American Urological Association

AUA NEWS

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INSIDE THIS ISSUE

Urology's Role in Environmental Stewardship

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In June of 2018 a striking image of an iceberg shaped single-use plastic bag appeared on the cover of *National Geographic*.[1] Its small tip, visible hovering just above the waterline, hid a much larger expanse of plastic billowing below the water's surface. "Planet or Plastic?" read the accompanying title. This arresting metaphor underscored the issue's theme–underappreciation for the profound impact of single-use plastics on the environment–and kicked off *National Geographic*'s multiyear Planet or Plastic campaign.

The research is unambiguous. Plastics plays an integral role in our daily lives but at significant costs to the environment and human health. Data on the adverse effects of plastics and their derivatives are accumulating. Wildlife and marine life are the first to succumb to its detrimental effects, but we are just now understanding how it is affecting us. Increased plastic exposure has been linked to compromised endocrine function, reproductive health and poor semen quality.[2,3] The longer term consequences remain to be seen. Plastic production increases every year, but only a scant 9% is recycled annually.[1] Millions of tons of unrecycled plastic litter landfills and oceans. Resistant to degradation, they may linger for several hundred years or longer, burdening future generations.

One may ask: How am I to make a difference and reduce consumption of single-use plastics? Small daily changes in our lives including in our workplaces may accumulate, rippling into larger beneficial effects. Each year American hospitals produce 6 million tons of medical waste, 30% of which is from operating rooms (ORs). A large portion of OR waste is recyclable due to the widespread use of sterile disposable products with accompanying packaging material.[4] Recycling these materials would result in substantially less plastic waste entering the environment. Moreover, OR recycling would produce major cost savings. On average, recycling costs $68 per ton to dispose compared to $121 per ton for solid waste. Many OR plastics also end up in red trash bags for which disposal costs hospitals much more at $963 per ton.

This begs the question: Why are we, the surgical community, not recycling as much as 1 million tons of OR plastic a year in the U.S.? Several factors may explain this trend. Some studies cite uncertainty regarding infectious risks and proper recycling techniques as the

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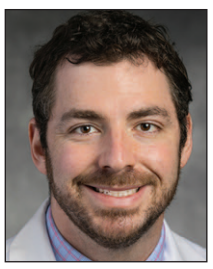
Healthy Men Should Undergo Baseline Prostate Specific Antigen Testing



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Prostate specific antigen (PSA) screening has fallen out of favor among many physicians over the past decade. This was in large part because of misinterpretation of data from randomized trials, particularly the Prostate Lung Colorectal and Ovarian (PLCO) Cancer Screening

▼ Continued on page 2

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Urology and the Environment

▼ Continued from page 1

most common barriers to recycling, even in hospitals with established recycling programs. Other data suggest that potentially recyclable items are commonly mistaken as nonrecyclable.[4]

Organizations such as the nonprofit Practice Greenhealth, a health care membership organization providing sustainability solutions, have made it their mission to help health care systems practice sound and impactful environmental stewardship. Practice Greenhealth publishes an annual report on the sustainability performance of 327 partnering hospitals that use their resources. In addition to providing guidance on appropriate waste segregation and management of recycling Practice Greenhealth offers information to improve identification of recyclable materials, altering OR packs to minimize waste, implementing reusable items when appropriate and smart energy management. In 2019 alone hospitals in the Practice Greenhealth network saved a collective $53 million while reducing more than 309 million kiloBTUs of energy, saving 146,750 tons of waste from the landfill and avoiding 182,370 metric tons of carbon emission.[5]

We in the urological community are positioned to lead environmental stewardship in the OR for several reasons. First, we use a large number of disposable items with layers of sterile, recyclable packaging including but not limited to ureteral stents, stone extraction devices and special single-use cautery devices. Second, we employ copious amounts of irrigation plastic bottles and bags during endoscopic cases, which may be safely opened and recycled without contamination. Finally, we have relationships with colleagues in industry with whom we can readily establish environmental stewardship partnerships. Our colleagues at Cook Medical and Boston Scientific have already made commitments and initiatives to reduce their global plastics footprints by decreasing the amount of plastic used in their packaging materials. Working together we can reduce our plastics environmental footprint without compromising the integrity of the devices we use to provide safe and excellent care for our patients.

We must start somewhere, and we perceive no better forum to begin than through the AUA, its membership and other members of the global urological community. For example, the AUA could develop initiatives to encourage environmental stewardship in the OR including digital educational platforms, and sponsor research grants with industry partners focused on improving the execution of OR recycling programs and methods of tracking their progress. As individuals, we can also work locally with environmental services and the OR staff at our hospitals to create successful recycling plans that will be most successful.

As members of the health care community we have an opportunity to do our part in reducing plastic waste, and blunting its ill effects on the environment and global health. We must hold ourselves accountable not only for ourselves, but also for future generations. ◆

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Baseline PSA Testing in Healthy Men

▼ Continued from page 1

Trial. In 2016 we demonstrated that approximately 90% of men in the control arm of PLCO had PSA testing.[1] This significant contamination means that the mortality difference between screening and control arms cannot be interpreted as evidence against PSA screening.

The realization of the extent of contamination contributed to professional guidelines subsequently changing from recommendations against PSA screening to recommending individualized decision making.[2] However, the decision aids incorporated in these new recommendations underestimate the benefits and overestimate the harms of PSA screening.[2,3] In our recent study we summarize the current evidence regarding PSA screening and highlight the critical importance of the followup interval used to examine screening's tradeoffs.[4]

To illustrate the importance of taking followup time into account, imagine the extreme example of examining the harms and benefits of screening 1 year after initiating a screening program. Obviously, there would be substantial harms (impotence, incontinence etc) and no mortality benefit within a year. While 1 year from initiating screening is obviously too short a duration to realize significant benefit policymakers have arbitrarily selected intervals of 9 or 13 years to examine tradeoffs of PSA screening. In fact, a duration of more than 20 years is needed to adequately assess the benefits of PSA screening for most men because of the prolonged natural history of screen detected prostate cancer. Many men begin screening in their 50s, and the median age of prostate cancer death is 80 years.

To assess these longer-term tradeoffs we used a microsimulation model that estimates the natural history of prostate cancer with and without prostate cancer screening that is calibrated to real-world cancer registry data and data from the European Randomized Study of Screening for Prostate Cancer screening trial. Even using very conservative assumptions we estimated that the number of excess diagnoses resultant from screening to prevent 1 prostate cancer death at 25 years was 11 with estimates well into the single digits depending on model parameters. It is important to note that these numbers are roughly equivalent to the number needed to treat to cause 1 case of urinary incontinence or impotence from prostate cancer treatments.[5]

We would suggest that this tradeoff–about 1 case of impotence or incontinence to prevent a death from prostate cancer–means engaging in screening is worthwhile for most men. These estimates also do not incorporate the prevention of metastatic disease associated with screening, nor do they include recent changes to prostate cancer

▼ Continued on page 5

AUA NEWS

October 2020 Volume 25 | Issue 10

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Man vs Machine: Comparative Effectiveness of Cognitive Targeted and Image Fusion Targeted Transperineal Prostate Biopsy



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Recent randomized validation of the diagnostic superiority of prebiopsy multiparametric (mp) magnetic resonance imaging (MRI) and subsequently mpMRI targeted prostate biopsy when compared to transrectal ultrasound (TRUS) guided systematic prostate biopsy alone has revolutionized the pre-existing prostate cancer diagnostic pathway.[1-3]

Routine prebiopsy mpMRI is now recommended in the evaluation of biopsy naïve men referred with a suspicion of prostate cancer in the 2019 American Urological Association and Society of Abdominal Radiology consensus guidelines.[4] The conversation has appropriately moved forward to evaluating the diagnostic utility of currently available mpMRI targeted biopsy techniques on the detection of clinically significant prostate cancer (csPCa) within this new cohort.

Briefly, these techniques include visual estimation (or cognitive), image fusion (or software registration) and direct in-bore MRI targeted biopsy. During visual estimation the operator reviews mpMRI imaging prior to adopting a cognitive MRI targeted approach with real-time TRUS guidance. Image fusion offers the operator a computer platform (various available) to contour the mpMRI prostate lesion(s), and these are subsequently overlaid onto the acquired real-time TRUS imaging. This can be in either a rigid or elastic (deformable) manner. Finally, direct in-bore biopsy is performed in real time within an MRI scanner. The target lesion is biopsied under the guidance of multiple periprocedural mpMRI acquired sequences.

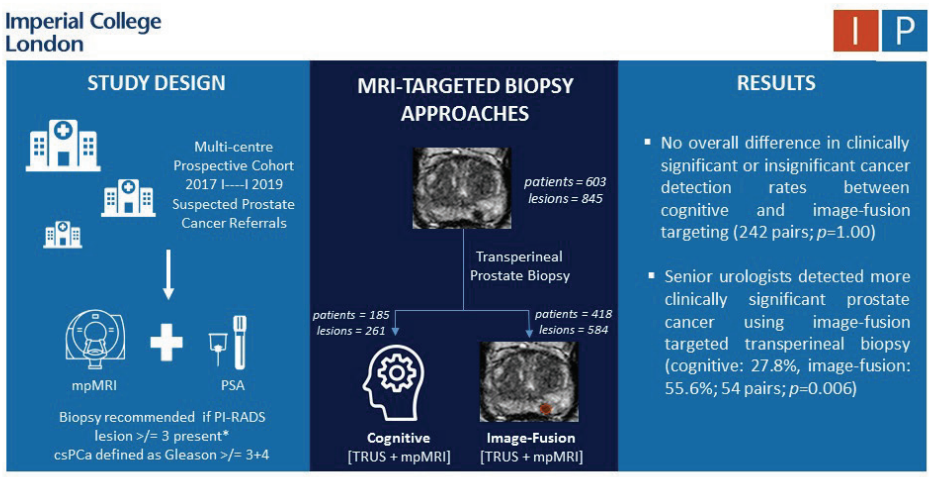

Figure. Study infographic. Asterisk indicates that where PI-RADS® lesion score was 3 PSA density of 0.12 ng/ml/ml or greater was required to trigger transperineal prostate biopsy.

In our recent award-winning presentation at the AUA 2020 virtual conference we aimed to compare cancer detection rates of visual estimation and image fusion targeted prostate biopsy approaches (see figure). Our multicenter prospective registry study identified 603 men who had undergone visual estimation or image fusion targeted transperineal prostate biopsy for a prebiopsy mpMRI (1.5T or 3.0T) PI-RADS® (v2.0) lesion score of 3 or greater. Men with a lesion score of 3 required a prostate specific antigen (PSA) density of 0.12 ng/ml/ml or more to be offered a transperineal prostate biopsy.

A standard operating procedure was used during all study prostate biopsies. This included a biplanar TRUS probe (Hitachi, Japan). Image fusion was performed with the BiopSee® platform (Medcom, Germany). Biopsies were taken stereotactically with continuous TRUS utilizing elastic registration. A minimum of 3 targeted cores were performed with the maximum number of cores at the discretion of the operating surgeon.

Results were analyzed using a propensity score matching (1:1; R version 3.5.3). This was performed by age, PSA, PSA density, prostate volume, number of target lesions, operator grade, PI-RADS score and number of cores (caliper=0.25). Operator experience included senior urologists, interns and others (eg specialist nurse practitioners). We compared detection rates of csPCa and insignificant prostate cancer (cisPCa; Fisher's exact) and median number of cores taken (Mann-Whitney U). Primary threshold of csPCa was set at any recorded Gleason 3+4 or greater.

Our study reported on 845 lesions (261 cognitive, 584 image fusion) in a total of 603 men (185 cognitive, 418 image fusion). For those biopsied median age was 66.7 years (IQR 60.5–72), PSA 7.5 ng/ml (IQR 5.5–10.8) and prostate volume 43 ml (IQR 32–59). There was no overall difference in csPCa or cisPCa detection rates between visual estimation and image fusion targeting biopsy (242 pairs, p=1.00).

However, senior urologists detected significantly more csPCa using image fusion targeted biopsy (27.8% cognitive, 55.6% image fusion, 54 pairs, p=0.006). There was no significant difference when biopsies were conducted by trainee urologists (143 pairs, p=0.1) or other operators (17 pairs, p=0.73). There was no difference between visual estimation and image fusion for prostates less than 40 ml (107 pairs, p=0.49), 40–80 ml (94 pairs, p=1.00) or greater than 80 ml (20 pairs, p=0.73). Similarly, there was no difference when there was a single target lesion (109 pairs, p=0.54) or more than 1 target lesions (133 pairs, p=0.54).

Furthermore, it is important to note that while we used propensity matching to minimize differences between comparator groups patients were not randomized to biopsy registration method. Therefore, there is potential residual confounding when interpreting our study findings.

In conclusion, we found no difference in overall cancer detection rates between visual estimation and image fusion mpMRI targeted transperineal prostate biopsy. However, when analyzed by operator experience senior urologists had a greater detection rate of clinically significant cancer using image fusion. When taken collectively, these findings suggest that for now the choice of mpMRI targeted prostate biopsy technique should be dependent on individual operator experience.

AUA Virtual Science Best Poster winner. ◆

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Molecular Analyses in Interstitial Cystitis/Bladder Pain Syndrome

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The pathophysiology underlying interstitial cystitis/bladder pain syndrome (IC/BPS) is still unclear, presenting significant challenges in diagnosing and managing this chronic, heterogeneous pelvic pain condition.[1] Molecular phenotyping may facilitate stratification of patients with IC/BPS into clinically relevant subgroups.

In an earlier pilot study our female pelvic health research group investigated gene expression profiles in bladder biopsy tissue from patients with IC/BPS and found that those with low anesthetic bladder capacity (BC, defined herein as 400 cc or less) had a significantly different gene expression profile when compared to those with nonlow BC (greater than 400 cc) and nonIC/BPS controls.[2] Herein, we extended our previous findings by evaluating microRNA (miRNA) and gene (mRNA) co-expression in patient bladder biopsy samples to compare 3 clinically distinct IC/BPS patient subgroups.

This molecular study was performed using samples previously collected and archived in our IRB approved tissue repository. Each patient provided informed consent to participate. Briefly, posterior bladder wall biopsies were obtained from female patients aged 18 to 80 years with IC/BPS via cystoscopically guided, cold cup biopsy technique at the time of a scheduled hydrodistension procedure during which anesthetic BC and Hunner's lesion (HL) status were recorded. Total RNA (miRNA and mRNA) was isolated from the bladder biopsies via standard protocols and assayed on both whole genome (mRNA) and miRNA expression arrays.

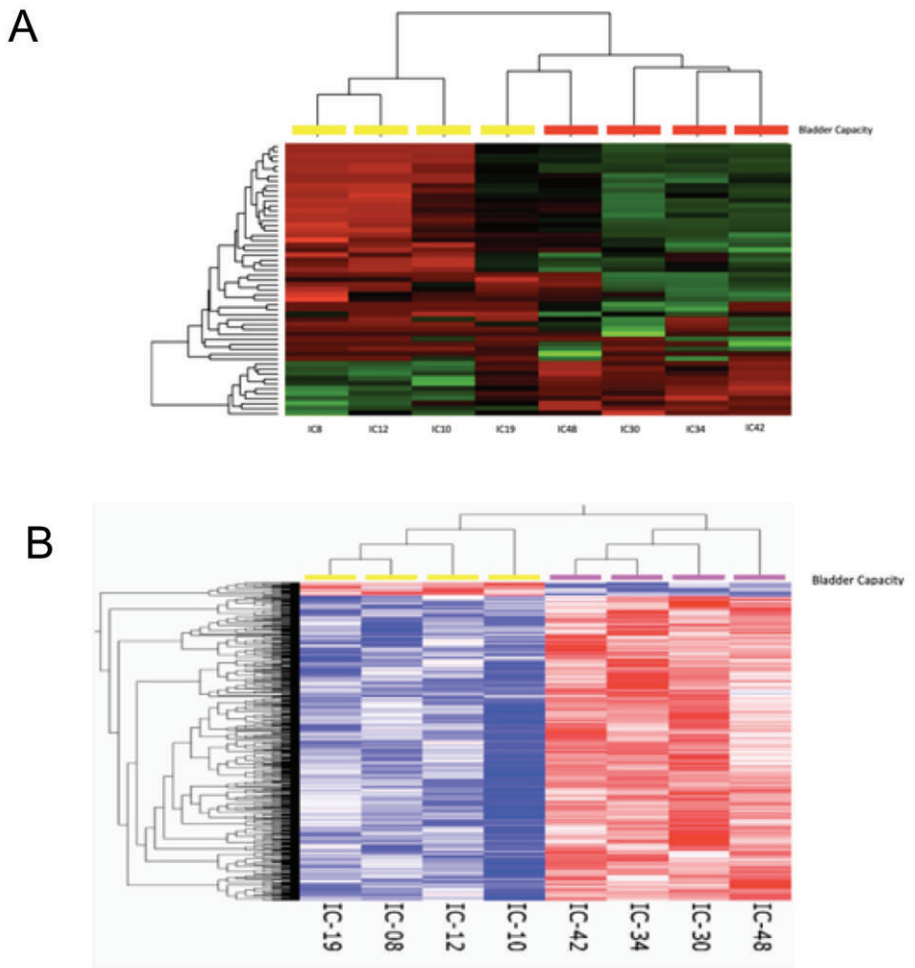

Figure 1. Hierarchical clustering of RNA expression profiles inpatients with IC/BPS bladder biopsy samples of the low vs nonlow bladder capacity comparison. (*A*) Heat map representation of miRNA expression profiles showing patients with low bladder capacity (yellow columns) and patients with nonlow bladder capacity (red columns), where red represents higher and green represents lower gene expression. (*B*) Heat map representation of mRNA expression showing patients with low bladder capacity (yellow columns) and patients with nonlow bladder capacity (magenta columns), where blue indicates higher and red represents lower gene expression.

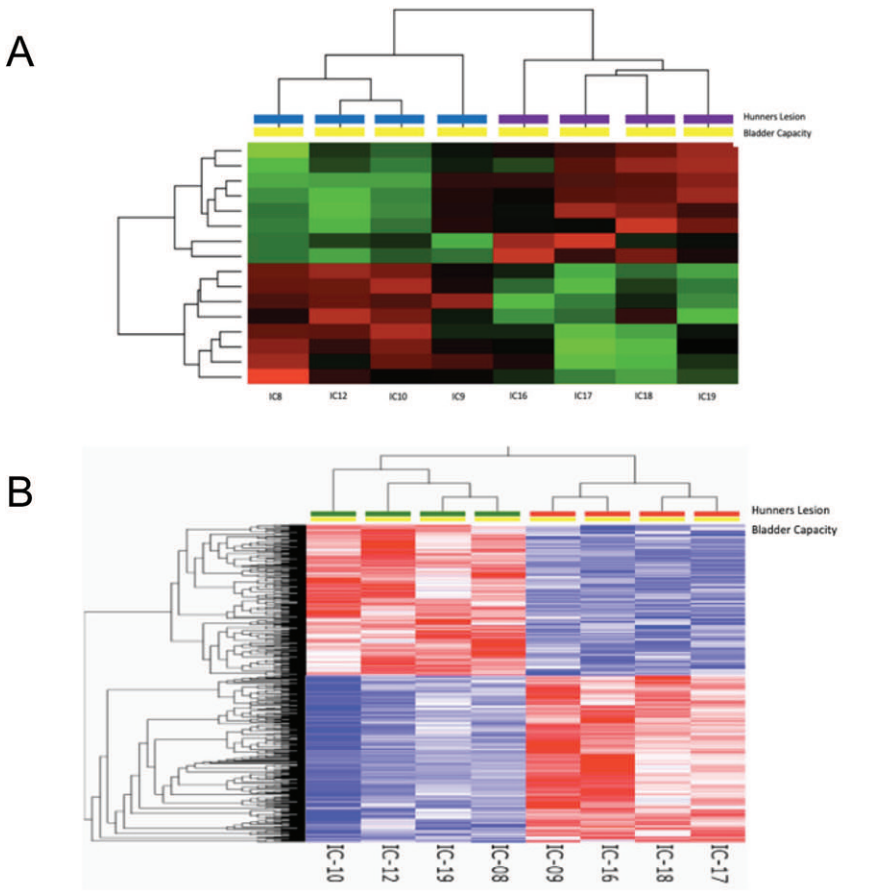

Figure 2. Hierarchical clustering of mRNA expression profiles in patients with IC/CPS bladder biopsy samples for HL positive vs negative comparison. (*A*) Heat map representation of miRNA expression profiles showing patients with low bladder capacity (yellow columns), patients who are HL positive (blue columns) and HL negative (purple columns), where red indicates higher and green lower gene expression. (*B*) Heat map representation of mRNA expression profiles showing patients with low bladder capacity (yellow columns), patients who are HL positive (green) and HL negative (red), where blue indicates higher and red lower gene expression.

Patients for this pilot study were selected from the repository based upon their membership in one of 3 IC/BPS subgroups. Group 1 included patients with low BC without HL, Group 2 low BC with HL and Group 3 nonlow BC without HL. In this molecular analysis 2 subgroup comparisons were made. Comparison 1 (Group 1 vs 3) evaluated co-expression in patients with low vs nonlow BC IC/BPS, and Comparison 2 (Group 1 vs 2) evaluated co-expression in patients with HL positive vs negative IC/BPS.

In Comparison 1, 54 differentially expressed miRNAs and 744 differentially expressed gene transcripts were identified. Hierarchical clustering of miRNA revealed 2 primary clusters, one consisting of 3 patients with low BC IC/BPS patient samples and the other consisting of all 4 nonlow BC samples and 1 low BC sample (fig. 1, *A*). Hierarchical clustering of mRNA revealed 2 primary clusters as well, which completely separated based on BC status (fig. 1, *B*). Using Ingenuity Pathway Analysis (IPA) software we identified 11 (of 54) of the differentially expressed miRNAs that mapped to 40 (of 744) of the differentially expressed genes within this comparison between patients with a low vs nonlow BC.

