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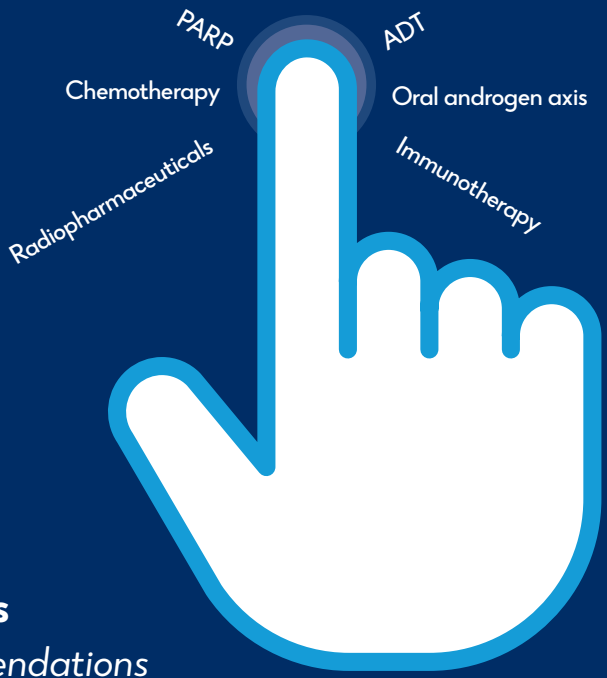
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CHOOSING THERAPIES IN PROSTATE CANCER

What to Consider When Selecting a Treatment for Patients

A discussion with Catherine Handy Marshall, MD, MPH p.14



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Conversations With the Uromigos

New ASCO Recommendations for Management of Patients with Metastatic Clear Cell Renal Cell Carcinoma p.8

PROFILES IN GU ONCOLOGY

Jérémie Calais, MD, MSc



An International Adventure Advances Cancer Imaging and Theranostics

Dr Calais is Director of the Theranostics Program and Clinical Research Program in the Ahmanson Translational Theranostics Division at UCLA. p.11

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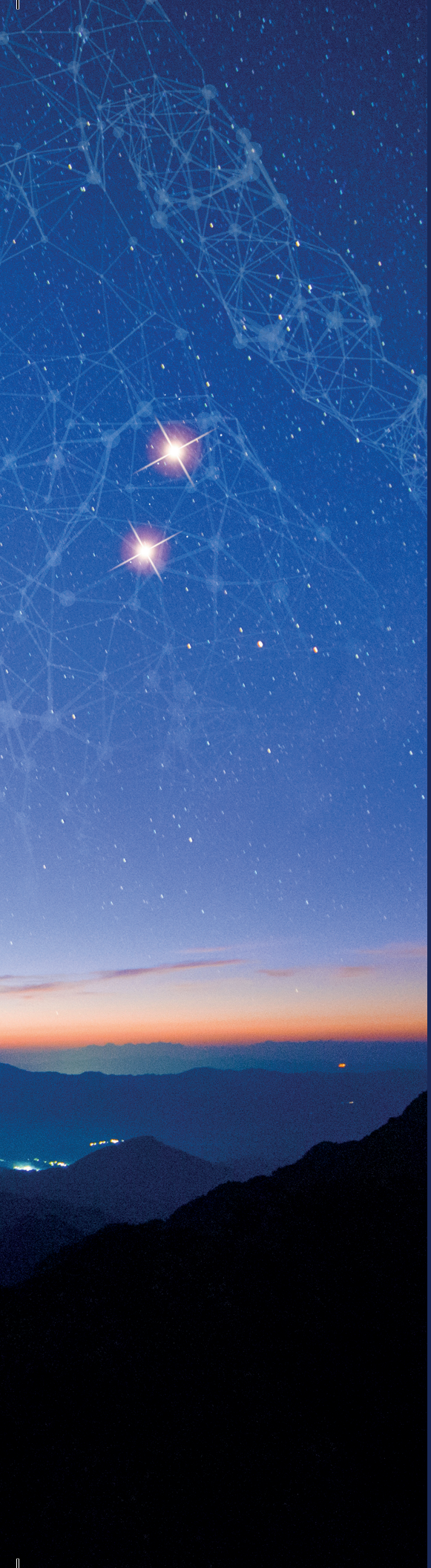
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Gallium Ga 68 gozetotide contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Ensure safe handling to minimize radiation exposure to the patient and health care workers. Advise patients to hydrate before and after administration and to void frequently after administration.

ADVERSE REACTIONS

The safety of gallium Ga 68 gozetotide was evaluated in 960 patients, each receiving one dose of gallium Ga 68 gozetotide. The average injected activity was 188.7 ± 40.7 MBq (5.1 ± 1.1 mCi). No serious adverse reactions were attributed to gallium Ga 68 gozetotide. The most commonly reported adverse reactions were nausea, diarrhea, and dizziness, occurring at a rate of < 1%.

DRUG INTERACTIONS

Androgen deprivation therapy and other therapies targeting the androgen pathway Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, can result in changes in uptake of gallium Ga 68 gozetotide in prostate cancer. The effect of these therapies on performance of gallium Ga 68 gozetotide PET has not been established.

You are encouraged to report suspected adverse reactions of prescription drugs to the FDA.

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ADVERSE REACTIONS

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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 safety of ILLUCCIX has been established based on studies of another formulation of gallium Ga 68 gozetotide in patients with prostate cancer [see Clinical Studies (14)]. Below is a display of the adverse reactions in these studies. The safety of gallium Ga 68 gozetotide was evaluated in 960 patients, each receiving one dose of gallium Ga 68 gozetotide. The average injected activity was 188.7 ± 40.7 MBq (5.1 ± 1.1 mCi). No serious adverse reactions were attributed to gallium Ga 68 gozetotide. The most commonly reported adverse reactions were nausea, diarrhea, and dizziness, occurring at a rate of < 1%.

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USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
ILLUCCIX is not indicated for use in females. There are no available data with gallium Ga 68 gozetotide injection use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. All radiopharmaceuticals, including ILLUCCIX, have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. Animal reproduction studies have not been conducted with gallium Ga 68 gozetotide.

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Risk Summary
ILLUCCIX is not indicated for use in females. There are no data on the presence of gallium Ga 68 gozetotide in human milk, the effect on the breastfed infant, or the effect on milk production.

Pediatric Use

The safety and effectiveness of gallium Ga 68 gozetotide in pediatric patients have not been established.

Geriatric Use

The efficacy of gallium Ga 68 gozetotide PET in geriatric patients with prostate cancer is based on data from two prospective studies [see Clinical Studies (14)]. Most patients in these trials were 65 years of age or older (72%). The efficacy and safety profiles of gallium Ga 68 gozetotide appear similar in younger adult and geriatric patients with prostate cancer, although the number of younger adult patients in the trials was not large enough to allow definitive comparison.

