levels will decline in AYA men.

The investigators used data from the National Health and Nutrition Examination Surveys (NHANES) from 1999 to 2016 to analyze serum testosterone level changes over time in 4045 AYA males. During the study periods, 3 different assays (Biotin-Streptavidin from 1999-2004, IS-Liquid Chromatography from 2011-2012, and High-Performance-Liquid-Chromatography Tandem Mass Spectrometry from 2013 onwards) were used. However, of note, they demonstrate comparable testosterone values with only some additional accuracy in the latest modality, Lokeshwar said.

After controlling for confounders—including year of study, age, race, BMI, comorbidity status, alcohol and smoking use, and level of physical activity—total testosterone was lower among men in the later (2011-2016) versus earlier (1999-2000) cycles ($P<0.001$). Mean total testosterone decreased from 1999-2000 (605.39 ng/dL), 2001-2004 (567.44 ng/ dL), 2011-2012 (424.96 ng/dL), 2013-2014 (431.76 ng/dL), and 2015-2016(451.22 ng/dL; all $P<.0001$).

Elevated BMI was associated with reduced total testosterone levels ($P<.001$), with the mean BMI increasing from 25.83 in 1999-2000, to 27.96 in 2015-2016 ($P=0.0006$). Lokeshwar noted that even men with a normal BMI (18.5-24.9) had declining total testosterone levels ($P<.05$) during the same time frames.

Potential causes include increased obesity/BMI, assay variations

According to Lokeshwar, potential causes for these declines could be increased obesity/BMI, assay variations, diet/phytoestrogens, declined exercise and physical activity, fat percentage, marijuana use, and environmental toxins.

“We’ve seen that lower values of testosterone have been associated with increased comorbidities and an increase risk for all-cause mortality. This decline specifically, in these young adult men, with increased obesity may lead to an increase in precocious cancer,” Lokeshwar said, adding such decreases can also result in a lower libido and an increased risk for erectile dysfunction.

“This is especially worrisome in this young adult age group, as many men feel stigma and are less likely to seek care for these low libido and erectile dysfunction.” Lokeshwar added. “Testosterone levels in AYA men are used as the benchmark normal levels for testosterone. This is very scary, because generally, when we think of normal values of testosterone, we treat based upon this age group. This may ultimately lead to the undertreatment of testosterone deficiency, which can have large ramifications and severe consequences.”

REFERENCE
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Gene-mediated therapy for high-grade NMIBC delivers positive results in trial

72.9% of patients with papillary disease achieve high-grade RFS at 3 months after initial treatment

Cheryl Guttman Krader, BSPharm
Urology Times® Corresponding Editor

Intervesical nadofaragene firadenovec (recombinant adenovirus interferon alfa with Syn3 [rAD-IFNα/ Syn3], FerGene) is a promising therapeutic option for patients who have bacillus Calmette-Guérin (BCG)-unresponsive high-grade non–muscle invasive bladder cancer (NMIBC), said Stephen A. Boorjian, MD, at the 2020 American Urological Association Virtual Experience.1

He reported results from a subgroup analysis of a multicenter, phase 3, open-label trial, demonstrating that the novel intravesical gene-mediated therapy was well tolerated, safe, and efficacious, specifically highlighting the findings from the cohort of patients with papillary disease.

“The optimal management for patients with BCG-unresponsive NMIBC continues to be investigated because many of these patients are either medically unfit for or unwilling to undergo radical cystectomy,” said Boorjian, Carl Roschen Professor of Urology at the Mayo Clinic in Rochester, Minnesota.

“In this phase 3 study, nadofaragene firadenovec demonstrated a clinically meaningful benefit in a patient population for whom nonsurgical treatment options have been limited.”

Nadofaragene firadenovec combines a recombinant adenovirus vector encoding the human IFNα2b gene with the excipient Syn3, which enhances transduction of the adenovirus vector into bladder cells. A phase 2 study completed several years ago investigated 2 doses of nadofaragene firadenovec (1.1 or 3 x 10^11 vp/mL) in 40 patients with BCG-unresponsive high-grade NMIBC. Its results showed that at 12 months after the first instillation, 14 patients (35%) were free from high-grade recurrence.

“Of particular interest in the phase 2 study, the 12-month, high-grade, recurrence-free survival rate among patients with papillary-only tumors was 50%,” Boorjian said.

The phase 3 study investigated nadofaragene firadenovec 3 x 10^11 vp/mL in patients with high-grade NMIBC who met the FDA definition for BCG-unresponsive disease. A total of 157 patients were enrolled, received at least 1 treatment, and were included in the safety population. Six patients who did not meet the definition of BCG unresponsiveness were excluded from the efficacy population, leaving an evaluable cohort of 103 patients with carcinoma in situ (CIS) and 48 patients with papillary disease.

The investigational gene-mediated therapy was instilled into the bladder with a targeted dwell time of 1 hour. Efficacy was evaluated based on findings from cystoscopy and urine cytology performed every 3 months, with biopsy if indicated, and a mandatory biopsy performed at 12 months after first instillation. Repeat treatments could be given every 3 months to patients who remained free from high-grade recurrence.

“The quarterly delivery schedule for this agent was favorable to both patients and providers,” Boorjian said.

The primary end point analysis showed that a complete response was achieved by 55 of 103 patients with CIS (53.4%), which occurred by 3 months after the first instillation. Among the 48 patients with papillary disease, 35 patients (72.9%) achieved high-grade recurrence-free survival at 3 months after their initial treatment.

Analyses of data collected at 12 months showed that, among patients who achieved a complete response, 21 (60%) of those with papillary disease and 25 (45.5%) of those with CIS remained free from high-grade recurrence.

Only 3 patients (6.3%) from the papillary disease cohort experienced progression to muscle invasive disease during the available follow-up. Within the CIS cohort, 5 patients (4.9%) progressed to muscle invasive disease.

The safety analysis for the phase 3 trial included all 157 enrolled patients who received at least 1 dose of nadofaragene firadenovec. It showed that the most common study drug–related adverse events (AEs) were irritative lower urinary tract symptoms, which were transient.

Three patients (1.9%) experienced a serious study drug–or procedure-related AE. Those AEs included single episodes each of sepsis, syncope, and hematuria. In addition, 3 patients (1.9%) discontinued the study drug because of a treatment-emergent AE. There were no deaths in the study.

Disclosure: Dr Boorjian is a consultant for Ferring, Sanofi, ArTara Therapeutics, and FerGene.

REFERENCE

Is low-intensity surveillance feasible for patients with high-risk NMIBC?

Study compares regimens for patients with high-risk non–muscle invasive bladder cancer

Louise Gagnon
Urology Times® Correspondent

Low-intensity cystoscopic surveillance of patients with high-risk, non–muscle invasive bladder cancer (NMIBC) was associated with similar bladder cancer outcomes compared with American Urological Association (AUA)-recommended, high-intensity surveillance.