Within Comparison 2, 16 differentially expressed miRNAs and 917 differentially expressed mRNAs were identified. Hierarchical clustering of miRNA and mRNA revealed clear separation based on HL status (fig. 2). Within this low vs nonlow BC comparison we found that 4 (of 16) differentially expressed miRNAs mapped to 13 (of 917) differentially expressed genes.

In Comparison 1 (low vs nonlow BC) upregulated genes were overrepresented in cell proliferation, progression through the cell cycle and inflammatory pathways. These findings suggest potential underlying biological themes for the low BC phenotype providing further support for our hypothesis that

▼ Continued on page 5

Molecular Analyses in IC/BPS

▼ Continued from page 4

anesthetic BC is a relevant delineator of IC/BPS disease.[2] In addition to overrepresentation of these same pathways in Comparison 2 (HL positive vs HL negative) oxidative stress may underlie the HL positive phenotype. These findings are consistent with previously published reports that have assessed molecular variation in IC/BPS based on HL status.[3–5]

This present study has identified significant molecular differences in IC/BPS associated with the low vs nonlow BC phenotypes as well as additional molecular findings that define the HL positive phenotype providing further support for our hypothesis that there are at least 3 unique subgroups of IC/BPS disease. The use of molecular profiling to identify distinct IC/BPS subgroups could be clinically useful for diagnosis and management.

AUA 2020 Virtual Science Best Poster winner. ◆

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Baseline PSA Testing in Healthy Men

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screening and diagnostics including the use of magnetic resonance imaging as a triage test before biopsy and active surveillance for low risk disease.

Based on these data it seems reasonable that PSA screening should be recommended for all healthy men with the goal of initiating a screening program designed to optimize the benefits of screening while reducing the harms. One such strategy is baseline PSA screening, where men undergo a first prostate cancer screening in their late 40s or early 50s with subsequent screening tailored according to established protocols such as those proposed by the National Comprehensive Cancer Network®. We would advocate that such a program be recommended for healthy men, particularly higher risk populations such as Black men and men with a strong family history of prostate cancer. ◆

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RECOMMENDED

Olaparib (LYNPARZA) is the only PARPi included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) as a Category 1† recommended option for men with HRRm mCRPC adenocarcinoma who have progressed on prior treatment with enzalutamide and/or abiraterone, regardless of prior docetaxel therapy.[6]

†Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

INDICATION

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in <1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The duration of therapy in patients who developed secondary MDS/AML varied from <6 months to >2 years. All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy, and some also had a history of more than one primary malignancy or of bone marrow dysplasia.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Occurred in <1% of patients exposed to LYNPARZA, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. A pregnancy test is recommended for females of reproductive potential prior to initiating treatment.

Females

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

Males

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

Venous Thromboembolic Events: Including pulmonary embolism, occurred in 7% of patients with metastatic castration-resistant prostate cancer who received LYNPARZA plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study. Patients receiving LYNPARZA and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

ADVERSE REACTIONS—HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients in clinical trials of LYNPARZA for **PROfound** were: anemia (46%), fatigue (including asthenia) (41%), nausea (41%), decreased appetite (30%), diarrhea (21%), vomiting (18%), thrombocytopenia (12%), cough (11%), and dyspnea (10%).

Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients in clinical trials of LYNPARZA for **PROfound** were: decrease in hemoglobin (98%), decrease in lymphocytes (62%), decrease in leukocytes (53%), and decrease in absolute neutrophil count (34%).

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

USE IN SPECIFIC POPULATIONS

Lactation: No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.

Among men with **BRCA1/2- or ATM-mutated mCRPC following progression on enzalutamide or abiraterone**

LYNPARZA more than doubled median rPFS vs retreatment with enzalutamide or abiraterone[1,7]

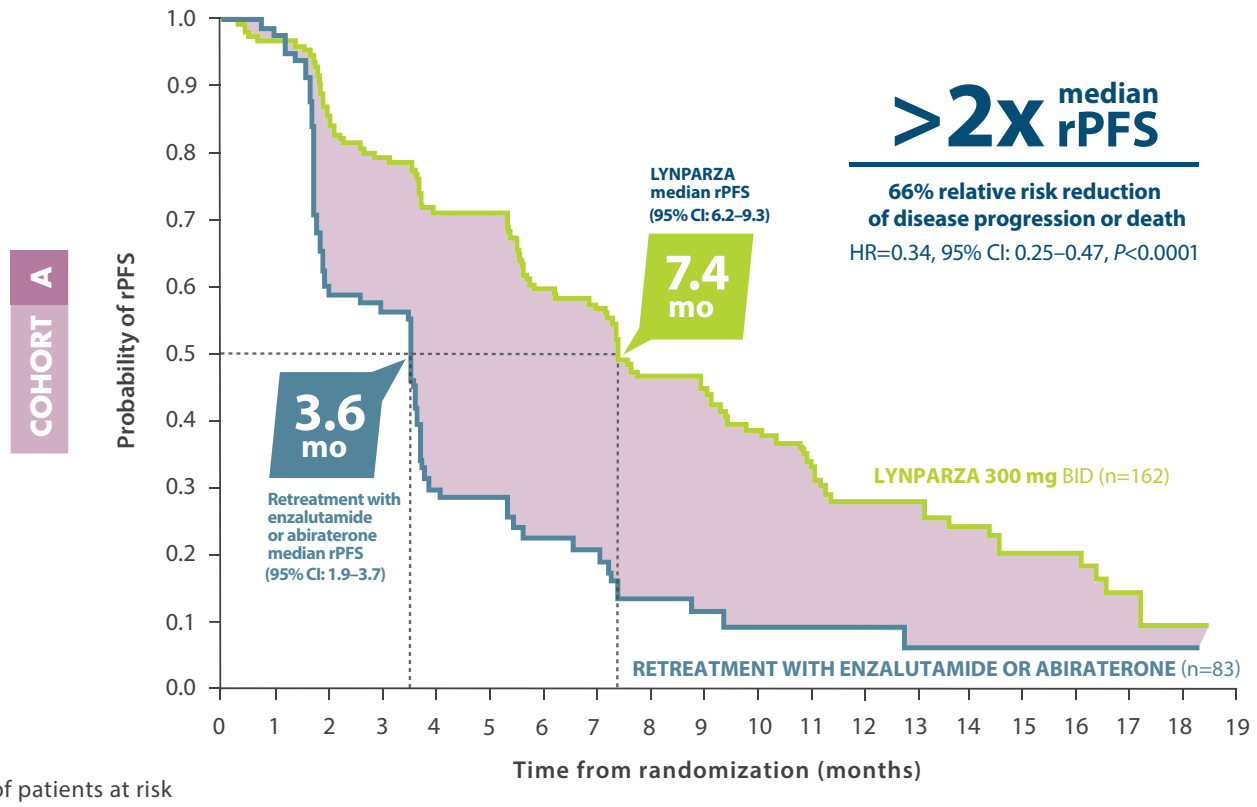
PROfound: A PHASE 3 trial of a PARPi in mCRPC[1,7]

TRIAL DESIGN[1,7]

- The PROfound trial was a prospective, multicenter, randomized, open-label, phase 3 trial of LYNPARZA in patients with HRRm mCRPC
- Key eligibility criteria: Metastatic castration-resistant prostate cancer; progression on prior enzalutamide or abiraterone treatment for metastatic prostate cancer and/or CRPC; a tumor mutation in at least 1 of 15 genes* involved in the HRR pathway
- Patients were divided by mutation: ***BRCA1/2* or *ATM* gene mutation (Cohort A [n=245]†‡) and other HRR gene mutations (Cohort B [n=142]‡§)**, and randomization was stratified by prior receipt of taxane chemotherapy and presence of measurable disease by RECIST 1.1
- Each cohort was randomized 2:1 to receive LYNPARZA (tablets, 300 mg per dose, twice daily) or an active comparator (retreatment with investigator's choice of enzalutamide or abiraterone)

*HRR gene mutations (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and/or *RAD54L*) were identified by tissue-based testing using the Foundation Medicine FoundationOne® clinical trial HRR assay performed at a central laboratory. No patients were enrolled who had mutations in 2 of the 15 prespecified HRR genes: *FANCL* and *RAD51C*.
†Patients with co-mutations (*BRCA1*, *BRCA2*, or *ATM* plus a Cohort B gene) were assigned to Cohort A.
‡All patients received a GnRH analog or had prior bilateral orchiectomy.
§*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*.
Although patients with *PPP2R2A* gene mutations were enrolled in the trial, LYNPARZA is not indicated for the treatment of patients with this gene mutation due to unfavorable risk-benefit ratio.

PRIMARY ENDPOINT: RADIOLOGICAL PROGRESSION-FREE SURVIVAL (rPFS)[1,7]



Number of patients at risk

LYNPARZA	**162**	**149**	**126**	**116**	**102**	**101**	**82**	**77**	**56**	**53**	**42**	**37**	**26**	**24**	**18**	**11**	**11**	**3**	**2**	**0**
Retreatment with enzalutamide or abiraterone	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0

>2x median rPFS

66% relative risk reduction of disease progression or death

HR=0.34, 95% CI: 0.25–0.47, *P*<0.0001

- rPFS in Cohort A was determined by BICR using RECIST version 1.1 and PCWG3 (bone) criteria
- Consistent results were observed in exploratory analyses of rPFS:
  - For patients who received or did not receive prior taxane therapy
  - For those with germline *BRCA* mutations identified using the Myriad BRACAnalysis CDx assay compared with those with *BRCA* mutations identified using the Foundation Medicine F1CDx assay

The PROfound study included additional secondary endpoints not present here.

From *The New England Journal of Medicine*, de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382(22): 2091-2102. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

EXPLORE THE DATA, including secondary endpoints, and testing recommendations at LYNPARZAprchcp.com

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS (CONT'D)

Hepatic Impairment: No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Renal Impairment: No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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

BICR=blinded independent central review; BID=twice a day; CI=confidence interval; CRPC=castration-resistant prostate cancer; GnRH=gonadotropin-releasing hormone; HR=hazard ratio; HRR=homologous recombination repair; HRRm=homologous recombination repair gene–mutated; mCRPC=metastatic castration-resistant prostate cancer; NCCN=National Comprehensive Cancer Network; PARPi=poly (ADP-ribose) polymerase inhibitor; PCWG3=Prostate Cancer Working Group 3; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=radiological progression-free survival.

References: 1. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. **2.** Zejula® (niraparib) [prescribing information]. Waltham, MA: TESARO, Inc.; 2020. **3.** Rubraca® (rucaparib) [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2020. **4.** Talzenna® (talazoparib) [prescribing information]. New York, NY: Pfizer Inc.; 2020. **5.** Teo MY, Rathkopf DE, Kantoff P. Treatment of advanced prostate cancer. *Annu Rev Med.* 2019;70:479-499. **6.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed May 21, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. **7.** de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med.* 2020;382(22):2091-2102.

MERCK AstraZeneca

LYNPARZA® (olaparib) tablets, for oral use

Initial U.S. Approval: 2014

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics.

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including *BRCA* mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection

Indication	Biomarker	Sample type	
		Tumor	Blood
Germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer*	*ATM*m, *BRCA1*m, *BRCA2*m, *BARD1*m, *BRIP1*m, *CDK12*m, *CHEK1*m, *CHEK2*m, *FANCL*m, *PALB2*m, *RAD51B*m, *RAD51C*m, *RAD51D*m, *RAD54L*m	X	
	g*BRCA1*m, g*BRCA2*m		X

* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test.

Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- HRR gene-mutated metastatic castration-resistant prostate cancer

Patients receiving Lynparza for mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

If a further dose reduction is required, then reduce to 200 mg taken twice daily.

Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors with Lynparza.

If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor.
- 150 mg twice daily when used concomitantly with a moderate CYP3A inhibitor.

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

In clinical studies enrolling 2351 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the incidence of Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) was <1.5% (28/2351) and the majority of events had a fatal outcome. Of these, 25/28 patients had a documented *BRCA* mutation, 2 patients had g*BRCA* wildtype and in 1 patient the *BRCA* mutation status was unknown. Additional cases of MDS/AML have been documented in patients treated with Lynparza in combination studies and in postmarketing reports. The duration of therapy with Lynparza in patients who developed secondary MDS/cancer-therapy related AML varied from <6 months to >2 years. All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy. Some of these patients also had a history of more than one primary malignancy or of bone marrow dysplasia.

Do not start Lynparza until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt Lynparza and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Lynparza.

Pneumonitis

In clinical studies enrolling 2351 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the incidence of pneumonitis, including fatal cases, was <1% (20/2351). If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Lynparza treatment and treat the patient appropriately.

Embryo-Fetal Toxicity

Lynparza can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Lynparza. Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

Venous Thromboembolic Events

Venous thromboembolic events, including pulmonary embolism, occurred in 7% of patients with metastatic castration resistant prostate cancer who received Lynparza plus androgen deprivation therapy (ADT) compared to 3.1% of patients receiving enzalutamide or abiraterone plus ADT in the PROfound study. Patients receiving Lynparza and ADT had a 6% incidence of pulmonary embolism compared to 0.8% of patients treated with ADT plus either enzalutamide or abiraterone. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Pneumonitis *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Venous Thromboembolic Events *[see Warnings and Precautions (5.4) in the full Prescribing Information]*

Clinical Trial Experience

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

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2351 patients; 1585 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In these trials, 55% of patients were exposed for 6 months or longer and 31% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anemia (37%), vomiting (34%), diarrhea (25%), decreased appetite (23%), headache (16%), neutropenia (15%), dysgeusia (15%), cough (15%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), thrombocytopenia (11%), and abdominal pain upper (10%).

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound *[see Clinical Studies (14.7) in the full Prescribing Information]*. This study was a randomized, open-label, multi-center study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Fatal adverse reactions occurred in 4% of patients treated with Lynparza. These included pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%).

Serious adverse reactions occurred in 36% of patients receiving Lynparza. The most frequent serious adverse reactions (≥2%) were anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%).

Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 22% of Lynparza patients. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (25%) and thrombocytopenia (6%) and the most frequent adverse reaction leading to reduction of Lynparza was anemia (16%). Discontinuation due to adverse reactions occurred in 18% of Lynparza. The adverse reaction that most frequently led to discontinuation of Lynparza was anemia (7%).

Tables 16 and 17 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 16 Adverse Reactions* Reported in ≥10% of Patients in PROfound

Adverse Reactions	Lynparza tablets n=256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and lymphatic disorders				
Anemia†	46	21	15	5
Thrombocytopenia‡	12	4	3	0
Gastrointestinal disorders				
Nausea	41	1	19	0
Diarrhea	21	1	7	0
Vomiting	18	2	12	1
General disorders and administration site conditions				
Fatigue (including asthenia)	41	3	32	5
Metabolism and nutrition disorders				
Decreased appetite	30	1	18	1
Respiratory, thoracic, and mediastinal disorders				
Cough	11	0	2	0
Dyspnea	10	2	3	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03

† Includes anemia and hemoglobin decreased

‡ Includes platelet count decreased and thrombocytopenia

In addition, adverse reactions of clinical relevance in PROfound that occurred in <10% of patients receiving Lynparza were neutropenia (9%), venous thromboembolic events (7%), dizziness (7%), dysgeusia (7%), dyspepsia (7%), headache (6%), pneumonia (5%), stomatitis (5%), rash (4%), blood creatinine increase (4%), pneumonitis (2%), upper abdominal pain (2%), and hypersensitivity (1%).

Table 17 Laboratory Abnormalities Reported in ≥25% of Patients in PROfound

Laboratory Parameter*	Lynparza tablets n†= 256		Enzalutamide or abiraterone n†=130	
	Grades 1-4 n= 247 (%)	Grades 3-4 n=247 (%)	Grades 1-4 n=124 (%)	Grades 3-4 n=124 (%)
Decrease in hemoglobin	242 (98)	33 (13)	91 (73)	5 (4)
Decrease in lymphocytes	154 (62)	57 (23)	42 (34)	16 (13)
Decrease in leukocytes	130 (53)	9 (4)	26 (21)	0
Decrease in absolute neutrophil count	83 (34)	8 (3)	11 (9)	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Postmarketing Experience

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

Immune System Disorders: Hypersensitivity (rash/dermatitis).

DRUG INTERACTIONS

Use with Anticancer Agents

Clinical studies of Lynparza with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

Effect of Other Drugs on Lynparza

Strong and Moderate CYP3A Inhibitors

Coadministration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Avoid coadministration of strong or moderate CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Strong and Moderate CYP3A Inducers

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Lynparza efficacy *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Avoid coadministration of strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, Lynparza can cause fetal harm when administered to a pregnant woman. There are no available data on Lynparza use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily *(see Data)*. Apprise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to Day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure ($AUC_{0\text{-}24h}$) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs, and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

Lactation

Risk Summary

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants from Lynparza, advise a lactating woman not to breastfeed during treatment with Lynparza and for one month after receiving the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Recommend pregnancy testing for females of reproductive potential prior to initiating treatment with Lynparza.

Contraception

Females

Lynparza can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for at least 6 months following the last dose.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Pediatric Use

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

Geriatric Use

Of the 2351 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily as monotherapy, 596 (25%) patients were aged ≥65 years, and this included 137 (6%) patients who were aged ≥75 years. Seven (0.3%) patients were aged ≥85 years. *[see Adverse Reactions (6.1) in the full Prescribing Information]*.

Of the 535 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab, 204 (38%) patients were aged ≥65 years, and this included 31 (6%) patients who were aged ≥75 years.

No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

Renal Impairment

No dosage modification is recommended in patients with mild renal impairment (CLcr 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min) *[see Dosage and Administration (2.5) in the full Prescribing Information]*. There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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5/2020 US-34783 6/20

The MIND Trial: Brain Training for Surgeons

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Elite sports players and their teams dedicate themselves to optimizing performance. Alongside trainers and coaches, sport psychologists play an increasingly important role. Various aspects of an athlete's performance are now routinely supported with cognitive interventions. Mental imagery techniques can be used to address different training needs, focus concentration and attention, goal-direct imagery, regulate arousal or improve technical performance

Surgical training has undergone a significant transformation in recent years. The growing inclusion of simulation based learning has supported progress toward proficiency based training models over the experiential focussed approach used previously. The potential role for the variety of simulation tools now available in delivering effective and more personalized training is well documented, but the role of adjuncts such as cognitive training is yet to be realized.

Motor imagery (MI) offers great potential for surgical education. It is the process of imaging the performance of a motor task without physical execution in order to improve that motor skill. MI has been shown to be effective in improving motor skill in sports as well as other fields including music and rehabilitation medicine. Based on the theory of functional equivalence neuroimaging studies have shown that MI results in similar patterns of activity in motor networks as motor planning and execution.[1]

Studies have previously investigated the role of MI in surgery. Overall the evidence does appear to support the utility of MI, but methodologies remain heterogenous and quality variable limiting the conclusions that can be drawn.[2] We have previously shown that evidence-based MI is effective for robotic technical skills training, yet like all studies our results were based on self-reported imagery questionnaires.[3] In the current study the direct effects of MI for surgical training on neural connectivity were assessed using functional magnetic resonance imaging (fMRI).

We recruited 4 intermediate level surgical trainees for comprehensive task and resting state fMRI experiments. Initially these trainees underwent a baseline fMRI protocol. This consisted of a resting state scan followed by a motor localization task to localize brain areas activated in actual and imagined hand movements. The localization task comprises alternating rest and task blocks. In each task block participants imagined or performed a simple hand movement mimicking a key step in laparoscopic suturing with either left or right hand.

The examined regions of interest (ROIs) were identified as those areas with significantly more activation during MI than motor execution. To analyze if there are persistent changes in the functional wiring of the brain after MI training statistical correlation between pairs of time courses of these ROIs (functional connectivity) were compared between the baseline and followup resting state scans.

Following the initial imaging baseline laparoscopic skill was assessed using a dry lab laparoscopic simulator. Each participant completed a suturing, and the video recorded performances were blindly assessed. The participants were then MI trained according to the PETTLEP model (see reference 3 for details). The MI training protocol was developed through collaboration with expert laparoscopic surgeons and psychologists experienced in MI training. Alongside technical instructions the script provided information on sensory cues to enhance the representation of the motor task in the participant's mind, a step that has been shown to be critical to successful MI. The importance of temporal congruence was also highlighted to the participants to enable them to direct and modify their MI. The task should take equally as long to perform mentally as it does physically. After this initial instruction session, participants continued MI training unsupervised in their own time. Participants then performed focussed MI training at least once a day for a period of 14 days. No physical laparoscopy training was undertaken.

After 14 days of training all participants were brought back for posttraining assessment. This consisted of a repeat fMRI identical to the baseline protocol. Technical skills were assessed on the same day by repeating the dry lab simulation suturing assessment. We identified 6 ROIs (fig. 1). Comparison of functional connectivity before and after training demonstrated a significant increase in the connectivity between the contralateral prefrontal and the premotor and motor areas (Brodmann 4/6, fig. 2). Connectivity between all other regions remained similar. Technical skill assessment scores (GOALS

▼ Continued on page 10

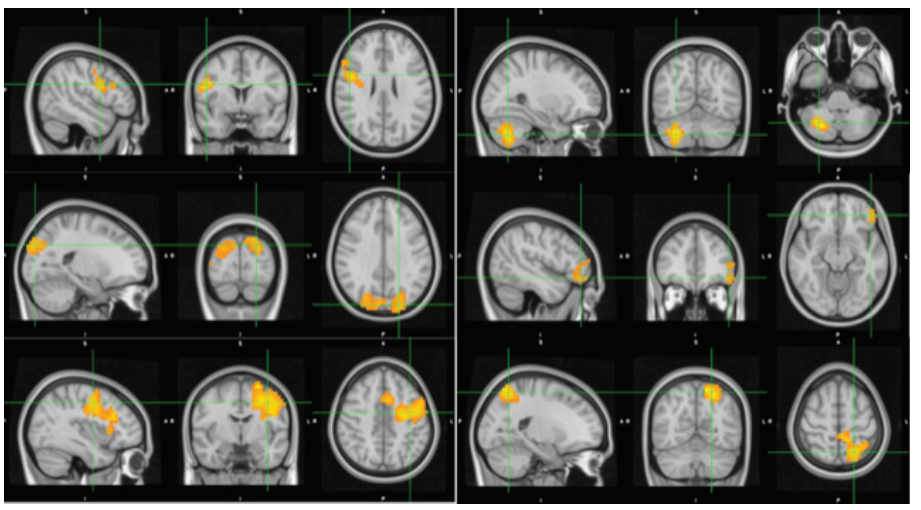

Figure 1.