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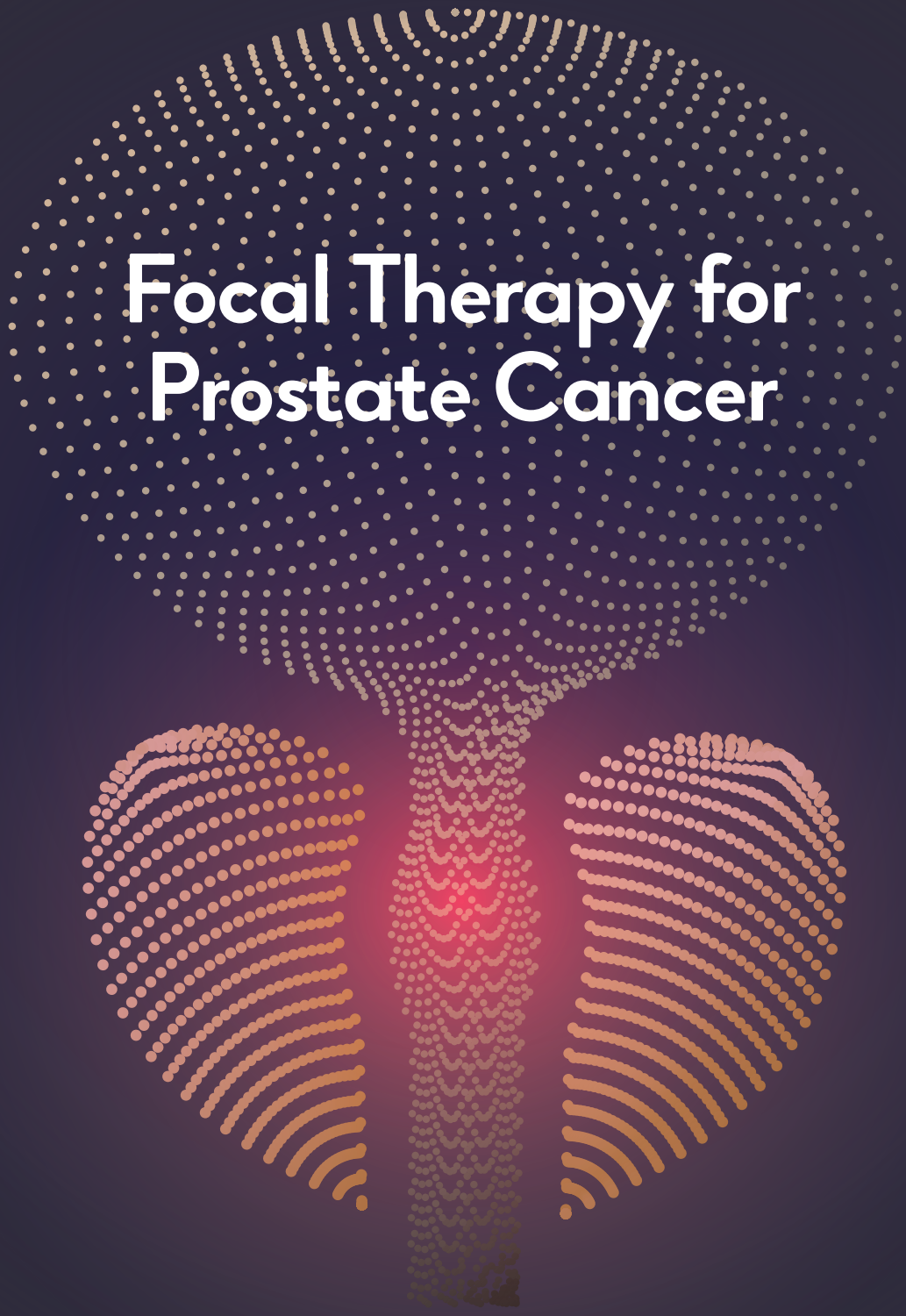
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Focal Therapy for Prostate Cancer



Akhil A. Saji, MD

PROSTATE CANCER IS the second highest malignancy-specific cause of mortality in American males[1] following lung and bronchus cancer, and current data show that the rate of diagnoses of new cases of prostate cancer has increased between 2015 and 2020.[2] According to data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER), in 2022 an estimated 268,500 American men with a median age of 67 years will be diagnosed with new-onset prostate cancer.[2] Moreover, based on SEER-estimated death models, approximately 35,000 patients will experience prostate cancer-related mortality this year.[2] Overall, prostate cancer represents one of the most commonly diagnosed malignancies in the United States (second only to breast cancer in females), affecting the lives of many older American men and the people who care for them.[2]

Therapy for localized prostate cancer consists of radical prostatectomy with pelvic lymph node dissection or radiation therapy,[3] and the complications of localized therapy have been well documented in several studies. For robot-assisted radical prostatectomy (RALP)—the most utilized surgical therapy—postoperative complications include development of bladder neck strictures, lymphocele, obturator nerve injury, ureteral injury, and development of deep vein thrombosis. The primary functional outcomes of concern after RALP are urinary incontinence and erectile dysfunction. Approximately 21% of patients will need to use at least 1 urinary incontinence pad per day following prostatectomy.[4] Postprostatectomy patients with moderate to severe urinary incontinence may require placement of a urethral sling or even an artificial urinary sphincter to achieve continence, adding further surgical morbidity to the procedure. Additionally, an estimated 50% to 70% of patients will have difficulty with erectile function following prostatectomy, although many of these outcomes are center- and high-volume-specific. Sparing of the neurovascular bundle plays a critical role in preserving erectile function.

Radiation therapy also causes complications with which clinicians should be familiar. Specific areas of concern include rectal toxicity and development of fistulas, such as rectourethral fistulas.[4] Although these complications are rare, they can cause significant morbidity. As discussed in the August 2022 issue of *GU Oncology Now,* investigators have explored and utilized techniques for avoiding rectal toxicity, such as hydrogel spacers. Compared with RALP, use of radiation therapy results in much lower urinary incontinence rates for patients with prostate cancer, but rates of lower urinary tract symptoms may increase after brachytherapy.[4] However, outcomes for erectile function remain similar, with around 56% potency in patients after treatment with combined external beam radiation therapy and brachytherapy boost.[5] Reviewing the complications of both primary treatment modalities tells us that patients with localized prostate cancer, and particularly those with lower risk categories of disease, may benefit from active surveillance, or at least delayed treatment1 to avoid the morbidity from treatment. However, some patients may still wish to seek treatment to become cancer free.

Despite the excellent oncologic outcomes reported by both surgical and radiation approaches to localized treatment of patients with prostate cancer, the associated morbidity led to an interest in developing gland-sparing modalities that yield less patient morbidity but a similar level of oncologic control. Most patients with prostate cancer have multifocal disease; however, the index (primary) lesion is thought to be the major contributor to the patient's disease course.[4] This assumption is based mainly on pathologic and genetic studies conducted over the past 2 decades. In a study of 961 prostatectomy specimens, Ohori et al demonstrated that the index lesion contributed to nearly 80% of the tumor burden; moreover, of the 377 specimens that contained extracapsular extension, 84% originated from the index lesion.[4,6] Genetic studies exploring the origins of metastatic prostate cancer resulting in mortality report that in most patients, these tumors are monoclonal in origin.[7] Thus, the basic premise of focal therapy is that by accurately identifying and treating the index prostate cancer lesion, patients can avoid the morbidity of prostatectomy or radiation while achieving similar oncologic benefits.

The basic premise of focal therapy is that by accurately identifying and treating the index prostate cancer lesion, patients can avoid the morbidity of prostatectomy or radiation while achieving similar oncologic benefits.

Patient selection is a critical component of the process of applying focal therapy. Specifically, patients must be willing to undergo surveillance and further treatment, even after the initial ablation procedure, is completed in order to monitor for disease progression or recurrence. The process of identifying the index lesion typically involves utilization of multiparametric prostate magnetic resonance imaging, which, owing to its high sensitivity but low specificity for detecting prostate cancer, must

be used in conjunction with prostate biopsy. Various patterns have been described for focal ablation, including ablation of an entire half of a gland (hemiablation), quadrant ablation, anterior ablation, and even targeted lesion ablation. Various energy sources have also been described in the literature, ranging from cryotherapy, high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE). These energy sources can be applied via transperineal, transrectal, or even transurethral routes, but the location of the index lesion plays a role in selection. For example, peripheral zone lesions are easily accessible via the transrectal approach and may be most amenable to a transrectal ablation; by contrast, an anterior zone lesion is best accessed via the transperineal approach.[4]

Cryoablation is a focal therapy approach that induces cell death via induction of rapid freezing of tissue, resulting in mechanical trauma to cell membranes via formation of intracellular ice crystals. This rapid freezing phase is followed by a cooling phase in which the extracellular compartment becomes depleted and leads to membrane rupture.[8] Although cryoablation has been around since the 1960s, its application to focal therapy for prostate cancer has only occurred within the past 20 years as the availability of new probes the size of a 17-gauge needle have facilitated targeted ablation.[4] The development of urethral warming devices has also resulted in lower urethral morbidity when applying cryoablation to the prostate. HIFU, another common technology, uses an ultrasound transducer to generate thermal energy by focusing several ultrasound beams at a target point, resulting in coagulative necrosis of the target tissue.[8] Finally, IRE uses a nonthermal approach to induce cell death by inducing a direct electric current into the target tissue, which produces nanopores within the cell membranes and causes targeted cellular apoptosis.[9] In renal tumors, IRE has been specifically useful in ablation of tumors near the renal hilum or other critical structures.