This is according to study findings presented at the 2020 American Urological Association Virtual Experience and published in PLOS One.1,2

“Less intensive surveillance may be reasonable for high-risk NMIBC patients,” said Michael E. Rezaee, MD, MPH, the study’s lead author and a urology resident at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire, in See SURVEILLANCE page 29

7/10/20   1:41 PM
Addition of avelumab to BSC after chemo improves OS in advanced UC

Treatment significantly extends overall survival in patients with advanced urothelial cancer

Beth Fand Incollingo
Managing Editor, CURE®

Avelumab (Bavencio) as a maintenance treatment after chemotherapy significantly extended overall survival (OS) in patients with advanced urothelial cancer, according to findings from the phase 3 JAVELIN Bladder 100 trial. The results of the study of best supportive care (BSC) with or without immunotherapy after frontline platinum-based chemotherapy were presented in a presscast in advance of the 2020 American Society of Clinical Oncology Virtual Scientific Program®.

Investigators reported that avelumab improved survival by 7.1 months compared with BSC alone in patients with unresectable locally advanced or metastatic urothelial cancer that had responded to or remained stable on chemotherapy. The results represent the largest survival benefit seen to date in advanced urothelial cancer in the maintenance setting, and the first showing efficacy of avelumab immediately after initial chemotherapy, a time when recurrence frequently occurs, ASCO stated in a press release.

Avelumab and other immunotherapies that inhibit PD-1 or PD-L1 are standard second-line treatments for patients in this population whose disease progresses after platinum-based chemotherapy, but only 22% to 55% of eligible patients receive it, with a minority of those gaining a durable clinical benefit, reported the study’s lead author, Thomas Powles, MD, a professor of genitourinary oncology and Director of Barts Cancer Centre in London.

The trial included 700 patients with unresectable locally advanced or metastatic urothelial cancer who had experienced no disease progression following 4 to 6 cycles of gemcitabine chemotherapy given with either cisplatin or carboplatin. Of the total population, 350 patients were randomized to receive maintenance avelumab at an IV dose of 10 mg/kg every 2 weeks along with BSC and 350 were assigned to BSC alone. The patients started their study treatment within 10 weeks of completing chemotherapy. They were further stratified into subgroups based on whether they had visceral vs non-visceral disease when they started chemotherapy, and whether they had experienced a complete or partial response to chemotherapy vs stable disease.

The primary end point was OS, assessed from randomization in 2 primary populations: all randomized patients and those with PD-L1-positive tumors as evaluated by the Ventana SP263 assay. Secondary end points included progression-free survival (PFS), and the subset of patients who did not receive chemotherapy, OS and PFS were assessed within the chemotherapy-naive population.

Researchers reported that avelumab significantly improved survival by 7.1 months compared with BSC alone in patients with locally advanced or metastatic urothelial cancer that had responded to or remained stable on chemotherapy.

Investigators reported that the primary end point of OS was significantly improved in the avelumab group (HR = 0.75, 95% CI 0.62-0.90, P = 0.002). At 12 months, the OS rate was 43% vs 28% in the BSC group.

In addition, avelumab demonstrated a significant improvement in PFS (HR = 0.73, 95% CI 0.60-0.89, P = 0.002). At 12 months, the PFS rate was 18% vs 9% in the BSC group.

Investigators also observed that high-risk patients who were surveilled less often underwent fewer transurethral resections (37 vs 99 per 100 person-years, P < 0.001). The majority (n = 520) underwent low-intensity surveillance (1-5 cystoscopies over 2 years) and the majority (n = 1022) underwent high-intensity surveillance, creating an opportunity to study the impact of such surveillance, explained Rezaee.

The study was comprised of 1542 VA patients diagnosed with high-risk NMIBC between 2005 and 2011, with follow-up taking place through 2014. The minority (n = 520) underwent low-intensity surveillance (1-5 cystoscopies over 2 years) and the majority (n = 1022) underwent high-intensity surveillance (≥6 cystoscopies over 2 years).

Risk of death did not differ significantly between groups

Investigators sought to assess if there was any difference in the risk of bladder cancer death between the 2 groups. They found that the risk of bladder cancer death did not differ significantly between the low-intensity (8.1%) and high-intensity (9.1%) surveillance groups at five years (P = 0.61).

Investigators also observed that high-risk patients who were surveilled less often underwent fewer transurethral resections (37 vs 99 per 100 person-years, P < 0.001).

“If they underwent fewer cystoscopies, they were taken to the operating room for a resection less often,” Rezaee said. “Fewer cystoscopies and resections did not translate into worse mortality risk in the low-intensity surveillance group.”

Florian R. Schroek, MD, senior author of the paper and chief of urology at the White River Junction VA Medical Center in Vermont, is in the beginning stages of designing a randomized trial to determine if less frequent cystoscopy is safe in patients with high-risk NMIBC. The present study is limited by its retrospective design and unmeasured confounders, restricting the implications of its results, explained Rezaee.

A randomized trial may serve to demonstrate which patients need more surveillance and which need less. “It is totally plausible to think that there are subgroups of high-risk patients who may need less surveillance while some patients may warrant even more surveillance,” he said. “We will be able to get more granular data from a prospective trial.

“We have been doing this [high-intensity surveillance] because it is habit, not because we know it’s the best thing to do,” said Rezaee. “There is no level 1 evidence to support the [AUA] guideline. We need to determine what the best surveillance strategy is.”

He pointed out that cystoscopies and subsequent resections are not benign procedures.

“The need for less frequent cystoscopy is also a wish of a lot of patients because it is not comfortable [to undergo],” he said. 91

REFERENCE
Intervention enhances antibiotics adherence for in-office cystoscopy

Quality improvement protocol increases compliance with American Urological Association guidelines

Jason M. Broderick
Associate Editorial Director, Urology Times®

A basic quality improvement protocol enhanced compliance with American Urological Association (AUA) guidelines for periprocedural antibiotic prophylaxis for high-risk patients receiving in-office cystoscopy, according to a study published in the Journal of Urology.1

The AUA best practice guideline for periprocedural antibiotic prophylaxis recommends the treatment when there is a greater than 10% potential infection rate. Because in-office cystoscopic procedures in high-risk cases are linked to a higher infection risk, antibiotic prophylaxis is indicated. Investigators from the division of urology in the department of surgery at the Virginia Commonwealth University School of Medicine in Richmond, Virginia, devised and evaluated a 4-step intervention to optimize appropriate delivery of antibiotics in this setting. Overall, the appropriate administration of antibiotics in this setting was increased by 49.1% (P < .0001) through use of the intervention.

“This study demonstrates that implementation of a 4-step QI initiative was able to significantly improve the rate of appropriate antibiotic administration in our population of patients undergoing office based cystoscopy according to published AUA guidelines,” lead study author Natalie Swavely, MD, and coauthors wrote. “This protocol can easily be incorporated into any urology practice.

The protocol also can easily be adapted to any changes in guideline recommendations based on emerging research.”

