There is good evidence to suggest that increasing fluid intake and making dietary lifestyle changes can prevent future stones or at least reduce aggressiveness of patients’ kidney stone disease, said Necole M. Streeper, MD, a urologist and assistant professor of surgery at Penn State Health in Hershey, Pennsylvania. The impact from simply drinking lots of water throughout the day is significant.

“High fluids intake is the most important factor for preventing kidney stone disease and for every 200 mL of water, the risk of stones is reduced by 13%,” according to a study published earlier this year.1

But what urologists, dietitians, and others should or should not recommend in the way of dietary changes is evolving. How clinicians present recommended lifestyle changes can affect whether patients incorporate the adjustments into daily life.
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Chairman’s Letter

The beginning of a new era for Urology Times®

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

It is no understatement to say that we at Urology Times® would not be able to fulfill the publication’s mission of delivering expert clinical analysis, practice advice, and policy perspectives without the contributions of our editorial advisory board. These urologists help keep our finger on the pulse of the specialty and ensure that we give our readers what they want. Especially important to these efforts have been our editorial consultants, who have, for many years served Urology Times® in a number of ways. To deepen our relationship with our advisers and enhance the publication further, I am very pleased to announce the appointment of Gopal H. Badlani, MD, and Michael S. Cookson, MD, as co-editors-in-chief of Urology Times®. Badlani previously served as an editorial consultant for Urology Times® and brings continuity to the position, and Cookson’s extensive credentials in the field of urologic oncology will be invaluable as this field continues to explode with numerous new and developing therapeutic and diagnostic products. I can’t wait to watch this collaboration take Urology Times® to even greater heights.

In addition, I must acknowledge and extend much gratitude to Stephen Y. Nakada, MD, and J. Brantley Thrasher, MD, for their many years of dedicated service to Urology Times®. Much of the publication’s sustained success can be attributed to their commitment and wise counsel, which helped lay the foundation on which our co-editors-in-chief will build. Their professionalism and drive for Urology Times® to succeed are very much appreciated.

Turning our attention to the current issue, this month’s cover feature parses the many and varying lifestyle modifications for the prevention of kidney stones. Reading the article, it’s clear that the successful prevention of kidney stones goes beyond merely drinking more water, and even doing that isn’t so easy for everyone to accomplish: “For people to make a plan of when they are going to drink fluid throughout the day is really important. Bathroom access can be a really big barrier. For example, classroom teachers have limited time for bathroom breaks during the day, so they have to think carefully about when they might be able to have access to the bathroom and when they might be able to go,” Charles D. Scales Jr, MD, MSHS, said in the article.

In prostate cancer, this issue leads off with a fascinating report on a recently published case series and a literature review looking at use of freehand transperineal prostate biopsy under local anesthesia. Also, be sure to read this month’s recap of a recent Around the Practice virtual live case review, in which an expert panel discussed a case of high-risk prostate cancer with oligometastasis at diagnosis.

Among other clinical highlights in this issue are reports from the recent 2021 New York GU 14th Annual Interdisciplinary Prostate Cancer Congress® on non-muscle-invasive bladder cancer and upper tract transitional cell carcinoma, as well as articles on recent research regarding 5-year surgical reintervention rates in patients with lower urinary tract symptoms, and an association between Peyronie disease and risk of developing psychiatric disorders.

In their Coding Q&A column, Jonathan Rubenstein, MD, and Mark Painter address several questions regarding trusurectal resection of the prostate. For Practice Matters, Robert A. Dowling, MD, evaluates the latest data from the Centers for Medicare & Medicaid Services pertaining to spending for Medicare Part B drugs. In this month’s installment of Speak Out, 3 urologists reminisce about the day they learned of a new drug. In this month’s installment of Speak Out, 3 urologists reminisce about the day they learned of a new drug.

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Tivozanib is officially launched in US kidney cancer market

The renal cell carcinoma (RCC) drug tivozanib (Fotidra) is now commercially available in the United States, according to AVEO Oncology, the developer of the VEGF tyrosine kinase inhibitor.1

The FDA approved tivozanib on March 10, 2021,2 for the treatment of adult patients with relapsed or refractory advanced RCC who have received 2 or more prior systemic therapies, based on data from the phase 3 TIVO-3 trial (NCT02627963). Results from the TIVO-3 presented during the 2020 American Society of Clinical Oncology Virtual Scientific Program3 showed that treatment with tivozanib led to a significant improvement in progression-free survival compared with sorafenib (Nexavar), with similar overall survival, in patients with relapsed/refractory metastatic RCC.

REFERENCES

FDA grants priority review to belzutifan for VHL-associated RCC

The FDA has granted a priority review designation to a new drug application (NDA) for the HIF-2α inhibitor belzutifan (MK-6482) for the treatment of patients with Von Hippel-Lindau (VHL)-associated renal cell carcinoma (RCC), not requiring immediate surgery.1

The NDA is supported by data from the phase 2 Study-004 trial (NCT01407788),2 which enrolled patients with VHL-associated RCC, as well as nonrenal lesions. The findings showed that at a median follow-up of 68.7 weeks (range, 18.3-104.7), belzutifan induced an objective response rate (ORR) of 36.1% in RCC lesions among 61 patients. The ORR comprised 22 confirmed partial responses (PRs). There were also 7 unconfirmed PRs. Overall, 91.8% (n = 56) of patients had at least some decrease in the size of target lesions.

REFERENCES

Study to explore BET inhibitor plus pembrolizumab and enalitamide

The first patient has been treated in a phase 2 trial examining a triplet regimen combining the investigational BET inhibitor ZEN-3694 plus pembrolizumab (Keytruda) and enalitamide (Xian-di) in patients with metastatic castration-resistant prostate cancer (mCRPC) who have become resistant to first-line treatment with an androgen receptor signaling inhibitor (ARSI).1

The patient was dosed at the University of California, San Francisco (UCSF), where the study is being led by principal investigator Rahul Aggarwal, MD, a medical oncologist and associate professor of hematology/oncology at UCSF. Aggarwal is also associate director for clinical research at the UCSF Helen Diller Family Comprehensive Cancer Center.

The open-label, nonrandomized phase 2 trial (NCT04471974) is accruing patients with progressed adenocarcinoma that is histologically confirmed at diagnosis, with ongoing development of mCRPC. At the time of enrollment, there must be evidence of progressive disease as shown by prostate-specific antigen (PSA) and/or radiographic progression (PCWG3 criteria).

The target enrollment for the trial is 54 patients. The primary end point of the trial is composite response rate. Secondary end points include objective response rate, duration of response, progression-free survival, overall survival, PSA30 response proportion, and safety. The estimated primary completion date for the trial is December 31, 2025.

REFERENCES

FDA accepts application for novel testosterone replacement therapy

The FDA has accepted a new drug application (NDA) for SOV2012-F1 (Kyzatrex), an oral testosterone undecanoate soft gelatin capsule, for the treatment of adult men with primary or secondary hypogonadism.1

The NDA is supported by findings from the pivotal phase 3 ReTUNE trial (NCT03198728),2 as well as a 6-month extension study of the ReTUNE trial (NCT04467697).3 Marius Pharmaceuticals, the manufacturer of SOV2012-F1, reported in a news release that more than 96% of patients in the pivotal phase 3 trial who completed 90 days of treatment reached average testosterone levels in the normal range. Regarding safety, the most common treatment-emergent adverse event (TEAE) was hypertension, whereas there were no serious TEAEs deemed related to the study drug across the phase 3 trials. Under the Prescription Drug User Fee Act, the FDA is scheduled to make a final decision on the NDA on or before October 31, 2021.

REFERENCES
**Freehand transperineal biopsy case series and review support widespread use**

Technique is safer and more accurate than transrectal biopsy, investigator says.

**Lisette Hilton**  
*Urology Times® Correspondent*

A recently published case series and a literature review looking at use of freehand transperineal prostate biopsy under local anesthesia demonstrate the feasibility of incorporating this safer, more accurate approach to prostate biopsy into the urology clinic workflow.

“Many centers around the world have adopted freehand transperineal prostate biopsy because it virtually eliminates sepsis, may improve detection rates of clinically significant prostate cancer, and can be easily integrated into a normal clinic workflow using only local anesthesia. If all urologists in the United States abandoned transrectal prostate biopsy for freehand transperineal prostate biopsy, the potential savings in health care costs of complications would be significant,” the author concluded in the review published online in the *Journal of Endourology.*

“[The transperineal biopsy] approach virtually eliminates sepsis complications, as shown both by review of the literature and the fact that of the 242 consecutive freehand transperineal biopsies performed, 212 (88%) received no antibiotic prophylaxis and none developed sepsis.”

**Richard Julius Szabo, MD**

Many urologists are switching to the transperineal approach because of the increasing rates of sepsis post transrectal prostate biopsy, despite use of empirical or targeted antibiotic prophylaxis, according to review author Richard Julius Szabo, MD, a urologist with Kaiser Permanente in Irvine, California; an associate clinical professor of urology at the University of California, Irvine, School of Medicine; and volunteer urology faculty at the Veterans Administration Healthcare System in Long Beach, California. Szabo also authored results of a case series of 242 consecutive freehand transperineal biopsies performed between August 26, 2016, and December 31, 2018, published online in the *Journal of Endourology.*

“This approach virtually eliminates sepsis complications, as shown both by review of the literature and the fact that of the 242 consecutive freehand transperineal biopsies performed, 212 (88%) received no antibiotic prophylaxis and none developed sepsis,” Szabo said. “Recent evidence also shows that when the transperineal approach is coupled with MRI/ultrasound fusion targeting, the yield of clinically significant cancer is 50% to 60% greater than the yield with transrectal MRI/ultrasound fusion targeting. This more accurate yield is even more pronounced in anteriorly located clinically significant prostate cancer that in 1 study was detected 3.5 times more frequently when employing the transperineal approach compared to the yield detected using the transrectal approach.”

**Technique is easily incorporated in clinic workflow**

Freehand transperineal prostate biopsy under local anesthesia is easily incorporated into a normal outpatient clinic workflow, he noted. An increasing number of academic centers in the United States are using the transperineal approach, including Johns Hopkins, Massachusetts General Hospital, Mayo Clinic, Northwestern University, the University of Connecticut, and the University of Michigan, according to Szabo. Soon patients will insist on this safer, more accurate approach to prostate biopsy, he said.

“Furthermore, the Centers for Medicare & Medicaid Services and major insurers will become aware that if all urologists in the United States switched to freehand transperineal prostate biopsy under local anesthesia, the potential savings in eliminating the estimated 39,400 admissions for posttransrectal biopsy sepsis will amount to between $341,676,800 and $752,540,000, a savings of $173 to $382 for every transrectal biopsy performed,” Szabo said. This does not include the additional savings in eliminating emergency department visits through the elimination of posttransrectal biopsy rectal bleeding, which occurs in 2.5% of cases, and the reduction in posttransrectal biopsy urinary tract infections and prostatitis, which occur in 5% to 7%, respectively, Szabo said.

Szabo conducted the case series using the PrecisionPoint Transperineal Access System (Perineologic), an FDA-approved needle guide that has been on the market since 2016. It maintains the biopsy needle in the ultrasound image sagittal plane and adjusts for anterior and posterior targeting while maintaining the coaxial introducer in the same skin puncture site, according to Szabo.

Limitations of the freehand transperineal prostate biopsy approach include that it takes an average 19.1 minutes to perform versus the transrectal approach, which takes an average 14.7 minutes. Pain scores with the transperineal approach were slightly higher at a pooled average of 3.17 out of 10.0 compared with 2.6 out of 10.0 for the transrectal prostate biopsy, according to Szabo.

“This might be ameliorated with improved local anesthesia techniques and periprocedural antianxiety or pain medication,” Szabo said.**

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**REFERENCES**


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**Eric A. Klein, MD on genomic testing for genitourinary cancers**

“Genomic testing is going to be a routine part of prostate cancer care and urologic cancer care going forward,” Eric A. Klein, MD, says. **Scan to watch the video.**
Apalutamide survival benefit in mCSPC is sustained in long-term follow-up

No difference was seen in health-related quality of life between treatment and placebo groups

Benjamin P. Saylor
Senior Editor, Urology Times®

Treatment with apalutamide (Erleada) plus androgen-deprivation therapy (ADT) reduced the risk of death by 35% versus ADT alone in patients with metastatic castration-sensitive prostate cancer (mCSPC).1

Final analysis findings from the phase 3 TITAN trial were presented at the 2021 Genitourinary Cancers Symposium by Kim N. Chi, MD, chief medical officer and vice president of BC Cancer in Vancouver, Canada.

In the randomized, double-blind, placebo-controlled TITAN trial (NCT02489318), 1052 patients with mCSPC were randomized 1:1 to receive apalutamide plus ADT or placebo plus ADT. Dual primary end points were radiographic progression-free survival (rPFS) and overall survival (OS).

Findings from the primary analysis of the trial were published in 2019.2 At a median follow-up of 22.7 months, both rPFS and OS reached statistical significance, according to Chi. The 2-year OS rates at the primary analysis were 82.4% in the apalutamide arm versus 73.5% in the control arm, translating to a 33% reduction in the risk of death (HR, 0.65; 95% CI, 0.53-0.79; P<.0001). After adjusting for crossover using a preplanned sensitivity analysis, investigators found a 48% reduction in the risk of death (HR, 0.52; 95% CI, 0.42-0.64; P<.0001).

The treatment effect on OS was found to favor apalutamide plus ADT across all prespecified subgroups except for patients who had received prior docetaxel.

“However, this subgroup comprised only 10% of patients, and among them, there have been relatively few events. A post hoc interaction analysis between treatment and prior use of docetaxel showed no significant interaction,” Chi noted. Health-related quality of life (HRQOL) was measured using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score. Chi reported that HRQOL was maintained in the treatment group, with no difference between the treatment and placebo groups.