The oncologic and functional outcomes of these 3 techniques are worthy of review. Most cryoablation studies use a hemigland ablation technique and stratify patients into low- and intermediate-risk prostate cancer groups.[10] Oncologic control rates in the majority of studies are promising, with rates of biochemical progression-free survival reported between 71% to 98%.[4,10] Furthermore, urinary continence rates are reported at 96% to 100%, and erectile potency rates range from 58% to 100%, suggesting improved performance compared to radiation or prostatectomy. The literature surrounding HIFU also shows similar data. One large prospective study exploring HIFU gland hemiablation involved 111 patients with localized prostate cancer.[11] At 24 months, the investigators preservation of urinary continence showed in 97% of patients and erectile potency in 78%. Oncologic outcomes were also promising, with 89% of patients avoiding radical therapy (reported as the radical treatment-free survival rate) at 24 months.

In summary, continued development and research into focal therapy for men with prostate cancer holds the promise of avoiding overtreatment of patients with lower risk localized disease while offering similar oncologic control and higher rates of functional outcomes.

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Akhil Abraham Saji, MD is a urology resident at New York Medical College / Westchester Medical Center. His interests include urology education and machine learning applications in urologic care. He is a founding and current member of the EMPIRE Urology New York AUA section team.

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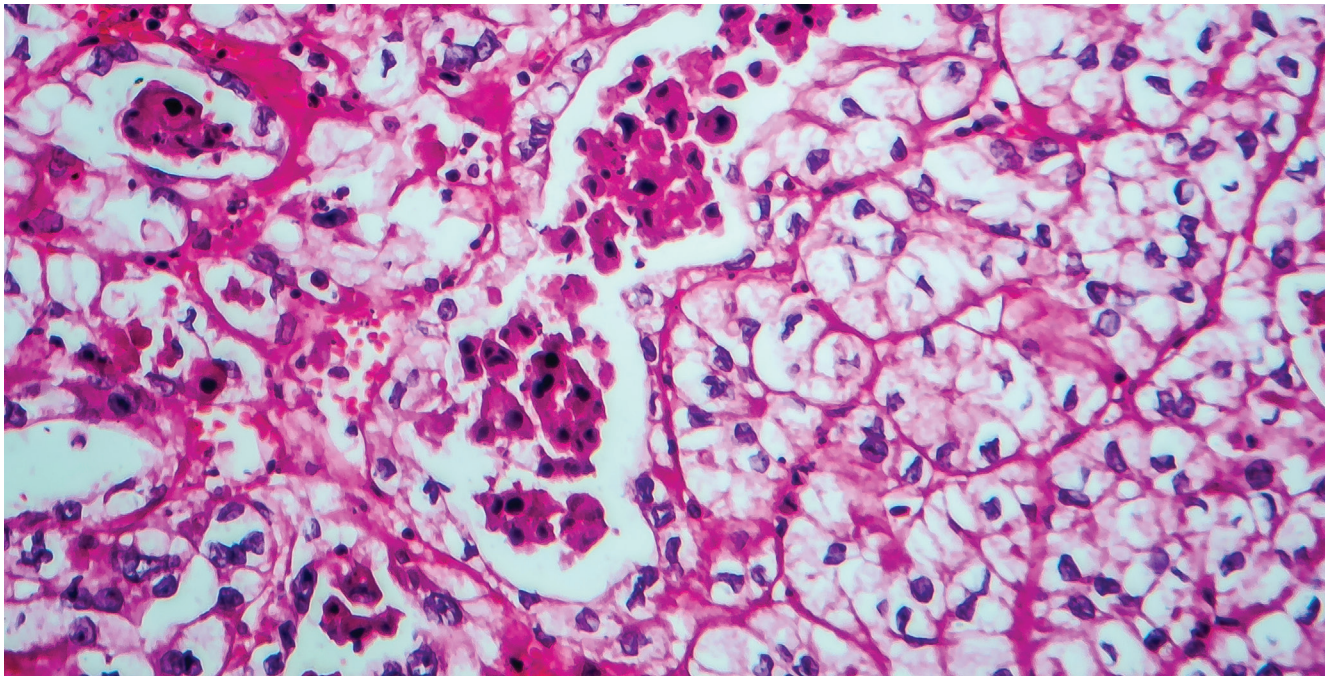
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New ASCO Recommendations for Management of Patients With Metastatic Clear Cell Renal Cell Carcinoma – Expert Discussion

Linda Brookes, MSc

ON JUNE 21, 2022, the American Society for Clinical Oncology (ASCO) released its first ever guideline for the management of metastatic clear cell renal cell carcinoma (ccRCC), intended for all health care practitioners, social workers, patients and caregivers.[1] The guideline explains that its focus on ccRCC, the most common form of kidney cancer, was motivated by the need for a guide to the increasing number of new therapeutic options, with the potential for disease control and extended survival that have emerged over recent years. The guideline was based on a review of English language, peer-reviewed literature published through March 2022, and written by a specially-convened ASCO Guideline Expert Panel.

Co-chair of the guideline panel, **W. Kimryn Rathmell, MD, PhD,** joined **Thomas Powles, MBBS, MD,** (Barts Cancer Centre, London, UK) and **Brian Rini, MD** (Vanderbilt University, Nashville, TN) in a discussion of the new recommendations from US and global viewpoints. Dr Rathmell is the Hugh Jackson Morgan Professor and Chair of Medicine at Vanderbilt University Medical Center (VUMC), and Physician-in-Chief and Professor of Biochemistry for Vanderbilt University Adult Hospital and Clinics.

Dr Rathmell made some general points about the guideline, in particular the omission of words like "mandatory," or,

"required" in support any of its recommendations. "We say, 'ideally,' she stressed. An important feature is the incorporation of the International Metastatic RCC Database Consortium (IMDC) risk classification throughout the guideline.[2] I hope that the IMDC classification will become more widely used in the community as a tool to make clinical judgments," Dr Rathmell said.

The ASCO panel identified six important clinical questions in the management of metastatic ccRCC. The first, how metastatic ccRCC is defined and diagnosed, was the one that instigated the most debate, Dr Rathmell admitted. "It isn't necessarily where all guideline groups start, but we felt that there was a lot of heterogeneity in how people approach diagnosing metastatic renal cell carcinoma," she explained. The guideline recommends comparing tissue in the metastatic site with primary histology using paired box gene 8 (PAX8), carbonic anhydrase IX (CAIX), or other traditional immunohistochemistry-type markers. Radiographic diagnosis may be used secondarily. "We understand that there are a lot of different caveats here, but I think we've all been burned when we've excluded histology in our diagnosis of metastatic RCC," Dr Rathmell said.

Dr Powell expressed concern that the recommendation to biopsy metastatic sites appears to apply to the majority of patients. From a global perspective, many locations, such as community hospitals, will struggle with that, he commented. "Most patients we're seeing who relapse within six months of a T3b tumor are not going to need that biopsy, and spending two months trying to get the tissue could actually be counterproductive," he suggested. Could the guideline recommendation result in fewer patients longer delays in starting systemic therapy, he asked. "If that proves to be true, then we'll need to revise our guidelines," Dr Rathmell responded, "But I also think that we need to be encouraging people to be as rigorous as they can be." There is a need to move away from the RCC NOS (not otherwise specified) diagnosis and be much more precise about the diseases being treated, she added.

The second clinical question covered by the guideline is the role of cytoreductive nephrectomy. "We knew everyone would have an opinion on this," Dr Rathmell admitted, "but we could not say that we no longer do cytoreductive nephrectomy, because that's not true and it's really not in the best interest of patients." So it remains an option in patients who have one IMDC risk factor and who can have most of their tumor burden removed at the time of surgery. Dr Rathmell stressed that "optimally," was used to describe the ASCO recommendation. "I hope that it came through clearly enough that people should at least think about getting cytoreductive nephrectomy, but that we can't advocate for it beyond that subgroup," she said. The guidelines are appropriately cautious, Dr Rini agreed, adding that he believes there is a role for cytoreductive nephrectomy in selected patients.