The 4-point intervention was composed of a “yes/no” checklist to identify patients who were high risk; the urology provider assessing the checklist and electronically place an antibiotics order; appropriate patients receiving single doses of the most commonly recommended antibiotics (ciprofloxacin, sulfamethoxazole/trimethoprim and gentamicin) through immediate nurse-directed administration; and, during the preprocedural time-out, a review of the checklist and antibiotic administration.

To assess the intervention, Swavely et al conducted a retrospective analysis to compare patients’ antibiotic adherence 3 months prior and 3 months after the intervention was implemented. Overall, the analysis included 307 patients, comprising 157 prior to implementation of the intervention and 150 after the protocol was put in place.

Among the 157 patients in the pre-intervention group, the median age was 58.27 years and 58.6% of patients were male. Patients were indicated for cystoscopy due to microscopic hematuria (15.9%), gross hematuria (12.1%), urinary retention (3.8%), lower urinary tract symptoms (12.7%), bladder cancer surveillance (17.8%), urinary incontinence (5.1%), neurogenic bladder (1.9%), stent removal (22.9%), upper tract cancer surveillance (3.2%), recurrent UTIs (1.9%), fistula (0.6%), urethral diverticulum (0.6%), and chyluria (1.3%).

The 150 patients in the postintervention group had a median age of 58.11 years and 75.3% of patients were male. Patients were indicated for cystoscopy due to microscopic hematuria (12.7%), gross hematuria (22%), urinary retention (5.3%), lower urinary tract symptoms (20.7%), bladder cancer surveillance (22%), urinary incontinence (1.3%), neurogenic bladder (2%), stent removal (11.4%), upper tract cancer surveillance (1.3%), and recurrent UTIs (1.3%).

In the pre-intervention cohort, 76.4% (n = 120) of patients were classified as high risk and thus indicated for antibiotic prophylaxis; however, only 31.7% (n = 38) of these patients were actually administered the treatment. In the post-intervention arm, 69.3% (n = 104) of patients were indicated for antibiotic prophylaxis based on their high-risk status. Of these patients, 80.8% (n = 84) actually received the treatment.

“Our quality improvement (QI) initiative was straightforward and easy to implement with buy-in from providers and clinic nursing staff. In addition, the QI initiative added minimal time and no increase in cost to our high-volume urology clinic at a tertiary care academic teaching hospital,” Swavely et al wrote in their conclusion.

REFERENCE

AVELUMAB
continued from page 29

objective response, and safety. Patients were followed for a median of more than 19 months.

Investigators found that avelumab plus BSC generated a median OS of 21.4 months compared with 14.3 months for BSC alone (hazard ratio [HR], 0.69; 95% CI, 0.65-0.86; 1-sided P = .0005).

In patients whose tumors were PD-L1-positive (n = 358), median OS had not yet been reached in the avelumab group and was 17.1 months in the BSC-alone group (HR, 0.65; 95% CI, 0.40, 0.79; 1-sided P = .0003). An OS benefit was also observed across all prespecified subgroups, although those with visceral disease prior to chemotherapy had worse outcomes than those who started with nonvisceral disease.

PFS was 38% better in the avelumab arm compared with the BSC-alone group across all study patients (3.7 vs 2.0 months, respectively) based on blinded independent central review (HR, 0.62-95% CI, 0.52-0.73) and was 44% improved in the avelumab group compared with the BSC-alone group in patients with PD-L1-positive tumors (HR, 0.56; 95% CI, 0.43-0.73).

“In urothelial cancer, patients have high PD-L1 expression and high tumor mutation burden. Response rates associated with immune therapy are pretty high,” Powles said. “This means that checkpoint inhibitors can work quite well in urothelial cancer.”

The investigators plan to continue to follow patients to see how long response is maintained. Adverse events (AEs) of grade 3 or higher occurred in 47.4% of patients who received avelumab plus BSC vs 25.2% in those who received BSC alone.

The most common grade 3 or higher AEs were urinary tract infection, anemia, hematuria, fatigue, and back pain. The safety profile of avelumab was consistent with previous studies of monotherapy, the authors stated.

“Avelumab frontline maintenance in patients whose disease has not progressed with platinum-based induction therapy is a new frontline standard of care for advanced urothelial carcinoma,” Powles said.  

REFERENCE
Abstract LB1.
Rechargeable neuromodulation system safe and efficacious through 1 year

Reduction in urinary urgency incontinence episodes “quite significant,” investigator says

Cheryl Guttman Krader, BSPharm
Urology Times® Contributing Editor

Results from 1 year of follow-up of patients enrolled in a pivotal clinical trial show that sacral neuromodulation (SNM) with a miniaturized, implanted rechargeable device (Axonics System) provides highly safe and durable effective treatment for urinary urgency incontinence (UUI), said Howard B. Goldman, MD, at the 2020 American Urological Association Virtual Experience.

Goldman, a professor of urology at Cleveland Clinic Lerner College of Medicine in Cleveland, Ohio, presented the research on behalf of the study investigators. He reported that reduction in UUI episodes observed at the study’s primary end point at 6 months were sustained through 1 year, and the safety profile of SNM with the rechargeable device was consistent with SNM experience reported in the literature.

“Patients also benefited with clinically significant improvements in quality of life, had a high level of satisfaction, and found the charging task user friendly,” Goldman said.

The rechargeable SNM system received FDA approval for treating UUI, urinary urge frequency, and urinary retention in November 2019. The pivotal trial supporting the system had a single-arm design and enrolled 129 patients at 19 centers in the United States and western Europe. Subjects were eligible for inclusion if they had 4 or more UUI episodes in a 3-day diary, including 1 or more episode per day. Individuals with more than a minimal level of stress incontinence, anatomic urinary tract obstruction, or an underlying neurological condition were excluded.

The trial’s participants ranged in age from 21 to 86 years (mean age, 59 years) and were almost entirely women (98%). Mean UUI episodes per day at baseline was 5.6.

The primary end point for the study assessed the rate of therapy responders at 6 months. Ninety percent of women, defined as participants achieving a 50% or greater reduction in UUI episodes per 3 days, achieved the end point. The therapy responder rate was 89% at 1 year.

“The reduction in UUI episodes was quite significant in the study cohort,” Goldman said.

“At 6 months it had decreased to 1.3 episodes per day and it was 1.4 at 1 year.”

Howard B. Goldman, MD

“All of the improvements were statistically significant and far exceeded the minimum 10-point change that is considered clinically significant," Goldman said.

At 1 year, 93% of patients said they were satisfied with the therapy, and 92% said they would undergo the therapy again with the same expected results (table). Questions pertaining to the charging of the device showed that it was considered easy by 89% of participants, and 96% rated the frequency and duration of charging as acceptable. Ninety-five percent of participants reported recharging the device no more than once a week, and 86% reported that the total charge time was 60 minutes or less.

There were few adverse events (AEs) in the series and no serious device-related AEs. The most common AE was uncomfortable change in sensation or magnitude of stimulation (5%).

No patient underwent surgical intervention for pain, but 3 patients underwent a revision and the device was explanted in 1 patient due to infection.