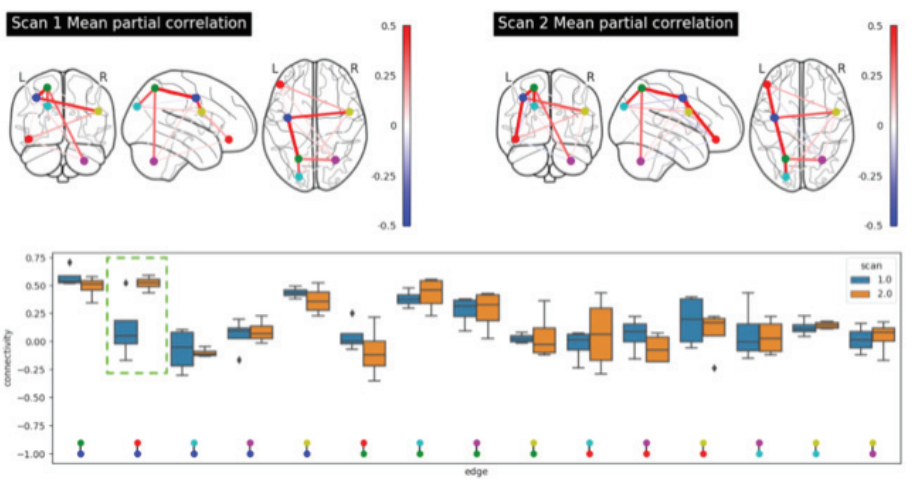

Figure 2.

MIND Trial for Surgeons

▼ Continued from page 9

and a suturing checklist) increased with training but did not meet significance (fig. 3).

Our analysis has shown that MI training for a surgical task results in measurable changes in functional connectivity in the intrinsic wiring of the brain alongside improvements in technical performance. Specific changes in functional connectivity between the frontal and motor cortices were observed. The effects of learning on structural brain plasticity are well recognized.[4] Previous studies support the results of this paper in showing that MI training like other forms of learning results in specific and robust modulation of functional connectivity. We have demonstrated for the first time that this process also occurs in complex tasks such as minimally invasive surgery. Our results provide important evidence for the use of cognitive tools in surgery, and we hope they will generate interest in developing their greater integration into clinical training.

AUA 2020 Virtual Science Best Poster winner. ◆

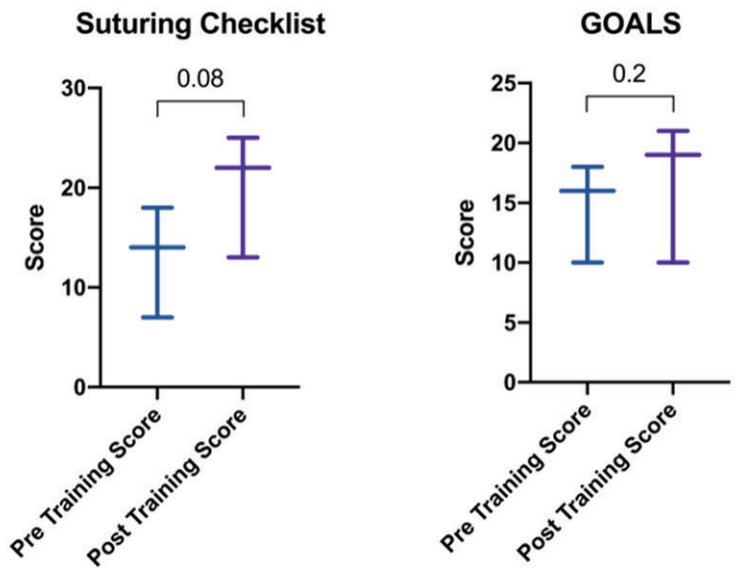

Figure 3.

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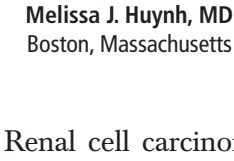
The Metabolomic Profile of Renal Cell Carcinoma



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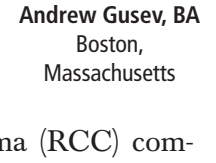
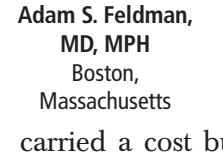


Andrew Gusev, BA
Boston, Massachusetts



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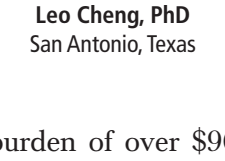

Leo Cheng, PhD
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Renal cell carcinoma (RCC) comprises approximately 85% of all kidney tumors.[1] While there are radiographic features on imaging that may help to differentiate malignant from benign tumors there are still instances where imaging can present a diagnostic challenge. This can subsequently lead to biopsy or unnecessary surgical intervention, and up to 30% of small renal masses undergoing partial nephrectomy demonstrate benign histology, which carried a cost burden of over $90 million between 2007 and 2014.[2]

The field of metabolomics aims to define the specific metabolic profiles associated with a tissue, cell, organ or organism under normal conditions in order to allow us to compare them to diseased states. Regular magnetic resonance spectroscopy and mass spectroscopy have been the traditional techniques for studying metabolomics, but they can be time consuming, require extensive tissue processing and may alter the natural state of tissues.

On the other hand, high resolution magic angle spinning (HRMAS) magnetic resonance spectroscopy (MRS) offers the unique advantage of allowing metabolomic analysis of intact tissues,[3] thereby presenting the opportunity to develop in vivo platforms with the ability to identify tumor histology based on metabolic profiles. This would in turn avoid the need for renal mass biopsies and unnecessary interventions such as surgery and their associated complications.

We investigated the metabolomic profile of RCC with HRMAS-MRS using radical nephrectomy or partial nephrectomy specimens from our frozen tissue bank. Metabolites within 60 spectral regions were analyzed and compared to those of benign parenchymal tissue adjacent to the malignant tumors. False discovery rates (FDRs) were used to account for multiple testing during identification of potential

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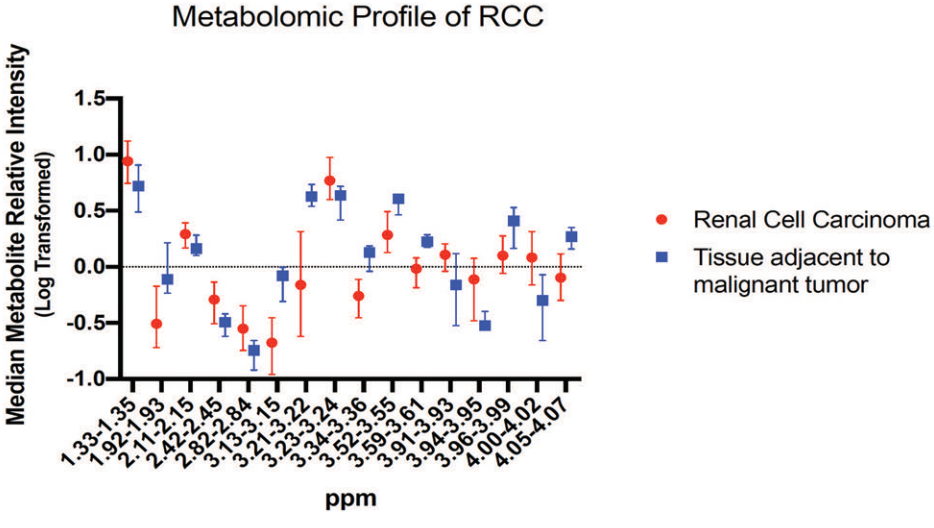

Figure. Median MRS intensities of spectral regions of interest for RCC and adjacent benign parenchyma.

Table. Odds ratios for risk of malignancy for metabolites identified as potential predictors of malignancy based on FDR p value (reference group: tissue adjacent to malignant tumor).

Region of Interest (ppm)	OR (95% CI)	p Value for OR
4.07-4.05 (Myo-inositol)	0.38 (0.18–0.82)	0.013
4.02-4.00 (TBD)	3.13 (1.10–8.85)	0.032
3.99-3.96 (Histidine, phenylalanine, phosphocholine, serine)	0.34 (0.16–0.71)	0.004
3.95-3.94 (Serine, phosphocreatine)	29.24 (2.47–345.94)	0.007
3.93-3.91 (Creatine, glycerophosphocholine)	8.17 (1.77–37.78)	0.007
3.61-3.59, 3.61-3.59 (Myo-inositol, glycerophosphocholine)	0.13 (0.03–0.490)	0.003
3.55-3.52 (Glycine)	0.59 (0.39–0.90)	0.014
3.36-3.34 (Scylla-inositol)	0.08 (0.02–0.42)	0.003
3.24-3.23 (Myo-inositol, Taurine)	1.35 (1.04–1.76)	0.027
3.22-3.21 (Phosphocholine, glycerophosphocholine, histidine)	0.41 (0.25–0.67)	<0.001
3.15-3.13 (Spermine, histidine, phenylalanine)	$3.72x10^{-5}$ ($7.42x10^{-8}$–$1.87x10^{-2}$)	0.001
2.84-2.82 (TBD)	7,161.72 (6.30–$8.14x10^{6}$)	0.013
2.45-2.42 (Glutamine)	121.56 (2.17–6,825.42)	0.02
2.15-2.11 (TBD)	3.96 (1.18–13.28)	0.026
1.93-1.92 (Acetoacetate)	0.38 (1.13–1.09)	0.072
1.35-1.33 (Lactate)	1.22 (1.03–1.45)	0.023

Metabolomic Profile of RCC

▼ Continued from page 10

predictors of RCC.

There were 38 RCC specimens (16 clear cell, 11 papillary, 11 chromophobe), and 13 of them had adjacent normal tissue specimens. Therefore, there were 13 matched pairs. Out of 60 spectral regions of interest (ROIs) 16 were identified as candidate predictors of RCC. The figure depicts the median MRS intensities of each ROI, and the table summarizes the odds ratios for risk of malignancy based on relative abundance. Those denoted as TBD (to be determined) are undergoing further study to definitively identify and associate specific metabolites to the corresponding spectral regions. There was a greater amount of serine and phosphocreatine (3.95–3.94 ppm) in RCC specimens with an odds ratio of 29.24 (95% CI 2.47–345.94, p=0.007) as well as glutamine (2.45–2.42 ppm, OR 121.56, 95% CI 2.17–6,825.42). There are also a number of metabolites in other spectral regions that differed in quantity between RCC and the tissue adjacent to the malignant tumor, the exact identities of which have yet to be elucidated. The greatest odds ratio for risk of malignancy was observed for metabolites in the 2.84 to 2.82 spectral region (OR 7,161.72, 95% CI 6.30–8.14x10^6, p=0.013).

Our study found glutamine in higher quantities in RCC samples relative to the adjacent benign parenchyma. Glutamine is an amino acid that is central to cellular metabolism due to its use in the biosynthesis of lipids, proteins, nucleotides and generation of adenosine triphosphate (ATP).[4] It is known that hypoxia inducible factor (HIF) causes increased glutamine use, which has led to interest into the development of glutaminase inhibitors to treat metastatic RCC. In a landmark paper regarding the molecular characterization of clear cell renal cell carcinoma, patients with a poorer prognosis were found to have increased glutamine transport and glutamine dependent lipogenesis.[5] Our results also indicated elevated levels of serine in the RCC samples. The serine biosynthesis pathway has been shown to be altered by constitutive HIF2 activity in clear cell RCC and has been implicated in other cancers as well.[6]

While our results are intriguing there are limitations to our study. Firstly, we were limited by the number of patients and specimens available, thus we analyzed all RCCs together as 1 group. Future work should be undertaken to characterize the metabolomic profile of each RCC subtype as well as that of benign tumors such as angiomyolipoma and oncocytoma. Secondly, we have only performed HRMAS-MRS in ex vivo samples. Once our ex vivo results have been validated on a larger number of samples, the next step would be to proceed to in vivo studies. The potential for in vivo characterization of renal masses by metabolomic profiling is very exciting as it would avoid subjecting the patient to the harms and complications of renal mass biopsy and other surgical interventions.

AUA 2020 Virtual Science Best Poster winner. ◆

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Cholesterol Lowering Therapy before Prostatectomy Lowers Cellular Proliferation Rates

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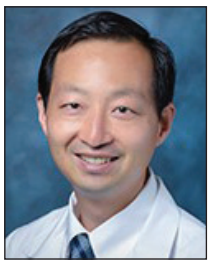

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Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer death among men in North America.[1] Epidemiological studies have demonstrated a strong association between cholesterol lowering therapy with statins and lower risk of death from prostate cancer with a greater risk reduction in men taking the most potent statins. Our study sought to evaluate the effects of aggressive cholesterol lowering therapy that addresses the 2 primary sources for serum cholesterol. Before prostatectomy we used a statin to decrease cholesterol synthesis in the liver and ezetimibe to bind intestinal cholesterol and inhibit absorption.

Men scheduled to undergo radical prostatectomy for clinically localized prostate cancer were enrolled in a prospective IRB approved study and treated with simvastatin 40 mg and ezetimibe 10 mg daily for 2 to 6 weeks. Participants were required to have at least some component of Gleason grade 3 prostate cancer and prostate specific antigen less than 20 ng/ml. Prostate biopsy and prostatectomy tissues were stained for hematoxylin and eosin (H&E) and antigen KI-67 (Ki-67), a nuclear protein associated with cellular proliferation. An expert pathologist annotated H&E slides from biopsy and prostatectomy samples for areas of normal tissue, low grade (Gleason grade 3) and high grade (Gleason grade 4 or 5) prostate cancer. From each annotated area 3, 50,000 μm^2 regions were randomly selected and percentage of Ki-67 staining cells was quantified by automated image analysis (QuPath, University of Edinburgh, United Kingdom). Student's unpaired t-test was used for statistical analysis.

A total of 35 patients were enrolled from a single institution. After starting treatment serum cholesterol levels decreased from a mean of 178.6 mg/dl to 119.7 mg/dl ($p < 0.0001$). As expected, serum high density lipoprotein levels did not significantly change ($p=0.29$). When comparing pretreatment biopsy to prostatectomy tissue, expression of Ki-67 decreased after cholesterol lowering therapy in normal prostate tissue with mean before vs after treatment Ki-67 expressions of 10.1% vs 2.7% ($p < 0.0001$). In Gleason grade 3 prostate cancer mean pretreatment Ki-67 expression was 12.7% and posttreatment expression was 5.8% ($p=0.04$). Ki-67 expression did not significantly change following cholesterol lowering therapy in high grade prostate cancer with before vs after treatment Ki-67 expressions of 13.1% vs 12.7% ($p=0.96$).

We conducted this prospective clinical trial because there was little direct evidence that cholesterol lowering treatment decreases the risk of prostate cancer. Earlier evidence was based on epidemiologic studies and preclinical models. Epidemiologic studies have consistently identified an association between statin use and lower risk of prostate cancer. A meta-analysis of 15 cohort and 12 case control studies concluded that statin use was associated with a 7% reduction in total incidence of prostate cancer and a larger (20%) reduction in advanced prostate cancer.[2] Preclinical models have demonstrated that cholesterol enriched diets promoted tumor growth in a xenograft mouse model for prostate cancer and that lowering serum cholesterol slowed prostate cancer growth.[3,4]

Various molecular mechanisms have been proposed. Prostate tissue growth is fueled by androgens of which cholesterol is a precursor.[5] The Hedgehog pathway is a cancer associated signaling pathway involved in proper cell differentiation, and cholesterol can activate oncogenic Hedgehog signaling through interaction with the Smoothened receptor, a G protein coupled receptor.[6] Furthermore, cholesterol is an important structural component of lipid rafts on cellular membranes, which provide a signal transduction mechanism for oncogenic signaling pathways.[7] There is also evidence that lowering cholesterol may modulate cancer progression by altering the antitumor immune response.[8–10]

Our prospective window of opportunity study demonstrated that cholesterol lowering therapy reduced cellular proliferation in normal prostate tissue and Gleason grade 3 cancers but not Gleason grade 4 cancers. It is possible that this study lacked statistical power to assess the high grade subgroup. These results suggest cholesterol lowering therapy may be useful for lowering the risk of progression for men with low risk disease such as those on prostate cancer active surveillance. The possibility of repurposing a commonly used cardiac drug with a well-established safety profile to reduce the risk of prostate cancer is attractive. These results argue for a definitive, large scale study with clinically meaningful oncologic endpoints.

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Correlation between Local Arteriosclerosis of Prostatic Arteries and Chronic Inflammation in Benign Prostatic Enlargement

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Recently, chronic inflammation has been implicated as a putative mechanism of benign prostatic enlargement (BPE). Metabolic syndrome, infectious agents and autoimmune disease could be considered causes of chronic inflammation in the prostate.[1] However, the involvement of chronic inflammation in the growth of the prostatic gland has yet to be clarified.

Our previous research showed that chronic ischemia due to local arteriosclerosis in the prostatic arteries was related to BPE in human surgical specimens.[2] However, since arteriosclerosis was also assumed to be a chronic inflammatory disorder it is also possible that chronic inflammation due to arteriosclerosis might play a central role in the growth of the prostatic gland.

Lectin-like oxidized low density lipoprotein (LDL) receptor-1 (LOX-1) was first isolated from vascular endothelial cells. After binding oxidized-LDL, a ligand of LOX-1, LOX-1 sends various intracellular signals worsening the arteriosclerosis by vascular endothelial cell injury, cell proliferation, infiltration of macrophages and proliferation of collagen via the activation of p38 and p44/42 mitogen activated protein kinases. LOX-1 is upregulated as arteriosclerosis and/or obesity progresses. Therefore, LOX-1 is considered to be related to the etiology of BPE due to its involvement in cell proliferation and chronic inflammation.

In the current study the relationship between local arteriosclerosis and LOX-1 was investigated to clarify the etiology of BPE due to chronic inflammation caused by arteriosclerosis. Moreover, the associations between local arteriosclerosis and chronic inflammation and the stromal increase induced by LOX-1 in the prostate were investigated.

This prospective observational study involved 50 consecutive patients with localized prostate cancer who underwent robot-assisted radical prostatectomy (RARP) at our institution. These patients were selected because actual local arteriosclerosis in patients with BPE could not be assessed by microscopy.

Furthermore, because the prostatic arteries are difficult to remove from the resected prostatic specimens after surgery the prostatic arteries were excised from the neurovascular bundles (NVBs) during the surgery (fig. 1, *A*).[2] Local arteriosclerosis was defined in this study as the presence of atheroma occupying 50% or more of the inner cavity of the prostatic artery (fig. 1, *B*).

To evaluate prostatic inflammation a standard inflammatory score using the standardized classification system of chronic prostatitis (CP-CPPS) of the National Institutes of Health was used. In addition, to assess the expression of several molecular markers induced by LOX-1 in the prostate, immunohistochemical examinations of the prostatic specimens acquired by a prostatic needle biopsy gun from the resected prostate were performed.

In the current research after confirming the increased size of the prostate with and without local arteriosclerosis, the association between local arteriosclerosis in the prostatic arteries within the NVBs and the degree of chronic inflammation in the prostate were evaluated. Moreover, the associations between local arteriosclerosis and expressions of several molecular markers induced by LOX-1 in the prostate were investigated.

The present results demonstrated that the weight of the prostate was significantly greater with than without arteriosclerosis (arteriosclerosis [–] : arteriosclerosis [+], 44±14 gm : 62±32 gm, p=0.006). The total inflammation score was significantly higher with than without arteriosclerosis (arteriosclerosis [–]: arteriosclerosis [+], 4.1±1.4 : 6.9±1.5, p <0.001). In addition, with respect to the inflammation subscores, the anatomical location score, the inflammatory grade score and the inflammatory extent score were significantly higher with than without arteriosclerosis (p <0.001, p=0.002 and p <0.001, respectively).

On immunohistochemical analyses for several molecular markers induced by LOX-1 in the prostate, LOX-1 and IBA-1, a marker of macrophages, were significantly expressed in patients

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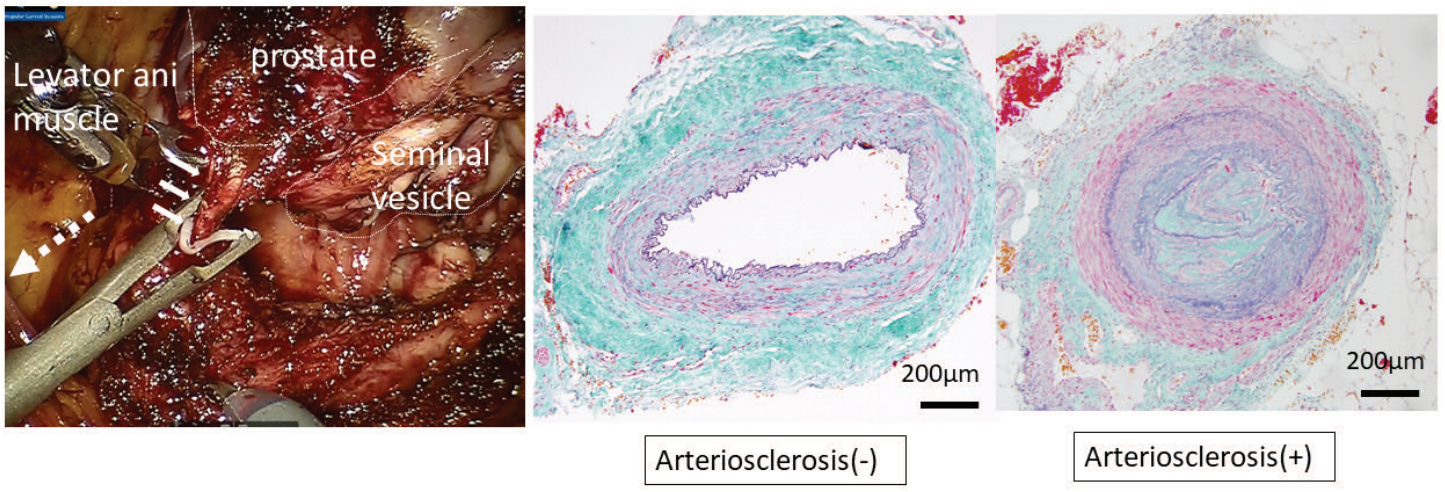

Figure 1. Removal of prostatic arteries (solid arrows) from neurovascular bundles during RARP where dotted arrow indicates the cranial direction (*A*) and prostatic arteries stained by Elastica-Masson staining (*B*).