The safety profile of apalutamide plus ADT was found to be consistent with previous reports, according to Chi.

“Importantly, cumulative incidence of any-grade treatment-emergent falls, fractures, and fatigue was similar between groups. The cumulative incidence of grade 3/4 treatment-emergent adverse events and serious adverse events was also similar between groups. As expected, the incidence of any-grade rash was higher in the apalutamide group than in the placebo group, but reached a plateau after about 6 months,” Chi said.2

REFERENCES
PSMA theranostic $^{177}$Lu-PSMA-617 is more active and safer than cabazitaxel

Prostate-specific antigen response of 66% was seen with LuPSMA, phase 2 data indicate

Jason M. Broderick
Associate Editorial Director, Urology Times®

The investigational radioligand therapy $^{177}$Lu-PSMA-617 (LuPSMA) demonstrated stronger clinical activity with fewer grade 3/4 adverse events (AEs) compared with cabazitaxel (Jevtana) in patients with metastatic castration-resistant prostate cancer (mCRPC), according to findings from the phase 2 TheraP trial published in The Lancet. 1

The findings, which were previously shared during the 2020 American Society of Clinical Oncology Virtual Scientific Program, 2 showed a prostate-specific antigen (PSA) response rate of 66% with LuPSMA compared with 37% with cabazitaxel, representing a 29% absolute greater PSA response rate ($P < .0001$). For sensitivity analysis per protocol, the difference observed was 23% ($P = .0016$).

Regarding safety, grade 3/4 AEs occurred in 33% vs 53% of the LuPSMA vs cabazitaxel arms, respectively. There were no LuPSMA-related deaths.

“This phase 2 study provides evidence that $^{177}$Lu-Lu-PSMA-617 is a potential alternative to cabazitaxel in men with metastatic castration-resistant prostate cancer, with greater activity but less severe [AEs] and improvements in patient-reported outcomes,” wrote first author Michael S. Hofman, MBBS, Peter MacCallum Cancer Research Center, Melbourne, Australia, and colleagues.

The radiolabeled small molecule LuPSMA is a theranostic that delivers $\beta$ radiation to PSMA-expressing cells. The TheraP trial enrolled 200 patients with mCRPC who progressed after docetaxel. Patients had undergone imaging with 68Ga-PSMA-11 and 18F-FDG PET/CT that confirmed high PSMA expression and no sites of FDG-positive/PSMA-negative disease. More than 90% of patients in each arm had received abiraterone acetate (Zytiga), enzalutamide (Xtandi), or both.

Patients were randomized in a 1:1 ratio to LuPSMA (n = 99) or cabazitaxel (n = 101). Study treatment occurred at 11 clinical locations in Australia. In the LuPSMA cohort, men received posttreatment single-photon emission CT/CT after each cycle, with those achieving an exceptional response having their treatment paused. Treatment would subsequently resume at the time of PSA progression.

PSA response rate was the study’s primary end point. A response was defined as ≥50% reduction. Key secondary efficacy end points included PSA progression-free survival (PFS), AEs, and overall survival ($OS$).

At the time of the data analysis, there were 173 progression events, 90 and 83 in the LuPSMA and cabazitaxel cohorts, respectively. LuPSMA delayed progression vs cabazitaxel ($HR, 0.63; P = .0028$), with a comparable benefit observed in radiographic PFS ($HR, 0.64; P = .0070$) and PSA-PFS ($HR, 0.60; P = .0017$).

The safety analysis included 98 men in the LuPSMA arm and 85 in the cabazitaxel arm. Grade 3/4 AEs occurred in 33% (n = 32) and 53% (n = 45) of the 2 arms, respectively.

**VISION trial**

Adding LuPSMA to best standard of care (BSC) improved OS in patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC), according to findings from the phase 3 VISION trial (NCT03511664). 3

LuPSMA also extended PFS when added to BSC versus BSC alone. No new safety signals emerged in the trial. Data from the study will be presented at a future scientific conference, according to Novartis, the developer of LuPSMA.

The open-label phase 3 VISION trial accrued patients with progressive PSMA-positive mCRPC who received at least 1 novel androgen axis drug (eg, enzalutamide [Xtandi]) or abiraterone acetate (Zytiga) and were previously treated with 1 to 2 taxane regimens. Patients were randomized to LuPSMA plus BSC or BSC alone. The coprimary end points of the trial were OS and PFS.

**Future of PSMA**

PSMA-PET imaging and PSMA theranostics are becoming a mainstay in the prostate cancer paradigm, Evan Y. Yu, MD, a professor in the Department of Medicine, Division of Oncology, University of Washington and Fred Hutchinson Cancer Research Center, told Urology Times® in a recent interview. 4

In December 2020, the FDA approved gallium 68 PSMA-11 as the first drug for PET imaging of PSMA-positive lesions in men with prostate cancer.

The FDA is currently reviewing a new drug application for the PSMA-targeted PET imaging agent 18F-DCFPyL for prostate cancer.

Under the Prescription Drug User Fee Act, the FDA is scheduled to make a decision on the application by May 28, 2021. 5

**REFERENCES**


**Emerging biomarkers and techniques in prostate cancer diagnosis**

Leonard G. Gomella, MD, of Thomas Jefferson University, Philadelphia, Pennsylvania discusses emerging biomarkers and the use of MRI for the early detection of prostate cancer.

Scan to watch the video.
Bipolar androgen therapy sensitizes CRPC to subsequent treatment

Patient-reported QOL data consistently favored BAT over enzalutamide, investigators report

Jason M. Broderick
Associate Editorial Director, Urology Times

Bipolar androgen therapy (BAT) demonstrated “meaningful clinical activity” and showed the capacity to sensitize castration-resistant prostate cancer (CRPC) to subsequent antiandrogen therapy, according to findings from the phase 2 TRANSFORMER trial published in the Journal of Clinical Oncology.1

The TRANSFORMER trial (NCT02286921) randomized asymptomatic patients with metastatic CRPC and disease progression on abiraterone acetate (Zytiga) to BAT or the antiandrogen therapy enzalutamide (Xtandi). The trial missed its primary end point, because BAT did not show superior clinical or radiographic progression-free survival (PFS) compared with enzalutamide. However, although the study was not powered to show equivalency, the results showed similar outcomes between the treatments in terms of median PFS (5.7 months in both groups), time to prostate-specific antigen (PSA) progression (2.8 months for BAT vs 3.8 months for enzalutamide), and the rate of patients with a 50% decline in PSA (PSA50; 28.2% vs 25.5%, respectively).

Further, crossover to the opposite arm was allowed at progression, and the PSA-PFS (interval from randomization to the time of PSA progression) for enzalutamide increased from 3.8 months following abiraterone to 10.9 months following BAT (HR, 0.45; P = .008). The PFS2 (PFS from randomization through crossover) was 28.2 months versus 19.6 months for those who crossed from BAT to enzalutamide versus those crossing from enzalutamide to BAT, respectively (HR, 0.44; P = .02). The median overall survival (OS) was 37.1 months versus 50.2 months, respectively (HR, 0.68; P = .225). The PSA50 was 77.8% versus 23.4%, respectively.

Most adverse events were grade 1/2

Safety data showed that most adverse events related to BAT were grade 1/2. The investigators also reported that patient-reported quality of life data consistently favored BAT over enzalutamide.

“Although the trial failed to demonstrate superior PFS with BAT over enzalutamide in postabiraterone CRPC, it demonstrated that BAT is safe, enhances [quality of life], and has efficacy comparable to enzalutamide in this patient population. However, the most important finding is that post abiraterone, BAT can markedly improve the magnitude and duration of response to enzalutamide when used as an intervening therapy,” wrote the authors, led by Samuel R. Denmeade, MD, of Johns Hopkins University, Baltimore, Maryland.

BAT involves “periodical oscillation between castration levels and supraphysiologic levels of testosterone in order to prevent the adaptation of prostate cancer cells to a low-androgen environment.” Between April 2015 and April 2018, the open-label TRANSFORMER trial randomized 195 patients in a 1:1 ratio to BAT (n = 94) or enzalutamide (n = 101). Across the overall study population, the median age was 71, 87% of patients were White, about 81% of patients had received abiraterone for more than 6 months, about 90% of patients had a Gleason score of 7 or higher, and the median number of metastases was 2. The mean PSA at baseline was 44.3 ng/mL in the BAT arm and 50.6 ng/mL in the enzalutamide arm.

At a median follow-up of 31.9 months, the median PFS was 5.7 months for both arms (HR, 1.14; P = .42). The median OS was 32.9 months with BAT versus 29 months with enzalutamide (HR, 0.95; P = .80).

“These results support further evaluation of sequential BAT [followed by] enzalutamide as a single therapy. Further study is warranted to define the potential for sequential treatment to produce significant survival improvement in men with CRPC,” the authors wrote in their conclusion.

REFERENCES

ENZALUTAMIDE NEARS EU APPROVAL FOR MCSPE

Jason M. Broderick
Associate Editorial Director, Urology Times

The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has recommended approval of enzalutamide (Xtandi) for the treatment of adult men with metastatic castration-sensitive prostate cancer.1

The CHMP based its recommendation on data from the phase 3 ARCHE trial (NCT02677896), in which the median radiographic progression-free survival in men with metastatic castration-sensitive prostate cancer was not reached with enzalutamide plus androgen deprivation therapy (ADT) and was 19.45 months with placebo and ADT, translating to a 61% reduction in risk of radiographic progression or death with enzalutamide (HR, 0.39; P < .0001).2-3 The European Commission will now review the CHMP recommendation and make a final decision.

The double-blind ARCHE trial enrolled 1150 patients with histologically verified metastatic castration-sensitive prostate cancer across North America, Europe, and the Asia-Pacific region who were randomized to receive enzalutamide at 160 mg daily or placebo.

References
Case review: High-risk prostate cancer with oligometastasis at diagnosis

Around the Practice is a monthly urologic virtual live event featuring case reviews from multidisciplinary experts, presented by Urology Times® in partnership with LUGPA. On February 17, 2021, a panel convened to discuss cases involving an incidentally discovered adrenal mass as well as localized, high-risk prostate cancer, with oligometastasis at diagnosis. What follows is an edited portion of the panel’s conversation regarding the prostate cancer case.

The panelists for this case included moderator Jason M. Hafron, MD; Byard Edwards, MD, PhD; Ajeet Gajra, MD, MBBS; Tyler Gunter, MD; and Christopher M. Pieczonka, MD.

HAFRON: This case involves localized high-risk prostate cancer with oligometastasis at diagnosis. The patient was a 64-year-old African American man who was given a diagnosis of Gleason score 4+3=7 adenocarcinoma of the prostate 13 years ago. The cancer involved 2 out of 12 cores. Pretreatment [prostate-specific antigen] PSA was 5.7 ng/mL. The patient was treated with primary brachytherapy in 2008 by his previous urologist. Adjuvant [androgen deprivation therapy] ADT was not administered at that time. The patient did great and had a serum PSA nadir at less than 0.2 ng/mL.

Unfortunately, in 2017 up to November of 2019, his PSA progressed. He had evidence of biochemical recurrence, with a PSA of 6.7 ng/mL. He was lost to follow-up for a period because of the coronavirus disease 2019 (COVID-19) pandemic, which is something we’re all challenged with today. Dr Pieczonka, how would you evaluate this patient?

PIEczONKA: It would depend on the insurance. If the patient is on Medicare, we could probably go right to an Axumin [fluciclovine F18] scan. If not, then I would have to potentially do a CT scan and a bone scan and then get the Axumin scan. In this particular case, until you prove otherwise, you want to make the diagnosis and find out if they’re a radiation failure or if they’re metastatic. I can tell you that all too often, what I see in my referral practice is that this patient would be started on ADT without trying to find where the underlying recurrent disease might be.

HAFRON: So based on your experience, you would ask the primary urologist to hold off on the ADT until you get the imaging?

PIEczONKA: Absolutely. I think this patient would be imaged, if possible, ahead of time.

Now, to be fully transparent, in our practice, these cases are still going to probably be at the level of the local urologist and they may not make it into the advanced clinic yet. We are not at the point that we’re pulling patients with biochemical relapse into our advanced prostate cancer clinic, although we’re having conversations about that. But one of the concerns on this would be the patient’s PSA is jumping through all of the ADT. Granted, this patient’s PSA is pretty high. But what if it was half of what you originally presented? You could put that patient on ADT and then you might have no idea where the recurrence was.

HAFRON: That’s an important point. Dr Gajra, you’re a hematologic oncologist. You’re also medical director at Cardinal Health, so you have a good perspective on PET imaging across the United States. I would like to hear where you think we’re going with PET imaging following biochemical recurrence.

GAJRA: We certainly see in our outreach and in our research here at Cardinal that urologists and urology practices are much more on the cutting edge of imaging than medical oncologists, and perhaps rightly so. In addition, Axumin certainly outdoes conventional imaging, but it still has low sensitivity, which is its Achilles’ heel. Also, at least based on our assessments, it almost seems across the United States that 50% of urologists, and even more medical oncologists, are not utilizing Axumin, either because they don’t have easy access to it or, especially with medical oncologists, it just hasn’t caught up to their work-up. But the field is already moving now, as you said, to prostate-specific membrane antigen (PSMA). There have been remarkable data. The CONDOR study (NCT03739684), which was a US-based study presented at [American Society of Clinical Oncology], was very well designed with input from the FDA. This study evaluated how newer radiopharmaceutical imaging modality (PyL PET/CT) may change clinical management for these men with biochemical recurrence. The other point being that in the CONDOR study, 64% of evaluable participants had an intended change in management after the PSMA scan. The vast majority, almost 80%, were because of detection of lymph nodes.