“Interestingly, 6 patients had magnetic resonance imaging during the year after implantation, which was full body in 4 participants, without any evidence of adverse events,” Goldman said.

The rechargeable SNM device is also approved for the treatment of fecal incontinence, and changes in fecal incontinence were evaluated prospectively in the pivotal trial. Data collected in the subgroup of patients who had fecal incontinence at baseline showed they experienced a statistically significant improvement at 6 months and even greater benefit at 1 year.

“Overall, 91% of patients who had bowel symptoms at study entry were satisfied with how that problem was helped as well,” Goldman said.

Disclosures: Dr Goldman is a study investigator and a consultant to Axonics Modulation Technologies. Axonics Modulation Technologies provided funding for the study.

REFERENCE

TABLE. AXONICS SYSTEM: PATIENT RESPONSES TO QOL QUESTIONNAIRE

<table>
<thead>
<tr>
<th>% of patients who answered</th>
<th>% of patients who answered</th>
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<tr>
<td>93% of patients said they were satisfied with the therapy</td>
<td>92% said they would undergo the therapy again with the same expected results</td>
</tr>
<tr>
<td>89% considered charging the device to be easy</td>
<td>96% rated frequency and duration of charging as acceptable</td>
</tr>
<tr>
<td>96% reported recharging the device no more than once a week</td>
<td>86% reported total charge time was 60 minutes or less</td>
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Source: Howard B. Goldman, MD
American Urological Association meeting moves from Washington to the web

**COMPiled by Benjamin P. Saylor**

Saylor is content managing editor for *Urology Times*.

Originally scheduled to be held in Washington, DC from May 15-18, this year’s American Urological Association annual meeting was among countless events worldwide that were affected by the coronavirus disease 2019 (COVID-19). The cancellation of the traditional in-person gathering led to the AUA posting “virtual education” materials online (www.auavirtual.org), as well as hosting live web presentations of meeting content in May and June.

In addition to the meeting’s traditional scientific program of poster and podium presentation abstracts, the AUA also conducted virtual editions of its “Crossfire” debates, panel discussions, state-of-the-art lectures, and more. Highlights included a keynote address from Anthony Fauci, MD, as well as the release of new clinical guidelines for advanced prostate cancer, microhematuria, and disorders of ejaculation, as well as an amendment to a guideline for benign prostatic hyperplasia. You can follow our continuing coverage of 2020 AUA materials for benign prostatic hyperplasia. You can follow our continuing coverage of 2020 AUA materials at www.urologytimes.com/conference/aua.

What follows is just some of the research highlighted at this meeting.

**Blue light cystoscopy enables earlier detection of invasive bladder tumors**

Analyses of data from a multi-institutional registry show that blue light cystoscopy (BLC) using hexaminolevulinate HCl (Cysview) detects invasive bladder tumors that are missed by white light cystoscopy (WLC). You can follow our continuing coverage of 2020 AUA materials at www.urologytimes.com/conference/aua.

Of the 3514 lesions, 494 (14%) were invasive (pT1) and 818 (23.2%) were not visible on WLC but detected using BLC (WLC-/BLC+). Of the 494 invasive lesions, 55 (11%, in 47 unique patients) were WLC-/BLC+. Further analyses of the invasive lesions showed that 13.8% of the pT1 tumors and 6% of the pT2 tumors were WLC-/BLC+, meaning they were not visible on WLC and detected only because of BLC. The 55 invasive WLC-/BLC+ lesions represented 7% of the WLC-/BLC+ lesions. They included 48 pT1 tumors and 7 pT2 tumors. During TURBT among the 47 patients with invasive WLC-/BLC+ lesions, 28 (60%) were found to have concomitant CIS, and 23 (49%) had at least one other T1 lesion.

**Intermediate 10-year data presented for MRI-guided laser focal therapy**

MRI-guided laser focal therapy manufactured by HALO Diagnostics showed tremendous precision and fewer side effects than standard treatment options in patients with localized prostate cancer, according to interim 10-year results from a phase 2 trial. The procedure yielded a 100% prostate cancer–specific survival rate. The safety profile showed that the rates of erectile dysfunction, infection, and incontinence were all under 1% with MRI-guided laser focal therapy. These rates show a tremendous benefit over standard whole-gland prostatectomy, which is associated with a 25% risk of urinary incontinence and 50% risk of erectile dysfunction.

At this analysis, the study included over 170 men with low-to-intermediate risk or recurrent prostate cancer who volunteered to enroll. Inclusion criteria were aged ≥45 years; clinical stage T2c or T2a; Gleason score of 3+3 or 3+4 or 4+3 or ≤3 biopsies cores with prostate cancer; and a PSA density of ≤0.375. At the 10-year follow-up, the overall survival rate was 98%, the prostate cancer–specific survival rate was 100%, and the metastasis-free survival rate was 99%. According to HALO Diagnostics, recruitment of equipment have FDA 510(k) clearance for use in patients with localized prostate cancer, as well as 86% of subjects could place and orient the device and 79% were able to remove it without assistance. Safety of the device was demonstrated, as there were no clinically important direct or reflexive effects on heart rate, rhythm, or blood pressure during stimulation, nor any untoward issues in the vagina due to the device.

Clinical utility was evaluated by analyses of changes in voids per 24 hours, urgent voids per 24 hours, changes in urinary urge, and incontinence-related quality-of-life questions from 3 validated questionnaires. In the ITT cohort, similar improvements in these parameters were seen in both the treatment and control groups. However, signals of treatment benefit were observed in an efficacy-analysis subgroup comprised of 11 women (7 treatment subjects, 4 controls). The study goal of 200 men has been achieved as of June 16, 2020. The study has been extended to 20 years. The final iteration of the device will be a self-contained unit. However, as of June 16, 2020, prn.to/2YJDcsE.

**Wearable neuromodulation device shows promise for overactive bladder**

A nonimplanted, intravaginal neuromodulation device (FemPulse) for treating overactive bladder symptoms demonstrated favorable results in a feasibility study assessing wearability, safety, and clinical utility, reported Suzette E. Sutherland, MD, MS, FPMRS, director of Female Urology at the University of Washington School of Medicine in Seattle.

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

In an intent-to-treat (ITT) cohort that included all 19 women who completed the study, the device was fit easily and was reported to be comfortable. In addition, it exhibited good self-manoeuvrability, as 86% of subjects could place and orient the device and 79% were able to remove it without assistance.

Safety of the device was demonstrated, as there were no clinically important direct or reflexive effects on heart rate, rhythm, or blood pressure during stimulation, nor any untoward issues in the vagina due to the device.

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

**REFERENCES**

A diagnosis of prostate cancer was life-changing news for over 170,000 people per year.

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It’s time to prepare for upcoming E/M coding changes

Deletion of code 99201 among evaluation/management coding changes for 2021

The year 2020 has been challenging for everyone. The Centers for Medicare & Medicaid Services (CMS) has made several unprecedented changes to adapt to the coronavirus disease 2019 (COVID-19) public health emergency (PHE), with other payors following suit. However, as stay-at-home orders are lifted, we are seeing several payors roll back or partially roll back some of the implementations regarding the use of telehealth. The health care system changes are only a fraction of the challenges each urology office is facing. We have been impressed with the innovation and outside-the-box thinking that many have taken on and shared with others to meet the challenges facing us. We encourage you to keep thinking and trying new things.