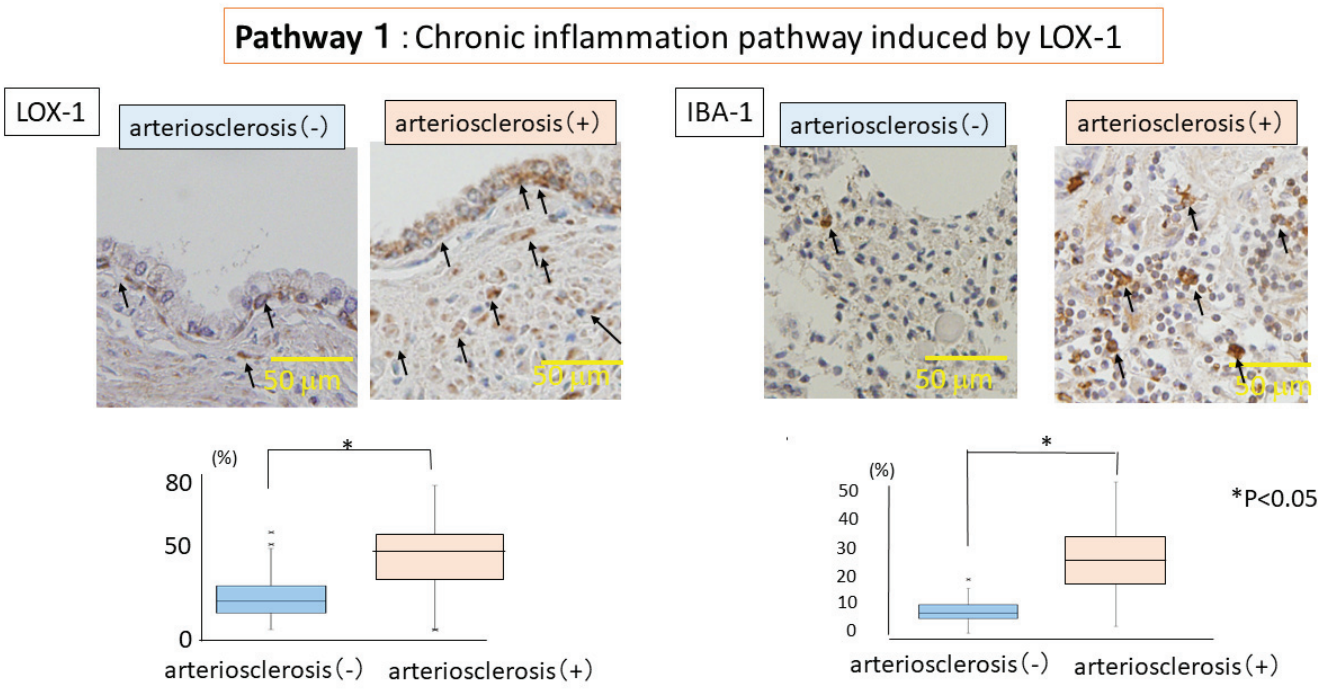

Figure 2. Association between LOX-1 expression and BPE chronic inflammation pathway. Significant expressions of LOX-1 and IBA-1 observed in arteriosclerosis group. * p <0.05.

Chronic Inflammation Induced by Benign Prostatic Enlargement

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with local arteriosclerosis (fig. 2). In addition, significant expressions of transforming growth factor beta 1 (TGF-β_1), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, p38 mitogen-activated protein kinases (MAPK) and ERK1/2 were observed in patients with local arteriosclerosis (fig. 3). These 4 molecular markers were involved in the stromal increase in the prostate.

In conclusion, LOX-1 is upregulated in the prostate by local arteriosclerosis. Therefore, LOX-1 might have an important role in the growth of the prostatic gland through 2 pathways (fig. 4). First, in the chronic inflammation pathway, migration and accumulation of macrophages occurs, leading to induction of chronic inflammation. As a result, tissue damage and remodeling occur in the prostate leading to BPE. Second, in the pathway related to the stromal increase, TGF-β_1 and NADPH oxidase are activated, leading to the activation of oxidation reduction signals, resulting in a stromal increase in the prostate leading to BPE.

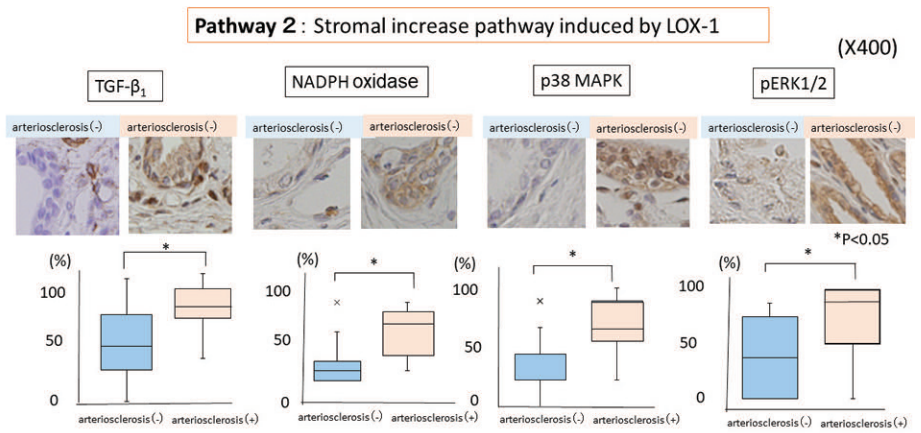

Figure 3. Association between LOX-1 expression and BPE stromal increase pathway. Significant expressions of TGF-β_1, NADPH oxidase, p38 MAPK and ERK1/2 observed in arteriosclerosis group. Asterisk indicates p <0.05.

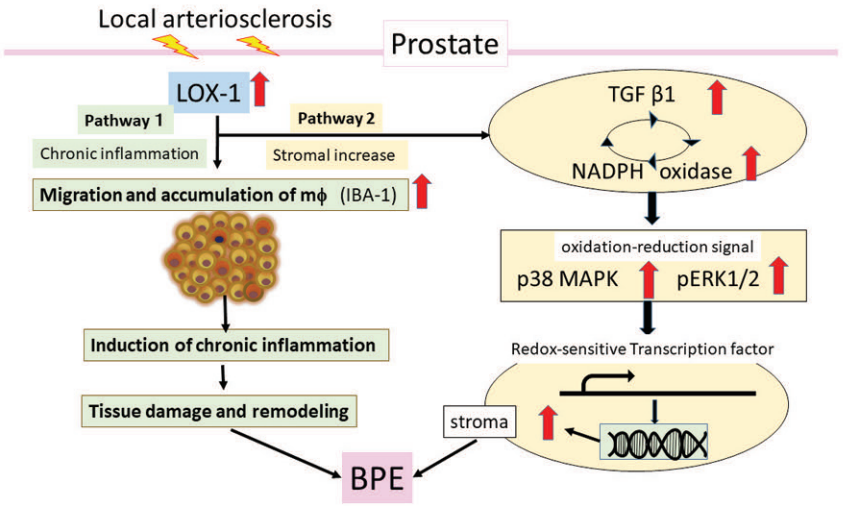

Figure 4. Possible mechanism of BPE induced by local arteriosclerosis. LOX-1 upregulated by local arteriosclerosis. In chronic inflammation pathway, migration and accumulation of macrophages occurs, leading to induction of chronic inflammation. As a result tissue damage and remodeling occur in prostate, leading to BPE. In stromal increase pathway TGF-b1 and NADPH oxidase are activated, leading to activation of oxidation-reduction signals, and stroma increases in prostate, leading to BPE.

AUA 2020 Virtual Science Best Poster winner. ◆

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Ultrasound for Detection of Inferior Vena Cava Tumor Thrombi Level in Kidney Cancer


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Radical nephrectomy with inferior vena cava (IVC) tumor thrombectomy requires extensive surgical planning to maximize the chance for success. Ideally, the cephalad extent and mobility of the tumor thrombus (TT) should be evaluated preoperatively (table 1). These factors influence surgical approach including involvement of other surgical specialties such as cardiothoracic and also appropriate operating room equipment such as bypass capability. Thrombus that invades the caval wall may require IVC resection and/or reconstruction.

Magnetic resonance imaging (MRI) is widely accepted as the imaging method of choice for preoperative TT staging.[1,2] Due to the fast growing nature of tumor thrombi it is recommended that imaging is obtained within 1 to 2 weeks of surgery.[3–5] Ultrasonography (US) is an inexpensive, accessible and noninvasive tool that can be used in the preoperative setting for real-time examination of IVC TT associated with kidney cancer.

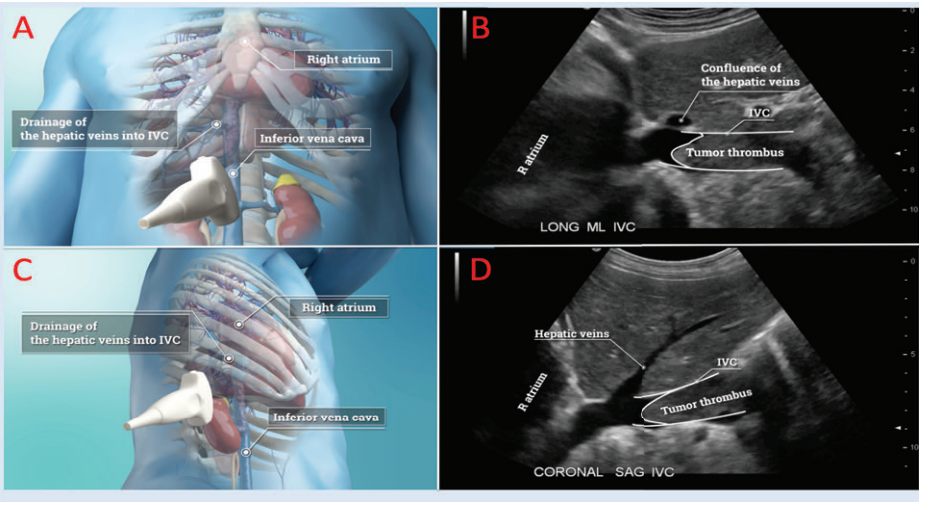

Figure. Schematic view of IVC TT in sagittal plane (*A*). Gray scale US image in sagittal plane demonstrates IVC TT and its relationship to hepatic veins and right atrium (*B*). Schematic view of IVC TT in coronal plane (*C*). Gray scale US image in coronal plane demonstrates IVC TT and its relationship to hepatic vein and the right atrium (*D*).

How is the Ultrasonography for IVC TT Done?

At Emory University the following protocol was followed for performing US for IVC TT. If possible the patients were asked to fast 6 to 8 hours before the procedure to decrease potential obscuration from gastrointestinal contents. First, sagittal images of the IVC were obtained with the patient in the supine

▼ Continued on page 15

IVC Tumor Thrombi Level Detection

▼ Continued from page 14

position. A curved array probe was positioned in the midline of the abdomen underneath the xiphoid process and slowly moved inferiorly until the IVC, right atrium and drainage of the hepatic veins into the IVC were in view. If the cephalad extent of the thrombus was below the confluence of the hepatic veins the distance was measured between them as this would be a critical factor in surgical planning (see figure).

To assess the mobility of the tumor the patient was asked to hold his or her breath and the TT was then examined to see if it moved within the IVC. The steps above were repeated in the sagittal plane for optimal view of higher level thrombi. Additionally, a transverse view of the IVC could be obtained. If a clear view of the IVC still had not been obtained at this point the patient was positioned into a lateral decubitus position so that he or she was lying on the side opposite the renal mass. We often found that lower level thrombi were better visualized coronally in this position. We also found that this was often the optimal position for obese patients.

Results

In our study we retrospectively identified 38 patients at our institution who had undergone US and MRI before undergoing open radical nephrectomy with tumor thrombectomy between 2010 and 2019. This is the largest study of its kind. We compared the findings between US and MRI, then compared the diagnostic accuracy of US and MRI individually to the intraoperative findings.

In this study US matched with MRI findings for TT level in 26 (68.4%) cases. When compared to operative findings US accurately identified the cephalad extent of TT in 30 (79.0%) cases while 5 (13.2%) cases were understaged and 3 (7.9%) were overstaged. MRI also agreed with surgical findings in 30 (79.0%) cases, understaged 5 (13.2%) and overstaged 3 (7.9%) cases. Importantly, cases overstaged and understaged by US and MRI were not necessarily the same (table 2).

Conclusion

The results of our current study demonstrate that US is comparable to MRI in accurately determining the cephalad extent of TT in patients with kidney cancer. Beside the utility in detecting the TT level another important benefit of US is its unique ability to detect tumor mobility using the surrogate marker of flow around the TT, which helps to inform the surgeon whether or not the thrombus can be manipulated below critical structures such as the hepatic vein confluence or the cavoatrial junction. Furthermore, in the era of value based cases US is far more affordable and accessible than MRI. It lacks some of the drawbacks of MRI such as wait time, incompatibility with some implanted devices, claustrophobia for some patients and the need for intravenous contrast.

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Table 1. Nieves tumor thrombus classification. *RV*, renal vein.

Level	Description
0	At level of RV
1	In IVC 2 cm or less above RV
2	In IVC 2 cm or more above RV
3	Above hepatic veins and below diaphragm
4	Above diaphragm

Table 2. TT levels staged by surgery vs US vs MRI

IVC TT Level	No. Surgical Findings (%)	No. US Findings (%)	No. MRI Findings (%)
0	2 (5.26)	3 (7.89)	1 (2.63)
I	9 (23.68)	8 (21.05)	11 (28.95)
II	21 (55.26)	22 (57.89)	21 (55.26)
III	4 (10.53)	4 (10.53)	2 (5.26)
IV	2 (5.26)	1 (2.63)	3 (7.89)

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Access to Male Fertility Preservation at NCI Cancer Centers

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The National Cancer Institute (NCI) was created in 1971 with the passage of the National Cancer Act by President Nixon. Decades of progress in cancer research since its passage have resulted in a new generation of cancer survivors who deal with a host of issues resulting directly from cancer therapy including infertility and sexual dysfunction. Additionally, in the United States specifically family planning is being pushed off to later ages, increasing any 1 person's chances of undergoing a gonadotoxic cancer therapy before completion of childbearing. Issues of infertility add to the emotional burden of cancer treatment and are heightened in comparison to fertility issues in the noncancer population.[1] Fertility options before cancer therapy initiation include oocyte, embryo, ovarian and spermatic cryopreservation.

Prior work has demonstrated a lack of information regarding sexual health and fertility on NCI cancer center websites, and this is especially true for information pertaining to men's health.[2] Given these known access gaps and the knowledge that these concerns are of major importance to patients with cancer and cancer survivors, our group used telephone interviews and systematic website searches to comprehensively characterize center specific and geographic care patterns at the 64 clinical NCI cancer centers in the United States. Additionally, we used the "find-a-provider" tool offered on the Society for the Study of Male Reproduction website to identify fellowship trained andrologists within 5 miles of the zip code of all 64 NCI cancer centers. This provider information was used to perform an ecological analysis between the United States population and cancer centers with referrals to urologists and fellowship trained andrologists.

Our phone and web based surveys revealed that online male fertility information on NCI center websites ranged from 40% to 79% among U.S. census regions. However, there were no significant differences among regions. A similar pattern was found for overall online sexual health information. Referral to a specific sperm bank or presence of a sperm bank on campus was low nationally, ranging between 43% and 71% of centers (see table for full results). The presence of an established referral to a specific urologist for issues of fertility or sexual function ranged from between 77% and 86% nationally also without a significant difference between U.S. census regions. However, we did find that the Northeast United States has a significantly greater clustering of fellowship trained andrologists within a 5-mile radius surrounding NCI centers compared to the other U.S. census regions (p=0.014).

Table. Access to online fertility preservation information, andrology referrals and sperm banking by U.S. census region.

	Northeast (14)	Midwest (14)	South (21)	West (15)
% Fertility information on website	50	79	48	40
% Online male fertility information	43	50	29	27
% Referral to specific urologist	86	79	77	86
% Referral to andrologist	79	79	67	80
% Referral to sperm bank	50	43	71	60
Avg No. andrologists in 5-mile radius	2.2	0.8	0.5	0.8

Logistic regression revealed that those NCI centers with online language related to fertility preservation and sexual health were more likely to have established relationships with sperm banks (3.48 OR 1.11–12.29). Our ecological analysis using 2015 data published by the U.S. Census Bureau revealed that 30% of reproductive aged males or over 18 million men in the United States fall outside of 100 miles of a NCI Cancer Center with a referral pattern to a fellowship trained andrologist (see figure).

Ensuring access to high quality information and care is imperative in the treatment of cancer in young adults. The term oncofertility was introduced in 2006 and signals a broad, multidisciplinary approach to improving outcomes in the reproductive domains for patients with cancer. Patients undergoing cancer treatment who had access to oncofertility expertise before treatment reported less treatment related regret, and increased physical and emotional well-being. Reproductive stress related to cancer treatment is linked to increased rates of divorce.[3,4] Our data can be used to address critical gaps in information, data and options that will better serve our patients.

We demonstrate that information regarding cancer and reproductive health as well as appropriate specialist referrals are not ubiquitous at our nation's top cancer hospitals. In the age of COVID-19 increasing outreach to the millions of patients outside the physical catchment areas via telehealth visits can be a major step in closing this access gap. Additionally, offering home sperm preservation kits prior to cancer therapy for men is an increasingly popular and easy option for obtaining gamete preservation before treatment. The strength of our work is in our methods, as we used telephone calls and web searches to collect data, the same tools used by patients seeking health care information. Empowering patients with information and strengthening offerings by providers will be the way forward in improving oncofertility care in the United States.

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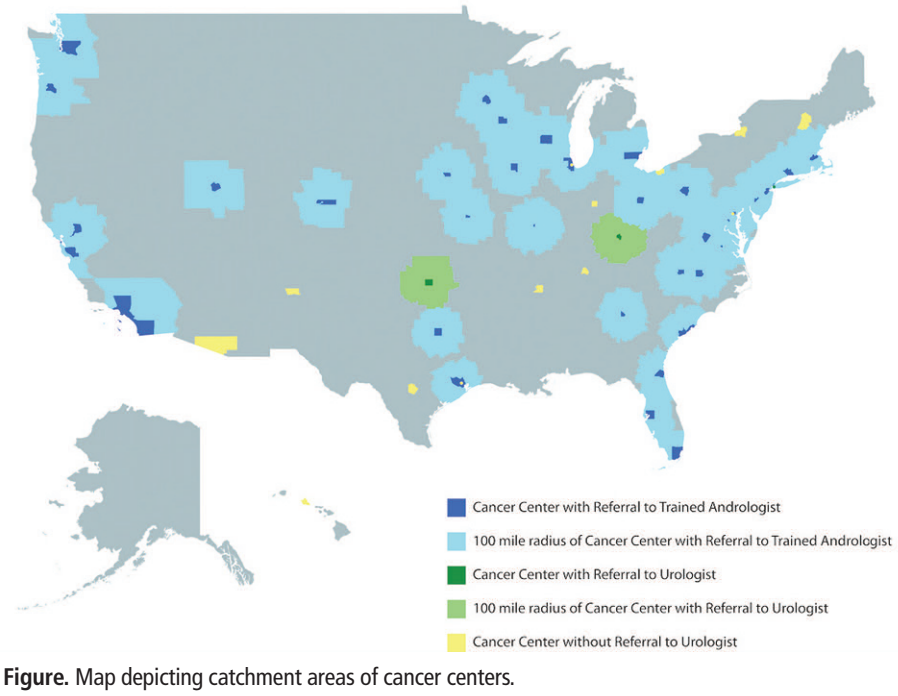

Figure. Map depicting catchment areas of cancer centers.

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Preoperative Gentamicin Underdosing in the Urology Patient



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Gentamicin is an aminoglycoside antibiotic that is commonly used to treat gram-negative infections. It is often the preoperative antibiotic of choice for urological procedures as it covers many uropathogens and possesses some antistaphylococcal activity. It is efficacious, inexpensive, long acting (half-life of 2-3 hours)[1] and is not associated with Clostridium difficile infection.[2] Gentamicin is among the few antibiotics that are readily accessible and effective at treating pseudomonas, which often creates biofilms on indwelling foreign bodies used in urology (ie ureteral stents and Foley catheters).

In 2013 the American Society of Health-Systems Pharmacists (ASHP) updated clinical guidelines for antimicrobial surgical prophylaxis to recommend administering a single high dose (5 mg/kg) of gentamicin instead of the previously recommended 1.5 mg/kg to 2 mg/kg dose.[1] This new recommendation emerged in response to data demonstrating that extended interval, high dose gentamicin is safe and effective when used for therapeutic indications.

Despite these guideline recommendations we recently demonstrated in a retrospective single center study of 2,134 urology patients that nearly 90% of patients received substantially less than the 5 mg/kg dose. Elderly patients (70 years old or older) and those who underwent endoscopic surgery were at significantly increased risk of being underdosed (OR 2.54, p <0.001; OR 6.21, p <0.001, respectively). On exploratory analysis of patients having only endoscopic surgery (1,694), men (OR 1.92, p=0.004), elderly patients (OR 3.15, p <0.001) and those who underwent upper tract endoscopy (OR 3.26, p <0.001) were more likely to be underdosed.

As demonstrated in the figure the risk of underdosing decreased significantly between 2017 and 2019 (5.6% per year, p <0.001) and the frequency of guideline concordant dosing increased (2.9% per year, p=0.001). However, the median gentamicin dose administered in 2019 remained well below 5 mg/kg at 2.1 mg/kg (IQR 1.7–3.8).