Question 3, "a big topic," reviews the options for first-line systemic treatment. including vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs), immune checkpoint inhibitors (ICIs), and combinations with anti-programmed death (PD-1) and anti-cytotoxic T-cell lymphocyte-4 (CTLA-4) agents. Knowing how to use those, in what order, and in which patient is complicated, Dr Rathmell noted. "We tried to make a best-case scenario of which type of combination or single agent to use in each IMDC risk group (poor, intermediate, favorable)," she explained.
According to the recommendations, however, some patients, especially those with favorable and intermediate risk, should be offered active surveillance. "We didn't want people to forget that surveillance can buy people a lot of time and good time," Dr Rathmell clarified. Recommended first-line treatment in patients with intermediate or poor risk is combination ICIs, such as ipilimumab plus nivolumab or an ICI plus a VEGFR-TKI. Select patients receiving systemic therapy in the first-line setting, including those with favorable disease, may receive monotherapy with either a VEGFR TKI or an ICI.

Dr Rini noted that the panel "didn't really take a stance on ipilimumab-nivolumab versus ICI-VEGFR TKI." Dr Rathmell explained that the panel had discussed this extensively, but there were no data to support one over the other.

Dr Rini asked about ipilimumab-nivolumab in favorable-risk patients. "They're clearly an immune-responsive subset, he pointed out. Dr Rathmell replied that although this was discussed, the panel did not include it in the guideline because of the lack of data showing which patients would benefit, or whether the additional toxicity associated with that combination warranted recommending that everyone should get it first.

Dr Powell pointed out that there is no clear survival signal for pembrolizumab plus lenvatinib, nivolumab plus cabozantinib, or pembrolizumab plus axitinib in this setting. European groups, particularly payers, are now pushing back strongly now, especially in favorable-risk patients, invoking an immunotherapy 'halo effect,' he said. We may be embarking on a journey that will inevitably involve additional toxicity as well as additional cost, he suggested. "Is it unreasonable to offer them single agent VEGF TKI therapy?" he asked. "There are definitely going to be scenarios where single agent VEGF TKI makes sense," Dr Rathmell agreed. Although the data do not show big differences in survival, some patients have remarkable responses to immunotherapy that are quite durable, she noted.

Dr Powell expressed surprise that the guideline includes interleukin 2 (IL-2) as a first-line option, which he regards as "a chapter from the past." Dr Rathmell acknowledged

that there was a lot of debate about whether to omit it, but because it remains an available therapy, the view was that it needed to be addressed. The recommendation for IL-2 is "weak", she noted, because the panel could not identify a patient base that would likely benefit from it. "We included practical information that the significant toxicity of the regimen has to be weighed in relation to newer immunotherapy. So I think we basically said, it's on the shelf but don't take it," she said.

Dr Rathmell stressed the importance of brain-directed local therapy with radiation, and /or surgery in patients with brain metastases.

The fourth question focuses on second- or later-line systemic therapy. "We did our best to help, but it gets much harder in the second and further line," Dr Rathmell admitted. "The recommendation is basically, do your best, and mostly single agents." Dr Rini pointed out that ongoing trials should provide more clarity about this setting.

Question 5 is about the optimal application of metastasis-directed therapy, The basic question is whether there are patients for whom metastasectomy or ablative type therapies is appropriate, Dr Rathmell explained. "There aren't any strong data for when to do it, but it's something that you can consider," she noted. Despite this, the recommendation for it is "strong."

"We're really talking here about oligometastatic single site resections, and we said that the evidence quality is 'moderate'." Dr Powell was concerned that this recommendation might be interpreted as a call for more of this therapy. Shouldn't we rather be doing clinical trials to generate the data needed, he asked. Dr Rini pointed out that many treatments are adopted into clinical practice without prospective randomized trials, for example, stereotactic radiotherapy. "But we should be doing more trials of metastasis drug therapy to prove whether it's useful or not, and to identify the patients who might benefit," he added.

The sixth and final clinical question covers the treatment of special subsets of metastatic ccRCC, including bone and brain metastases and sarcomatoid carcinomas. Dr Powell and Dr Rini called attention the "strong" recommendation for giving bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors to patients with bone disease, agents they themselves use only sporadically. Dr Rathmell replied that there appeared to be good enough evidence for prevention of skeletal-related events.

Dr Rathmell also stressed the importance of brain-directed local therapy with radiation, and /or surgery in patients with brain metastases. The decision about the type of radiation therapy is left to the individual provider. Dr Powell described this recommendation as a very good addition to the guideline. "I think we need to move away from whole brain and towards stereotactic radiation to the head," he commented.

In ccRCC with sarcomatoid features, "we'd like to have biomarkers and more biologically segmented groups of ccRCC, but right now, we only have sarcomatoid and not sarcomatoid," Dr Rathmell acknowledged.

However there was sufficient evidence to point to ICI-based combination therapy first-line (ipilimumab-nivolumab) or an ICI plus a TKI in sarcomatoid ccRCC, she said. Dr Rini pointed out that supporting data are strongest for ipilimumab-nivolumab, although all the data are retrospective with no central pathology review. Dr Powell predicted more data with immunotherapy will be coming soon.

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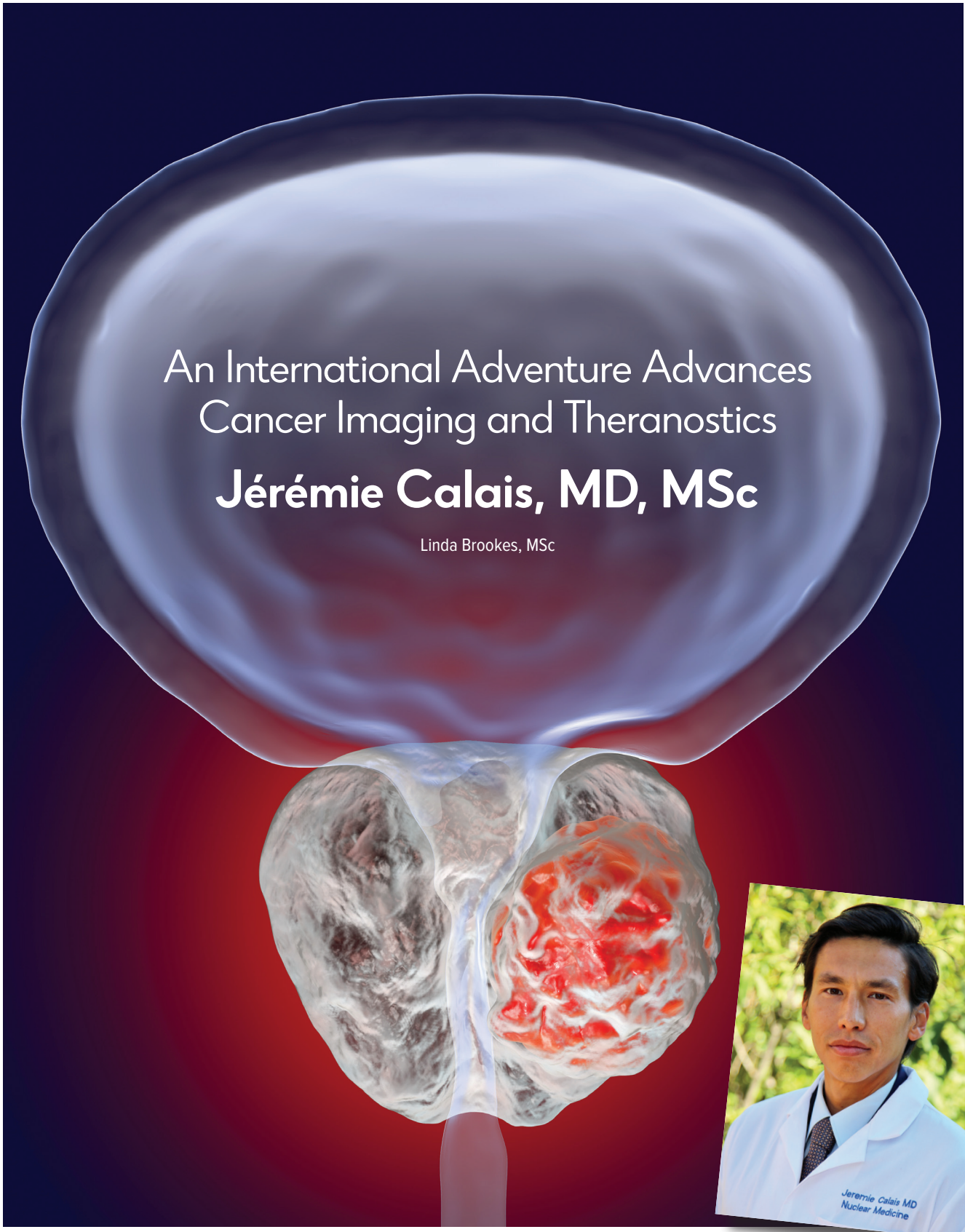