We have to realize that PSMA PET, for example, has been approved and used in countries like Australia for over 3 years now, so in that way, we are lagging behind because the FDA laid down very stringent guidelines for what they wanted to see in a trial. The CONDOR trial met all these criteria. Last December, the FDA approved Gallium-68 (Ga-68) PSMA-11 PET/CT, albeit only at the University of California, Los Angeles (UCLA), and the University of California, San Francisco (UCSF). Certainly, we expect later this year that that will become more widespread.

Basically, PSMA PET does conventional imaging with CT and bone scan because it has both high sensitivity and high specificity. The proPSMA study, which was published in the Lancet,1 is a prospective, randomized, multicenter study of PSMA PET/CT in men with high-risk prostate cancer being considered for radical prostatectomy or radiotherapy with curative intent. It found that PSMA PET/CT is superior to conventional imaging, providing superior accuracy, to the combined findings of CT and bone scanning. There was also a novel study that actually used both Axumin and gallium PSMA.2 It’s a smaller, proof-of-principle type study where 50 patients with prostate cancer biochemical recurrence after radical prostatectomy underwent Axumin and gallium PSMA PET/CT scans. Detection rates were significantly lower with Axumin than with gallium PSMA PET/CT.

HAFRON: Thank you, Dr Gajra. That was great. Dr Edwards, what is your perspective?

EDWARDS: We’re not doing PET imaging in our group for historical reasons. But everything Dr Gajra said was right on. If you look at the statistics, as soon as PSMA PET is rolled out, I assume it will take over. It’s clear all the studies show it is superior.

HAFRON: Dr Gajra, you brought up the CON-
in the COVID-19 world, we’re not inserting looks to be some sort of oligometastatic disease, we would get germline testing done, and we ease, particularly with this type of recurrence, regards to sensitivity and specificity. I feel these agents are probably going to be more handling and such, but in terms of diagnostic efficacy, the results for these are very similar with to aggressive SABR vs standard of care with pal- liation as necessary. They didn’t design it as a superiority study, but on their update, they did detect a survival difference in favor of SABR. Median survival was almost doubled. Five-year survival was more than doubled. And so there is presumably across many disease sites this oligometastatic setting where local therapy can be beneficial. They didn’t have enough patients to analyze subgroups to detect a benefit for prostate cancer in particular. But we do have a couple other recent studies, first, STOMP (NCT01538427) and more recently, ORIOLE (NCT02680987), that looked at this just in prostate cancer. They both included patients with 3 or fewer metastases in a controlled primary, and randomized them to aggressive SABR vs standard of care with pal- liation as necessary. We should be able to keep the risk of complica- tion on the sigmoid relatively low. That could potentially be worth trying. More concerning, though, is this patient has a PSA of 44 ng/mL, and I would wager it’s pretty unlikely that this is his only site of disease. So we could try it, but he’s likely to progress elsewhere.

HAFRON: The local radiation oncologists weren’t comfortable with giving more radiation. What line of therapy would you recommend next? Dr Pieczonka, what would you do with this patient?

PIECZONKA: I love the fact that stereotactic radiation was performed up front, because if you swing and you hit it out of the park, you might give the patient, at the very least, a long disease-free interval, or perhaps delay the need for ADT. I think when it recurred the second time, I think that patient needs to have something else done. Quite honestly, in our practice, this patient would be screened for clinical protocol. We have a variety of different clinical protocols and some of them are starting to become quite precision guided. I can think of 2; we have clinical protocols and the big pharmaceutical players are in this market. They’re looking at patients who have homologous repair deficiencies. Those
patients potentially could be put on ADT with some sort of androgen receptor-targeted therapy plus or minus a PARP inhibitor or placebo. AstraZeneca is now in this market with patients who have PTEN abnormalities. PTEN abnormalities happen in roughly 20% of these types of patients with metastatic disease. They have a targeted drug called capivasertib, which is not FDA approved and is being used with abiraterone.

If I didn’t have access to clinical protocol, this patient would get combination ADT with some sort of androgen receptor (AR)-targeted therapy. They would absolutely not get ADT monotherapy. And, at least in my practice, I have a pretty frank conversation with the patients who are found to be metastatic and tell them to resist the temptation to receive intermittent therapy, which raises the questions: would you do intermittent therapy with ADT monotherapy alone? Would you do intermittent therapy with AR-targeted therapy with ADT?

I just went through this with one of my patients recently. He received radiation, he ended up recurring. PSA is undetectable. Now, he’s on apalutamide with leuprolide acetate injection. He asked me, “Do I need to stay on this lifelong?” I said yes. We had a pretty honest conversation about it.

HAFRON: Dr Gajra, if this patient were in your clinic, what would you recommend?

GAJRA: I agree with Dr Pieczonka. So assuming that we have hormone-sensitive disease because the patient has never been treated with ADT, we have data on enzalutamide from ARCHES in terms of ADT plus enzalutamide (NCT02677896). We have very similar data with apalutamide from the TITAN trial (NCT02489318). Both of these suggest significant improvement in progression-free survival. I like these 2 trials because they categorically, in a preemptive manner, plan for low-volume patients, and about a third of the patients on each of those trials had low-volume disease. Those patients got the same amount of benefit. They derived even more benefit than high-volume patients with the addition of enzalutamide and apalutamide, respectively. Which AR agent you choose depends on individual comfort. There are physicians who have used enzalutamide for so long, they’re reluctant to learn a new agent, and then there are physicians who think, “If it’s new, it might be better.” And some are finding differences in the toxicity profile as they gain experience with both drugs.

In my practice, I think this would be the time when I would also conduct germline and somatic testing for HRD genes if this has not been previously performed. As for the question regarding intermittent therapy, I have never been impressed by the results although they continue to exist within guidelines. The overall evidence is weak and those studies have major flaws. It can be a disservice to the patient. Every once in a while, there’s a young patient who will really force your hand. We talk about M0CRPC, but M0CRPC is a transient entity in my opinion, because it only exists because of the limited sensitivity of current imaging. That is a whole entity that’s going to disappear.

HAFRON: I think those are great points. I think the mistake that urologists make is treating with monotherapy. I think that’s a bad habit we have to get rid of. If you look at the National Comprehensive Cancer Network or the American Urological Association guidelines, combination therapy, ADT plus androgen receptor are the new standard of care. In terms of chemotherapy, there’s really no role for it with disease of this low volume. Do you agree with that, Dr Gajra?

GAJRA: Absolutely. Based on CHAARTED (NCT00309985) we saw low-volume disease not achieve benefit and subsequently, there have been other studies. STAMPEDE (NCT00268476) did find benefit to addition of docetaxel as well as abiraterone acetate to ADT. There is a meta-analysis out there that shows that patients with low-volume disease also get benefit from docetaxel. But for me, as a medical oncologist, I wouldn’t offer that for low-volume disease. I trust the US data better, because STAMPEDE was a mishmash of all kinds of patients, categories, stages. So I agree; I wouldn’t offer chemotherapy and I wouldn’t offer abiraterone either, mainly to minimize their respective toxicities, especially the steroid with abiraterone. I would offer enzalutamide or apalutamide.

HAFRON: I think another treatment that urologists frequently use inappropriately is bicalutamide (Casodex). Most recently, the American Urological Association made a very strong statement about complete androgen blockade with bicalutamide where first-generation AR is no longer indicated.¹ The only indications for bicalutamide are for prevention of flare. As urologists, we really have to stop using bicalutamide inappropriately. ADT plus bicalutamide is no longer recommended, and based on trials such as ARCHES, TITAN, and ENZAMET (NCT02446405), clearly, we see a survival benefit in all these trials in using ADT with an AR-targeted therapy.²³

ABOUT THE PANELISTS

HAFRON is the chief medical officer at the Michigan Institute of Urology PC; an associate professor of urology at the Oakland University William Beaumont School of Medicine; and the director of robotic surgery at Beaumont Hospital Royal Oak in Rochester, Michigan.

EDWARDS is a radiologist in community practice in Nashville, Tennessee.

GAJRA is vice president and senior medical director of Cardinal Health Specialty Solutions in Dublin, Ohio, and a clinical professor of medicine at the State University of New York Upstate Medical University, Syracuse.

GUENTER is an assistant professor of radiation oncology at the University of Oklahoma College of Medicine, Oklahoma City.

PIECZONKA is a urologist in community practice in Syracuse, New York.

REFERENCES


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Prostate Cancer / JOURNAL ARTICLE OF THE MONTH

Functional and oncological outcomes vary among surgeons
Trend persists even after adjusting for surgical volume and experience

For men undergoing surgery for localized prostate cancer, which is often diagnosed at an early, curable stage, functional outcomes are as important as oncological outcomes. Patient and tumor characteristics are often the subject of postsurgical outcomes studies. But, despite the commonly held belief that surgeon-related factors are an important determinant of surgical outcomes, the studies evaluating the effect of surgeon-related factors are infrequent and opaque.

In a recent update of a previously reported trial,1,2 Nyberg et al examined the effect of heterogeneity in surgeon experience and caseload on the outcomes after radical prostatectomy. A previous report on the Laparoscopic Prostatectomy Robot Open (LAPPRO) trial (a prospective, nonrandomized, multi-center trial) comparing open radical prostatectomy (ORP) and robot-assisted laparoscopic prostatectomy (RALP) procedures demonstrated that there was no difference in the rate of urinary incontinence or oncological outcomes, and modestly improved erectile function after RALP.

The trial was conducted at 14 Swedish centers by 68 surgeons; however, the previous report only included surgeons who had performed at least 100 RPs before participating in the trial. In the current report, the authors included all participating surgeons to determine the influence of surgeon-related factors (including previous experience and current caseload) on the outcomes and to determine whether surgeon heterogeneity affected the comparative outcomes of ORP and RALP. The outcome measures included urinary incontinence, erectile dysfunction (ED), and cancer recurrence (prostate-specific antigen > 0.25 ng/mL) at 24 months after surgery.

Of the 3443 evaluable patients for this analysis, 826 underwent ORP and 2617 underwent RALP. A model including surgeons with at least 20 procedures during the study was developed that adjusted for the baseline patient and tumor characteristics to account for any differences in the case mix. Additional analyses included the subgroup of experienced surgeons (> 250 cases) and the annual caseload of surgeons during the study.

Among the main cohort of surgeons with 20 or more cases during the study period (n = 25), significant heterogeneity was noted in the incontinence rates, ranging from 5% to 30% (P < .001).

The rate of ED also varied significantly, ranging from 61% to 93% (P < .001). Similarly, wide variation was noted in the rate of recurrence (from 4% to 35% (P < .001)). The subgroup of surgeons with prior experience with more than 250 RPs (n = 12), significant heterogeneity was noted in the incontinence rates, ranging from 5% to 30% (P < .001).

The authors also evaluated whether the baseline patient/tumor characteristics and surgeon-related factors could explain the difference in the outcomes of ORP and RALP. After adjusting for baseline patient and tumor characteristics only, the difference in incontinence rate was significantly lower after ORP than after RALP.

Adjusting for the annual caseload increased the difference in favor of ORP whereas adjustments for previous experience reduced the difference in incontinence rate. Regarding ED, there was no statistically significant difference between ORP and RALP at baseline, but adjusting for surgeons’ experience alone, or in combination with current caseload resulted in improvement (less ED) in favor of RALP. In terms of recurrence rates, there was no significant difference between ORP and RALP at baseline, and additional adjustments for surgeons’ caseload or experience did not change this outcome.

Data raise several questions
This report demonstrates a large and significant variability of functional and oncological outcomes among individual surgeons, without clearly demonstrating the superiority of either ORP and RALP. The most important factor affecting the heterogeneity of functional outcomes appears to be the surgeon’s prior experience, whereas current caseload had a significant impact on oncological outcomes.
High TMB predicts immunotherapy response in bladder cancer

Jason M. Broderick
Associate Editorial Director, Urology Times®

A retrospective analysis led by investigators from The University of Texas MD Anderson Cancer Center found that high tumor mutation burden (TMB-H) is only a biomarker for clinical response to immune checkpoint inhibitors in some tumor types, according to findings published in the *Annals of Oncology.*1,2

Regarding the most common genitourinary cancers, the study showed that TMB-H status was predictive of clinical response to immune checkpoint inhibitors in patients with bladder cancer, but not in patients with prostate cancer.

“This study represents the most comprehensive analysis to date of TMB as a biomarker for response to immune checkpoint blockade,” lead author Daniel J. McGrail, PhD, postdoctoral fellow in Systems Biology at MD Anderson, said in a news release. “Our results do not support applying high TMB status as a universal biomarker for immunotherapy response, suggesting that additional tumor type-specific studies are needed to clarify how best to apply TMB status in cancer types where it does not appear to be associated with outcomes.”

The anti–PD-1 immune checkpoint inhibitor pembrolizumab (Keytruda) received a tumor-agnostic approval from the FDA in June 2020 for the treatment of adult and pediatric patients with unresectable or metastatic TMB-H solid tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options.3

The approval was based on the phase 2 KEYNOTE-158 trial (NCT01704287), which included 755 patients with evaluable TMB, 102 (13%) of whom had tumors that were classified as TMB-high. Results showed that the overall response rate (ORR) with pembrolizumab in these patients was 29%, comprising a 4% complete response rate and a 25% partial response rate. Of note, there were solid tumor types not represented in the trial, including prostate, breast, and brain cancers.

“The FDA approval of pembrolizumab for patients with high TMB certainly provides an important option for many patients,” senior author Shiaw-Yih Lin, PhD, professor of systems biology, MD Anderson, said in the news release. “However, we felt that it was important to look more closely at TMB status in a broader group of cancer types and establish approaches to harmonize TMB across various assays to enable clinicians to best utilize the recent FDA approval.”