The underlying cause of widespread underdosing is not yet known, but it is likely multifactorial. First, we suspect that relatively few physicians are aware of the ASHP guidelines and perioperative gentamicin dosing recommendations. In addition, physicians may be improperly calculating aminoglycoside dosing weights since they differ from therapeutic dosing weights. Per ASHP guidelines patients who weigh less than 120% of their ideal body weight (IBW) should be dosed according to their actual body weight and patients who weigh more than 120% of their IBW should be dosed according to their adjusted body weight.[1] Dosing patients according to their IBW can lead to underdosing.

Second, physicians may be unaware of the therapeutic benefits of high dose gentamicin and the theoretical risk of propagating antimicrobial drug resistance with low dose gentamicin. High dose gentamicin takes advantage of 3 key features of the drug–concentration dependent bacteriocidality, rapid drug excretion and a unique pharmacological phenomenon called the postantibiotic effect (PAE).[3] PAE describes continual bacterial killing and suppression of bacterial growth that persists after the drug is eliminated from the body. This allows for a gentamicin-free period during which the antibacterial properties of the drug remain active but the risk of drug toxicity is reduced.

PAE is thought to result from aminoglycosides irreversibly binding bacterial ribosomes despite unmeasurably low drug concentrations. For maximal efficacy while the drug is in circulation the ratio of peak serum concentration to bacterial minimum inhibitory concentration should be higher than 10:1.[2] Higher serum concentrations are best achieved with high dose administration. For urology patients higher drug concentrations can be especially beneficial as they translate to higher urine concentrations. Previous studies demonstrate that urine gentamicin concentration exceeds plasma gentamicin concentration by up to 100-fold within an hour of drug administration and can remain at therapeutic levels against most uropathogens for at least 72 hours thereafter.[2] In addition, single high dose administration kills sensitive bacteria faster and more profoundly than scheduled intermittent lower doses, which may prevent adaptive bacterial resistance.

Last, urologists, pharmacists and anesthesiologists may be hesitant to administer high dose preoperative gentamicin because of a presumed dose dependent risk of nephrotoxicity associated with aminoglycosides. Despite these concerns, the incidence of adverse events is extremely low.[1] Several clinical studies have demonstrated that the risk of nephrotoxicity with single high dose administration for therapeutic indications is equal to or less than that of intermittent, conventional low dose administration.[3] Previous research in over 1,500 orthopedic surgery patients found that the rate of nephrotoxicity among patients receiving 4.5 mg/kg of preoperative gentamicin was 2.5%. The majority of the cases of nephrotoxicity involved minimal kidney injury, which was transient and reversible. There was no difference in the risk of nephrotoxicity between patients who received ASHP guideline concordant preoperative gentamicin (1,590) and those who did not receive preoperative gentamicin (2,587).[4]

We similarly observed a minimal risk of kidney injury in our cohort. Using the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria to define postoperative kidney injury we compared the relative risk of nephrotoxicity in urology patients who received guideline concordant high dose gentamicin to those who received a lower dose. Among 735 patients with recorded preoperative and postoperative serum creatinine values we identified no cases of sustained kidney injury following high dose gentamicin administration. We found that there was no significant difference in the

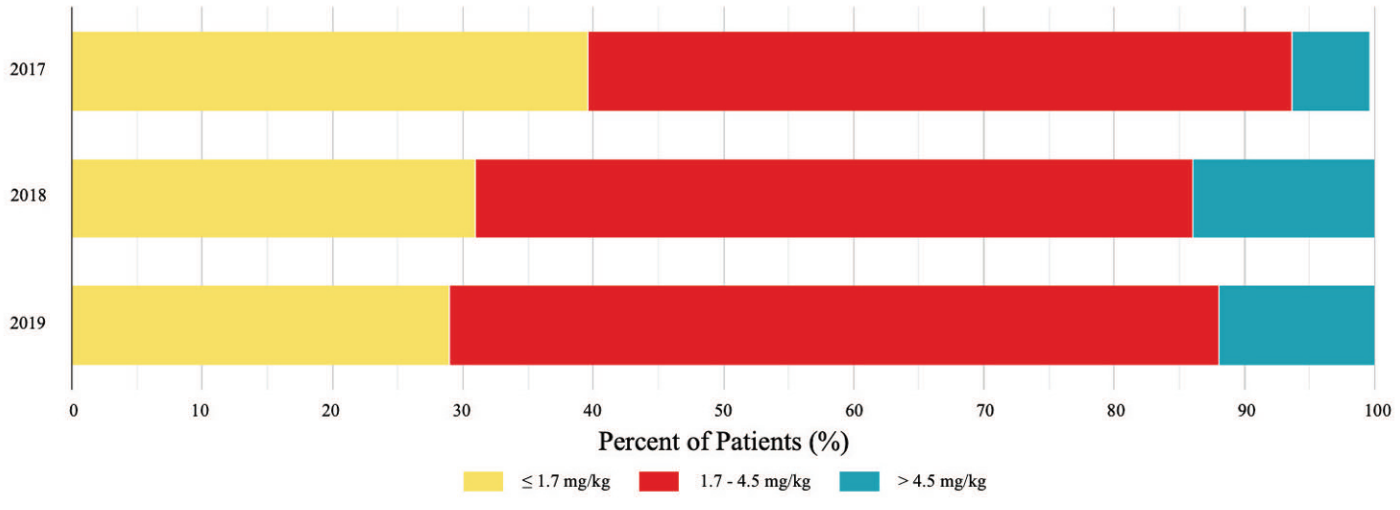

Figure. Trends in gentamicin dosing over time.

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Preoperative Gentamicin Underdosing

▼ Continued from page 17

risk of minimal kidney injury between those who received a dose less than 4.5 mg/kg and those who received a higher dose (OR 0.89, 95% CI 0.26–3.0, p=0.75). On sensitivity analyses, excluding patients with preexisting chronic kidney disease (p=0.73), patients 70 years old or older (p=0.16) and those with creatinine values from greater than 30 days (p=0.24) and greater than 60 days (p = 0.72) preoperatively and postoperatively did not change our conclusions.

While our study adds to the literature on the safety of high dose gentamicin administration for perioperative prophylaxis much work is needed to educate perioperative teams about current recommendations. Future initiatives should focus on improving physician and pharmacist adherence to aminoglycoside dosing guidelines, and additional research is needed to investigate if gentamicin underdosing is associated with an increased risk of postoperative infection and/or bacterial drug resistance.

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Predictive Factors of Peripheral Nerve Evaluation Success in a Contemporary Series

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Peripheral nerve evaluation (PNE) involves a 3-day to 7-day trial of sacral neuromodulation to determine candidates for permanent system implant in a single operation. Several advantages to the PNE test include its ability to be performed in-office under local anesthesia without the need for perioperative antibiotics. PNE success rates, typically defined as conversion to a permanent implant, are reported between 40% and 50% using a single, nontined temporary lead.[1]

Compared to PNE, advanced evaluation with a permanent tined lead is approximately 77% successful but requires a 2-staged approach in the operating room under light sedation.[2] With the availability of in-office fluoroscopy and a refined technique more contemporary data on PNE success rates are needed. The purpose of this study was to evaluate a recent series of PNE cases to determine success rates–specifically, predictive factors toward PNE screening success and persistent functional response following permanent implant.

A retrospective review of all patients who underwent Medtronic InterStim™ PNE at a large, tertiary academic center from 2015-2019 was performed. Patients with refractory urgency-frequency syndrome, urgency urinary incontinence (UUI) and/or fecal incontinence (FI) were included, whereas patients with chronic urinary retention were excluded. All unipolar leads (Medtronic basic evaluation lead model 305901) were placed percutaneously in-office under local anesthesia utilizing fluoroscopy by one of 4 female pelvic medicine and reconstructive surgery fellowship-trained urologists. Observable motor (plantar toe flexion and/or anal bellows) and patient-reported anatomical sensory responses (perineum involving vaginal/scrotal, perianal/rectal, or none) were recorded. Clinical response was documented via bladder diary during a 7-day trial period.

Patients demonstrating an optimal response (50% or more objective symptom improvement) during basic evaluation proceeded to single-stage implant. Conversion rates to permanent implant after a successful PNE trial were reviewed. As most studies define PNE success as conversion to implantation and recognizing that a proportion of successful PNE trials have suboptimal responses following permanent implant, we also evaluated for persistent symptom improvement at 1 month or more following single-stage implant as a marker for a positive screening test. Multivariable logistic regression determined patient and PNE related predictors of PNE success and predictors of continued functional success at 1 month or more postoperative followup.

Included were 102 patients (87 females and 15 males). All 102 patients had urgency frequency syndrome (overactive bladder), 88 patients (86.2%) had urgency urinary incontinence and 11 patients (10.8%) had fecal incontinence (table 1). We included 13 patients (12.7%) with a prior neurologic diagnosis including 5 patients with Parkinson's disease, 5 with unspecified dementia and 3 with transverse myelitis, myasthenia gravis or myotonic dystrophy. Bilateral unipolar leads were placed in 95 patients (93.1%). The majority of patients (80.4%) demonstrated plantar toe flexion and anal bellows, and 66 patients (64.7%) reported perineal sensation during PNE (table 1).

A total of 78 patients (76.5%)

▼ Continued on page 19

Table 1. Clinical demographics and testing factors for patients undergoing PNE

Patient Factors	
Age: Mean (SD) Range	 65.9 (15.8) 24–89
No. female (%)	87 (85.3)
BMI, kg/m² (SD)	29.4 (5.4)
Median ASA® (mode)	3 (3)
No. coronary artery disease (%)	16 (15.7)
No. congestive heart failure (%)	3 (2.9)
No. hypertension (%)	60 (58.8)
No. hyperlipidemia (%)	44 (43.1)
No. chronic obstructive pulmonary disease (%)	7 (6.9)
No. diabetes mellitus type 2 (%)	23 (22.5)
No. cerebrovascular accident (%)	11 (10.8)
No. obstructive sleep apnea (%)	25 (24.5)
No. current smoker (%)	4 (3.9)
No. neurologic diagnosis (%): Parkinson's Unspecified dementia Transverse myelitis Myasthenia gravis Myotonic dystrophy	13 (12.7) 5 5 1 1 1
No. urgency incontinence (%)	88 (86.3)
No. fecal incontinence (%)	11 (10.8)
PNE testing factors	
No. bilateral leads (%)	95 (93.1)
No. at least bellows (%)	88 (86.3)
No. at least plantar toe flexion (%)	83 (81.4)
No. bellows and plantar toe (%)	82 (80.4)
No. sensation (%): Perianal/rectal Perineal/vaginal/scrotal None	 29 (28.4) 66 (64.7) 7 (6.9)

Peripheral Nerve Evaluation Success

▼ Continued from page 18

were PNE responders (50% or more symptom improvement) and 24 patients (23.5%) were PNE nonresponders (less than 50% symptom improvement). Patient predictors of PNE success included younger age (p=0.014), urgency urinary incontinence (p=0.021), fecal incontinence (p=0.017) and absence of a neurologic diagnosis (p=0.04). Intraprocedural testing factors associated with PNE success included presence of plantar toe flexion and anal bellows (p=0.038), and perineal sensation (p=0.027) (table 2).

Of the 78 PNE responders who proceeded to permanent system implant 68 patients (87.2%) maintained an optimal response at 1 month or more followup (66.7% of the total 102 patient cohort). Median postoperative followup time was 4 months (range 1 to 39 months). On multivariate logistic regression the only statistically significant predictor of persistent implant success was absence of a neurologic diagnosis (p=0.013, table 3).

This retrospective review of patients undergoing PNE revealed a 76.5% response rate comparable to previously reported tined lead placement (77%).[2] Patients with an underlying neurologic condition were more likely to fail PNE screening. Of the 24 PNE nonresponders 8 patients (33.3%) had either Parkinson's disease or unspecified dementia. These findings are supported by Crites-Bachert et al who previously demonstrated that patients with an equivocal or failed PNE outcome were more likely to have a neurological insult[3] and Amundsen et al who suggested that neurologic conditions may be associated with decreased cure rates.[4]

This study also evaluated for persistent symptom improvement at 1 month or more following single-stage implant as a marker for a positive screening test. While most studies define PNE screening success as conversion to a permanent implant there is a small proportion of patients who demonstrate suboptimal responses following single-stage implant.

Potential etiologies for a successful PNE trial followed by suboptimal permanent implant responses may include slightly altered positioning of the permanent lead compared to the test stimulation or possible placebo effect from the shorter 3-day to 7-day PNE trial period. Therefore, we chose to evaluate responses at the 1-month or more interval following permanent implant to better define PNE trial success. In this group of 102 unselected patients undergoing PNE there were 78 PNE responders (76.5%) of whom 68 (87.2% of PNE responders or 67% of total cohort) maintained an optimal therapeutic response at 1 month or more (see figure).

In the current study the only statistically significant predictor of persistent implant success was absence of a neurologic diagnosis (p=0.013). No additional factors predictive of a successful PNE carried over to suggest a successful implant, however the presence of UUI and FI trended toward statistical significance (table 3). When defining PNE success as a screening tool we suggest that success of the permanent implant at followup such as 1 month postoperatively be considered when defining PNE success rates, as a small percentage of PNE responders do not translate into optimally functioning implants. With the recent introduction of a redesigned basic evaluation PNE lead (Medtronic model number 306001), which is purported to have a lower rate of migration, the future success rates of the PNE evaluation may prove even higher.

This contemporary series of unselected patients undergoing PNE with fluoroscopy revealed

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Table 2. Patient and testing factors predictive of PNE success

	PNE Responders (78)	PNE Nonresponders (24)	p Value
Age: Mean (SD) Range	 64.2 (16.3) 24–87	 71.4 (12.6) 39–89	 0.014
No. female (%)	66 (84.6)	21 (87.5)	0.14
BMI, kg/m² (SD)	29.7 (5.4)	28.6 (5.6)	0.12
Median ASA (mode)	3 (3)	2.5 (2)	0.16
No. coronary artery disease (%)	13 (16.7)	3 (12.5)	0.36
No. hypertension (%)	47 (60.3)	13 (54.2)	0.25
No. hyperlipidemia (%)	34 (43.6)	10 (41.7)	0.81
No. diabetes mellitus type 2 (%)	21 (26.7)	2 (8.3)	0.21
No. cerebrovascular accident (%)	8 (10.3)	3 (12.5)	0.42
No. obstructive sleep apnea (%)	22 (28.2)	3 (12.5)	0.71
No. neurologic diagnosis (%): Parkinson's Unspecified dementia Transverse myelitis Myasthenia gravis Myotonic dystrophy	5 (6.4) 1 1 1 1 1	8 (33.3) 4 4	0.04
No. urgency incontinence (%)	69 (88.5)	19 (79.9)	0.021
No. fecal incontinence (%)	11 (14.1)	0 (0)	0.017
No. bilateral leads (%)	72 (92.3)	23 (95.8)	0.37
No. at least bellows (%)	67 (85.9)	21 (87.5)	0.41
No. at least plantar toe flexion (%)	63 (80.8)	20 (83.3)	0.056
No. bellows and planar toe (%)	63 (80.8)	19 (79.2)	0.038
No. sensation (%): Perianal/rectal Perineal/vaginal/scrotal None	 20 (25.6) 55 (70.5) 3 (3.8)	 9 (37.5) 11 (45.5) 4 (16.7)	 0.027

Table 3. Predictors of PNE success and persistent optimal response at 1 month or more followup.

	PNE and Implant Responders (68)	PNE and Implant Nonresponders (34)	p Value
Mean age (SD)	64.5 (15.9)	68.6 (15.4)	0.20
No. neurologic diagnosis (%): Parkinson's Unspecified dementia Transverse myelitis Myasthenia gravis Myotonic dystrophy	4 (5.9) 1 1 1 1	9 (26.5) 4 5	0.013
No. urgency incontinence (%)	61 (89.7)	27 (79.4)	0.054
No. fecal incontinence (%)	10 (14.7)	1 (2.9)	0.081
No. bellows and plantar toe (%)	56 (82.4)	26 (76.5)	0.59
No. sensation (%): Perianal/rectal Perineal/vaginal/scrotal None	 17 (25) 48 (70.6) 3 (4.4)	 12 (35.3) 18 (52.9) 4 (11.8)	 0.158

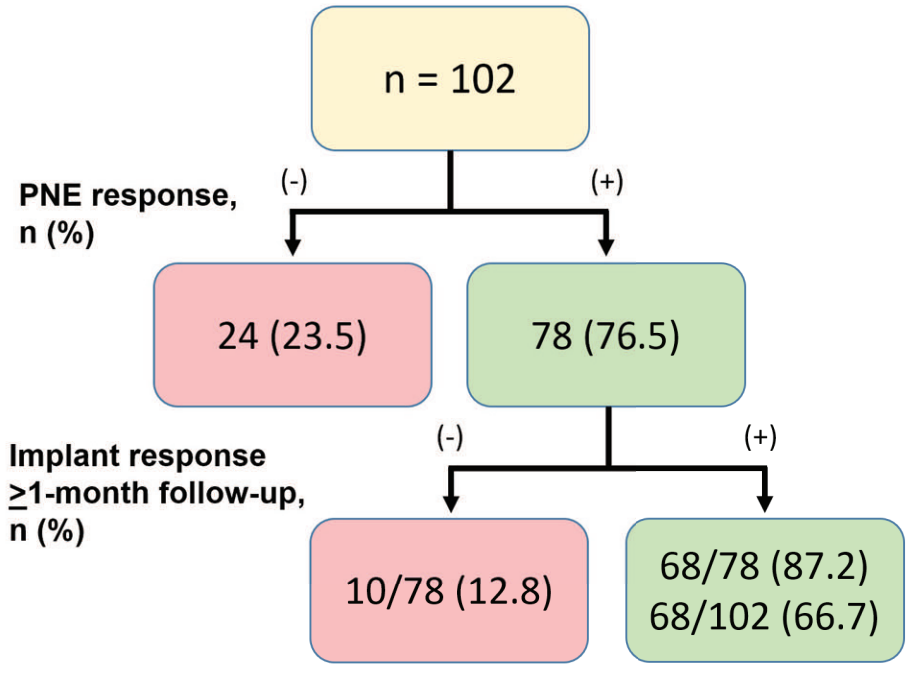

Figure.

Peripheral Nerve Evaluation Success

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screening rates equivalent to available reports on staged implant. Predictors of PNE success included younger age, urgency incontinence, fecal incontinence and absence of a neurologic condition. In all, 67% of patients maintained an optimal therapeutic response at 1 month or more with a median followup of 4 months. PNE conversion rates to permanent implant may not be the ideal outcome and evaluation for continued improvement at a minimum of 1 month postpermanent implant may be considered as an indicator of successful screening.

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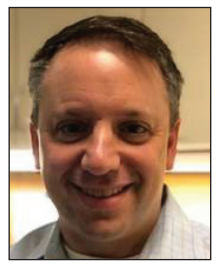
Feasibility and Success of a Nonopioid Pathway after Ureteroscopy



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The opioid epidemic in the United States continues and physician prescribing patterns are implicated as a significant factor leading to the current environment. In response, surgical specialties have begun to implement nonopioid protocols after surgery.[1] Recently, the American Urological Association published a position statement on opioid use intended to guide urologists on pain management and opioid prescribing.[2] Specifically, the statement encourages patient education, the use of nonopioid forms of pain control, and prescribing the fewest number and lowest potency of opioids when they are required. In addition, the AUA's Quality Improvement Patient Safely Committee is currently preparing a white paper describing the rationale and strategies for reducing urological postoperative opioid prescribing. Still lacking are specific AUA guidelines on opioid use after specific urological procedures.

In light of the increased use of ureteroscopy in the last 2 decades and in efforts to decrease the impact of physician overprescribing, we began making concerted efforts to discharge patients without opioids after ureteroscopy in November 2016.[1,3] Our efforts are based on the belief that the morbidity from this procedure is secondary mainly to the presence of the indwelling ureteral stent. We hypothesized that multimodal approaches focusing on nonsteroidal anti-inflammatory drugs (NSAIDs) when possible and additional adjunct medications can manage stent related symptoms as well if not better than approaches with opioids. Avoiding opioids will also decrease immediate postoperative morbidities like nausea and vomiting, and limit the risk of developing long-term use and addiction, particularly in opioid naïve patients.

A treatment algorithm was developed to determine eligibility and select patients for the perioperative nonopioid pathway (fig 1). Charts of patients who underwent ureteroscopy with stent placement during the study period were retrospectively reviewed. Patients with chronic kidney disease (CKD) stage 2 or greater, allergies to NSAIDs, history of ureteroscopy requiring opioids, or current or previous

▼ Continued on page 21

Nonopioid Pathway after Ureteroscopy

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opioid tolerance were excluded. All patients were counseled preoperatively about stent related symptoms, and the intent and rationale for using NSAIDs without opioids.

Intraoperatively near the procedure completion intravenous ketorolac was administered by the anesthesia team. The postoperative discharge nonopioid pathway medications included 4 days of diclofenac 50 mg twice daily and adjunct medications such as acetaminophen, phenazopyridine and tamsulosin. Patients were given detailed discharge instructions focusing on stent related symptoms and concerns that would warrant seeking medical advice. Our main outcomes were adverse events while the stent was in place captured by emergency department (ED) visits, telephone calls for genitourinary symptoms and/or pain medications refill requests.

Our original study results in 2018 demonstrated the feasibility of the nonopioid pathway. In this cohort of 210 patients 73% were discharged without an opioid prescription. As our nonopioid approach continued we expanded our results over a 3-year period to assess the continued feasibility of this pathway. Out of 391 patients included in the analysis 357 (91.3%) were safely discharged without opioids and 34 (8.7%) received opioids. Again we saw that both groups had a low and similar number of postoperative visits to the ED. The nonopioid group had fewer telephone calls made to the urology clinic for stent related symptoms or for pain medication refill requests (fig 2).