For this article, we are going to focus on a “burning” question that we have been asked repeatedly: With all that is happening, is CMS going to move forward with the adoption of new guidelines for E/M office coding?

Recall that the final rule for 2020, released in November 2019, included a commitment to adopt the upcoming changes in evaluation and management (E/M) codes, revise the relative value units (RVUs) for office and other outpatient E/M codes, and add or adopt codes to address additional time and impacts on certain specialties.

History (H) and physical (P) examination will no longer follow the requirements currently included in the guidelines for 1995 or 1997. Instead, the new guidelines require only that the documentation include a medically necessary and appropriate H and P.

CMS also partially adopted the proposed documentation changes for 2021 E/M codes to allow for services provided via telehealth during the PHE. In short, our qualified “yes” regarding whether or not CMS will adopt the E/M changes for 2021 is based on what CMS has published. In addition, the American Medical Association (AMA) has indicated they will proceed with an updated publication of the office and other outpatient Evaluation and Management Services Guide, required for use under HIPAA. Our answer is qualified because CMS has not yet issued the final rule and, as we have seen, the agency could make alterations at the last minute.

We will focus on a few highlights of the upcoming changes and the preparations we recommend for the remainder of this year.

First, code 99201 will be deleted. Second, and more importantly, history (H) and physical (P) examination will no longer follow the requirements currently included in the guidelines for 1995 or 1997. Instead, the new guidelines require only that the documentation include a medically necessary and appropriate H and P.

Definition of time amended

The other change adopted for the PHE was the amended definition of time. Although the 2021 updates in current procedural terminology will take things a step further by including revised time ranges for each E/M new and established office visit, the concept has already been implemented during the PHE for telehealth visits. Currently, time can be used as the overriding factor if you spend over 50% of the E/M face-to-face visit time in counseling and/or coordination of care, and document it.

Under the new definition (again, currently allowed for telehealth visits), you can use time to select the appropriate level of service.
reported regardless of how much time you spent in counseling and/or coordination of care. In addition, the new definition of time allows you to count the total time spent during the date of service in support of the E/M encounter. For documentation, you will need to record total time. This includes time spent directly with the patient, reviewing records, discussing with other providers, coordinating care, and so on.

We do not yet know the extent of detail you may need to document. As is the case today, you are not required to document time unless it is to be used to determine the level of service charged. Further, although time is appropriate for some encounters, most urology encounters would be more accurately and efficiently reported by reviewing the medical decision making required.

The new definition of time allows you to count the total time spent during the date of service in support of the E/M encounter.

The new guidelines rely primarily on the medical decision making documented. These proposed changes were not adopted for the PHE but will be adopted on January 1, 2021, for all new (99202-99205) and established (99211-99215) office visit codes. The new guidelines for medical decision making will require some education as the changes published by the AMA have been revised. The changes to this portion of the E/M office new and established patient guidelines include the same main categories of Number of Problems, Amount of Data, and Amount of Risk. What has changed is the way in which these categories will be divided by level.

Number of Problems is now based on severity of problem, with little accommodation for the number of problems addressed. Amount of Data is grouped by category, and the number of categories and amount of data for each category are used to determine the appropriate level of service. Amount of Risk is similar to the existing risk table, but has been simplified by grouping the former three columns of risk into one table representing the risk of morbidity from additional diagnostic testing or treatment.

We urge you to take time this fall to educate yourself on these changes. The American Urological Association and Physician Reimbursement Services will be offering courses on the new system over the remaining months of 2020, as well as providing support in 2021. Further, follow up with your EMR vendor to ascertain what changes if any are being made to your system to accommodate these updates. Although change is always difficult, we feel that these changes will be of great benefit to urologists once they are implemented. Get ready and embrace this challenge.
Cybercrime on the rise during COVID-19 pandemic

An active strategy of prevention and preparedness is essential for all practices

According to several reports, the FBI has experienced a 100% increase in cybersecurity complaints since the coronavirus disease 2019 (COVID-19) pandemic began. Some of the increase is thought to be due to criminals capitalizing on fears, tests, and scam treatments for the virus. Some may be due to nation states attempting to steal valuable scientific research. Much of the rise in complaints may be a consequence of the general shift to remote work: more people online, more activities online, more email, and more challenges for companies in maintaining safe external access to their systems.

According to Interpol, “Cybercriminals are taking advantage of the widespread global communications on the coronavirus to mask their activities. Malware, spyware and Trojans have been found embedded in interactive coronavirus maps and websites. Spam emails are also tricking users into clicking on links which download malware to their computers or mobile devices.”

As urology practices have adapted to the pandemic, increased their telehealth practice, and moved staff to remote locations, they may be more vulnerable to cybercrime. In this article, we will reflect on lessons learned from cyberattacks that result in data breaches, including those on health care entities.

According to the Identity Theft Resource Center, 2019 saw a 17% increase in the number of data breaches over 2018. A data breach is defined as “an incident in which an individual name plus a Social Security number, Driver’s License number, medical record or financial record (credit/debit cards included) is potentially put at risk because of exposure.” The US Department of Health & Human Services Office for Civil Rights (OCR) makes available, as required by law, a list of breaches of unsecured, protected health information affecting 500 or more individuals. As of June 1, 2020, a total of 3,705,374 individual records involving four large health plans have been reported to the OCR (Table 1). The vast majority of these breaches involve health care providers (hospitals, physicians), and the notable exception in 2015 of over 100 million records involving four large health plans (Table 2). In the last 5 years, the most common type of breach has been hacking (Table 3), and the most common location of the information is email, followed closely by network servers (Table 4).

<table>
<thead>
<tr>
<th>Breach year</th>
<th># Breaches</th>
<th># Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>3250</td>
<td>242,577,254</td>
</tr>
<tr>
<td>2019</td>
<td>200</td>
<td>13,162,158</td>
</tr>
<tr>
<td>2018</td>
<td>199</td>
<td>5,932,276</td>
</tr>
<tr>
<td>2017</td>
<td>18</td>
<td>134,773</td>
</tr>
<tr>
<td>2016</td>
<td>329</td>
<td>16,658,080</td>
</tr>
<tr>
<td>2015</td>
<td>270</td>
<td>113,307,814</td>
</tr>
<tr>
<td>2014</td>
<td>314</td>
<td>19,073,551</td>
</tr>
<tr>
<td>2013</td>
<td>277</td>
<td>7,018,839</td>
</tr>
<tr>
<td>2012</td>
<td>218</td>
<td>2,854,525</td>
</tr>
<tr>
<td>2011</td>
<td>200</td>
<td>13,162,158</td>
</tr>
<tr>
<td>2010</td>
<td>199</td>
<td>5,932,276</td>
</tr>
<tr>
<td>2009</td>
<td>18</td>
<td>134,773</td>
</tr>
</tbody>
</table>

As urology practices have adapted to the pandemic, increased their telehealth practice, and moved staff to remote locations, they may be more vulnerable to cybercrime.