For their analysis, the investigators used data from The Cancer Genome Atlas to examine over 10,000 tumors across 31 tumor types. They specifically assessed the interaction between TMB status and tumor immunogenicity, which they defined as “infiltration of immune cells (CD8+ T cells) into the tumor.” Across the 31 tumor types, there was a subgroup of cancers showing a strong relationship between TMB status and T-cell infiltration, and a second subgroup in which the correlation between these 2 factors was not strong.

In tumors where the correlation was strong between T-cell infiltration and TMB status (eg, bladder, lung, melanoma), clinical outcomes were improved in patients with TMB-H status. The ORR to immunotherapy was 39.8% among those who were TMB-H, which the investigators reported was significantly higher than the ORR in individuals with low TMB.

In contrast, among tumors without a strong correlation between TMB status and T-cell infiltration (eg, prostate, breast, and glioma), TMB status was not predictive of the success of immunotherapy. The ORR with immune checkpoint agents was 15.3% among patients in this subgroup with TMB-H status. This rate was lower than the ORR with immune checkpoint agents in patients with TMB low status.

“While TMB status does show value in predicting response to immune checkpoint blockade in several cancer types, this was not generalizable across all cancers,” McGrail said. “For those cancer types where a high TMB does not appear to increase immunogenicity, additional prospective studies are needed to determine if TMB status can be an effective clinical biomarker and at what threshold.”

REFERENCES


OUTCOMES continued from page 16

general. How do we identify surgeons with clearly better outcomes and train the ones in need of improvement? Who should have the responsibility or authority (the department or the hospital) to collect such data? If the surgeons’ outcomes data are to be placed in the public domain, what necessary steps would be required to ensure that the data are robust and the public is sufficiently educated to use that information properly?

It is important to note that the variability in functional and oncologic outcomes in this study persisted even after adjusting for surgical volume and experience. This clearly suggests that surgical volume alone is insufficient to promise improved outcomes after RP. There must be some other unmeasured or intangible factors that influence the functional and oncologic outcomes such as advanced training, hand-eye coordination, and tissue handling.

In a patient-centric approach, monitoring and reporting surgical outcomes, albeit challenging, may become necessary. Further efforts such as anonymous review of surgical videos and intervention such as additional training, peer review, and feedback may be warranted to reduce the significant heterogeneity in outcomes noted among surgeons.4

REFERENCES


Bladder Cancer / CLINICAL UPDATES

Gomella discusses the state of the treatment paradigm for NMIBC

BCG remains the standard of care, but excitement is growing for new treatments

Matthew Fowler
Assistant Editor, CancerNetwork®

At the 2021 New York GU 14th Annual Interdisciplinary Prostate Cancer Congress® held virtually in March, Leonard G. Gomella, MD, FACS, the Bernard W. Godwin Jr Professor of Prostate Cancer and chairman of the Department of Urology at Thomas Jefferson University in Philadelphia, Pennsylvania, discussed the current state of the treatment paradigm in non–muscle-invasive bladder cancer (NMIBC) and highlighted novel agents on the horizon.1

BCG

Managing NMIBC starts with the resection of all visible disease and a focus on the existing standard of care, intravesical BCG, according to Gomella.

“Non–muscle-invasive bladder cancer management is something commonly encountered by urologists,” Gomella explained in his presentation at the congress. “Initial management is to resect all visible disease and think about enhanced cystoscopy as a way to complete that process. If [the disease is] high-grade, consider intravesical BCG therapy; [and with] low-volume disease, just do follow-up cystoscopy.”

The standard approach utilized by most care providers for BCG intravesical immunotherapy is known as the SWOG protocol, in which patients receive an initial 6-weekly induction dose, followed by 3 weekly doses at 3 months and every 6 months following initial treatment for up to 2 or 3 years.

Along with having a robust response, patients typically tolerate BCG therapy well. Some common adverse events associated with BCG treatment include fever, hematuria, and granulomatous prostatitis.

Although BCG is the current standard of care for NMIBC, BCG failures do exist. Specifically, recurrence and progression can happen with treatment via BCG, with 1- and 5-year recurrence rates of 15% to 61% and 31% to 78%, respectively. As for progression, the 1- and 5-year rates are as high as 17% and 45%, respectively. These existing data strengthen the need for additional therapeutic options for patients with NMIBC.2

“There’s no question that BCG is probably the best-known immuno-oncology agent,” Gomella said. “In reality, we’ve been using BCG for bladder cancer certainly since the FDA approval way back in 1990, and it’s really become the standard of care for non–muscle-invasive bladder cancer.”

After BCG failure

Among patients eligible for BCG, data suggest up to 40% may not respond to treatment or will become refractory to BCG. For high-risk patients who fit this description, Gomella explained that radical cystectomy should be considered as the first option. If patients are unwilling to undergo cystectomy or prefer another therapy, Gomella said that intravesical chemotherapy represents an option, although he noted its limited success.

For intravesical chemotherapy, monotherapy treatment is less efficacious than BCG, with paclitaxel, docetaxel, doxorubicin, epirubicin, and valrubicin (Valstar) among the drugs used in this treatment. Gomella noted that valrubicin is the only drug that has received FDA approval for this indication.

In addition, systemic pembrolizumab (Keytruda) to treat patients with BCG-refractory bladder cancer was recently approved by the FDA in response to data from the phase 3 KEYNOTE-057 study (NCT02625961).3

The median duration of response was 12.7 months (range, 0.0-20.5+ months), with 75% of patients experiencing a complete response (CR) duration of 6 or more months and 53% of patients showing a CR duration of 9 or more months.

“If you have a high-grade BCG failure, valrubicin and systemic pembrolizumab currently are the FDA-approved salvage medications,” Gomella said. “Again, cystectomy should always be considered and at least presented to the patient.”

Emerging agents

Several investigational agents are generating excitement in the field. The FDA granted a priority review designation to the protein-fusion drug Vicineum (VB4-845) in February 2021 for the treatment of patients with high-risk, BCG-unresponsive NMIBC.4

The intravesical therapy nadofaragene firadenovec has shown promise in BCG-unresponsive NMIBC. In a phase 3 trial, the CR rate with nadofaragene firadenovec was 53.4% at 3 months in patients with carcinoma in situ (CIS) with or without concomitant high-grade Ta or T1 disease (CIS ± Ta/T1).5 The 12-month CR rate was 24.3% and the median duration of CR was 9.69 months. Further, 45.5% of patients with an initial CR were still free of high-grade recurrence at 1 year.

Also of note, data from the phase 2/3 QUILT 3.022 study (NCT03022825) shared at the 2021 Genitourinary Cancers Symposium in February showed that the combination of N-803 (Anktiva), a novel IL-15 superagonist complex, and BCG achieved CRs in 71% (51/72) of patients with BCG-unresponsive, high-risk NMIBC with CIS with or without Ta or T1 disease.6

REFERENCES


Management of upper tract transitional cell carcinoma with mitomycin gel

59% of patients receiving treatment achieved a complete response at primary disease evaluation.

Audrey Sternberg
Managing Editor, Oncology®

In a presentation at the 2021 New York GU 14th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies, hosted by Physicians’ Education Resource, LLC, presenter Scott G. Hubosky, MD, discussed optimal strategies for treating patients with upper tract transitional cell carcinomas.

To do this, Hubosky mostly focused on the use of mitomycin gel (UGN-101; Jelmyto) as adjuvant therapy because of its ability to reach all surfaces of the luminal space of the upper urinary tract.

“We’re trying to see if we can extend our reach for conservative management,” said Hubosky, who is vice chair of quality improvement and safety of Jefferson University Hospitals in Philadelphia, Pennsylvania. “We were able to chemoblade these lesions. What this tells us is that we’re able to extend our reach with conservative management, and this is appealing.”

Mitomycin gel was approved in 2020 based on results of the pivotal phase 3 OLYMPUS trial (NCT02793128), which looked at patients with low-grade tumors who underwent weekly treatments, which is done during surgery with a retrograde ureteroscopic manipulation for kidney stones, the stricture rate is less than 1%,” Hubosky said. “It’s more than just ureteroscopic manipulation. Other things to keep in mind are the tumor location—you’re more likely to get a stricture if you’ve got a primary ureteral tumor.”

Other concerns for avoiding ureteral stricture include different energy sources, such as certain lasers that penetrate at a deeper level in the tissue. Hubosky recommended against using lasers that penetrate deeply in the ureter because many of these patients will see repeated procedures and manipulations of the tissue throughout the course of their disease.

Additionally, patients with Lynch syndrome tend to get tumors in the upper ureter more often than in the renal pelvis compared with patients who have sporadic upper tract tumors. “That’s going to put them at risk for ureteral strictures,” said Hubosky. “These patients have other things going on that really predispose them to ureteral stricture formation, such as other pelvic surgeries and pelvic radiation.” This is due to that fact that other cancers are likely present, such as colorectal cancer or endometrial cancer.

REFERENCES
Recurrence rates and patterns with robot-assisted radical cystectomy (RARC) were similar to historical data reported for open radical cystectomy in patients with bladder cancer, according to a large retrospective database analysis. The study reviewed data for 2107 patients who had received RARC. At a median follow-up of 26 months (interquartile range, 11-55), 521 (25%) had received RARC. At a median follow-up of 26 months, 521 (25%) had received RARC.

The investigators observed that worse relapse-free, local recurrence-free, distant metastasis-free, and overall survival occurred in patients with higher disease stage, positive lymph nodes, and positive soft tissue surgical margins (log rank P < .01 for all comparisons). Additionally, statistical analysis showed that disease stage (pT3 and node-positive status had a significant association with relapse-free, local recurrence-free, distant metastasis-free, and overall survival (P < .01).

“Disease stage remains the main variable associated with disease relapse and survival following radical cystectomy. Robot-assisted radical cystectomy was not associated with different patterns or higher relapse rates compared to historic open radical cystectomy data,” wrote the investigators, led by Ahmed Elsayed, MD, of Roswell Park Comprehensive Cancer Center in Buffalo, New York.

The 5-year relapse-free survival rate was 66% and the 5-year local recurrence-free survival rate was 84%. The 5-year distant metastasis-free survival and overall survival rates were 74% and 60%, respectively.

The investigators did not note a significant difference between these rates and historical data for open radical cystectomy.

Several limitations to the research were listed in the paper, including the retrospective nature of the analysis, the heterogeneity of the patients/physicians/protocols among the cases in the IRCC database, insufficient data available (eg, variant histology), and the lack of a comparative open radical cystectomy cohort.

In their conclusion, the investigators wrote, “RARC does not seem to exhibit a different relapse pattern compared to the ORC literature. Disease stage and adverse features remain the main predictors of relapses and survival after RARC.”

REFERENCE


doi:10.1097/JU.0000000000001380

ASCVD RISK IS HIGHER IN GU CANCER SURVIVORS

Cancer survivors, particularly those who had gonitourinary (GU) tumors, have an elevated 10-year risk of cardiovascular disease compared with the general population, according to research findings reported in *PLoS One*. The results showed that 35.1% of cancer survivors had an elevated 10-year risk of atherosclerotic cardiovascular disease (ASCVD) compared with 23.4% of individuals with no cancer history. The average estimated 10-year ASCVD risks were 8.3% vs 5.1%, respectively.

The 10-year risk was highest in GU cancer survivors, including bladder/kidney (odds ratio [OR], 2.727), prostate cancer (OR, 9.45), and testicular cancer (OR, 11.47).

“The good news is that we’re getting really good at treating cancer and we have more survivors, but we need to start thinking more carefully about the noncancer risks following a diagnosis, one of which is cardiovascular disease,” senior author Ashley Felix, PhD, an associate professor of epidemiology at The Ohio State University, Columbus, said in a news release.

The investigators applied statistical modeling to data from the National Health and Nutrition Examination Survey that was accrued between 2007 and 2016 for patients aged 40 to 79 years with no history of CVD. The study included data from 15,095 individuals with a mean age of 55.2 years. Overall, 12.3% (n = 1604) of patients self-reported a history of cancer. Patient characteristics showed that 53% were female, 71.7% were non-Hispanic White, and 9.9% were non-Hispanic Black.

The investigators noted that age was a significant modifier in the link between a history of cancer and the 10-year risk of ASCVD. Among this line, patients who received a cancer diagnosis between ages 60 and 69 had significantly higher odds of having an increased 10-year ASCVD risk (OR, 2.24); however, cancer history did not appear to affect the odds of elevated 10-year ASCVD risk in other age-defined subgroups.

Also commenting on the study in the news release, lead researcher Xiaochen Zhang, a PhD candidate in Ohio State’s College of Public Health, said, “The good news is that those younger individuals have a lot of time to make lifestyle changes that could move their cardiovascular risk in a positive direction.”

References


STONE PREVENTION
continued from page 1

What the guidelines say
The American Urological Association (AUA) recommends that patients with kidney stones increase fluid intake to produce more than 2.5 L of urine output daily.2

“The AUA recommends doing a metabolic evaluation, which is a 24-hour urine, that gives us the information that we need to know what recommendations to make,” Streeper said. “If a patient has hypercalciuria, or high amounts of calcium in the urine, then we would recommend they follow a normal calcium diet and limit their sodium intake. If somebody has high oxalate in their urine, or hyperoxaluria, we recommend that they limit the amount of oxalate-rich foods in their diet and do a normal calcium diet. For patients who have low levels of citrate, or hypocitraturia, we recommend that they increase their fruit and vegetable intake and limit how much animal protein they get. Then, for high amounts of uric acid in the urine, hyperuricosuria, we recommend they limit their animal protein.”