Brian Rini, MD

An International Adventure Advances Cancer Imaging and Theranostics

Jérémie Calais, MD, MSc

Linda Brookes, MSc



DR JÉRÉMIE CALAIS is Director of the Theranostics Program and of the Clinical Research Program in the Ahmanson Translational Theranostics Division and Associate Professor in the Department of Molecular and Medical Pharmacology (DMMP) at the University of California, Los Angeles (UCLA). He leads a clinical research program of nuclear medicine and theranostics, combining radionuclide imaging and therapy. The program has been primarily involved in conducting clinical trials to determine the impact of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging and PSMA radionuclide therapy on care and outcome of patients with prostate cancer. Dr Calais is especially well known for his work on ^{68}Ga-PSMA–11, the first PSMA PET agent to receive regulatory approval for prostate cancer imaging in the US in 2020.[1] Originally developed by the University of Heidelberg, clinical development of ^{68}Ga-PSMA–11 on which approval was based, was carried out by Dr Calais and colleagues at UCLA and researchers at the University of California, San Francisco (UCSF).[2,3]



Left, Dr Jérémie Calais with his wife and children.

Dr Calais joined UCLA from Paris in France in 2016. He admits that when he first arrived in the US, he was not anticipating staying for very long. He was looking forward to spending one or two years living a new adventure abroad and working outside his "comfort zone," he says. That he ended up staying longer than he intended was due to "pure luck and opportunism," he told *GU Oncology Now*, during an interview about his life and career to date. The luck was that he fell in love with the outdoor lifestyle that Santa Monica offered him, and the opportunity was that he was offered to lead exciting professional projects as he arrived right just at the time of the theranostics booming in the US.

Growing up in France, Dr Calais had no family connections with professional medicine, and his early ambition was to just play soccer. "I played at competitive, non-professional level and it was a big part of my life for many years," he recalls. As well as sport, however, he was also good at science, particularly biology, at school. "So when I realized that I needed to do something in my life other than playing soccer, I decided to go for medicine," he says. "At first, he intended to specialize in sports medicine.

In 2003, he started his first year of medical school at Paris Diderot University (now Paris Cité University). "In France you enter medical school straight after high school, much earlier than in the US," he explains. "After the first year there is a ranking exam, the result of which determines whether you can progress to the second year." Only 10-20% of candidates pass this exam, "so anyone can get into the first year of medical school, but to get past that and into the second year is tough," he notes.

It takes much longer to qualify in medicine in France than in the US. Six years are spent at medical school, the last three years in attendance at a hospital attached to the university, which for Dr Calais was the Faculty of Medicine Xavier Bichat (named after Marie François Xavier Bichat, 1771-1802, known as "the father of modern histology"). A medical internship (residency) of 4 years followed at the University of Rouen School of Medicine and at the Henri Becquerel Cancer Center. In 2014, Dr Calais completed his internship and successfully defended his medical thesis (on FDG uptake in PET/CT in non-small cell lung and esophageal cancers treated with radiation therapy). In the same year, he was awarded the *Diplôme d'Etat de docteur en médecine* (DE), and became board certified by the French Society of Nuclear Medicine.

Dr Calais spent two more years in Paris to get more training, choosing to specialize in nuclear oncology. He also obtained an MSc in biomedical imaging from the University of Paris-Sud (now Paris-Saclay), the equivalent to the first 2 years of a PhD in the US. He did not complete his PhD because in 2016, he moved to UCLA, which he calls "the start of a new adventure."

Dr Calais explains why he made the move. "The life of a doctor can be sometimes linear," he says. "After you are done with your training, you usually get a long-term position, either in private practice or public hospital and you follow the track. I was seeking a non-linear pathway and wanted to have a little bit of adventure outside of my 'doctor career' life in France by going abroad before moving to a more long-term position with 10 to 20 years of commitment in one place."

"I wanted to experience something different than Paris, but with a professional project that would still advance my clinical career," Dr Calais adds. He believes that the way physicians are trained in France, "the clinical knowledge we have," makes it easy for them to adapt to working in other countries.

Language ability restricted where he could go, however. "I was able to speak a little English at that time, but no other languages, so it had to be an English-speaking

country." And as he and his wife were both Parisians "with a really strong network and a great quality of life in Paris," they preferred to relocate to another large city. "There were only a few cities my wife would have followed me to in the US: New York, Los Angeles, San Francisco, Chicago, Miami and that's probably it," he admits. "Los Angeles is different from Paris but is still a great city to live in and we're very happy here," he says.

Dr Calais was already in contact with his mentor at UCLA, Johannes Czernin, MD, Chief of the Ahmanson Translational Theranostics Division, Professor of Molecular and Medical Pharmacology/Nuclear Medicine. Dr Czernin himself had relocated from Europe when he moved from the University of Vienna to UCLA in 1989. Dr Calais was appointed assistant professor in his department. "I arrived at the time of the rise of new theranostics techniques, focused mostly on PSMA," Dr Calais recalls. He worked first with colleagues from Germany, Drs Wolfgang Fendler, Ken Herrmann and Matthias Eiber, who eventually had to return home. "Dr Czernin wanted to develop PSMA PET and therapy and our German colleagues were instrumental in starting things up here, based on their expertise from Germany. Then PSMA PET works so well and the technique is so effective that referring physicians were sending us more and more patients and it became quite big very rapidly, so there was a real need for someone to handle all the new work," Dr Calais explains.

Dr Calais was appointed to his current position of director of clinical research program in 2018. He attributes this to "the combination of the opportunity, my being there at the right time, the emergence of this new, practice-changing technology, and my doing a good job at using it, selling it to physicians, and planning."

"Dr Czernin gave me a lot of confidence and, gradually, a lot of projects," he acknowledges. "Things went very well for me. We did about '5000' PSMA PET ^{68}Ga PSMA-11 scans in 4 years and the FDA approval was a whole new adventure. We initiated many clinical trials to answer many clinical questions. " He also worked on ^{177}Lu-PSMA-617 (Pluvicto, Novartis), the first targeted radioligand therapy approved for treatment of PSMA-positive metastatic castration-resistant prostate cancer.[4]

"There are still many clinical questions that we are trying to answer to improve the use of PSMA-targeted imaging and therapy," Dr Calais admits. "What are the best thresholds, what are the best indications, what do you do with that information? Maybe one day we will have the same questions in other diseases with other targets using similar approaches," he suggests. "We're not there yet, and that's exactly why we're doing these studies."

Dr Calais appreciates the way research in the life science environment is conducted in the US. "You benefit from the whole US university resource and financial support and power that you get here," he says. "You get many more initiatives, credits, and resources to be a health care researcher. Innovation is rewarded with money by industry. That is why the US is attractive for researchers, and people come here," he declares.

For the future in his field, Dr Calais hopes to see more applications of artificial intelligence (AI) tools in PET imaging. He is confident that it will further refine the ability to more accurately identify and stage prostate cancer and locate metastases; it will be used as an imaging biomarker to help guide therapy. Dr Calais has been working with PYLARIFY AI™ (Lantheus), the first AI platform approved by the US FDA in 2021.[5] It uses a deep learning algorithm to assist in standardized quantification of prostate cancer images acquired using PSMA PET/CT.