Our study highlights that the majority of appropriately selected patients (more than 90%) can be safely discharged without opioids following ureteroscopy with ureteral stent placement. This requires thorough preoperative counseling that includes setting expectations about stent related symptoms as well as providing the rationale for avoiding opioid use. While the optimal approach to the management of this patient population has not been determined we believe that the first and maybe most important step is to simply make the effort to change practice patterns and the current culture. We hope our results will support and encourage other urologists to consider nonopioid pathways after ureteroscopy.

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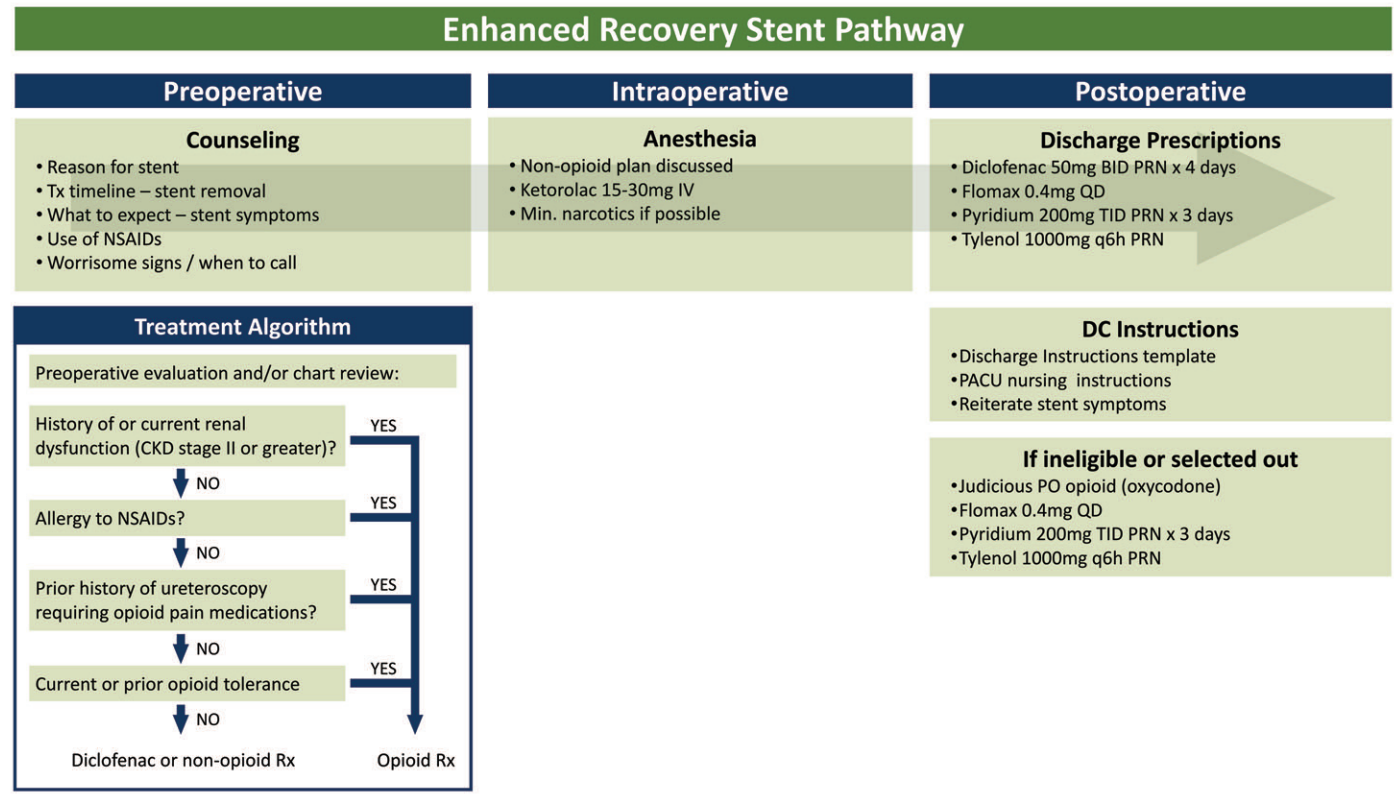
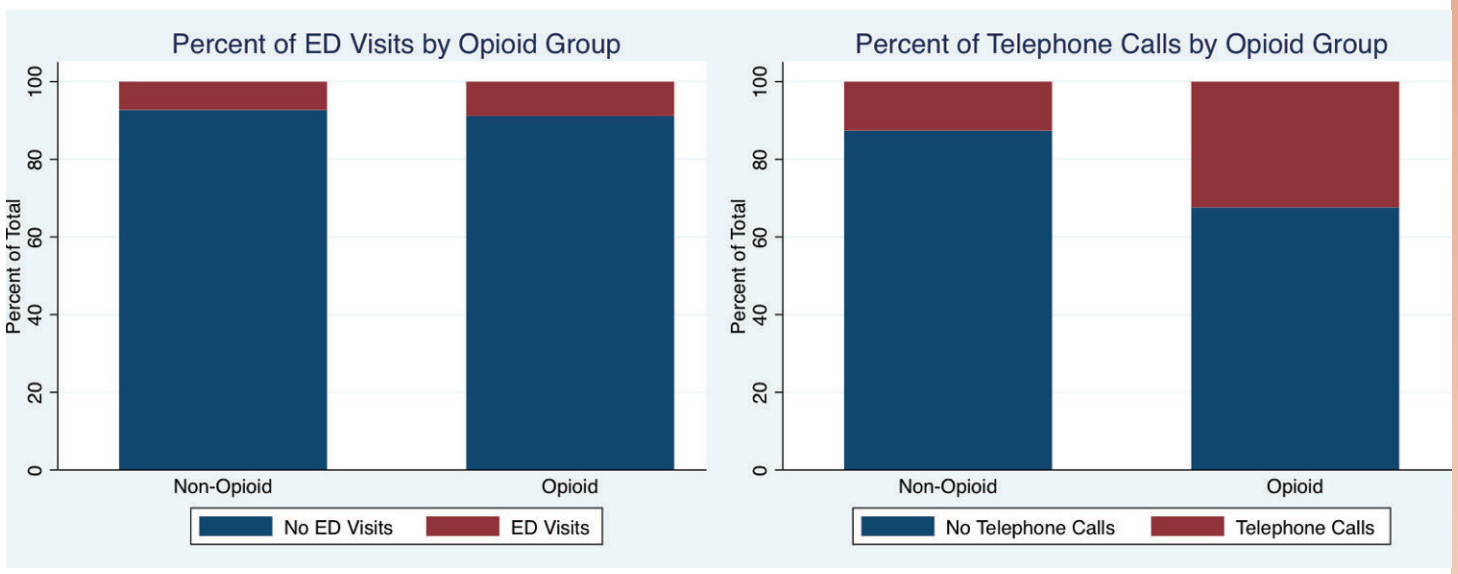


Figure 1.



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Floor vs Intensive Care Unit Management of Isolated Low Grade Renal Trauma




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There is a clear trend toward conservative/nonsurgical management of low grade (AAST [American Association for the Surgery of Trauma] grade I/II) renal trauma.[1] However, it is still unclear whether intensive care unit (ICU) admission and/or transfer to a level 1 trauma center are necessary. A recent study showed that management of renal trauma was similar across tiered trauma centers, and the odds of intervention vs nonoperative management were similar in a level 1 center vs a nonlevel 1 trauma center.[2]

A study on blunt splenic injury showed that ICU use varied widely across trauma centers due to a lack of protocol, and ICU admission was used primarily so that swift intervention could be implemented if clinical decline occurred.[3] Up to 77% of patients admitted to the ICU for blunt splenic injury did not receive any critical care procedure and there was no clear correlation between ICU admission and mortality. This management can lead to resource overuse and could also be occurring in the setting of low grade renal trauma.

In a recent study from a level 1 trauma center 36% of patients with renal trauma were found to have unnecessary transfer of patients to higher level trauma centers with 60% of those overtriaged patients having an AAST renal trauma grade of I/II.[4] No data exist on overtriage to the ICU for patients with renal trauma. Given the lack of data and no established evidence-based protocols patients are potentially being mismanaged and may incur a longer than necessary hospital stay, creating unnecessary costs and taking up valuable hospital resources. Even with the established nonoperative management of most renal trauma and data suggesting that a more liberal management protocol (omitting bed rest and serial hematocrit checks) is appropriate,[5] patients with low grade renal trauma are still being admitted to the ICU and transferred to higher level trauma centers. This suggests that it is necessary to reassess and implement guidelines for proper admission/transfer of patients with renal trauma.

The aim of this study is to determine whether ICU management/interhospital transfer is necessary in low grade renal trauma (AAST grade I/II), focusing on patients with isolated renal trauma. Our hypothesis is that floor management and early discharge as well as management at a lower level trauma center are safe for isolated low grade renal trauma.

After receiving approval from the institutional review board at the University of Washington we completed a retrospective cohort study with the prospectively collected data from the Harborview Trauma Registry from January 2005 to April 2018. All cases of grade I/II renal trauma were extracted from the database (586). Isolated low grade renal trauma was defined as having no other coinciding abdominal injury (solid organ, vasculature etc) in addition to the renal trauma. Patients with a nonabdominal (head, face, neck, chest, spine, extremity) Abbreviated Injury Score (AIS) less than 3 were selected to ensure ICU admission was due to renal trauma and not another injury (133). AIS descriptions in the registry were reviewed and all patients with any evidence of nonrenal abdominal injury (spleen, liver, pancreas, vasculature etc) were excluded, leaving the study sample of 77 patients with isolated low grade renal trauma.

Patients were classified into floor or ICU patients based on admission status (table 1). Demographics such as gender, race, trauma type (blunt or other) and trauma mechanism (motor vehicle, fall or other) were recorded. In addition, we analyzed blood product/vasopressor administration, all interventions and operating room procedures, and postdischarge complications

Table 1- Demographics of Study

n(%), Mean[IQR]		Floor (n=31)	ICU (n=46)
Age	Overall Mean	32.93 [20]	41.26 [46.25]
Count	0-18	7 (22.5)	10 (21.7)
	19-64	23 (74.2)	24 (52.2)
	65+	1 (3.2)	12 (26.1)
Sex (Male)		22 (70.9)	36 (78.2)
Race			
	White	20 (64.5)	37 (80.4)
	Black	3 (9.7)	3 (6.5)
	Other/N.A.	8 (25.8)	6 (13.1)
Trauma Type			
	Blunt	29 (93.5)	46 (100)
	Other	2 (6.5)	0
Trauma Cause			
	Motor Vehicle	15 (48.8)	18 (39.1)
	Fall	5 (16.1)	16 (34.8)
	Other	11 (35.5)	12 (26.1)

(table 2). Postdischarge status (alive/dead) was reviewed to see if admission status would affect mortality from renal trauma. Outcomes and admission status were stratified by age due to the potential impact age may play in ICU admission or receiving an intervention. Injury Severity Score (ISS) was stratified

Table 2- Admission Status and Outcomes

n(%), Mean [IQR]		Floor (n=31)	ICU (n=46)
Transferred to HMC		14 (45.1)	26 (56.52)
Transfer <72 hr. stay		14 (100)	19 (73.07)
Mean LOS in Hours		43.4 [20.75]	71.9 [45.94]
By Age Group	0-18	25.1 [15]	42.6 [21.56]
	19-64	49.6 [22.88]	63.9 [51.19]
	65+	27.8●	112.6 [81.88]
Mean ICU LOS (Hrs.)		NA	37 [23]
Mean ISS		7.7 [4]	8 [3.75]
Blood Product Admin		0	3 (6.52) ♦
Vasopressor Admin		0	0
Post-Discharge Complications⊖		2 (6.45)	3 (6.52)
Alive post-discharge		31 (100)	46 (100)
HMC discharge. to…			
	Home	31 (100)	41 (89.13)
	SNF♣	0 (0)	5 (10.87)

by age and admission status to see if it influenced admission decisions (fig. 1).

Our primary outcome of a 100% postdischarge survival rate suggests that floor or ICU admission had no impact on overall mortality in isolated low grade renal trauma. Along with this, those younger than 65 years old without preexisting renal conditions suffered no postdischarge complications. In addition, 96.1% of patients younger than 65 years old did not receive blood products or vasopressors (no patient received vasopressors) and mean ICU length of stay was only 37 hours. All these factors suggest that patients younger than 65 years old with isolated low grade

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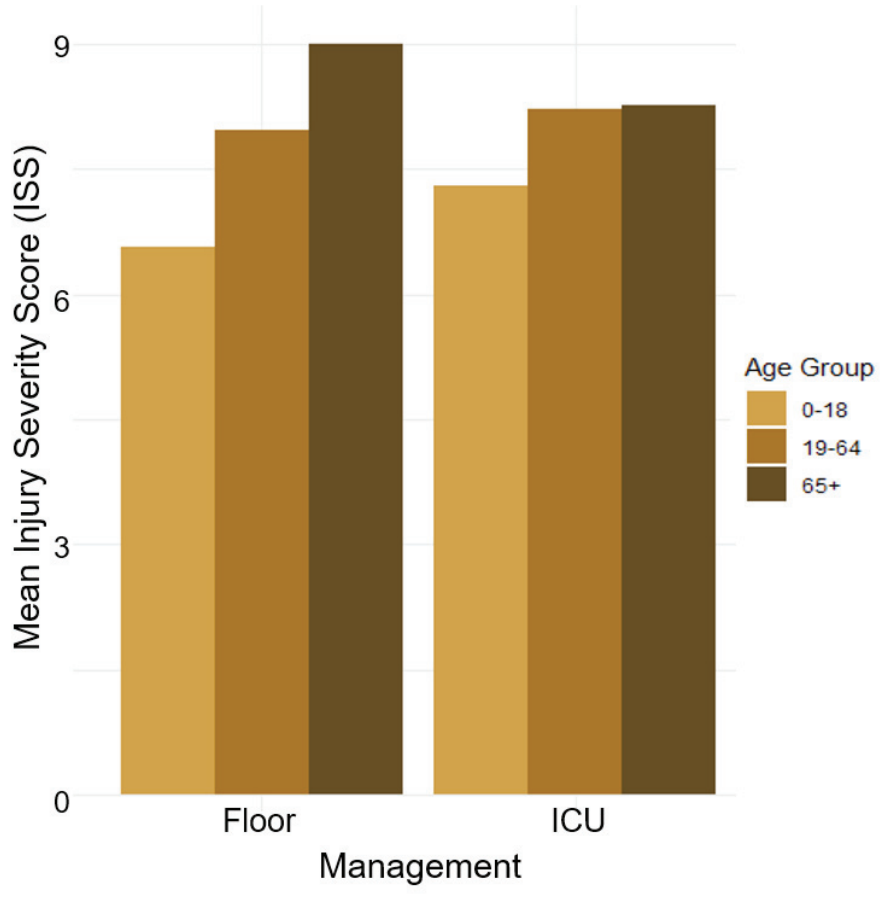

Figure 1. Mean ISS scores by age and admission.

Floor vs ICU Management of Renal Trauma

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renal trauma do not require ICU admission.

About half (52%) of the total number of patients with isolated renal trauma were transferred to our level 1 trauma center. In the 0 to18 and older than 65 year old groups most of the patients (65% and 70%, respectively) were transferred. Of the transferred patients 56% were admitted to the ICU (fig. 2), and 82% of the transferred patients who were admitted were discharged from the floor/ICU within 72 hours.

We are unable to decipher what drove the ICU admission for the entire cohort and especially for the transferring patients. When comparing ISS scores between floor and ICU patients stratified by age no considerable difference was seen for the 19 to 64 years old age group (7.63 for floor and 7.72 for ICU). Furthermore, average ISS scores did not differ considerably (7.65 for floor and 7.97 for ICU), suggesting that injury severity did not impact admission status (fig. 1).

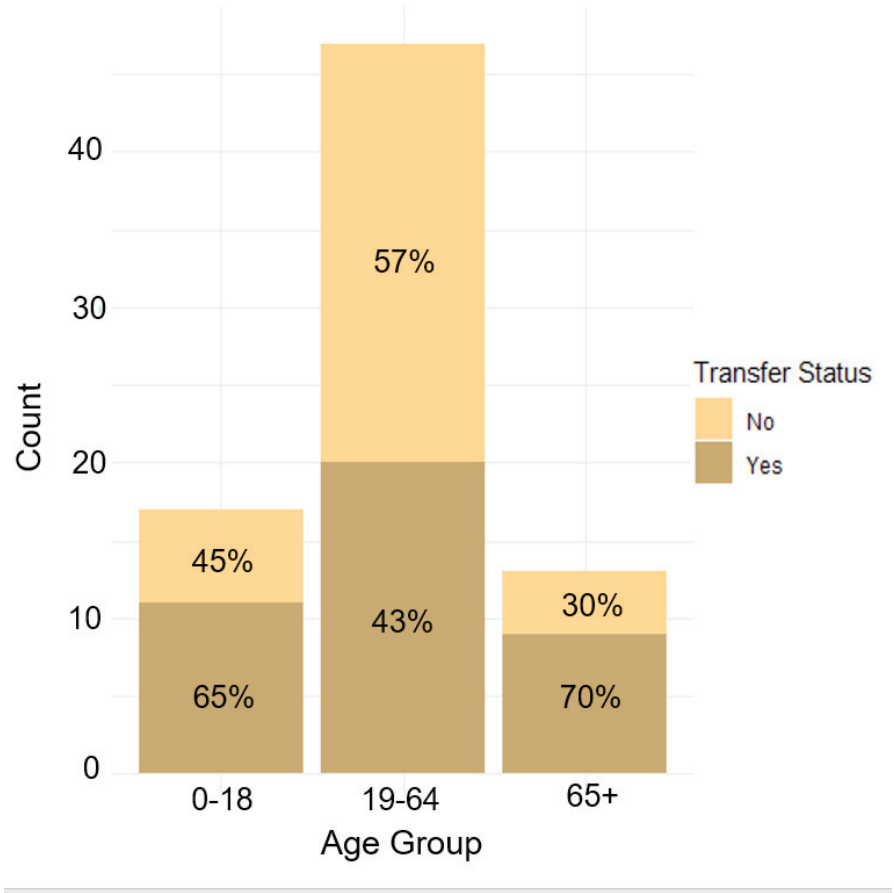

Figure 2. Transfer status by age.

Overall, given the low complication rate, rapid discharge and lack of intervention ICU care and transfer to a level 1 trauma center are unnecessary in optimal management of isolated low grade renal trauma. Further studies to confirm these findings will help establish guidelines and protocols for proper resource use. ◆

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Pretreatment Absolute Monocyte Count and the Effect of Pembrolizumab

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Background and Objectives

Immune checkpoint inhibition (ICI) is a novel approach for cancer therapy that has advanced treatment options in chemo resistant urothelial carcinoma (UC). One ICI, the programmed cell death protein-1 (PD-1) antibody pembrolizumab, exhibited antitumor activity in patients with advanced UC in the phase Ib KEYNOTE-012 study[1] and phase II KEYNOTE-052 study.[2] Furthermore, pembrolizumab was shown to have overall survival (OS) benefits over chemotherapy including paclitaxel, docetaxel or vinflunine as second line therapy for platinum resistant UC in the phase III KEYNOTE-045 study.[3]

However, there is still no reliable biomarker available for predicting worse clinical outcome in patients with chemo resistant UC treated with pembrolizumab. We focused on absolute monocyte count (AMC), reported to reflect high tumor associated macrophages, which promoted tumorigenesis and tumor progression and may be a biomarker for predicting prognosis in various malignancies. Our aim was to evaluate whether high pretreatment AMC (pre-AMC) could predict subsequent clinical outcomes in patients with chemo resistant UC treated with pembrolizumab.

Materials and Methods

We retrospectively reviewed 93 patients who were treated with pembrolizumab for chemo resistant UC between December 2017 and April 2019 at our 6 institutions. We excluded 3 patients who had a short observation period (less than 2 months). The remaining 90 patients were assessed in the present study (table 1). The mean age was 72.4 years, the mean followup period was 6.73 months and the mean number of pembrolizumab administration was 5.67. Diagnostic imaging including computerized tomography of the chest/abdomen/pelvis with or without intravenous contrast was performed every 2 or 3 courses of pembrolizumab. We investigated the association between pre-AMC levels and their

Table 1. Cohort description

n (%)	High pre-AMC group (n=53)	Low pre-AMC group (n=37)	p value
Sex			0.278
Male	40 (75.5)	25 (67.6)	
Female	13 (24.5)	12 (32.4)	
Mean age (years)	71.3±9.91	73.2±8.61	0.495
Mean progression-free duration (months)	16.0±40.0	12.1±12.0	0.607
Performance Status			0.199
0 or 1	50 (94.3)	37 (100)	
2	3 (5.7)	0 (0)	
Smoking history			0.544
Yes	28 (52.8)	20 (54.1)	
No	23 (43.4)	17 (45.9)	
Unknown	2 (3.8)	0 (8.2)	
Primary lesion of main tumor			
Pelvis	11 (20.8)	7 (18.9)	
Ureter	10 (18.8)	11 (29.7)	
Bladder	32 (60.4)	19 (51.4)	
Radical operation for primary tumor			0.198
Yes	36 (67.9)	29 (75.7)	
No	17 (32.1)	8 (54.3)	
Liver metastasis			0.09
Yes	9 (17.0)	2 (5.4)	
No	44 (83.0)	35 (94.6)	
Adverse events (Grade 3 or 4)			0.172
Yes	10 (18.8)	11 (29.7)	
No	43 (81.2)	26 (70.3)	
Number of chemotherapy			0.338
≤5 courses	35 (66.0)	22 (59.5)	
6 courses≤	18 (34.0)	15 (40.5)	
Salvage chemotherapy			0.02
Administered	42 (79.2)	21 (56.8)	
Not administered	11 (20.8)	16 (43.2)	

▼ Continued on page 24

Pretreatment Absolute Monocyte Count

▼ Continued from page 23

prognosis. We defined patients with AMC greater than 342 as the high pre-AMC group according to a calculation by receiver operating curve analysis.