Not all guidelines agree on exactly how much to increase fluid intake, according to Charles D. Scales Jr, MD, MSHS, associate professor of surgery (urology) and population health at Duke University School of Medicine in Durham, North Carolina. “The American College of Physicians’ and European Association of Urology’s guidelines recommend patients drink 2.5 to 3 L daily.1,4

“I typically counsel my patients to drink about ten 10-oz glasses of fluid, which is about 3 L of fluid, on a daily basis, assuming they have normal kidney function and don’t otherwise have a reason, like heart failure, that they could not increase their fluid intake.”

CHARLES D. SCALES JR, MD, MSHS

which is about 1000 to 1200 mg daily, according to Scales.

Recommendations in the AUA guidelines that are based primarily on expert opinion include having a low nondairy animal protein component to the diet, according to Scales. “I usually recommend maybe 1 small serving of animal protein a day that is not from a dairy source. I also recommend a diet that is rich in fruits and vegetables,” Scales said. “For someone who has made oxalate stones in the past, I typically will recommend they limit their dietary oxalate sources.”

Considering recent data
Such recommendations from guidelines are not inflexible for Ben H. Chew, MD, MSc, director of clinical research at the Stone Centre at Vancouver General Hospital and associate professor of urology at the University of British Columbia in Vancouver, Canada.

“Not every physician will do the whole metabolic evaluation to look at patients,” Chew said. “I’m leaning more toward not doing one, too, which is a little bit controversial.”

Use of the test is low in the United States. Only 7.4% of the 28,836 patients identified by investigators in one study as being at high risk for recurrence had 24-hour urine testing. Chew instead uses limited blood tests to make sure patients do not have hyperparathyroidism or hypercalcemia, then makes the same 5 lifestyle recommendations to most of his patients with stones. His first, second, and third recommendations are to drink more water, fourth is to make sure patients have normal amounts of oxalate and calcium in their diets, and the fifth emphasizes a healthy, balanced diet—one doctors recommend to reduce risks for hypertension, diabetes, and high cholesterol.

“If I recognize that a low-oxalate diet versus a normal-oxalate diet is controversial and there will be arguments amongst dietitians and stone experts,” Chew said. Restricting oxalate is not necessary, according to Chew, when all patients really need to do is combine the oxalate with calcium. So, tell patients to have spinach, Chew said, but to add a little cheese on top or a glass of milk.

“If you have unopposed calcium or unopposed oxalate, they will get absorbed into the bloodstream, where they will get filtered by the kidney and then combine with other calcium and oxalate that is already there to form a kidney stone,” Chew says. “You want calcium and oxalate to make the crystal, stay in the gastrointestinal tract so that you can excrete that out in the stool, and still absorb the nutrients. Definitely don’t have a calcium-free diet or avoid dairy because that is part of a healthy, balanced diet, both for stones as well as for bone health. We know that [patients with] kidney stones are also at higher risk for getting osteoporosis.”

Recommending that patients with stones go on a low-calcium diet is based on outdated information, according to Scales.

“That diet has been overturned based on the epidemiologic and the physiologic evidence that shows that low-calcium diets actually increase oxalate absorption,” Scales said.

Chew emphasizes a healthy, balanced diet to all his patients with stones. Urologists often treat stones as a separate entity, as kidney stone disease, according to Chew.

“Epidemiologically, we realize it is part of a whole syndrome. We know kidney stone disease is associated with the metabolic syndrome. We know it comes with diabetes, high blood pressure, being obese, and having high lipids. We know that the more of those 4 things you have, the more likely you are to get kidney stones,” Chew said. “When I see young patients, I think they should be warned to basically follow up with doctors because this could be their sentinel event. I think there is a real opportunity for us to help patients change their lives, not just for kidney stones but also to prevent high blood pressure, diabetes, for which a lot of the risks are modifiable.”

Helping patients make lifestyle changes
Educating patients about how to prevent kidney stone formation requires more than a handout. It takes time and effort, Streeper said. Although Streeper does the educating and is in practice with a dietitian and nephrologist who help to care for her patients with kidney stones, she said other practices might recruit advanced practice providers to help change patient behavior.

“I always try to pick out and give patients no more than 3 recommendations to do, and I prioritize the 3 recommendations.”

NECOLE M. STREEPER, MD

30 | Urology Times | APRIL 2021
Expanding Kidney-Sparing Options For Patients With Low-Grade Upper Tract Urothelial Cancer

If you are a US healthcare professional, view the iPub® at the link below to expand your knowledge of this topic.

urologytimes.com/interactive-tools/jelmyto

In this iPub®, Dr. Gordon Brown and Dr. Phillip M. Pierorazio:

Discuss the recent guidelines updates that have expanded the recommended use of kidney-sparing procedures

Explain the current limitations of radical nephroureterectomy and endoscopic management

Review the results of a pivotal trial that evaluates the efficacy and safety of a primary tumor therapy for low-grade upper tract urothelial cancer (LG-UTUC)

Describe the first and only FDA-approved treatment for LG-UTUC

Join these leading experts:

Gordon Brown, D.O.
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Phillip M. Pierorazio, M.D.
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Johns Hopkins University
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VIEW THE TODAY AT:
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High-power super pulse thulium fiber laser yields encouraging results

Laser performs efficiently for ablating a variety of stone types, investigators report

Cheryl Guttman Krader
Urology Times® Contributing Editor

North American urologists analyzing outcomes from their initial experience treating urolithiasis with the high-power super pulse thulium fiber (HPTF) laser (Solvite) are encouraged by the results. Findings from their retrospective review that included 76 patients treated for a total of 118 upper urinary tract stones showed that the technology performed efficiently for ablating a variety of stone types and had a safety profile similar to that of the holmium:yttrium-aluminum-garnet (Ho:YAG) laser that is considered the current gold standard.1

Details on patient characteristics, intraoperative data, and clinical outcomes are summarized in a paper published online in Urology. Wilson R. Molina, MD, professor of urology at Kansas University Medical Center in Kansas City, Kansas, was one of the treating urologists in the multicenter study and helped to develop the HPTF laser. He told Urology Times®, “The Ho:YAG laser, which has been around for more than 2 decades, is proven great technology for stone treatment, and its capabilities have been enhanced in recent years with the introduction of high-power lasers and pulse modulation. However, the HPTF laser offers several practical and technical advantages that give it the potential to be a real breakthrough in stone treatment. “Experience with the HPTF laser is limited, we are still in the process of understanding how to optimize its parameters for treating different stone types, and there is a need for prospective randomized trials comparing the HPTF and Ho:YAG lasers. Preliminary, however, the HPTF laser is clearly promising new technology for treatment of urolithiasis,” Molina added.

Other centers contributing to the first North American HPTF laser series were the Ohio State University, Columbus; University of British Columbia, Vancouver, Canada; and Mayo Clinic, Phoenix, Arizona. The 118 stones treated included 32 located within the ureter, and 49, 25, and 12 in the lower, mid-, and upper poles, respectively. Three-fourths of the procedures involved retrograde intrarenal surgery, dusting was the most common technique (67%), and most cases (79%) were done using a 200-μm fiber. Mean operative time approached 1 hour.

“Findings from laboratory studies and initial clinical experience indicate that when it comes to ablation efficiency, the HPTF laser is better than the Ho:YAG laser.”

WILSON R. MOLINA, MD

STONE PREVENTION

continued from page 30

videors to educate and guide patients in making lifestyle changes.

It is important to go beyond telling patients what to do and help them figure out how to do it. Patients might face occupational barriers to increasing their fluid intake, for example.

“Patients and when they might be able to access to the bathroom day, so they have to think carefully about when they might be able to have access to the bathroom and when they might be able to go.”

Another tip is to limit the recommendations to a doable amount because patients often feel overwhelmed by all they must do, Streeper said.

“I always try to pick out and give patients no more than 3 recommendations to do, and I prioritize the 3 recommendations,” Streeper said.

Apps and technology can help patients stay on track with changes, including increasing fluid intake. Streeper and colleagues have been studying a stone-specific technology called sipIT, to determine whether it helps patients drink more water. The device is a watch that connects with a smart water bottle. Together, the devices alert patients in real time if they are not achieving their fluid intake goals.2,7

Scales and colleagues are recruiting for the PUSH trial (NCT0244189), a randomized trial in the Urinary Stone Disease Research Network, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases that focuses on increasing participants’ adherence to fluid goals for stone prevention. The multicomponent behavioral intervention, focusing on adherence, leverages a smart water bottle sold as the HidrateSpark water bottle (Hidrate) as a study platform, with the primary endpoint being recurrence of symptomatic kidney stones at a 2-year time point.7

REFERENCES


Urology Times® April 2021
Mental disorder risk is elevated in men with Peyronie disease

Increased risks of receiving diagnosis of substance use disorder and self-injurious behavior are seen

Jason M. Broderick
Associate Editorial Director, Urology Times*

Men with Peyronie disease (PD) have increased risk of developing psychiatric disorders, according to findings from a population-based cohort study published in the Journal of Urology.1

The results showed that men with PD were at elevated risk of receiving a diagnosis of any psychiatric outcomes (HR, 1.4), as well as substance use disorder (HR, 1.4), anxiety disorder (HR, 1.9), depression (HR, 1.7), and self-injurious behaviors (HR, 2.0). There was not elevated risk of alcohol misuse (HR, 0.9).

“PD may be a serious but partially hidden public health concern. We reported for the first time that men with PD had increased risks of being diagnosed with several psychiatric outcomes, including self-injurious behaviors,” wrote the investigators, led by Ralf Kuja-Halkola, of Karolinska Institutet, Stockholm, Sweden.

The investigators conducted a longitudinal cohort study using data from Swedish national registers. The analysis included 8105 men with PD and 3.5 million comparison subjects without PD. The patients in the PD cohort were born between 1933 and 1996 and had received their diagnoses between 1997 and 2013.

In the PD cohort, 13.4% of men had received diagnoses of adverse psychiatric outcomes compared with 10.7% in the control cohort. The rates of anxiety disorder, depression, and self-injurious behaviors were 4.1% vs 3.2%, 6.4% vs 4.1%, and 3.6% vs 2.5%, respectively.

“Although many urologists are aware of the impact of PD on mental health, they rarely assess these issues formally. We suggest that the PD care at urology clinics would be improved by implementing 2 simple practices: confirm a documented mental health status and refer those without a documented mental health status to primary care,” the investigators wrote.

There were 2 accompanying editorial commentaries simultaneously published in the Journal of Urology. In the first, Martin Gelbard, MD, Department of Urology, Men’s Health University of California, Los Angeles, wrote, “For the urologist, these data reinforce the benefit of inquiring about psychological issues in their patients with Peyronie disease, and for general health care providers, the need to tactfully explore sexual function of patients with the above problems. Additionally, troubled patients may find much needed support when their health care providers use this extremely informative data set to show them they are not alone in feelings that may be difficult to express.”2

In the second commentary, Brian Le, MD, Department of Urology, University of Wisconsin School of Medicine and Public Health in Madison, noted that he found the findings useful but urged caution when interpreting the results for clinical practice.3

“From a practical standpoint, this study certainly would encourage urologists to consider a psychiatric evaluation if there are any hints of this in your clinical evaluation, because it may affect patient expectations and perceptions of outcomes of PD treatment. However, we should also keep in mind that the population attributable risk of PD for being diagnosed with a psychiatric disorder is 2.7%, which puts into question the efficacy of widespread screening of all men with PD for psychiatric disorders,” wrote Le.4

REFERENCES


LASER continued from page 32

mean laser time was 10.8 minutes, and total laser energy used was 12.5 kJ.

There were 11 intraoperative complications, all related to ureteral access sheath and none related to the laser itself. In addition, 1 patient developed renal collecting system bleeding that was controlled with laser coagulation settings. All patients had same-day discharge excluding 3 who developed sepsis. As assessed using ultrasound or CT scan, stone-free rates among patients who presented for follow-up were 67% at 6 weeks and 79% at 12 weeks.

Compared with the Ho:YAG laser, the HPTF laser is more portable, quieter, and can be installed without any special energy infrastructure requirements because it can be plugged into a conventional 120-V power outlet. From a technical perspective, the HPTF laser can be operated with a broader range of pulse energy and frequency settings that provide opportunity for optimizing lithotripsy. Because its 1940-nm wavelength is at the peak of water absorption and it is associated with less stone retropulsion, energy is delivered more efficiently with the HPTF laser.

“Findings from laboratory studies and initial clinical experience indicate that when it comes to ablation efficiency, the HPTF laser is better than the Ho:YAG laser,” Molina said.

As another advantage, the HPTF laser seems to be associated with less fiber burn-back than the Ho:YAG laser, indicating the potential for the fibers to last longer. In addition, the HPTF laser can be used with smaller fibers that could potentially improve scope navigation and better irrigation flow.

“Already HPTF procedures are being done with a 150-μm fiber, whereas 200 μm is the smallest fiber that can be used with the Ho:YAG laser,” Molina said.

The features that distinguish the HPTF laser from the Ho:YAG laser, however, come with 2 sides to the coin. Because it causes less stone retropulsion, the HPTF laser will not perform as well as the Ho:YAG for the popcorn technique. In addition, the increased adjustability of the HPTF laser settings will likely make treatment parameter optimization more complex.

“We have to start from scratch to develop the best settings because we cannot extrapolate those used for Ho:YAG laser lithotripsy. With so much versatility, identifying the best settings for the HPTF laser will probably take more time,” Molina said.

Disclosure: Molina is a consultant for Olympus of the Americas.

REFERENCE

AUGUST 2021 | Urology Times® | 33
Combination of belzutifan plus cabozantinib is active in advanced RCC

Treatment shrank tumors in 88% of patients and led to a disease control rate of 90%.