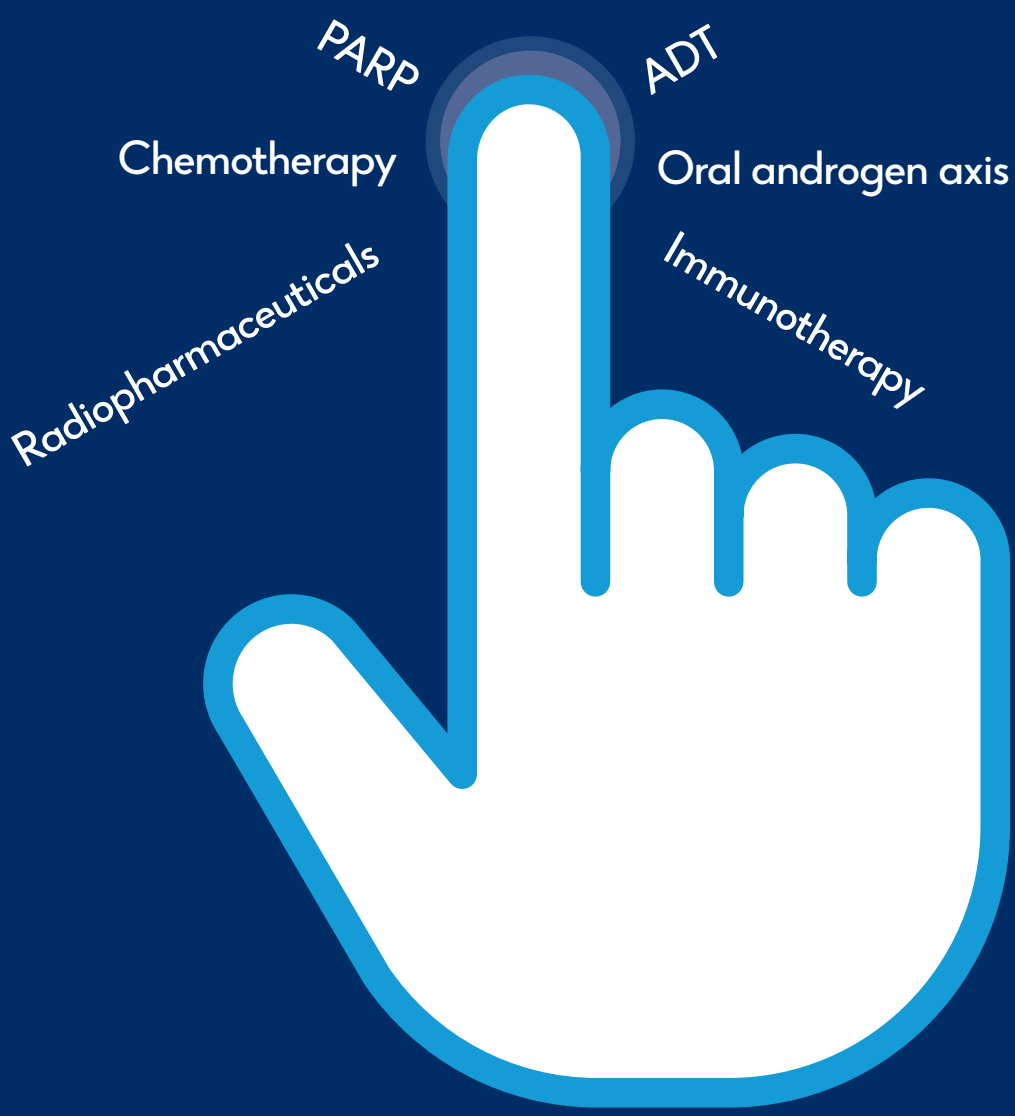
Dr Calais is also looking at the promise of new radionuclide agents for treatment of prostate cancer and neuroendocrine tumors such as additional lutetium PSMA beta-emitters like ^{177}Lu-PNT2002 (^{177}Lu-PSMA-I&T), ^{177}Lu-rhPSMA-7.3, and ^{177}Lu-rhPSMA-10.1. Actinium and lead-labelled alpha-emitting agents including ^{225}Ac-PSMA-617 and ^{212}Pb-NG001 are in development. High-energy, short-range emissions will be able to pinpoint tumor targeting more efficiently, he explains.

As to the future in his personal life, Dr Calais says his family is now settled in Santa Monica, He and his wife now have a Santa Monica-born daughter, in addition to their son. "We love it here; we love the lifestyle, the weather, the outdoors," he declares. "We're always at the beach or hiking, and we love visiting all the national parks in the US." He likes the water, he loves his bike, he does triathlons. And he still plays soccer.

Linda Brookes, MSc is a freelance medical writer/editor based in New York and London.

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CHOOSING THERAPIES IN PROSTATE CANCER

What to Consider When Selecting a Treatment for Patients

A discussion with Catherine Handy Marshall, MD, MPH

MULTIPLE CONSIDERATIONS come into play when physicians evaluate the best oral hormonal treatment for their patients with prostate cancer. The goals and concerns of the individual patient and his lifestyle also factor into these decisions as does the aim to help patients become active partners in their own care and well-being.

In this interview, Catherine Handy Marshall, MD, MPH, serves as our guide to demystifying the complexities of the decision-making process, offering a practical approach that clinicians can apply when thinking through decisions and explain their choices to patients. Dr. Marshall is an assistant professor of oncology in the Department of Oncology, in the Division of Genitourinary Oncology , at the Johns Hopkins University School of Medicine in Baltimore. Her work has been published in such journals as *The New England Journal of Medicine, European Urology, Future Oncology,* and *Prostate Cancer* and Prostatic Diseases. Her research focus is on prostate cancer, genetics, and cardiovascular disease.

Dr David Ambinder: **There are a wide variety of therapies available for treatment of patients with prostate cancer. What are some of that are associated with significant side-effect profiles?**



Catherine H Marshall, MD, MPH

Dr Catherine Marshall: When I talk with my patients about available medications and their options for therapy, I break down the treatments into a few buckets:

1. Androgen-deprivation therapy (ADT) - this includes the therapies that suppress testosterone production by the testes which are the LHRH agonists and antagonists.
2. Oral androgen axis–targeting agents - abiraterone, enzalutamide, darolutamide, apalutamide, and sometimes bicalutamide
3. Chemotherapy—docetaxel and cabazitaxel mostly. Sometimes also carboplatin is included in this list
4. Immunotherapy—sipuleucel-T but also programmed death 1 inhibitors for rare subsets of patients with microsatellite instability-high cancer, or cancer with a high-tumor mutational burden
5. Radiopharmaceuticals-these include radium-223 and now lutetium-177–prostate-specific membrane antigen-617, better known as ^{177}Lu-PSMA
6. Everything else-this includes PARP (poly adenosine diphosphate-ribose polymerase) inhibitors for a subset of patients[1]

Depending on the patient and state of disease, we might be talking about using therapy from 1 or more of those buckets at a given time. For example, as a medical oncologist, almost all patients I see will end up requiring ADT at some point in the treatment of prostate cancer. I discuss the potential side effects, which include injection site reaction and the side effects of testosterone suppression. I also break these side effects down into short term (eg, hot flashes, weight gain) and longer term (eg, bone health, metabolic disease) categories.

What are some of the important considerations when deciding how to counsel a patient about a treatment's side-effect profile before starting them on hormone therapy, i.e, abiraterone?

For the oral androgen axis–targeting agents, I first talk about some of the

side effects they share as a drug category, given that they all target the hormonal pathways in some manner. Typically, these effects include fatigue, hot flashes, and cardiometabolic toxicities. For abiraterone, specifically, I also talk about side effects from prednisone. This can be particularly important for certain patients who need to monitor their glycemic control. Then, I talk more about some of the major unique differences between the drugs. For example, use of abiraterone initially requires regular laboratory monitoring because of the risk of hepatoxicity. Seizures and fatigue are more pronounced with enzalutamide, while rash is more common with apalutamide.

With cytotoxic chemotherapy, I begin by talking about the shared side effects of chemotherapy—primarily docetaxel and cabazitaxel for the treatment of prostate cancer—as well as the logistical differences between receiving chemotherapy compared with one of the oral agents. Then I talk specifically about the individual side effects of treatment, like neurotoxicity and alopecia with docetaxel. The side effects are usually a major reason why we might not choose chemotherapy when there are alternative options available.