Multiple urology practices affected by breaches

There are 10 organizations in the OCR data that can be identified from their business name as urology practices, affecting a total of 750,840 individuals. The breaches involved unauthorized access to servers, a group email to hundreds of patients, a stolen and unencrypted laptop computer, and paper medical records in storage (Table 5). Eight of these resolved breaches (2 are still under investigation) resulted in corrective action plans or resolution agreements or both, but there is no mention of civil monetary penalties.

| Source: Adapted from OCR data by Robert A. Dowling, MD |
What lessons can urologists learn and apply from this information and these statistics? As I first described in an earlier column, there are some general principles to follow:

- Know the law, the rules, and the consequences. If you are a small organization, you should have access to an attorney with contemporary knowledge of this subject matter.
- Engage an IT professional with experience in health care information technology. Like medicine, IT is highly specialized and your employee or partner should understand the risks and prevention strategies specific to your business and your specialty. For example, is your urodynamic machine secure? This is an example of specialty-specific issues that need to be considered.
- Hold your vendors responsible for their contribution to your risk. Be certain that you have business associate agreements in place and review them regularly.
- Review common areas of vulnerability. Have you formally trained your staff how to recognize a phishing attack? Do they know what procedures to follow to send protected health information via email? Consider bringing your entire organization onto an encrypted email platform, which is standard in corporate America today.
- Paper and film is another area of risk: do you have shredding practices firmly in place? Is off-site storage secure? Is there an opportunity to stop printing on paper altogether for certain functions? Is that fax machine printing instead of sending directly to a file folder? Do your physicians still insist on "printing the last progress note"?
- Have a data backup plan in place and practice restoring it. This is not a simple matter, but is an important strategy in the event of loss or loss of access (ransomware, for example).

Bottom line: The pandemic has highlighted the fact that health care organizations remain at risk for hacking attacks and breaches of sensitive information. Practicing in the modern era involves recognizing these risks, an active strategy of prevention and preparedness, and partnership with expert professionals in law and health information technology.

REFERENCES

TABLE 5. Office for Civil Rights Breach Data from Known Urology Practices

<table>
<thead>
<tr>
<th>Practice</th>
<th>Individuals affected</th>
<th>Breach year</th>
<th>State</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>131,825</td>
<td>2020</td>
<td>DE</td>
<td>Under investigation</td>
</tr>
<tr>
<td>2</td>
<td>3000</td>
<td>2020</td>
<td>NJ</td>
<td>Under investigation</td>
</tr>
<tr>
<td>3</td>
<td>279,663</td>
<td>2017</td>
<td>TX</td>
<td>An unauthorized user obtained remote access to the servers of the covered entity (CE). The protected health information (PHI) potentially affected included names, addresses, dates of birth, social security numbers, and medical information.</td>
</tr>
<tr>
<td>4</td>
<td>17,634</td>
<td>2017</td>
<td>WI</td>
<td>No description</td>
</tr>
<tr>
<td>5</td>
<td>839</td>
<td>2017</td>
<td>MN</td>
<td>An employee sent a group email to patients that allowed all recipients to see the email list, thus exposing the names and/or email addresses.</td>
</tr>
<tr>
<td>6</td>
<td>300,000</td>
<td>2016</td>
<td>OH</td>
<td>Electronic protected health information (ePHI) contained on the CE’s computer server was compromised by an unauthorized third party. The PHI involved in the compromised server included full names, Social Security numbers, dates of birth, home addresses, drivers’ licenses, claims information, credit/bank account numbers, and treatment notes.</td>
</tr>
<tr>
<td>7</td>
<td>9300</td>
<td>2015</td>
<td>OK</td>
<td>An unencrypted laptop computer used by a former physician was stolen from his vehicle. The laptop contained PHI, including patients’ first and last names, medical record numbers, and dates of birth, and, in some cases, patients’ age, physicians’ names, and diagnosis, treatment, and/or billing codes.</td>
</tr>
<tr>
<td>8</td>
<td>6500</td>
<td>2015</td>
<td>MT</td>
<td>Unknown individuals broke into a locked storage unit at a secure storage facility where medical records were stored.</td>
</tr>
<tr>
<td>9</td>
<td>1144</td>
<td>2014</td>
<td>TN</td>
<td>A nurse practitioner (NP) of the CE left the practice to start their own clinic. An administrative assistant of the CE provided the NP with lists of patient information that contained the names, addresses, gender, age, and first and last dates of service.</td>
</tr>
<tr>
<td>10</td>
<td>835</td>
<td>2014</td>
<td>NY</td>
<td>No description</td>
</tr>
</tbody>
</table>

Source: Adapted from OCR data by Robert A. Dowling, MD

TABLE 4. Office for Civil Rights Breach Data by Location of Information, 2016-2020

<table>
<thead>
<tr>
<th>Location of breached information</th>
<th># Breaches</th>
<th># Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Email</td>
<td>1754</td>
<td>81,093,318</td>
</tr>
<tr>
<td>Network server</td>
<td>364</td>
<td>53,504,536</td>
</tr>
<tr>
<td>Paper/Films</td>
<td>296</td>
<td>2,465,605</td>
</tr>
<tr>
<td>Other</td>
<td>123</td>
<td>3,057,526</td>
</tr>
<tr>
<td>Electronic medical record</td>
<td>83</td>
<td>705,718</td>
</tr>
<tr>
<td>Laptop</td>
<td>74</td>
<td>1,795,942</td>
</tr>
<tr>
<td>Other portable electronic device</td>
<td>63</td>
<td>1,647,648</td>
</tr>
<tr>
<td>Desktop computer</td>
<td>51</td>
<td>630,639</td>
</tr>
<tr>
<td>Other</td>
<td>184</td>
<td>7,117,919</td>
</tr>
</tbody>
</table>

Source: Adapted from OCR data by Robert A. Dowling, MD
How to fill the gap between retirement, Social Security

Withdrawals from pretax retirement accounts among ways to bridge income

Q: I am looking to retire next year at age 60, but I don’t want to take Social Security until age 70 when my benefit maxes out. What is the best way to bridge the income gap between when I retire and when Social Security kicks in?

A: It is common for individuals or couples who do not “need” Social Security immediately to delay taking their benefits to maximize payouts. To do this, they need to find ways to fund their lifestyle while they wait to reach age 70. There are many ways you can fund this income gap, and some are more effective than others.

Taking Social Security at different ages changes the benefit amount paid out to you. Normal retirement age depends on the year you were born but currently falls between ages 65 and 67. If you claim Social Security at your full retirement age, you are entitled to 100% of your Social Security benefits. However, you can choose to claim your benefit before your full retirement age at a reduced amount, or you can delay claiming your benefit beyond your full retirement age and receive greater than 100%.