“Belzutifan is a first-in-class HIF-2 alpha antagonist that inhibits the transcription factor HIF-2 alpha, and cabozantinib is approved by the FDA for the treatment of renal cell carcinoma,” said Choueiri, director of the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute/Brigham and Women’s Hospital in Boston, Massachusetts. “We believe that targeting the underlying pathology of ccRCC, targeting the transcription factor HIF-2alpha with belzutifan, and targeting downstream with the VEGF receptor inhibitor, among other kinases, cabozantinib could be an effective treatment for patients with metastatic ccRCC.”

Investigators for the ongoing trial (NCT03634540) analyzed 41 patients for efficacy. The confirmed objective response rate (ORR) was 22% (9 of 41); all responses were partial responses. Investigators also observed another 5 (12%) unconfirmed partial responses. Twenty-eight (68%) patients had stable disease as best responses. The median duration of response was not reached, and all confirmed responses were still ongoing as of data cutoff of October 15, 2020. The median time from enrollment to data cutoff was 8.9 months. The investigators are still enrolling a cohort of untreated patients into the study.

Eligible patients were assigned to 120 mg belzutifan plus 60 mg cabozantinib orally once daily for 21 days. This efficacy analysis includes patients who received at least 1 dose of treatment and had an opportunity for at least 6 months of follow-up.

The progression-free survival (PFS) rate was 78% at 6 months and 65% at 12 months. Choueiri noted that 95% of patients were alive at 6 months.

“The median should not be considered real, given only 1 patient was at risk at month 17, but the median PFS here was 16.8 months,” he said.

David A. Braun, MD, PhD, a physician and investigator with Dana-Farber, urged caution. He delivered a discussant on Choueiri’s presentation.

“The median follow-up was only about 11 months and the minimum follow-up only 5.6 months,” he said. “This is interesting and potentially exciting, but we really need to have further follow-up. When we look at the PFS curve, which looks impressive, it’s a median of 16.8 months. But, again, there are very few patients who are out that far. It’s definitely preliminary.”

Nearly all (98%) patients experienced any-grade treatment-related adverse events (TRAEs). Grade 3-4 TRAEs included hypertension (34%), hyperkalemia (24%), anemia (10%), and ACE inhibitor-induced angioedema (9%). Grade 3-4 events were not dose-limiting. The most common grade 1-2 TRAEs were fatigue (90%), hypertension (86%), hypokalemia (71%), and bradycardia (66%).

ACE inhibitor-induced angioedema is an important safety concern with cabozantinib. Investigators recommend monitoring patients for this adverse event.

The most frequent grade 3-4 TRAEs were hypertension (12%) and hyperkalemia (9%). Grade 3-4 TRAEs were not dose-limiting. The most common grade 1-2 TRAEs were fatigue (90%), hypertension (86%), hypokalemia (71%), and bradycardia (66%).

In 38% of patients, treatment-related adverse events (TRAEs) led to drug discontinuation. Grade 3-4 TRAEs included hyperkalemia (9%), hypertension (5%), and bradycardia (5%). The most common grade 1-2 TRAEs were hyperkalemia (71%), hypertension (66%), and bradycardia (47%).

Grades 3-4 adverse events included hyperkalemia (9%), hypertension (5%), and bradycardia (5%). The most common grade 1-2 adverse events were hyperkalemia (71%), hypertension (66%), and bradycardia (47%).

Tivozanib was approved by the FDA based on data from phase 3 TiVo-3 trial. Results from the study presented during the 2020 American Society of Clinical Oncology Virtual Scientific Program2 showed that tivozanib demonstrated a significant improvement in PFS compared with sorafenib (Nexavar), with similar OS, in patients with highly relapsed/refractory metastatic RCC. Results showed that the final HR for OS was 0.87 (P = .003).

Moreover, an updated analysis of the data found that, with a median follow-up of 38 months for tivozanib and 40 months for sorafenib, the median OS was 16.4 months for tivozanib and 19.2 months for sorafenib.

References

PHASE 3 TRIAL TO EXPLORE RCC COMBINATION

Jason M. Broderick | Associate Editorial Director, Urology Times

Following the recent FDA approval of tivozanib (Fotivda) in renal cell carcinoma (RCC), the VEGF-tyrosine kinase inhibitor (TKI) is now being explored in combination with the PD-1 inhibitor nivolumab (Opdivo) in the phase 3 TiNi-vo-2 trial in patients with relapsed/refractory RCC.1

On March 10, 2021, the FDA approved tivozanib for the treatment of adult patients with relapsed or refractory advanced RCC who have received 2 or more prior systemic therapies.2 TiVo-2 is randomizing patients with RCC who progressed after receiving immunotherapy to either tivozanib alone or in combination with nivolumab.

The target enrollment of the open-label TiVo-2 trial is 326 patients with advanced RCC and disease progression following treatment. The international trial is accruing patients at sites in the United States, Latin America, and Europe. The primary outcome measure is progression-free survival (PFS) and secondary endpoints include overall survival (OS), overall response rate, duration of response, and safety.

Tivozanib was approved by the FDA based on data from phase 3 TiVo-2 trial. Results from the study presented during the 2020 American Society of Clinical Oncology Virtual Scientific Program2 showed that tivozanib demonstrated a significant improvement in PFS compared with sorafenib (Nexavar), with similar OS, in patients with highly relapsed/refractory metastatic RCC. Results showed that the final HR for OS was 0.87 (P = .003).

Moreover, an updated analysis of the data found that, with a median follow-up of 38 months for tivozanib and 40 months for sorafenib, the median OS was 16.4 months for tivozanib and 19.2 months for sorafenib.

References
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Study compares outcomes with common surgeries for LUTS related to BPO

Lower reintervention rate is observed in patients undergoing open simple prostatectomy

Belzutifan

Jason M. Broderick
Associate Editorial Director, Urology Times

A comparative study of 5-year surgical reintervention rates in patients with lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO) showed that, compared with transurethral resection of the prostate (TURP), photoselective vaporization of the prostate (PVP) had a significantly higher reintervention rate, whereas open simple prostatectomy (OSP) had a significantly lower reintervention rate.1

The retrospective study, conducted by investigators in Germany, compared reintervention rates in the 4 standard surgical interventions for BPO-related LUTS: TURP, OSP, PVP, and laser enucleation of the prostate (LEP). Regarding LEP, there was no difference in overall reintervention rates observed between the treatment and TURP.

“The surgical reintervention rate after surgery for LUTS due to BPO is a robust criterion of the quality of treatment. Open simple prostatectomy remains superior to transurethral resection with respect to long-term efficacy,” wrote the authors, led by Christian Gilfrich, MD, of St Elisabeth-Hospital Straubing in Straubing, Germany.

For their study, the investigators examined claims data from AOK, the largest provider of statutory health insurance in Germany. Overall, the study data were compiled from the records of 43,041 male patients with LUTS. Between 2011 and 2013, the patients were treated with TURP (n = 34,526), OSP (n = 1631), PVP (n = 3050), or LEP (n = 1814).

Across the total study population, the median age was 72 years (interquartile range, 66-77). The extent of comorbidity varied among the treatment-defined patient subgroups, with the highest degree of comorbidity in patients treated with PVP.

Increased hazard of reintervention is seen with PVP

Overall, within 5 years of primary surgery, there were 5050 first reinterventions performed. Statistical modeling showed that relative to TURP, there was an increased hazard of reintervention with PVP (HR, 1.31; P < .001); in contrast, the hazard of reintervention was significantly lower with OSP compared with TURP (HR, 0.43; P < .001). When specifically focusing on LUTS recurrence, these hazard data were further amplified: PVP versus TURP (HR, 1.52; P < .001), and OSP versus TURP (HR, 0.38; P < .001).

The investigators also evaluated reinterventions for urethral stricture and bladder neck contracture. With these reinterventions, the hazards for PVP and TURP did not vary, whereas OSP again had a significantly lower hazard than TURP (HR, 0.45; P < .001).

Some of the potential limitations of the study noted by the investigators were the use of data from a single provider, the inherent limitations of a retrospective analysis, and the lack of extensive clinical information provided on claims data.

In their concluding remarks, the authors stressed the significance of the long follow-up period captured by their data. “To our knowledge, this is the only study to date with a 5-year follow-up for the most established approaches in LUTS surgery,” the authors wrote. “Our findings underline the importance of long-term studies, because a continuous increase in reinterventions was evident up to the fifth year from initial surgery for all 4 approaches.”

REFERENCE


BELZUTIFAN

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3 TRAEs were fairly common (60%) but there was no incidence of grade 4/5 TRAEs.

Six (12%) patients discontinued belzutifan because of treatment-emergent AEs and 8 (15%) discontinued cabozantinib. Seven (13%) patients experienced serious TRAEs.

In July 2020, the FDA granted breakthrough therapy designation to belzutifan for the treatment of patients with von Hippel-Lindau (VHL) disease–associated RCC with nonmetastatic RCC tumors smaller than 3 cm in size unless immediate surgery is required. The agency also granted orphan drug designation to belzutifan for VHL disease.2 Both designations were based on data from a phase 2 trial evaluating patients with VHL-associated ccRCC that were presented at the 2020 American Society of Clinical Oncology Annual Meeting.

Results showed that the agent induced a confirmed ORR of 27.9%; all responses were partial response. Notably, most (86.9%) of the patients in the trial experienced a reduction in the size of their target lesions.3 Previous data from a phase 1/2 trial (NCT012974738) showed encouraging single-agent activity with belzutifan in patients with heavily pretreated ccRCC, a benefit that was observed across all International Metastatic RCC Database risk groups analyzed.4

In 53 patients enrolled to the dose escalation/expansion cohort of the trial, the ORR was 24% with the agent, while the disease control rate was 80%. The ORR consisted of 13 confirmed partial responses. Moreover, the median PFS reported with belzutifan in the overall patient population studied was 11 months. At 1 year, 49% of patients remained progression free.5

REFERENCES


Part B data reveal increased usage of denosumab and mitomycin

Leuprolide acetate remains the most commonly used androgen suppression drug

ROBERT A. DOWLING, MD

Dowling is the president of Dowling Medical Director Services, a private health care consulting firm specializing in quality improvement, clinical informatics, and health care policy affecting specialty care. He is the former medical director of a large, metropolitan single-specialty urology group in Fort Worth, Texas.

Growth in drug costs and spending for Medicare beneficiaries remains an area of concern for patients, policy makers, providers, payers, and regulators. The concerns exist in part because of a perception that the current reimbursement system encourages overutilization and price increases. According to the Centers for Medicare & Medicaid Services (CMS), between 2006 and 2017, Medicare Part B fee-for-service drug spending per enrollee grew at 8.1% annually, more than twice as high as per capita spending on Medicare Part D (3.4%) and nearly 3 times as high as overall retail prescription per capita drug spending (2.9%).

Spending is not increasing for all Part B drugs; in an article last year citing 2018 spending data, I reported that of 17 Part B drugs commonly used by urologists, only 3 drugs increased in spending faster than Part B spending overall. In fact, spending on a small number of specialty drugs is driving most of the increases through high prices, high utilization, or both.

Nevertheless, in 2020 CMS finalized a new “1 size fits all” rule—the Most Favored Nation Model for Medicare Part B Drugs and Biologicals—wherein it proposed indexing payments for Part B drugs to the reduced amounts paid by peer countries and testing a flat add-on fee to replace the current model of average sales price plus a percentage. This proposed rule would have a large impact on urology and oncology practices and met fierce resistance from a number of associations; at the time of this writing, CMS has not appealed an injunction that halted implementation of the rule. In this article, I will update the spending and costs for Medicare Part B drugs commonly used by urologists in the office setting in the context of even greater scrutiny by policy makers and regulators.

CMS recently released detailed drug spending data for 2015 to 2019. “Spending” in this context includes the estimated total costs, such as deductible, coinsurance, and Medicare spending. Total spending in 2019 for 585 Part B drugs was $37.3 billion, up more than 12% from 2018. (Note that CMS revised 2018 total spending figures in 2019; using the revised figure, spending increased over 18%.) Spending on any single drug may increase because of increased utilization, higher price, or both. Although it is not possible using this particular data set to determine what fraction of total spending is accountable to urologists, or the spending by indication for any individual drug, we can examine trends in the drugs commonly administered and billed by urologists in the office setting.

Denosumab has largest total spend among urologists

Seventeen drugs commonly used by urologists account for less than 7% of total Medicare Part B drug spending. Of these 17 drugs used in the urology office for Medicare beneficiaries (Table), the drug with the largest 2019 total spend—as in 2018—was denosumab (Xgeva) at $1.6 billion; in 2018, it was mainly due to decreased utilization, gentamicin sulfate, valrubicin, goserelin acetate, and degarelix acetate. Among the 7 drugs where spending declined in 2019 over 2018, it was mainly due to decreased utilization in 5 (triptorelin pamoate, interferon alfa-2b, histrelin acetate, sipuleucel-T [Provenge], and testosteron cypionate) and mainly to decreased average price in 2 (gencitabine HCL and ceftriaxone).

Total spending in 2019 for 585 Part B drugs was $37.3 billion, up more than 12% from 2018. (Note that CMS revised 2018 total spending figures in 2019; using the revised figure, spending increased over 18%.) Spending on any single drug may increase because of increased utilization, higher price, or both. Although it is not possible using this particular data set to determine what fraction of total spending is accountable to urologists, or the spending by indication for any individual drug, we can examine trends in the drugs commonly administered and billed by urologists in the office setting.