Sipuleucel-T side effects are mainly around the time of reinfusion of the cellular product and most often include infusion reactions and chills, fevers, and flu-like symptoms. For patients who need a central venous catheter, I also discuss possible side effects related to the catheter, like infection and clotting. If I'm using PD-1 inhibitors for the subset of patients with MSI-high disease or high tumor mutational burdens, I discuss the spectrum and time course of auto immune toxicities that can arise.

The radiopharmaceutical treatments can cause cytopenias, and in patients who have baseline cytopenias related to chemotherapy or the disease, this is a common reason why I do not prescribe these. 177Lu-PSMA has the unique side effect of dry mouth because of PSMA expression in the salivary glands. Radium-223 also causes more gastrointestinal side effects like nausea and diarrhea.

For the PARP inhibitors, olaparib is approved for use in men with alterations in one of 15 genes in the homologous recombination repair pathway who have disease that has progressed after one oral therapy, while rucaparib is approved for men with BRCA1 or BRCA2 gene alterations who have disease that has progressed after treatment with an oral agent and a taxane. Those differences in the approval are one of the main reasons why I choose one over the other as the side effects of the class are similar. Fatigue, cytopenias, and gastrointestinal toxicities are the most common. Studies with rucaparib also reported elevated transaminases which should be monitored on therapy.

Are there any considerations specifically related to side-effect profiles that you weigh before choosing one type of hormone therapy over another?
Absolutely! Fluid retention and the requirement for concomitant use of prednisone sometimes leads me away from choosing abiraterone. If a patient has seizures or significant fatigue at baseline from ADT, I tend to not select enzalutamide. For patients very worried about side effects, or in whom I'm very worried about side effects, I will sometimes start treatment at a low dose and monitor for side effects for the first 1 to 3 months. If there are no significant side effects, then I will consider titrating up to the recommended dose after the first few months.

Are there any important adjuncts (medications, supplements, holistic approaches) that can help mitigate the side effects of oral hormonal agents?
Exercise! I suggest exercise for all of my patients taking hormonal agents. Exercise really does help offset many of the side effects of the medication, but it can be harder to get patients to begin exercise programs after treatment has started. I still recommend calcium and vitamin D supplements for all of my patients receiving ADT, although that may change in the future after the large trial recently published in *The New England Journal of Medicine* did not find that supplementation lowered the risk of fractures among people without vitamin D deficiency or low bone mass or osteoporosis.

How often do you screen your patients on hormone therapy for side effects? Are there any particular lab tests that should be done routinely?
I see each patient at least once every 3 months. If they have other comorbidities, I may ask them to come in sooner than that—usually about 4 to 6 weeks after starting a new drug. Now that it is easy for some patients to communicate with me through their electronic medical record, I also encourage them to use it to report any new symptoms or to ask questions as they arise. With the expansion of telemedicine during the COVID-19 pandemic, I do some of these visits as telemedicine visits as well.

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https://pubmed.ncbi.nlm.nih.gov/35210863



David Ambinder, MD is a urology resident at New York Medical College / Westchester Medical Center. His interests include surgical education, GU oncology and advancements in technology in urology. A significant portion of his research has been focused on litigation in urology.

Prostate Biopsy Complications and Alternatives

Akhil A. Saji, MD

THE ADVENT OF transrectal (TR) ultrasound resulted in a dramatic shift in the late 1980s as urologists transitioned from finger-directed prostate biopsies to ultrasound (US)-guided biopsies.[1] Initially, biopsies were conducted using a 6-core biopsy template, which was soon expanded to 12 cores in conjunction with patients undergoing routine screening for prostate-specific antigen (PSA).[2] Although mortality from the disease is not common, it is estimated that 35,000 males will experience prostate cancer-related mortality in 2022.[3] Furthermore, approximately 270,000 men are expected to receive a new diagnosis of prostate cancer each year. According to data from 2013, an estimated ~1.3 million diagnostic biopsies are performed in the United States annually to establish these diagnoses.[1,4] In this article, we will discuss the complications of modern prostate biopsy techniques and explore upcoming alternatives for establishing a prostate cancer diagnosis.

Most prostate biopsies conducted are done via the TR route under local or general anesthesia; however, there has been growing interest in utilizing the transperineal (TP) route due to its beneficial impact on rates of infection. A large-scale meta-analysis comparing TR with TP biopsies found equivalent diagnostic yield, rates of gross hematuria, and urinary retention for the 2 modalities.[5] Patients who received TR biopsies were at higher risk for developing systemic inflammatory response syndrome (SIRS) suspicious for systemic infection as well as higher rates of rectal bleeding.[5] By comparison, patients who had TP biopsies had much lower rates of SIRS and minimal rectal bleeding; however, they had significantly higher rates of perineal discomfort and pain.[5]

Multiple steps are often required to prepare patients for a TR prostate biopsy. Although use of an enema for bowel preparation does not affect diagnostic accuracy, the resulting lower stool burden in the rectal vault may assist the urologist in performing a timelier and more accurate biopsy. The American Urological Association (AUA) guidelines recommend antimicrobial prophylaxis prior to TR biopsy using a combination of first-, second-, or third-generation cephalosporin plus aminoglycoside or, alternatively, a fluroquinolone.6 In patients with contraindications for either regimen, use of aztreonam (Cayston®) should be considered.[6] Patients undergoing TR prostate biopsy without general anesthesia commonly receive a local anesthetic through injection of a prostatic block (eg, lidocaine). The most frequent approach involves injecting 5 mL of anesthetic at the junction of the seminal vesicle and the base of the prostate under transrectal ultrasound (TRUS) guidance. Systematic TR prostate biopsy involves obtaining a total of 12 cores; these samples are drawn primarily from the peripheral zone, with some also drawn from the lateral and medial components of the prostate. Most guidelines recommend focusing on the lateral aspects of the prostate as well as the apex to maximize the amount of prostatic peripheral zone that can be sampled.[7] Additional topics of interest include lesion-specific biopsies directed at concerning areas noted on multiparametric prostate MRI (mpMRI) and abnormal nodules detected through digital rectal examination.

There are 2 primary ways in which mpMRI of the prostate is used to detect clinically significant prostate cancer. After the radiologist provides a 3-dimensional map of clinically suspicious lesions graded using the American College of Radiology's PI-RADS® (Prostate Imaging Reporting & Data System®) system, the urologist can perform a targeted biopsy in 1 of 2 ways: In a fusion-based biopsy system (either TR or TP), the fusion magnetic resonance imaging (MRI) image is aligned to the live TRUS images to allow simultaneous tracking of the suspicious lesions. The biopsies can then be performed using a combination of TRUS and MRI guidance. Alternatively, if a fusion system is unavailable, the urologist can perform a "cognitive" biopsy. In this case, the 3-dimensional location of the suspicious lesion on MRI is found on US using cognition, after which it is biopsied. The most commonly utilized fusion systems are UroNav (Philips) and Artemis with ProFuse (innoMedicus).[1] Currently, no significant evidence exists to suggest that MRI/US fusion techniques are superior to cognition-based techniques.[7] Currently, for patients who have not received any prior prostate biopsy, all major guidelines recommend combining use of mpMRI-directed prostate biopsy in conjunction with a systematic prostate biopsy.[7]

What about the TP technique? Apart from the reduced rate of infectious episodes mentioned earlier, other potential benefits include serving as a modality for biopsy in patients without rectal access, or in those suspected to have tumors in the prostatic apex, which may not be easily accessed via the TR route.[1] The diagnostic accuracy of the TP route is also reported to be superior. In a meta-analysis conducted by Tu et al, 315 patients undergoing TR MRI fusion biopsy were compared with 328 patients undergoing TP MRI fusion biopsies. The pooled diagnostic sensitivity was higher for the TP arm (86%) than the TR arm (73%).[8] The primary downsides of the TP approach are logistical. Due to the positioning required (dorsal lithotomy), as well as the uncomfortable nature of placing needles through the perineum, most patients will require some level of anesthetic support.[1]

Despite the many advances in prostate biopsy, there is still tremendous interest in noninvasive testing modalities to establish a diagnosis of prostate cancer.