The earliest someone can start claiming their benefits is age 62. If you start claiming benefits at age 62, your benefit will be reduced to 75% of your entire monthly benefit, assuming a full retirement age of 66. In other words, you will get 25% less income per month. Claiming early is usually only advisable in situations of financial hardship, when a stream of income is needed immediately.

The longest you can delay past your full retirement age is age 70. For each year you delay taking your benefit, you will increase your eventual payout by 8% compounded. Delaying claiming your benefit from your full retirement age until age 70 can significantly and permanently increase your Social Security income and financial security. By delaying from full retirement age 66 to age 70, you can increase your Social Security benefit to 136% of your normal retirement age benefit.

Claiming Social Security early is usually only advisable in situations of financial hardship.

Waiting until age 70 to claim your Social Security benefit is no easy task, but there are some ways you can bridge the income gap created by delaying:

Work part-time. Many physicians slowly phase themselves into retirement. Would your employer allow you to work reduced hours or, if you own your own practice, can you reduce your workload? Looking for a new challenge? Explore new fields of interest. A 2009 study found that people who pursued post-retirement bridge employment in their previous fields reported better mental and physical health than those who retired fully.

Exhaust cash. This is straightforward. If you have cash saved up beyond your emergency fund, using this cash to fund your lifestyle can be an effective strategy.

Make withdrawals from pretax retirement accounts. Social Security may be a taxable benefit. You may need to include it in your income and pay taxes on it. By delaying, you have less income, which may result in you being in a lower tax bracket. You can then make distributions from your pretax retirement accounts, such as 401(k)s and traditional individual retirement accounts, while minimizing the tax impact. Additionally, with these pretax accounts, at age 72 you will be required to start taking required minimum distributions (RMDs).

This is when the Internal Revenue Service forces a percentage of your balance to be distributed. In some cases, this distribution can amount to substantially more income than you need and potentially push you into a higher tax bracket. Lowering the balance of these retirement accounts during this income bridge period can reduce the size of RMDs later that may otherwise put you in an inconvenient position.

Tax loss harvesting. If you have an investment that has lost value, you can sell that investment to capture the loss. You can then use that captured loss to offset gains in another investment that you sell. Not only is this good tax management, but the two sales will also generate cash you can use as income.

Overall, delaying Social Security can lead to a significant increase in benefits and can provide an extra layer of long-term financial security. To bridge the income gap this strategy creates, you will need to be smart about how you generate cash to maintain your lifestyle. Some of the techniques we discussed take significant planning to execute correctly. For this reason, we recommend you consult your financial advisor or tax professional before taking action.

REFERENCE

FINANCIAL TIPS
- By delaying from full retirement age 66 to age 70, you can increase your Social Security benefit to 136% of your normal retirement age benefit.
- One way to delay taking Social Security is to continue working but on a part-time basis.
- If you have cash saved up beyond your emergency fund, using this cash to fund your lifestyle can be an effective strategy to help you delay taking Social Security.

JEFF WITZ, CFP
Witz is educational program director at MEDIQUS Asset Advisors, Inc. in Chicago, Illinois. He welcomes readers’ questions and can be reached at 800-883-8555 or witz@mediqus.com.

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The end of an era: When it comes time to close your practice

Giving notice to patients, winding down revenue cycle among considerations

A physician’s practice is more than a sign on a door. It’s a link to the community, it’s people, sometimes generations of them, who relied on medical wisdom here to help them feel better or maybe even to survive. It’s memories, it’s even family but, now, you want to close it in order to find your way to opening a new chapter. But, of course, it’s not as simple as making the decision and then turning off the lights.

Relying on you a final time

It begins with your patients.

“There are abandonment laws and you have an obligation to give them time to find another physician,” said Erin Whaley, partner in law firm Troutman Sanders. “You don’t have to recommend someone but it’s something to consider.”

For Charles Dinerstein, who closed his vascular surgery practice in 2012, he did provide recommendations, which he estimates took care of 10% to 15% of his patients. Whaley recommended giving 30 days’ notice at the minimum to patients and Dinerstein gave about 6 months.

You also won’t just be in touch with new physicians when it comes to records—you need to keep records for a certain amount of time, depending on your state. For Dinerstein, he said it’s 8 years in his state as he had his practice in Freehold, New Jersey.

“You need to answer the question of where the electronic medical record (EMR) will be retained and who responds to that request,” Whaley said. “Engaging a third party with a medical custodian to respond on a physician’s behalf may be the answer.”

Consider costly EMR contracts as well when it comes to the timing of your retirement.

“A reason to start looking at retirement a few years in advance is because some of those contracts have longer terms that automatically renew. If the provider says they want to retire in 6 months and the EMR contract renewed for 3 years that could create some expenses for physicians that could have been avoided with more planning.”

For your employees, there needs to be consideration for time they would need but also for their retirement plan, that it follows its needs for them moving forward.

“There are employment law considerations with respect to terminations that will vary depending on the size of the practice,” Whaley said. COBRA obligations, accrued PTO and benefit plans or retirement funds must be also considered for post closure and whether those need to be wound down, she said.

“A lot of tears were shed on both sides many times when I told patients I was retiring…” Dinerstein said. “It was a different job where you could see patients for many years. I look back and think looking back they would have done it differently. “You go from a high intensity job to playing golf and tennis—that may not cut it for these physicians…They maybe could have been a consultant. I think they’re not. They’re bored and very anxious. They probably could have been a consultant. I think looking back they would have done it differently.”

“Insurance also shouldn’t end on your last day as claims are also possible. Dinerstein had tail insurance, and you want to make sure with your broker that you are covered for years after. But, of course, you may not be retiring alone.

“If you have a partner in the business and you are both retiring, then closing the practice has similar considerations, but the potentially complicating factor is how to split any assets from the practice,” Whaley said. “If they are going to sell all of their exam tables, if they own the building, etc. Hopefully it’s spelled out in the corporate documents for the practice.”

A rush of memories

Finally, be prepared in another way—for the next step and for the emotional component.

“We talk about this on a regular basis...,” said Stephen A. Timoni, partner in law firm Lindabury, McCormick, Estabrook & Cooper, P.C. “Are you psychologically ready for it? When a physician stops practicing, it can be tough. I had a client retire...they were very active and did very complex surgeries and then they’re not. They’re bored and very anxious. They maybe could have been a consultant. I think looking back they would have done it differently. “You go from a high intensity job to playing golf and tennis—that may not cut it for these physicians...I think you should start planning 2 years in advance to consider different alternatives and the one that’s right for you,” Timoni added.

Of course, even when you do, there’s still that last word goodbye. Be ready because it probably won’t be easy. “A rush of memories mean so much.”

ERIC BUTTERMAN

Butterman is a contributor to Urology Times® sister brand Medical Economics®, where this article was first published.
What has been your experience with telemedicine?

**SMITH**

Before COVID-19, we called patients back, but we never did video or phone consults. Now we do both. Telemedicine will have an important place now in urologic care of patients. Initially, it was intimidating. How would timing come off? How would the back-and-forth work conveying information? But we quickly felt comfortable, especially with video. With face-to-face interaction, especially in pediatric urology, you can have them point to the affected area. I’ve even done it on postop. ‘Point the camera at the area. Oh, it looks great.’ It helps with [video] managing patient flow and educational aspects of care.