FIGURE. Common Drugs Used to Suppress Androgens in Urology: Medicare Part B Spending

* Generic drug has more than 1 brand name

Source: Adapted from Centers for Medicare & Medicaid Services data by Robert A. Dowling, MD

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>2019 Total Spending (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolide acetate*</td>
<td>$301,640,199</td>
</tr>
<tr>
<td>Degarelix acetate</td>
<td>$18,588,840</td>
</tr>
<tr>
<td>Goserelin acetate</td>
<td>$9,534,611</td>
</tr>
<tr>
<td>Triptorelin pamoate</td>
<td>$9,857,943</td>
</tr>
<tr>
<td>Histrelin acetate</td>
<td>$1,974,606</td>
</tr>
</tbody>
</table>

*Generic drug has more than 1 brand name
In the androgen suppression market (Figure), leuprolide acetate was still the most commonly administered drug with spending in 2019 of $302 million (11% higher than 2018). Over the last 5 years, growth in spending per dose of leuprolide acetate has decreased 1.4% annually. In 2019, growth in spending per dose of leuprolide acetate was still the most common — $18,588,840 (–0.62% 4.48% 5.14% 1.69% 84.37%).

**Urology market share is derived from detailed provider utilization data in the most recently available year (2018). The share is based on a random sample of 35% of all Medicare beneficiaries (for privacy reasons). Nevertheless, it is a good approximation of the market share of the drugs administered and billed by urologists.**

**Generic drug has more than 1 brand name.**

**REFERENCES**


### TABLE. Commonly Administered Drugs by Urologists: 2019 Medicare Part B Spending

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Brand</th>
<th>Generic</th>
<th>Number of Manufacturers</th>
<th>Total spending, 2019</th>
<th>Total units, 2019</th>
<th>Total beneficiaries, 2019</th>
<th>Average spending per dosage unit, 2019</th>
<th>Average sales price, 2019</th>
<th>Change in total spending, 2018-2019</th>
<th>Change in average spending per dosage unit, 2018-2019</th>
<th>Change in average sales price, 2018-2019</th>
<th>Annual growth rate in average spending per dosage unit, 2015-2019</th>
<th>Urology market share, 2018 **</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9097</td>
<td>Prosta* **</td>
<td>Denosumab*</td>
<td>1</td>
<td>$1,605,208,840</td>
<td>91,759,929</td>
<td>589,684</td>
<td>$17.49</td>
<td>$18.92</td>
<td>9.19%</td>
<td>13.28%</td>
<td>3.75%</td>
<td>4.49%</td>
<td>4.98%</td>
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<td>J9085</td>
<td>Ostar*</td>
<td>Onabotulinum toxA*</td>
<td>1</td>
<td>$306,463,548</td>
<td>63,742,503</td>
<td>146,030</td>
<td>$5.75</td>
<td>$6.13</td>
<td>5.76%</td>
<td>5.19%</td>
<td>–5.59%</td>
<td>0.89%</td>
<td>3.85%</td>
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<td>J9017</td>
<td>Eligard*</td>
<td>Leuprolide acetate*</td>
<td>2</td>
<td>$301,640,199</td>
<td>1,400,127</td>
<td>166,794</td>
<td>$215.44</td>
<td>$229.67</td>
<td>5.44%</td>
<td>10.95%</td>
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<td>J0243</td>
<td>Provence</td>
<td>Spizolone (Lactated ringers)</td>
<td>1</td>
<td>$176,936,557</td>
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<td>$42,172.96</td>
<td>$44,510.66</td>
<td>–12.32%</td>
<td>–6.15%</td>
<td>7.05%</td>
<td>6.30%</td>
<td>64.03%</td>
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<tr>
<td>J0775</td>
<td>Xaflex</td>
<td>Colloconazole clavulanate disodium</td>
<td>1</td>
<td>$60,506,760</td>
<td>1,342,638</td>
<td>8535</td>
<td>$45.07</td>
<td>$46.97</td>
<td>17.30%</td>
<td>26.51%</td>
<td>7.85%</td>
<td>4.68%</td>
<td>3.28%</td>
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<tr>
<td>J9155</td>
<td>Firmagon</td>
<td>Depeptide acetate</td>
<td>1</td>
<td>$18,588,840</td>
<td>5,037,048</td>
<td>12,249</td>
<td>$3.69</td>
<td>$3.87</td>
<td>–0.62%</td>
<td>4.48%</td>
<td>5.14%</td>
<td>1.69%</td>
<td>34.37%</td>
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<tr>
<td>J0380</td>
<td>Mitomycin*</td>
<td>Mitomycin*</td>
<td>5</td>
<td>$17,917,209</td>
<td>179,278</td>
<td>6446</td>
<td>$97.71</td>
<td>$107.28</td>
<td>77.01%</td>
<td>38.66%</td>
<td>–21.67%</td>
<td>13.89%</td>
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<tr>
<td>J0202</td>
<td>Zoladex</td>
<td>Goserelin acetate</td>
<td>2</td>
<td>$9,857,943</td>
<td>22,665</td>
<td>2919</td>
<td>$434.94</td>
<td>$496.86</td>
<td>–3.94%</td>
<td>7.62%</td>
<td>13.27%</td>
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<td>J3315</td>
<td>Trelstar</td>
<td>Triptorelin pamoate</td>
<td>2</td>
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<td>41,243</td>
<td>5487</td>
<td>$231.18</td>
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<td>–31.29%</td>
<td>–43.91%</td>
<td>–18.36%</td>
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<td>73.13%</td>
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<tr>
<td>J0957</td>
<td>Valstar*</td>
<td>Valstar*</td>
<td>2</td>
<td>$9,123,540</td>
<td>7202</td>
<td>363</td>
<td>$1876.64</td>
<td>$1835.48</td>
<td>–1.50%</td>
<td>7.68%</td>
<td>9.51%</td>
<td>4.51%</td>
<td>61.64%</td>
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<tr>
<td>J9214</td>
<td>Intron A</td>
<td>Interferon alfa-2b, recombinant</td>
<td>1</td>
<td>$6,475,080</td>
<td>207,605</td>
<td>964</td>
<td>$31.19</td>
<td>$33.96</td>
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<td>52.57%</td>
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<tr>
<td>J9021</td>
<td>Gemcitabine HCL*</td>
<td>Gemcitabine HCL*</td>
<td>14</td>
<td>$4,401,978</td>
<td>886,356</td>
<td>16,555</td>
<td>$5.03</td>
<td>$5.15</td>
<td>–3.12%</td>
<td>–22.56%</td>
<td>–20.07%</td>
<td>–10.93%</td>
<td>0.31%</td>
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<tr>
<td>J0701</td>
<td>Opro Testosterone*</td>
<td>Testosterone cypionate*</td>
<td>16</td>
<td>$2,483,943</td>
<td>93,193,316</td>
<td>56,213</td>
<td>$0.03</td>
<td>$0.03</td>
<td>–0.03%</td>
<td>–11.00%</td>
<td>7.76%</td>
<td>–2.52%</td>
<td>47.92%</td>
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<tr>
<td>J0696</td>
<td>Ceftriaxone*</td>
<td>Ceftriaxone in Is-Q-Slim Dietis</td>
<td>15</td>
<td>$2,267,029</td>
<td>3,344,860</td>
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<td>$0.57</td>
<td>–1.58%</td>
<td>–7.88%</td>
<td>–6.49%</td>
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<tr>
<td>J9225</td>
<td>Vantas</td>
<td>Histrelin Acetate</td>
<td>1</td>
<td>$1,974,606</td>
<td>550</td>
<td>548</td>
<td>$3590.19</td>
<td>$3677.72</td>
<td>–26.86%</td>
<td>–19.04%</td>
<td>10.69%</td>
<td>5.16%</td>
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<tr>
<td>J1680</td>
<td>Gentamicin sulphate*</td>
<td>Gentamicin sulphate*</td>
<td>5</td>
<td>$272,138</td>
<td>104,743</td>
<td>73,238</td>
<td>$1.16</td>
<td>$1.79</td>
<td>–6.50%</td>
<td>12.11%</td>
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<tr>
<td>J002</td>
<td>Testosterone enantate</td>
<td>Testosterone enantate</td>
<td>2</td>
<td>$80,270</td>
<td>1,609,804</td>
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<td>$0.05</td>
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<td>–5.85%</td>
<td>24.19%</td>
<td>31.91%</td>
<td>1.76%</td>
<td>56.83%</td>
</tr>
</tbody>
</table>

*Generic drug has more than 1 brand name.** Urology market share is derived from detailed provider utilization data in the most recently available year (2018). The total spending in this file is lower than the total spending in the dashboard data for the same year because this file does not include all sites of service or all beneficiaries (for privacy reasons). Nevertheless, it is a good approximation of the market share of the drugs administered and billed by urologists.

Source: Adapted from Centers for Medicare & Medicaid Services data by Robert A. Dowling, MD.
CODING Q&A / Business

Can CPT code 51798 be billed as part of a TURP?

Medical necessity must be documented on the chart to bill code 51798.

Q: I read the article “What is Included in the Global Period for TURP?” The article stated that the urinary catheter is included. Can you please also note whether 51798 is included? I read a post on a coding website that says that 51798 is considered diagnostic and not therapeutic, so it can be billed during the global period. Can you please confirm this?

A: Common Procedural Terminology (CPT) 52601 (transurethral electrosurgical resection of prostate, including control of postoperative bleeding, complete [vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included]) is assigned a 90-day global by Medicare. A 90-day global procedure means that the work for the procedure and associated care have already been factored into the payment for the code, typically including 1 day preoperative work, work on the day of the procedure, and the work that is typical for 90 days beginning the day after surgery.

What we did not include in our previous article are services not part of the global surgical package. The list of services not included in the global of a major surgery like a transurethral resection of the prostate (TURP) include the initial evaluation of the problem resulting in the decision for surgery, services of other physicians, visits unrelated to the diagnosis unless it is a complication, treatment of an underlying condition, diagnostic tests and procedures (including postvoid residual [PVR]), distinct surgical procedures that are not reoperations or for complications, treatment of complications requiring a trip to the operating room, and a more extensive surgery due to failure of the initial surgical treatment.

However, the important question is not whether it is a billable service, but whether there is medical necessity for the service. There is no medical necessity to performing a PVR on a patient during the normal recovery from a TURP merely because the patient arrives for a visit. If there is medical necessity documented on the chart, such as a patient who presents with symptoms concerning for urinary retention, CPT 51798 can be billed if performed.

There is no medical necessity to performing a PVR on a patient during the normal recovery from a TURP merely because the patient arrives for a visit.

Q: Can you please tell me whether it is appropriate to bill 51700 for urinary retention 2 weeks after TURP?

A: Medicare has defined work included in a global period to include postsurgical pain management by the surgeon, supplies (except for those identified as exclusions), dressing changes, local incision care, removal of cutaneous sutures and staples, lines, wires, tubes, drains, casts, and splints and insertion, irrigation, and removal of urinary catheters included in the work of the procedure.

In addition, complications that do not require additional trips to the operating room are included. Therefore, placing a catheter to irrigate obstructing blood clots (CPT 51700) is specifically included in the payment for the TURP if this complication is managed outside an operating room. It would not be appropriate to bring a patient to an operating room merely to make it a billable service.

Q: Our hospital has been denied CPT code 52601 because the operative report does not mention the word complete. Although the operative note described the procedure in detail and the pathology report showed benign prostatic hyperplasia (BPH) tissue, why do we need to state the word complete? What does it mean in the CPT description?

A: CPT 52601’s description reads: “Transurethral electrosurgical resection of prostate, including control of postoperative bleeding, complete [vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included].” It is interesting that the coder would deny billing CPT 52601 without the word complete in the operative description, because we can all agree that surgeons do the best and what is most medically appropriate for their patients and want the best outcomes.

When billing a TURP, it is in the best judgment of the physician to remove the tissue needed to maximize patient outcomes, and the completeness of a TURP would be described within the body of the operative note rather than in the description. It is possible that the coder means well but may not fully understand the procedure being performed or may possibly be misinterpreting the word complete within the descriptor of this code. When reading the CPT code description, the word complete is followed immediately without further punctuation to list other services (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy).
We know relationship building is critical to improving patient outcomes, and strong communication is especially important. Good communication can result in not only more efficient, effective care but also greater patient satisfaction with treatment, and this is particularly true with older patients.

Although the manner in which physicians communicate with patients is incredibly important for better outcomes, the means by which they do so also have a big impact on care. One of the primary ways provider-patient communication has evolved, particularly this past year as a result of coronavirus disease 2019, is through the rise of technology-driven communications, specifically virtual care and telehealth.

Many may argue that virtual care and telehealth will never fully replace in-person care for older individuals, and research shows that is likely true, even after increased adoption during the pandemic. According to a June 2020 survey of adults aged 50 to 80 years by the University of Michigan, more than 50% of respondents still perceive office visits as providing higher overall quality of care, and barriers to adoption and accessibility of technology remain for many older individuals. Even if they do not become the primary sources of health care for older individuals in the immediate future, telehealth is providing an opportunity to improve communications to meet the needs of this rapidly growing patient population.

**Filling the gaps in care**
An obvious way technology can improve patient care for better outcomes, the means by which they do so also have a big impact on care. One of the primary ways provider-patient communication has evolved, particularly this past year as a result of coronavirus disease 2019, is through the rise of technology-driven communications, specifically virtual care and telehealth.

Many may argue that virtual care and telehealth will never fully replace in-person care for older individuals, and research shows that is likely true, even after increased adoption during the pandemic. According to a June 2020 survey of adults aged 50 to 80 years by the University of Michigan, more than 50% of respondents still perceive office visits as providing higher overall quality of care, and barriers to adoption and accessibility of technology remain for many older individuals. Even if they do not become the primary sources of health care for older individuals in the immediate future, telehealth is providing an opportunity to improve communications to meet the needs of this rapidly growing patient population.

**TECHNOLOGY**
In the case you describe above, we recommend requesting modifier –52 to the 52601. We recommend having a discussion with the hospital coder and explaining this nuance, and feel free to show them this article.