Results

The high pre-AMC group consisted of 53 cases (58.9%). In the 85 cases with measurable lesions, at the point of maximum effect the sum of the target lesion longest diameter (SLD) was decreased in 27 cases (31.8%) compared to baseline. SLD decreased in 9 cases (17%) in the high pre-AMC group, which was significantly lower than that in the low pre-AMC group (18 cases, 48.6%, p=0.001). The disease control rate defined by RECIST v1.1 at best response in the high pre-AMC group was 30.6%, which was significantly lower than that in their counterpart (61.1%, p=0.003). A higher population of the high pre-AMC group was significantly administered salvage chemotherapy as compared to those in the low pre-AMC group (p=0.02). Pre-AMC in the PD group was not significantly higher than that in CR・PR・SD group (p=0.055). The 12-month progression-free survival (PFS) rate for the high pre-AMC group was 11.8%±5.2%, which was significantly lower than that for their counterpart (41.4%±0.9%, p<0.001, see figure).

Multivariate Cox regression analysis revealed that pre-AMC level greater than 342 (p=0.007) and liver metastases (p=0.028) were the independent indicators for disease progression (table 2). Furthermore, the 12-month cancer-specific survival (CSS) rates for the high pre-AMC group was 45.9%±8.1%, which was significantly lower than that for their counterpart (89.7%±5.8%, p <0.001, see figure). Multivariate analysis revealed that the pre-AMC level of greater than 342 was the only independent indicator for cancer specific death (p <0.001, fig. 3). The change of AMC level before and after pembrolizumab was elevated in 41 cases (45.6%). However, there was no association between clinical outcome of PFS and CSS and the change of AMC level.

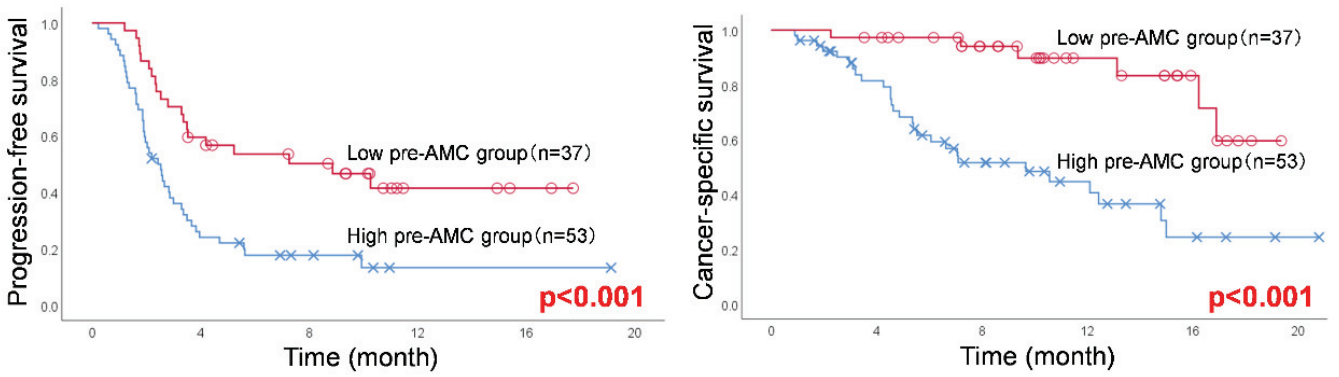

Figure. PFS and CSS according to pre-AMC.

Table 2. Cox regression analysis

	Progression			Cancer-specific death		
	Univariate p value	Multivariate HR (95% CI)	p value	Univariate p value	Multivariate HR (95% CI)	p value
Sex	0.499			0.065		
Male						
Female						
Age	0.535			0.437		
<70 years						
70 years≤						
Performance status	0.718			0.334		
0 or 1						
2						
Smoking history	0.215			0.728		
Yes						
No						
Primary lesion of the main tumor	0.959			0.051		
Upper tract						
Bladder						
Radical operation for primary tumor	0.795			0.286		
Yes						
No						
Liver metastases	***0.01***		***0.028***	0.87		
Yes		2.25 (1.16-4.38)				
No		1				
Adverse events (Grade 3 or 4)	0.168			0.1		
Yes						
No						
Number of chemotherapy	0.081			0.071		
≤5 courses						
6 courses≤						
Salvage chemotherapy	0.517			0.138		
Administered						
Not administered						
Pre-AMC	***<0.001***		***0.007***	***<0.001***		***<0.001***
<342		1			1	
342≤		2.38 (1.09-5.18)			8.4 (1.04-66.7)	

Conclusion

Elevated pre-AMC could identify a population with a poor response to pembrolizumab treatment among patients with chemo resistant UC.

AUA 2020 Virtual Science Best Poster winner. ◆

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Cost-Effectiveness Analysis of Pelvic Organ Prolapse Treatments


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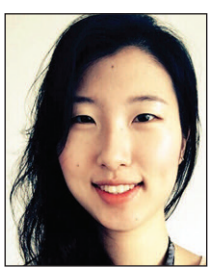
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Pelvic organ prolapse (POP) is a common disorder; 11% of women will undergo surgical treatment for POP or urinary incontinence (UI) in their lifetime.[1] The annual burden of cost for treatment of this disorder is significant. In 1997 the cost was estimated at $1 billion in the United States,[2] and it is expected that contemporary costs are higher. The traditional surgical treatment for uterovaginal prolapse using a vaginal approach has been a vaginal hysterectomy (VH) with vaginal vault suspension[3,4] as it was believed that the risk of recurrent apical prolapse is reduced with removal of the uterus as well as reduction in lifetime risk of uterine cancer.[5]

However, there is a growing interest nationally in uterine sparing procedures for several reasons. First, the risk of future cancers has been shown to be extremely low with a lifetime cervical cancer risk of 0.1% and endometrial cancer risk of 0.2%.[6] Secondly, preserving the uterus allows for future pregnancies,[7] and there is potential for maintenance of positive body image and sexuality for women.[5]

From a surgical standpoint there is reduced morbidity with uterine preservation related to a higher risk of significant blood loss with

▼ Continued on page 25

Cost-Effectiveness of Vaginal Hysteropexy vs Hysterectomy

▼ Continued from page 24

hysterectomy.[8] Interestingly, contemporary randomized controlled studies have shown that recurrence rates between VH with vault suspension and vaginal hysteropexy (HP) with sacrospinous (SS) ligament fixation have equivalent short-term and medium-term recurrence rates.[9,10]

In this study recurrent apical prolapse rates were 10% following VH and 6% following HP at 1 year. Uterine preservation may therefore be a good option when considering surgical intervention options for POP for the aforementioned benefits. In addition, when considering the impact on society as a whole the role of cost to the health care system should be considered when determining surgical treatment options. The objective of our study was to perform a cost-effectiveness analysis of HP vs VH with vaginal suspension for the treatment of uterine prolapse.

An IRB exempt cost-effectiveness analysis was performed on 4 different strategies for uterine prolapse including VH with uterosacral ligament suspension (VH-US), VH with sacrospinous ligament fixation (VH-SS), HP with sacrospinous ligament fixation (HP-SS) and HP with uterosacral ligament suspension (HP-US). Recurrence rates, repeat surgery for surgical failures and complication rates associated with each surgery were modeled. When possible, outcomes from the Detollenaere randomized control trial comparing VH and HP with 12-month followup were used (table 1).[9] Parameter values were modeled using published Health Utility Indices (table 2). Cost data reflect Stanford Hospital costs billed to insurance providers including HP-SS $41,637.33, HP-US $41,466.00, VH-SS $50,258.00, and VH-US $50,258.00. Cost-effectiveness was defined as an incremental cost-effectiveness ratio (ICER) of less than $50,000 per quality adjusted life year (QALY). Base case, threshold and 2-way sensitivity analyses were performed.

We found that sacrospinous hysteropexy was the most cost-effective strategy followed by uterosacral hysteropexy. Sacrospinous hysteropexy (HP-SS) and uterosacral hysteropexy (HP-US) were found to be cost-effective at a willingness-to-pay threshold of less than $100,000 per QALY in the base case scenario. The ICER for HP-US compared to HP-SS was $90,441.25 while VH-US and VH-SS were dominated strategies.

Tornado plots and univariate sensitivity analyses were performed on all variables. A sensitivity analysis varying cost (fig. 1) showed that vaginal hysterectomy strategies became the most cost-effective option when the cost of sacrospinous hysteropexy exceeded $52,500 and uterosacral hysteropexy cost exceeded $49,500. The driver for a more expensive uterosacral ligament procedure is the 1% to 3% risk of genitourinary injury which can lead to a repeat surgery costing approximately $50,000.

When a sensitivity analysis was

▼ Continued on page 26

Table 1. Model outcome probabilities

	Probability				Source
	Vaginal hysterectomy with uterosacral suspension	Vaginal hysterectomy with sacrospinous fixation	Uterosacral hysteropexy	Sacrospinous hysteropexy	
Complications of initial surgery					
Intraoperative or postoperative transfusion*	3.7%	2.2%	0.0%	0.0%	[10,12]
Genitourinary tract injury	2.7%	0.0%	2.7%	0.0%	[10,12]
Dyspareunia	6.9%	6.9%	12.3%	12.3%	[9,13]
Neuropathy	6.9%	12.4%	6.9%	12.4%	[12]
Recurrent apical prolapse rates at 12 months**	10.0%	10.0%	6.0%	6.0%	[10]
Subsequent surgery for treatment of recurrent apical prolapse	3.2%	3.2%	3.9%	3.9%	[10]

Table 2. Model utility values

	Utility Value	Range	Source
Baseline apical prolapse	0.83	0.2 -0.95	[14]
Surgical success	0.88	0.25-1.0	[14]
Surgical failure	0.86	0.2-0.95	[14]
Intraoperative/postoperative transfusion	0.76	0.2-0.9	[15]
Genitourinary tract injury	0.75	0.2-0.9	[16]
Postoperative dyspareunia	0.90	0.2-0.95	[17]
Postoperative neuropathy	0.66	0.2-0.9	[16]
Need for subsequent surgery (recurrent prolapse or genitourinary injury)	0.83	0.2-0.95	[16]

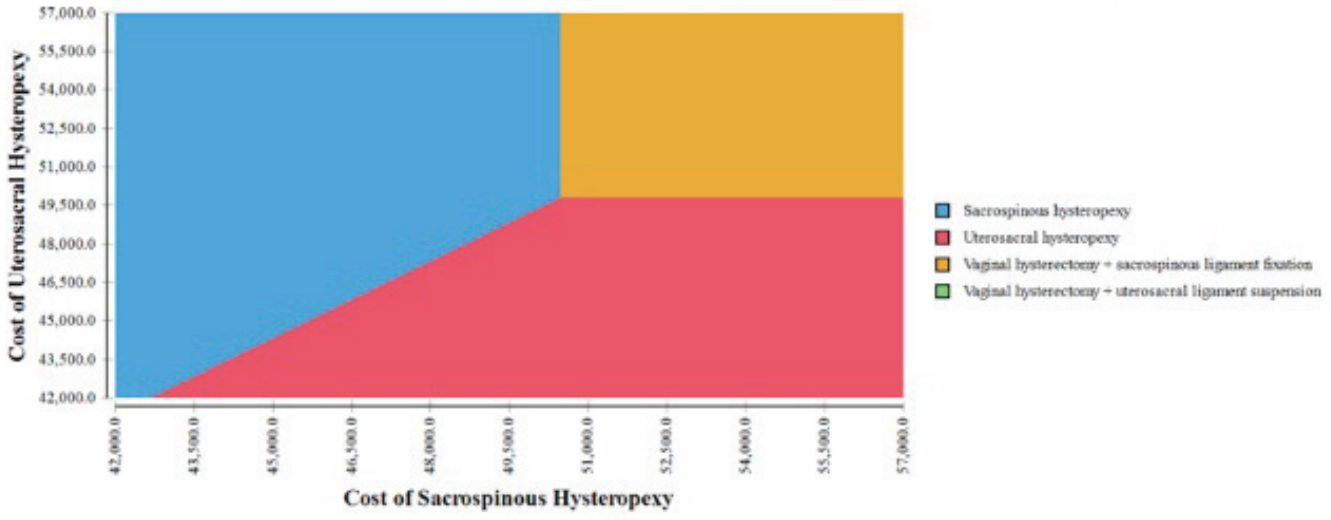

Figure 1. Two-way sensitivity analysis varying costs of sacrospinous hysteropexy and cost of uterosacral hysteropexy.

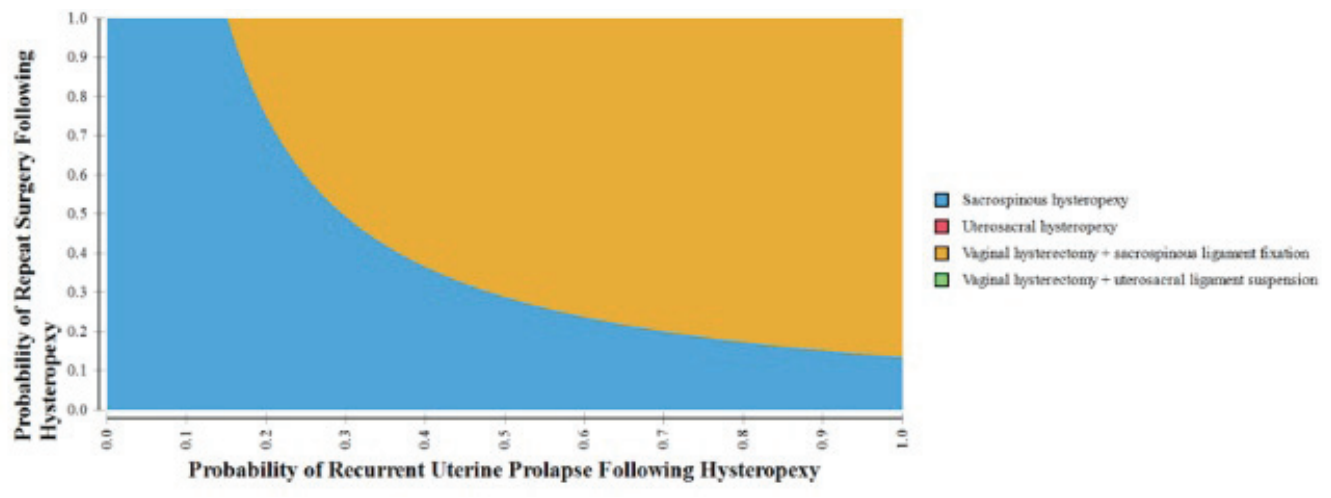

Figure 2. Two-way sensitivity analysis varying costs of recurrent vaginal prolapse after hysteropexy and repeat surgery after hysteropexy failure.

Cost-Effectiveness of Vaginal Hysteropexy vs Hysterectomy

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performed varying prolapse recurrence (fig. 2) we found that vaginal hysterectomy procedures become cost-effective when prolapse recurrence rates following hysteropexy procedures were 30%, and 50% of these patients underwent repeat surgery. Vaginal hysterectomy procedures also became cost-effective when the prolapse recurrence rates following hysteropexy procedures were 40%, and 35% of these patients underwent repeat surgery.

Our study suggests that even if we assume there are higher rates of recurrence and repeat POP surgery following hysteropexy for transvaginal surgical management of apical prolapse, sacrospinous hysteropexy is the most cost-effective surgery until prolapse recurrence rates surpass 30% and repeat surgery rates for recurrent prolapse surpass 50%. These thresholds are much higher than what is reported in contemporary studies, indicating that in clinical practice hysteropexy is the most cost-effective strategy. Our results should only be used as a guide in the context of existing clinical guidelines. Clinical decision-making for individual patients should also account for other factors, such as medical history, comorbidities and patient preference. ◆

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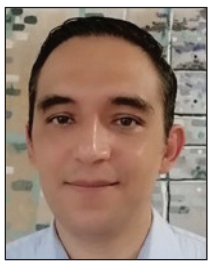
CASE *Report*

Translocation Renal Cell Carcinoma



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Background

Based on the International Agency for Research on Cancer in 2018 kidney cancer is the fifteenth most common type of cancer around the world with 403,262 cases. In recent years immunohistochemistry is the most widely used tool for categorizing renal tumors subtypes.[1] The aim of this report is to show a rare case of microphthalmia transcription factor (MiT) renal cell carcinoma.

Case Presentation

A 31-year-old male came to the emergency room (ER) after 7 days of abdominal pain, vomiting and diarrhea. The patient had no history of cigarette smoking, urinary symptoms or chronic diseases. After stabilization in the ER an abdominal ultrasound was performed that showed a renal mass in the upper pole of the left kidney. Noncontrast magnetic resonance imaging confirmed the upper pole mass in the left kidney. A week after controlling the initial symptoms the patient underwent surgery and a left laparoscopic radical nephrectomy was performed without intraoperative complications.

The pathology department reported a renal cell carcinoma (RCC) 10.9 cm in size with diffuse papillary patterns and fusocellular focus compatible with the MiT family.

Microscopy reported an epithelioid pattern characterized by cells with enlarged, pleomorphic and irregular nuclei. Nucleolar prominence with abundant clear to eosinophilic cytoplasm was arranged in solid, trabecular and diffuse patterns and psammoma bodies. Immunostaining for TFE3 was positive. The tumor was limited to renal parenchyma without extension to Gerota's fascia, suprarenal gland, renal pelvis or vascular structures.

The patient is in good condition 9 months after surgery with no tumor activity and is under oncology department surveillance.

Discussion

Translocation associated renal cell carcinoma (tRCC) is an uncommon subtype of RCC characterized by gene rearrangements in the TFE3 or TEEF loci which are members of the MiT family. These members of the MiT family regulate gene expression and cell differentiation such as melanocytes and osteoclasts.[2] Xp11 tRCC was originally described as a RCC subtype in the 2004 WHO classification. In 2016 it was renamed MiT family in the WHO classification including the new subtype t(6;11) RCC.[3]

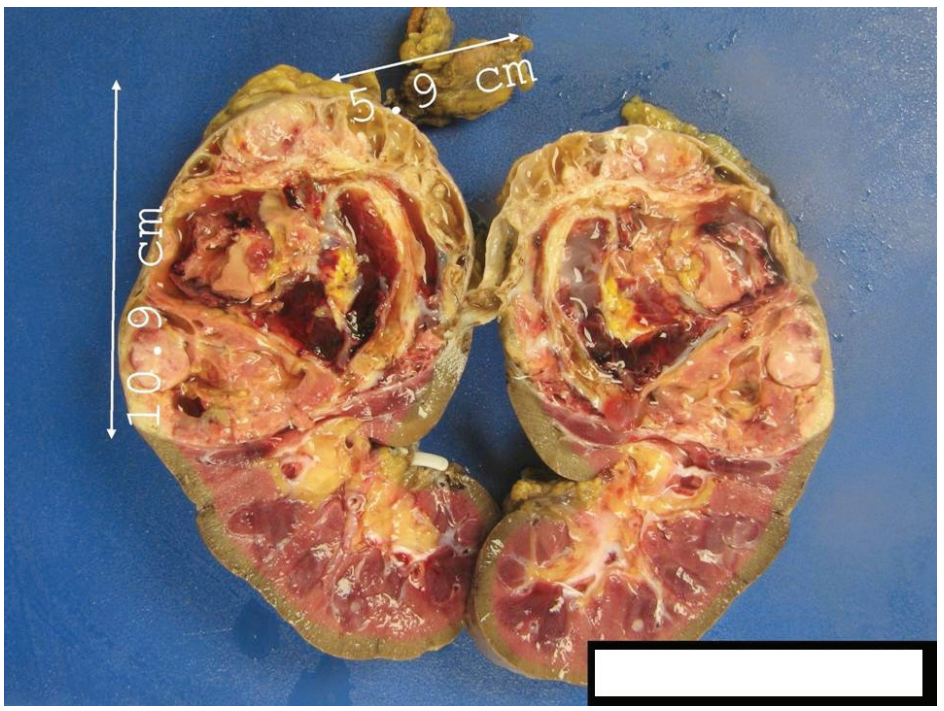

Figure 1. Renal mass macroscopic pattern.

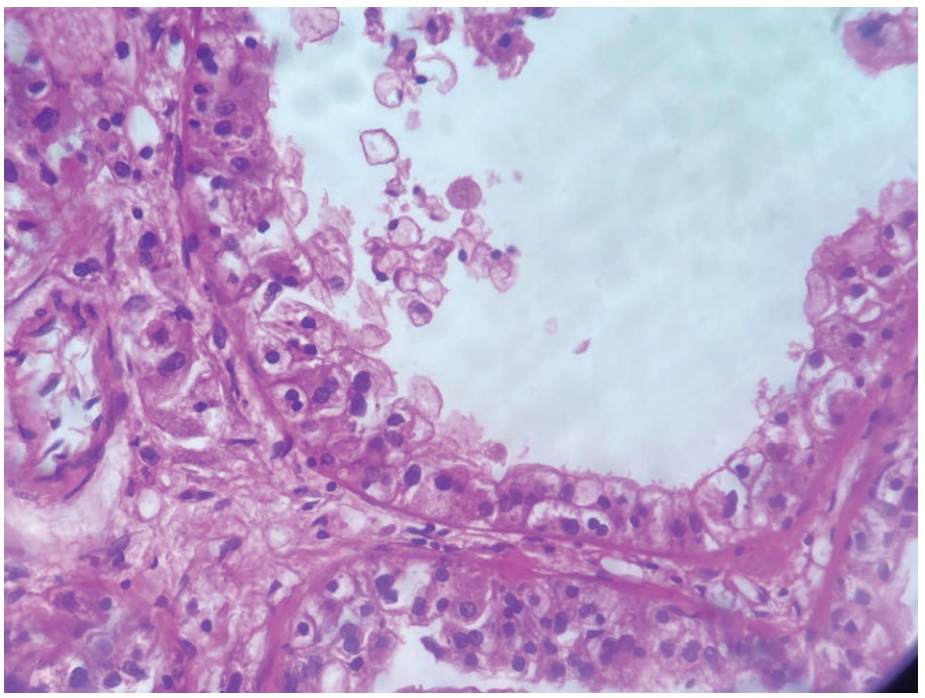

Figure 2. Mixed solid/fusiform and alveolar/tubular pattern of renal mass.