With pediatrics, often it’s not just one kid families have to wrap up when they need to see us. They’ve got several children to bring. If we can handle things over the phone, they’re elated.

Sometimes you can look at lab results and prescribe preliminary medication. Then you can see how it works before patients come in. That can streamline the management of disease. You can provide educational links to patients before we talk about a particular procedure. That can save time.

Facial recognition and communication are important when you’re going to do a procedure. You need the video-conferencing.

Most of our patients, even the elderly, seem to access their charts online. On the site, there’s an easy link to connect to a video consult. ‘My Chart’ has a prompt that allows them an easy video consult link.

Craig Smith, MD / Winfield, Illinois

**PATEL**

We didn’t do telemedicine before the pandemic. My experience now is fairly positive. It’s for reviewing labs, discussing people’s prognoses and potential outcomes, as well as the direction of therapy.

In urology, if patients need certain examinations, the initial consult can be telemedicine. Eventually, they’ll need an in-person visit because nothing replaces that physical examination.

Cognitive appointments, especially if you know the people, work well because these people don’t necessarily need a physical exam if their symptoms are stable.

It’s also good because older patients are at higher risk for coronavirus and many are anxious about possible exposure coming in. If physical exams are not critical for decision making, for example, if you’re following a patient’s PSA, you can check laboratory data by telemedicine. Eventually, they’ll probably need a physical examination but maybe that can be delayed until the environment is safer.

**GARY KALSER, MD**

Telemedicine works best on video. With audio only, you miss face-to-face communication. Body language is important, otherwise you don’t know whether they’re grasping concepts. It’s also more personal. Without that connection, they’re probably less likely to follow those things they should.

I expect we’ll continue telemedicine when coronavirus is no longer an issue, but probably not to the same extent. I have patients who travel who may request video appointments, which I would do sometimes. Other patients are less mobile and can’t always get here. It’s better to do a video conference than just keep rescheduling them and eventually have them drop out.

Gary Kalser, MD / Clermont, Florida

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House-passed HEROES Act promises relief for physicians

Bill would improve Medicare Accelerated and Advance Payment Program

YEHUDA A. SUGARMAN
Sugarman is federal affairs manager for the American Association of Clinical Urologists.

The US House and Senate are far from reaching consensus on a fourth coronavirus relief package, but the passage of the Health and Economic Recovery Omnibus Emergency Solutions Act (HR 6800), or HEROES Act, in the US House of Representatives on May 15, 2020, may provide some clues as to what physicians can expect, or perhaps hope for, in a final package. The $3 trillion supplemental spending package covers many sectors of the economy, including much-needed assistance to state and local governments. Similar to previous relief packages, it also includes considerable investment in the US health care system and coronavirus disease 2019 (COVID-19) response efforts.

$100 billion appropriation for Provider Relief Fund

The provision of the HEROES Act with the most direct impact on health care providers is an appropriation of $100 billion, on top of the $175 billion that has already been appropriated, for the Provider Relief Fund. The fund, initially established under the Coronavirus Aid, Relief, and Economic Security (CARES) Act passed in April, has provided 2 rounds of payments to hospitals and providers for COVID-19-related expenses and lost revenue.

In addition, the bill provides new guidance clarifying how funds from the program should be allocated to recipients. Following the first distribution of provider relief funds on April 10, there was considerable confusion and criticism surrounding the formula used to determine how much each provider received. Thus, regulators codified a new algorithm into the HEROES Act that will provide the Department of Health & Human Services with a more equitable and efficient system for distributing relief funds to providers.

The new guidance requires providers to apply for grants, on a quarterly basis, for all expenses and lost revenue relating to COVID-19 via a new program established at the Health Resources and Services Administration. Eligible expenses would be reimbursed at 100% whereas lost revenue would be reimbursed at 60%, with the latter being dependent on the availability of funds. The program does not require providers to pay back the funds they receive, with the caveat that they may not submit bill balances (surprise billing) to their uninsured patients.

The HEROES Act makes key improvements to the Medicare Accelerated and Advance Payment (AAP) Programs, which have provided necessary liquidity for many Medicare providers and suppliers impacted by the pandemic. According to data released by the Centers for Medicare & Medicaid Services (CMS) in early May, about $19.6 million in loans were allocated for urologists as part of AAP. (The $100 billion in total AAP loans provided by CMS is separate from and in addition to the $100 billion in grants distributed to providers as part of the CARES Act, which do not need to be repaid.)

The provision of the HEROES Act with the most direct impact on health care providers is an appropriation of $100 billion, on top of the $175 billion that has already been appropriated, for the Provider Relief Fund.

If HEROES is enacted, the terms of those loans would be considerably more favorable for the entities receiving payments. The bill would lower the interest rate on loans from above 10% to 1%, extend the repayment period (1 year before claims are offset and 2 years to repay the full outstanding balance), and reduce the per-claim recoupment rate to no more than 25% of Medicare reimbursement claims. It also would ensure that Part B premiums are not adversely impacted by this program.

A less publicized, but important, measure in the act would postpone implementation of the Medicaid Fiscal Accountability Regulation (MFAR) until after the end of the COVID-19 emergency. The controversial MFAR rule, proposed in November 2019, tightens regulations surrounding state-based Medicaid supplemental payment programs, which could lead to significant Medicaid cuts.

States and provider groups have opposed MFAR, arguing that it undermines existing financing and supplemental payment arrangements, will increase state budget deficits, and jeopardizes access to care for Medicaid patients, particularly in underserved areas. Postponing MFAR would help preserve Medicaid programs and prevent additional regulatory burdens at a time when many physician practices are struggling to meet the needs of their patients and staff.

Workplace safety for health care workers

As physician practices begin to reopen for nonurgent procedures and surgeries, providers will be at an increased risk of contracting the novel coronavirus. HEROES seeks to address this by requiring the Occupational Safety and Health Administration (OSHA) to issue emergency temporary standards for certain at-risk industries, including employees in the health care sector who are “at occupational risk of exposure” to COVID-19. Within 2 years, OSHA would be required to develop a permanent infectious disease standard.

In the interim, the temporary standards would require covered employers to protect workers from exposure to COVID-19 by developing and implementing an infectious disease control plan that is at least as protective as the measures issued by any OSHA state plan to protect workers from novel pathogens. HEROES also contains whistleblower protections for workers who report health and safety hazards, including a lack of personal protective equipment, in the workplace.

Various health care organizations and medical groups including the American Medical Association, the American Hospital Association, the Association of American Medical Colleges, and the American College of Physicians have endorsed the HEROES Act in whole or in part.

Although the Senate is not expected to take up the House-passed act for consideration, they will likely consider some additional form of relief. The provider community should stay engaged in the process and advocate for the inclusion of the measures discussed in this article in whatever legislative package emerges from the Senate.
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