**REFERENCES**

Send coding and reimbursement questions to Jonathan Rubenstein, MD, at urology_times@mmhgroup.com.

Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.
TELEHEALTH / Business

communication is by making it more accessible. Physicians can meet in person with a limited number of patients each day, and many older individuals face transportation challenges. Telemedicine in the form of traditional, video-enabled doctor visits alleviates many of those challenges and makes it easier for patients to connect with physicians or support staff between appointments. According to the same University of Michigan poll, 72% of respondents expressed interest in using telehealth for follow-up questions with a doctor they had already seen. Offering telemedicine as a supplemental method of communication with patients helps open more channels of communication throughout the care journey.

One of the most significant advantages to virtual care is the real-time lens it provides into a patient’s home life and social determinants that may exist.

Enlisting support
Another benefit of virtual communication is its ability to drive better care plan adoption among patients. For example, a study looked at patients’ understanding of newly prescribed medications after hospital discharge. It found that although 86% of patients were aware they had been prescribed new medications, only 64% could identify the name of the medication and merely 11% could recall being told of potential adverse effects. Digital communication can better ensure patient adherence through increased follow-ups, whether through physicians and support staff personally checking on a patient’s status or automated call or text messages about medication reminders or lifestyle changes. Increased engagement can also enable providers and patients to bring more stakeholders into the conversation, including family members or caretakers.

Real-time window
One of the most significant advantages to virtual care is the real-time lens it provides into a patient’s home life and social determinants that may exist. Whether it is the clutter that may increase a patient’s risk of falling or the isolation that may negatively affect mental health, the information providers can gather by connecting with a patient in their home environment can have an important impact on care plan adherence and overall health outcomes. Most importantly, these real-time insights enable providers to intervene more quickly and collaborate with other members of the patient’s care team to develop solutions before deterioration or hospitalization occur. With close to 75% of Medicare hospital readmissions being identified as preventable, the real-time insights gained from various aspects of virtual care can play an important role in necessary proactive care management.

Higher satisfaction
Many aspects of virtual care can lead patients to feel more in control of their health care journeys. Empowering patients to decide where, when, and how they prefer to engage with their care team means they are more likely to have a satisfying care experience. Best of all, increased payer reimbursement and revenue sources for telehealth means practices no longer can have greater confidence in pursuing virtual health, and reap the many benefits of virtual patient communications, a win-win for all stakeholders involved.

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How to avoid common cybersecurity mistakes

Formal staff training is crucial for medical practices, expert says

Medical Economics® spoke with Dave Grootwassink, general manager of the cybersecurity practice for Alaris Threat Mitigation Consultants, about what medical practices need to do to stay safe.

Q: What are the most common cybersecurity mistakes medical practices make?

A: The biggest one is not getting formal training to their people, because that’s where most of this stuff starts. Assuming a practice has the basic stuff in place, like a good firewall, infections and breaches are going to come from somebody doing something like clicking on an email, going to a bad website, or something like that. And, you know, bad websites aren’t necessarily porn.com, because infections can get into websites, and it’s not terribly unusual. If you train your people correctly, and they recognize things that don’t look quite right, then you can kind of keep that chink in the armor closed.

Typically, what a breach will do is somebody will get a little tiny infection, somebody opens an email attachment. And some of these email attachments are really insidious PDFs that look like an invoice or something. If they’ve spoofed the email address that it’s coming from, it may look like it’s coming from one of your regular vendors.

There are bugs and holes and things like PDFs that you can use to exploit and put a little piece of malware on your computer. And that little piece of malware then goes out and talks to a command-and-control server out somewhere and then starts downloading the real bad stuff. So, I’d say that the first mistake they make is they don’t do training.

The other thing that they don’t do is a real risk evaluation. A good risk assessment will point out, where do we need to take a look? And where do we need to correct things? Because there’s a lot of stuff that people don’t realize is going on between devices. Every medical device out there has an operating system in there that may or may not have been patched for years. There are still medical devices out there that the underlying operating system is Windows XP, and it hasn’t had a security patch in 10 years. If they train the people and do a good risk assessment, followed up by a mitigation plan, that will take care of 90% of the issues.

Ransomware will go in and happily encrypt your backups, too. You have to be very careful about how you do backups. I always recommend offsite cloud-based backup systems, and there are a handful out there that are actually HIPAA compliant.

Q: When a practice is hit with ransomware, how difficult is it to get everything back up and running? And how long does that process take?

A: If you have good backups, a couple of days. But I can’t stress how important it is for good multi-version backup systems that are not attached to the network.

The best way to get back on your feet is proper preparation. If you’ve got everything backed up, and you use a backup system that allows multiple versions—there are some backup systems commercially available that will keep a record and keep backups of all the changes for a period of time or for an amount of space, depending on what that particular arrangement that you have with the backup provider. If you’ve got a good backup in place, and one that has multiple versions, because I’ve run into places where they have a backup system, and they’ve successfully backed up the encrypted file, and the original file is gone. If you have backup that keeps multiple versions. When the file is encrypted from ransomware, and that file is backed up, you have the previous ones available. And some of the other things I’ve seen with ransomware is when people have attached backup systems, they can be as simple as those little drives you plug into your USB ports. The ransomware will go in and happily encrypt your backups, too.

You have to be very careful about how you do backups. I always recommend offsite cloud-based backup systems, and there are a handful out there that are actually HIPAA compliant. So, if you have good backup in place, you can bring yourself back usually to a good spot and it’ll take a little bit of time. The bigger the practice, the bigger and the more systems involved certainly will take more time. But if backups are in place, it can be done.

With that said, I’ve seen where [hackers] are actually exfiltrating all your files, too, and if you don’t pay the ransom, not only do you not get your files back, but they go out and they post them on various sites in the internet in public, which opens up another whole bunch of problems for practices.

To really combat things like that, you need to have monitoring of what’s going on in your network. When I go in and I set a practice up, one of the things that I install in the practice is something called a honeypot. I set a device up to look like a crippled PC or a crippled server that doesn’t have good security on it. That way, if anything ever hits it, or tries to get into it, I know that they are in there and that the entire network is compromised. We can shut things down and take care of it before everything goes to hell.

Q: How are the cyber threats evolving? And do practices need to change their defense tactics to keep up?

A: From a technical point of view, they change all the time; it’s a whack-a-mole. The good news is, the fundamentals always have to be there: threat assessment, remediation, and putting policies in place to deal with the threats in training. If you keep up with the training, and keep up with your patching, and you do a new threat assessment periodically—it should be done at least once a year or whenever something new comes into the practice. That basic blocking and tackling is what the practices need to do.
What is your clearest memory from the day you received your residency match?

"Personally, I had a lot riding on it because I was in a relationship with another doctor. We had to choose residency programs based upon cities where we both would be happy. It was complicated because we took our top 3 programs in the top 3 places we wanted to live. Then, because urology was an early match, I had to rank my list first and hope I got where my spouse wanted to go.

She was sacrificing more than me, perhaps, because urology matched first, then her match came second. Incredibly, obviously, I was thrilled to match in urology, number 1, because I knew I wanted to be a urologist and even back then it was extremely competitive. Number 2, I was thrilled to match in the city my spouse wanted, even though we were still waiting for her match to happen.

Then we got it. It was a home run. We both ended up matching our first choice, which was Boston.

I was also excited to train at Boston University, because I had been very inspired by the mentors I would train with there, so I was excited to match with that particular program.

Then she ended up matching where she wanted, which was Boston Children’s, probably the most difficult match in the country at the time, and it was nerve-racking.

It was eager anticipation with some fear and trepidation. When it came through, it was a relief. When it was finally through, I remember being relieved that I matched. I remember relief with that. I also remember a good bit of anxiety about embarking on 2 years of surgical residency before starting urology.

The program I went to was 2 years of general surgery first. With urology, you get either 1 or 2 years of surgical prelim, and I didn’t know which I would get. I wanted to match, so I figured I’d take what I got.

I’m not sure anybody signs up for 2 years of general surgery on purpose. Most people would rather do just 1, then get right into urology, but it really wasn’t bad. In the program I went to, you actually did surgery during general surgery. So, looking back on it, I don’t regret it.

My dad was in the Army, so I moved around growing up. My dad was from New Jersey and I got stationed in New Jersey when I was in the Air Force. I got to medical school in New Jersey, then matched residency in New Jersey, and then got a job in New Jersey, so I’ve been here ever since.

It was a good day, for sure. To have everything come together and know where you’re going and know you’ve matched. Maybe some people are more confident, but you’re never sure, and I was really happy to get a spot."

John Watson, MD / Hamilton, New Jersey

"It’s not really a vivid memory. It was important, knowing where you were going for the next 6 years. It was a big commitment. A lot of people were around.

Everyone was excited. You were watching everybody else going through their ‘Academy acceptance speech,’ except you didn’t have to go to the podium.

It was exciting, and it was nice that it was over too, because you were kind of waiting to see. It was never a guarantee. As much as you felt you had a chance, everybody, myself included, went to multiple programs to interview with your own list of preferred spots, from top to bottom. You were only going to receive 1 ‘yes.’ "

Craig Smith, MD / Naperville, Illinois

"As much as you felt you had a chance, everybody, myself included, went to multiple programs to interview with your own list of preferred spots, from top to bottom. You were only going to receive 1 ‘yes.’"

"By that time, I was bleeding orange and blue. I was a University of Illinois Champaign undergrad, University of Illinois, Chicago Medical School. Now I was entering University of Illinois residency, Chicago. It was 5 years, 4, and 6.

I did leave Illinois for fellowship and my first job, so I didn’t have to clone the blue and orange, but then back home to Illinois."

Craig Smith, MD / Naperville, Illinois
Was this patient with stones properly informed of a bladder mass?

Jury apportions fault among the plaintiff as well as the defendants

On October 23, 2015, the plaintiff, a 49-year-old man, presented to the emergency department complaining of back and flank pain. A physician and a third-year resident treated him. The patient underwent a CT scan, which confirmed the presence of kidney stones.

In his report, the interpreting radiologist also described the presence of a 2.7-cm mass in the bladder. The resident informed the patient only about the kidney stones. The patient was discharged, with written instructions describing “kidney stones” and advising him to follow up with a urologist within 5 days. The patient passed the kidney stone the next day, and never followed up with a urologist. The patient had no further symptoms until the end of 2016, when he began experiencing incontinence and erectile dysfunction. By February 2017, the patient finally saw a urologist; the urologist sent him for an ultrasound.

The radiologist interpreted the 2017 ultrasound and compared it with the 2015 CT scan. The radiologist reported that the mass was now considerably larger. It was so large that it occupied almost the entirety of the bladder. A biopsy confirmed the mass was malignant.

In May 2017, the patient began chemotherapy to shrink the mass. A cystoscopic procedure was attempted, but the mass was too large to be extracted. In July of that year, the patient’s bladder and prostate were removed. To replace his bladder, a piece of his colon was removed and sutured to create a pouch that was then connected to his ureter and urethra.

The patient and his wife brought a medical claim against the hospital, emergency department physician, and the resident, claiming the defendants failed to inform the patient about the mass seen on the 2015 CT, which led to delayed cancer diagnosis and subsequent surgeries, including removal of his bladder and prostate. The defendants all denied negligence, and the matter proceeded to trial.

Patient testifies about bladder issues, erectile dysfunction

At trial, the patient testified that no one informed him about the mass seen on the 2015 CT scan during the emergency department visit. He testified about his bladder issues and how he suffered erectile dysfunction. He described intense mental distress, for which he had sought treatment, a disruption of his normal activities, and occasional incontinence. He sought damages for past and future pain and suffering.

The defense expert testified that patients are expected to follow their physicians’ orders and that the patient was comparatively negligent for failing to follow the instructions to see a urologist.

The patient’s wife testified that no one informed her about the mass while they were at the hospital in 2015. The wife also testified about her husband’s erectile dysfunction and its consequent problems—such as the couple’s lack of intimacy—that affected the marriage. She sought damages for loss of consortium.

The plaintiff’s emergency department physician expert testified that the defendants were negligent for failing to verbally tell the patient in an adequate and transparent manner about the mass finding on the CT scan, and for failing to ensure that he understood the finding. At the time of trial, the patient continued to be monitored by his urologist. The patient’s treating urologist explained how the size of the tumor at the time of diagnosis prevented simple local resection.

The plaintiff’s urology expert testified that the patient remained at risk of developing recurrent cancer or metastatic disease. The urologist also testified as to metabolic abnormalities associated with the makeshift bladder, which could lead to other problems. The urologist expert testified that had the malignant mass been diagnosed properly in October 2015, it would have been removed cystoscopically, and the patient’s bladder and prostate would have been saved.

During the defense presentation, the defense emergency physician expert testified that the defendants’ care was reasonable, that the patient was informed in writing of the kidney stones, told about the mass, and instructed to follow up with a urologist. The defense expert further testified that patients are expected to follow their physicians’ orders and that the patient was comparatively negligent for failing to follow the instructions to see a urologist.

Following a 7-day trial, the jury returned a $10 million verdict for the plaintiff. The jury apportioned fault and found the resident 60% liable, the emergency department physician 25% liable, and the patient 15% liable. Accordingly, the award was reduced to $8.45 million.

LEGAL PERSPECTIVE: Many states allow a plaintiff who is partially at fault to still recover, as long as their fault does not exceed the fault of defendants. In this instance, the jury found the patient partially to blame for his failure to follow his physician’s instructions. But, because his fault did not exceed that of the defendants, he was still entitled to recover on his medical claim.
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I am a patient.

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Edward Cohen M.D., F.A.C.S.* Chief Executive Officer and Chairman Genesis Healthcare Partners and UROLIFT® SYSTEM PATIENT

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*Dr. Cohen is a paid consultant of NeoTract|Teleflex. Results may vary.
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