Xp11 tRCC comprises 1% to 4% of adult RCC with an average

▼ Continued on page 27

Case Report

▼ Continued from page 26

onset age of 40 to 50 years.[3,4] The predominant histological pattern of tRCC (TFE3/Xp11) is characterized by cytological and architectural heterogeneity as well as features similar to all subtypes of RCC, a papillary architecture with clear cells and psammoma bodies. Epithelioid clear cells have voluminous, clear to eosinophilic cytoplasm. The nuclei are enlarged with a prominent eosinophilic nucleolus.[1-4] TFE3 immunostaining should be used cautiously due to the frequent false positive and false negative results. Currently, the gold standard for the correct diagnosis of TFE3 rearrangement identification is by FISH assays on formalin fixed and paraffin embedded tissue sections. However, Xp11 tRCC can be confused with several neoplasms, mainly clear cell and papillary RCC. Cathepsin K is the most reliable immunohistochemical marker, observed in roughly half of all Xp11 tRRC.[4,5]

Treatment and optimal therapy for tRCC are not yet determined. Radical surgery remains the best option for localized tumors, including in patients with positive regional lymph nodes. Therapies targeting vascular endothelial growth factor receptors, immunotherapy and MET targeted therapies signaling pathway are options. To date there are no data regarding predictive markers. The outcome of Xp11 tRCC is variable from indolent to fast aggressive behavior. In general terms Xp11 tRCC has a worse prognosis than papillary RCC and is similar to clear RCC. Some studies have reported that Xp11 tRCC in children have an indolent course while in young adults behavior is aggressive in a high percentage of cases. Larger tumor size correlates with aggressive behavior ($p < 0.05$). Aggressiveness correlates with necrosis but not with the nucleolar grade.[4,5]

Conclusion

In recent years the number of subtypes of renal epithelial tumors has increased rapidly. The MiT family tRCCs are tumors with a variable clinical behavior. Although MiT tRCCs are rare, they should be considered a differential diagnosis for RCC with epithelioid patterns, especially in children and young adults. ◆

1. Kim M, Joo JW, Lee SJ et al: Comprehensive immunoprofiles of renal cell carcinoma subtypes. Cancers (Basel) 2020; **12**: 602.
2. Xie L, Zhang Y, Wu CL et al: Microphthalmia family of transcription factors associated renal cell carcinoma. Asian J Urol 2019; **6**: 312.
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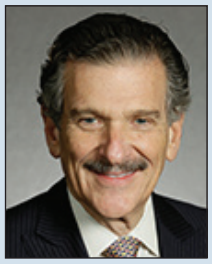
5. Pei J, Cooper H, Flieder DB et al: NEAT1-TFE3 and KAT6A-TFE3 renal cell carcinomas, new members of MiT family translocation renal cell carcinoma. Mod Pathol 2019; **32**: 710.

FROM THE *Urology Care Foundation*

An Open Letter of Thanks to Friends of the Foundation



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

As we reflect on what has thus far been a very difficult year, we are excited to share with you some bright news about the remarkable accomplishments and growth of the Urology Care Foundation.

While focusing our efforts on responding to the COVID-19 pandemic, the Foundation launched a resource center on our website. Moreover, at the same time we chose to move forward with our continued support of innovative research and our specialty's young urology researchers. Together with the AUA, we recognized 21 researchers as recipients of the Urology Care Foundation Research Scholar Awards. These awards provide clinical and postdoctoral fellows or early-career faculty $40,000 per year for 1 to 2-year mentored research training, and are critically important in developing future research leaders and improving patients' lives.

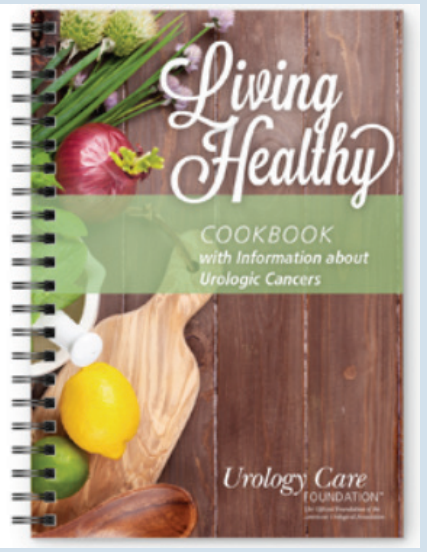
We congratulate this year's recipients as they aim to tackle the most pressing urological challenges facing patients in a very uncertain time.

Patient Education Accomplishments

The Foundation continues to grow as the world's single largest repository for medically approved urological patient education. Currently, the Foundation offers more than 400 patient education pieces on topics ranging from pediatric urological conditions to ones affecting male and female geriatric patients. These materials are available in a variety of formats, including downloadable and printable patient guides and fact sheets, as well as assessment tools, infographics, videos and podcasts.

We are also pleased to announce that our newly printed *Living Healthy Cookbook with Information about Urologic Cancers* has finally arrived! This educational cookbook includes recipes from several celebrity chefs including Chef Mary Nolan, Chef Wolfgang Puck and Chef Paul Wahlberg, and is designed to help those directly and indirectly affected by urological cancer.

Our patient education pieces are free and can be shipped for



free within the United States. Visit UrologyHealth.org/Order today to order materials or download materials by visiting UrologyHealth.org/Download.

Our flagship website, UrologyHealth.org, is fast becoming the leading go-to source for patient information and tools. Here you will find an abundance of relevant content, including our recently updated COVID-19 patient resource center. This resource is filled with information to help guide patients through their health care journey during this pandemic. Whether it's listening to podcasts, watching videos, or reading about urological conditions or procedures, it's no wonder that UrologyHealth.org is currently garnering an astounding 1 million visits per month.

To further support the growing need for patient education in languages other than English, we are translating the majority of our resources. As a result, the Foundation's patient education materials have been translated into Arabic, Brazilian Portuguese, Hindi, Italian, Punjabi, Spanish and Urdu. Through this action, we are empowering millions of patients worldwide with information and decision tools to help them understand and navigate their disease, diagnosis and treatment options.

Thank You

We recognize this work would not be possible without the steadfast support of our AUA members' time, energy, commitment and monetary contributions. With individuals like you, we continue to be a vital force in the efforts to create a future free of urological disease. Despite the difficult nature of 2020, I want to pause and reflect on these positive outcomes and express my sincere gratitude.

On behalf of the entire Foundation, we thank you again for your continued support. Together, we are advancing urological research and education to improve patients' lives. To learn more about contributing to the Foundation, please visit www.UrologyHealth.org. ◆

FROM THE *Chief Executive Officer*

Research Advocacy Update

Michael T. Sheppard, CPA, CAE
Linthicum, Maryland

It is hard to believe that autumn is already upon us. As the leaves begin to change colors and the air gets cooler, it is also time for us to begin planning for the coming year, including planning our budgets for 2021. In Washington, D.C. it is appropriations season, meaning that millions of medical research dollars are in play. The AUA, through our Research Council, our Research Advocacy Committee, our Patient & Research Advocacy staff and our many patient advocacy partners, works diligently throughout the year to ensure that urological research is appropriately represented in the government's many funding portfolios.

Our priority is to support federal funding for biomedical research to increase and maintain the urology physician-scientist and researcher workforce to catalyze the advancement of clinical practice and reduce the burden of urological disease. In 2019 we joined other urology research advocates in celebrating numerous successes on this front, including a 10-year reauthorization for the Patient-Centered Outcomes Research Institute and a $2.6 billion funding increase for the National Institutes of Health (NIH) that included an 8% funding boost for the National Cancer Institute over fiscal year 2019 funding.

In 2020, as the nation's attention turned to funding around efforts to combat the COVID-19 pandemic (including the development of a vaccine) the AUA, like many others, has shifted efforts to stay fluid with the situation. Our work to promote the value of urological research continues, and in 2020 we have:

- Maintained involvement in key research focused coalitions, including One Voice Against Cancer and the Defense Health Research Consortium, to ensure that funding for urological research is not only protected but continues to increase;
- Strengthened relationships with NIH agencies to ensure urology remains at the forefront of strategic funding decisions, which includes submitting feedback to the National Institute of Diabetes and Digestive and Kidney Diseases strategic plan and responding to agency requests for information as appropriate to reinforce urology's perspective; and
- Organized strike force meetings with key members of the AUA Board of Directors, Research Council, and Research Advocacy Committee members and NIH institutes to further highlight the burdens of urological conditions and emphasize the value in partnering with the AUA to promote research opportunities.

The AUA also launched a new stakeholder driven coalition in 2020 called Friends of the Prostate Cancer Care Community (FoPCCC). The coalition is comprised of 27 organizations representing patients, physicians, researchers and industry. The mission of this group is to identify and address gaps in prostate cancer advocacy, policy, awareness, education and research. The community strives to promote equity–of access, outcomes and information–to the highest possible quality of care, and informed decision making for men at risk for or diagnosed with prostate cancer.

In addition to the FoPCCC, the AUA leads the Bladder Health Alliance, a coalition comprised of more than 30 patient, physician and research organizations who work collaboratively to improve awareness about conditions impacting bladder health and removing stigma associated with these conditions. The Alliance was formed in 2013 and convenes annually to plan and promote Bladder Health Month activities and support research funding campaigns.

For more information about the AUA's advocacy efforts, visit www.AUAnet.org/ActNow. ◆

AUA RESIDENTS & FELLOWS *Committee News*

An Unexpected and Expedited Transition to Virtual Residency Interviews and Recruitment

Ahmad M. El-Arabi, MD
South Central Section Representative, AUA Residents & Fellows Committee
Kansas City, Kansas

This year has brought many changes, but one that is least expected is the new folder created on my iPhone® labeled "Meetings." Here we can find the Zoom, Skype® and Houseparty apps. These video conferencing and chat applications have replaced the face-to-face encounters we are all so sorely missing. We have come to expect seeing faces arranged in a grid reminiscent of the intro to *The Brady Bunch*. Virtual conferences. Virtual classrooms. Virtual happy hours. And as a consequence of the CoVID-19 pandemic, residency programs have had to adapt and forgo in-person interviews for virtual interviews.

While the thought of virtual interviews was not on the horizon for many residency programs, the question I pose is: Will virtual interviews become the norm? On the plus side, no more flying across the country and staying at a hotel just to spend a day in an uncomfortable suit touring a hospital that looks the same as every other, all to turn around in less than 24 hours and head home. On the downside, common technical snafus and fewer body language cues can make the online process feel impersonal. Given the current climate of rising student debt our forced transition to virtual interviewing during the CoVID-19 pandemic permits us to rethink how urology programs can structure recruitment now and in the future.

Virtual interviews have been proposed in recent years as a way to reduce applicant financial burden. Whitley et al found the median total cost of travel, food and hotels for urology applicants to be roughly $9,000 during the 2017 to 2018 match year.[1] While this amount pales in comparison to the greater than $100,000 of debt the average medical student carries into residency Nikonow et al found that nearly two-thirds of applicants did not receive any financial aid for interviews and only a third believed their financial aid departments provided adequate financial planning.[2]

Urology as a specialty has often been a pioneer in the use of technology in advancing our surgical field.

Furthermore, nearly a quarter of urology applicants indicated that their financial situation limited the number of interviews they attended. How can we as a specialty use these unprecedented times as an opportunity to recruit the best candidates regardless of their financial situation?

Urology as a specialty has often been a pioneer in the use of technology in advancing our surgical field. For this reason I feel the urological community is well suited to become leaders in implementation of technology in the resident interview and recruitment process. For instance, social media is no longer optional. In order to engage with medical students on the platforms they use the most, social networking is a critical component of resident recruitment. Residency programs must develop and maintain a professional social media presence that highlights the strengths of the program but also lends a sense of the culture of the program.

Regardless of advantages or disadvantages of virtual interviews we must embrace the unknown. While there will undoubtedly be hiccups through this recruitment process, I foresee this becoming a springboard for the seamless implementation of virtual interviews and social media recruitment for years to come.

In the end, I beg everyone to follow the number 1 rule of virtual interviews. Please put on pants. ◆

1. Whitley J, Joyner B and Kieran K: If it's not the money, and it's not the time…: investigating barriers to the recruitment of underrepresented minorities in urology residency programs. J Urol, suppl., 2019; **201**: e511.
2. Nikonow TN, Lyon TD, Jackman SV et al: Survey of applicant experience and cost in the urology match: opportunities for reform. J Urol 2015; **194**: 1063.

Invitation to the 21st Fall Scientific Meeting of the Sexual Medicine Society of North America

Alan W. Shindel, MD, MAS
Scientific Program Chair, SMSNA
San Francisco, California

Hossein Sadeghi-Nejad, MD, FACS
President, SMSNA
Hackensack, New Jersey

As Scientific Program Chair and President and of the SMSNA (Sexual Medicine Society of North America) it is our distinct pleasure to invite you to the 21st Annual (and first ever Virtual) Fall Scientific Meeting of the Sexual Medicine Society of North America.

The global pandemic has forced us to cancel our in-person meeting. However, we are optimistic that our redesigned virtual meeting will incorporate all of the elements that make SMSNA the preeminent North American meeting for sexual medicine clinicians and researchers. The virtual format also has the potential to increase accessibility to sexual medicine clinicians and researchers around the world. We are excited to be pioneering this new way to host scientific meetings!

Our meeting will be a weeklong affair. Original research will be presented in abstract form starting on Monday, November 9 and continue through Thursday, November 12. We will be offering free registration to medical students, residents and fellows. There will be a prosthetic urology course on Sunday morning that is sure to be a big draw, and we hope you will encourage all your trainees to attend. Our high impact courses, mental health symposium, and advanced practice nurse/physician assistant session will be held on the afternoon of Friday, November 13. The meeting will start in the evening with the Presidential Lecture, entitled "YouTube in Sexual Medicine: A Critical Evaluation," followed by our annual business meeting.

The plenary session will start Saturday, November 14. We will feature concomitant virtual rooms presenting talks, debates and panel discussions by leading experts in the field of sexual medicine. Our intention is to have "something for everyone" while simultaneously encouraging cross-pollination of ideas between basic scientists, clinicians and mental health professionals. Our membership is diverse in terms of background and discipline but united in our concern and advocacy for sexual wellness. A recurring theme of the meeting will be integration of different approaches to issues in sexual wellness. A specific example will be our "Collaboratory" on premature ejaculation, featuring considerations germane to basic scientists, clinicians and patients. We will also emphasize the essential nature of integrating the experience and expectations of our patients with those of their sexual partners.

Our basic science symposium will be divided into 2 sessions this year. The theme of both will be "LUTS and ED: Identifying Common Themes and Mechanisms." The dual purpose of the genitourinary system ensures that issues with either urination and/or sexual function will oftentimes overlap. Is this a simple matter of proximity, or are there fundamental molecular pathways that may modulate this complex interplay? Discover the evidence at our basic science symposium.

Our mental health committee has organized an exceptional program that will be of interest to fellow mental health practitioners

▼ Continued on page 30

21st Fall Scientific Meeting of SMSNA

▼ Continued from page 29

and also medical specialists. The theme of holistic assessment will be featured prominently with the intention that all practitioners who care for the sexual well-being of patients will come away with a more robust understanding of what our colleagues do for our patients and clients.

COVID-19 must by necessity be the highlight of what has been an incredibly eventful year. How has COVID-19 affected sexuality and sexual medicine practice? Our team of experts will discuss what we know about COVID-19 and sex and what the future of sex looks like in a postpandemic world.

Also, 2020 has been a year where we have been forced to confront our differences–politically, economically and with regards to health. We strongly believe that creating connections across differences is essential if we hope to survive and thrive not just as sexual medicine specialists but as citizens of the world. To that end, we will feature talks about the things that distinguish us from one another in hopes of better understanding the core values that bind us all.

When considering differences it is also worthwhile to take a moment to consider the diversity of human sexual expression. As in years past our meeting will feature information and content related to the care of people who endorse a lesbian, gay, bisexual, and/or transgender (LGBT) identity. We will also consider the particular concerns and needs of patients who engage in nonnormative sexual practices, use pornography and/or who have been the victims of sexual violence. This content will be of great interest for the practitioner who desires to "meet patients where they are" and to provide the best possible care to all patients.

Is the infrapubic approach superior to the penoscrotal approach for penile implant surgery? Is testosterone the optimal therapy for postmenopausal women with sexual dysfunction? Is collagenase the only appropriate injection agent for Peyronie's disease? Join our mentor/mentee debates to find out! The 2020 annual meeting will feature a number of high profile debates between leading experts in sexual medicine and their trainees. These sessions promise to be entertaining and informative, and will cover a large gamut of issues in human sexuality and sexual wellness.

Patients have high expectations from penile surgery. The risk of litigation must always be a consideration for the busy implant surgeon. To aid our membership in planning for the unfortunate event of legal action we will feature a session incorporating input from a legal expert and a panel of experienced implant surgeons. Planning for what is to some extent an inevitable consequence of medical practice can make all the difference in terms of outcome.

As always, SMSNA benefits from the rich experience of our friends around the world. The International Society of Sexual Medicine Session at the 2020 SMSNA is an international symposium that will feature state-of-the-art content from experts from around the globe. Come network with international colleagues and see what is new.

We look forward to seeing you in cyberspace! ◆

HAVE YOU *Read?*

Daniel Shoskes, MD
Cleveland, Ohio

Hilliard RW, Haskell J and Gardner RL: Are specific elements of electronic health record use associated with clinician burnout more than others? JAMIA Open 2020; https://doi.org/10.1093/jamia/ocaa092.

We are routinely told that physician burnout is due to our own lack of resiliency and that yoga plus mandatory wellness modules are the cure. Is the technology meant to simplify our lives helping or hurting?

This study combined data from a statewide clinician survey on burnout with Epic electronic health record (EHR) data from the ambulatory sites of 2 large health systems, with a combined data set including 422 clinicians. They examined whether specific EHR workload and efficiency measures were independently associated with burnout symptoms, using multivariable logistic regression and controlling for clinician characteristics.

Clinicians with the highest volume of patient call messages had almost 4 times the odds of burnout compared with clinicians with the fewest (adjusted OR 3.81, 95% CI 1.44–10.14, p=0.007). No other workload measures were significantly associated with burnout. No efficiency variables were significantly associated with burnout in the main analysis. However, in a subset of clinicians for whom note entry data were available, clinicians in the top quartile of copy and paste use were significantly less likely to report burnout, with an adjusted odds ratio of 0.22 (95% CI 0.05–0.93, p=0.039).

High volumes of patient call messages were significantly associated with clinician burnout, even when accounting for other measures of workload and efficiency. In the EHR "patient calls" encompass many of the inbox tasks occurring outside of face-to-face visits and likely represent an important target for improving clinician well-being. The authors conclude that increased workload is associated with burnout and that EHR efficiency tools are not likely to reduce burnout symptoms, with the exception of copy and paste.

STARRT-AKI Investigators for the Canadian Critical Care Trials Group, Australian and New Zealand Intensive Care Society Clinical Trials Group, United Kingdom Critical Care Research Group et al: Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med 2020; 383: 240-251.

As urologists we do not initiate renal replacement therapy for acute kidney injury but it certainly impacts many of our patients. The issue of how early to begin treatment for these patients with dialysis is controversial.

The authors conducted a multinational, randomized, controlled trial involving critically ill patients with severe acute kidney injury. Patients were randomly assigned to receive an accelerated strategy of renal replacement therapy (in which therapy was initiated within 12 hours after the patient had met eligibility criteria) or a standard strategy (in which renal replacement therapy was discouraged unless conventional indications developed or acute kidney injury persisted for more than 72 hours). The primary outcome was death from any cause at 90 days. Of the 3,019 patients who had undergone randomization 2,927 (97.0%) were included in the modified intention to treat analysis.

At 90 days 643 patients (43.9%) in the accelerated strategy group and 639 (43.7%) in the standard strategy group (relative risk 1.00, 95% CI 0.93–1.09, p=0.92) had died. Among survivors at 90 days continued dependence on renal replacement therapy was confirmed in 85 of 814 patients (10.4%) in the accelerated strategy group and in 49 of 815 patients (6.0%) in the standard strategy group (relative risk 1.74, 95% CI 1.24–2.43). Adverse events occurred in 346 of 1,503 patients (23.0%) in the accelerated strategy group and in 245 of 1,489 patients (16.5%) in the standard strategy group (p <0.001).

The authors conclude that among critically ill patients with acute kidney injury, an accelerated renal replacement strategy was not associated with a lower risk of death at 90 days than a standard strategy.

Burton CS, Gonzalez G, Vaculik K et al: Female lower urinary tract symptom prevention and treatment strategies on social media: mixed correlation with evidence. Urology 2020; doi: 10.1016/j.urology.2020.06.056.

Dr. Google, followed closely by its graduate student Dr. Twitter, continues to inform and misinform our patients. How well do they do for women with lower urinary tract symptoms?

In this study the authors performed a digital analysis of anonymous online posts on social media sites collected by a social media data mining service. A total of 1,000 posts about pelvic organ prolapse, stress urinary incontinence, overactive bladder, urinary tract infection and interstitial cystitis/bladder pain syndrome were randomly selected. They analyzed these posts for recommendations regarding the prevention and treatment of these diseases, which were then compared to recommendations in available clinical guidelines and assessed for level of evidence.

Of the 1,000 posts 158 contained 239 prevention strategies. Among posts on pelvic organ prolapse there were 41 strategies identified, of which 25 (61%) had no evidence. For urinary tract infection 14 of 58 (29%) had no evidence, including recommendations for dietary modifications and urinary alkalization. For overactive bladder 8 of 28 (29%) had level 4 or no evidence. For stress urinary incontinence 12 of 34 (36%) prevention strategies such as laser rejuvenation and bladder training had no evidence. Interstitial cystitis had the highest number of prevention strategies and most were low or nonevidence-based (70 of 79, 89%).

The authors conclude that prevention and treatment strategies are common in online discussions of pelvic floor disorders, but at least a third of these recommendations have no evidential support. There is a role for further online education and social media engagement by health care specialists to promote evidence-based practices. ◆

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