Despite the many advances in prostate biopsy, including a rapid transition to implementation of TP biopsy as recommended by the most recent urology guidelines,7 there is still tremendous interest in noninvasive testing modalities to establish a diagnosis of prostate cancer. Benefits of noninvasive modalities include the ability to perform active surveillance with less morbidity and less utilization of resources such as hospital visits or operating room time. Additionally, such modalities can be used to monitor disease status (ie, recurrence) or response to treatment. One such modality is liquid prostate biopsy (analyzing body fluids such as urine or blood) employing underlying technology to analyze circulating tumor cells (CTCs), cell-free DNA (cfDNA), circulating RNA, or even extracellular vesicles.[9] The basic concept behind CTCs involves detection of blood-borne cancer cells that are released into the circulation by the primary tumor or metastatic tumors. The primary limitation of CTC technologies is the rarity of such cells within the systemic circulation, with an estimate of ~1 tumor cell per 1 billion cells.9 In contrast to CTCs, cfDNA focuses on detection of nucleic acids released during apoptosis of cancer cells. Many of these DNA strands carry mutational segments specific to the tumor of interest. CTC utilization in the localized prostate cancer setting is relatively uncharacterized primarily owing to the widespread utilization of PSA.[9]

Despite limited data focusing on utility for patients with localized prostate cancer, some interesting projects were presented at the AUA's 2022 annual meeting. A recently available urine-based liquid biopsy tool called miR Sentinel™ (miR Scientific) shows promise. The liquid biopsy uses noncoding RNAs isolated from the urinary exosome of patients thought to have prostate cancer. One presentation at AUA 2022 discussed a series of 763 biopsy-naive patients with prostate cancer undergoing biopsy for diagnosis. When compared to results from miR Sentinel, the liquid biopsy had 92.2% sensitivity and predicted clinically significant prostate cancer in 93% of cases.[10]

Overall, continued research and development into liquid biopsy technologies will likely enable greater access to prostate cancer while simultaneously offering the ability to decrease cost and decrease the morbidity of prostate cancer diagnosis through prostate biopsy.

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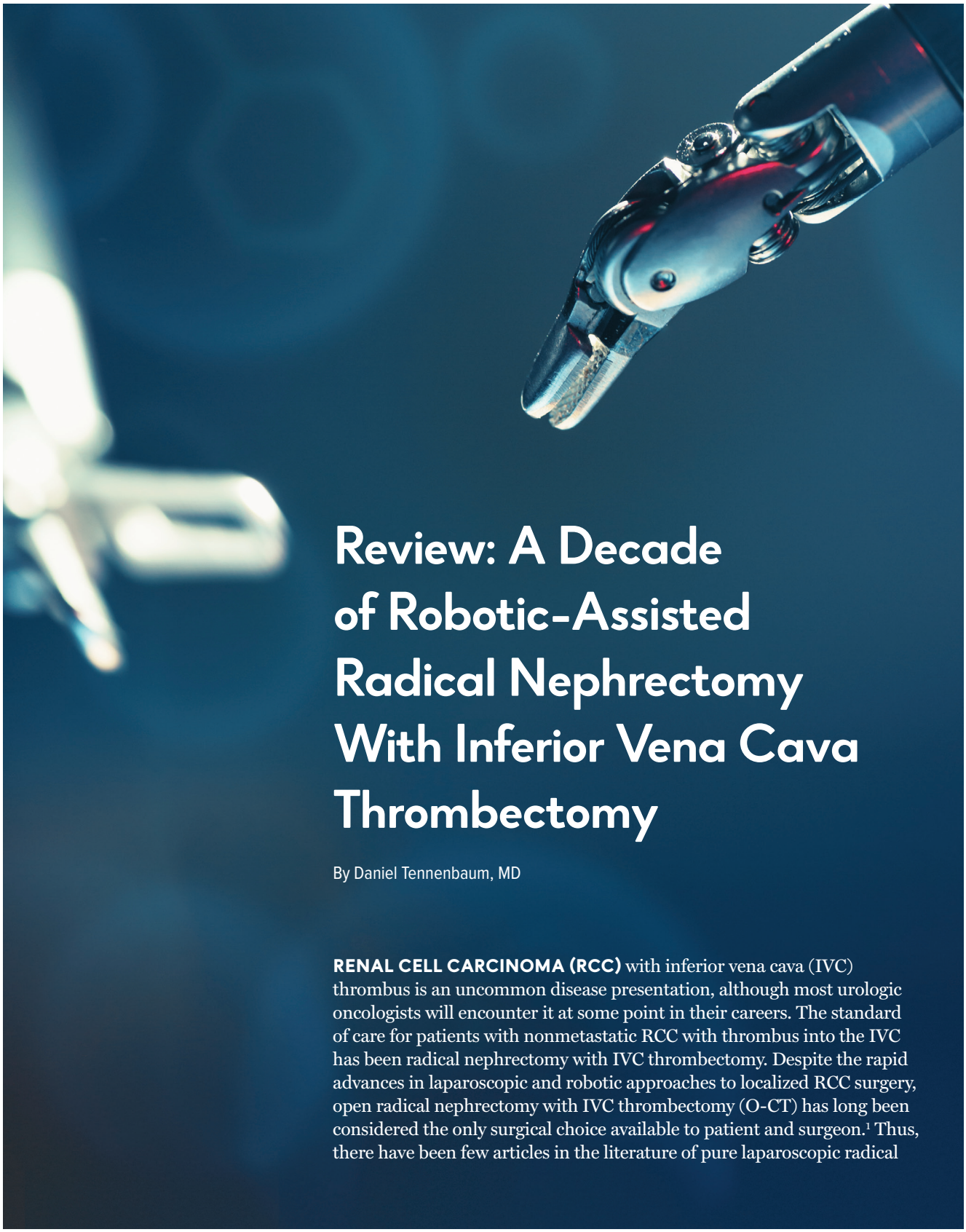
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Review: A Decade of Robotic-Assisted Radical Nephrectomy With Inferior Vena Cava Thrombectomy

By Daniel Tennenbaum, MD

RENAL CELL CARCINOMA (RCC) with inferior vena cava (IVC) thrombus is an uncommon disease presentation, although most urologic oncologists will encounter it at some point in their careers. The standard of care for patients with nonmetastatic RCC with thrombus into the IVC has been radical nephrectomy with IVC thrombectomy. Despite the rapid advances in laparoscopic and robotic approaches to localized RCC surgery, open radical nephrectomy with IVC thrombectomy (O-CT) has long been considered the only surgical choice available to patient and surgeon.[1] Thus, there have been few articles in the literature of pure laparoscopic radical



nephrectomy and IVC thrombectomy, with the first case reported in 2011 by Abaza et al.[2] In the decade since, there continue to be single-institution reports of the feasibility of robot-assisted laparoscopic radical nephrectomy with IVC thrombectomy (R-CT), with limited high-quality evidence such as a randomized multi-institutional study. Therefore, the multi-institutional group headed by Garg et al sought to assess the safety and feasibility of R-CT and provide an accumulated understanding of the first decade of its use in a systematic review published in the *Journal of Urology*.[3]

The authors conducted a retrospective review of appropriate studies in the PubMed database to compare the perioperative outcomes with R-CT and O-CT. They separated their findings into single-arm studies reporting on R-CT (n=21), as well as comparative studies comparing R-CT with O-CT (n=7). Only 4 of the comparative studies evaluated R-CT versus O-CT, while 3 studies compared various robotic techniques.

Of the 21 single-arm studies, only 9 (43%) included a cohort of >10 patients. A total of 329 patients from the single-arm studies were analyzed: 75% had right-sided tumors, of whom 61% had level II tumor thrombi extending into the IVC >2 cm above the renal vein.[4] A level I, tumor thrombus <2 cm above the renal vein occurred was found in ~15% of the patients, while level III tumor thrombi above the hepatic veins but below the diaphragm was documented in 20% of the cohort. Only 2.5% of the R-CT cohort had a level IV tumor thrombus extending above the diaphragm. Notably, 12% of the cohort had metastatic disease at the time of surgery.

Most of the single-arm studies reporting outcomes data described surgery performed by highly experienced robotic surgeons using a multidisciplinary approach. Almost one-third of all patients underwent angioembolization before surgery to try to reduce the tumor burden before starting the planned intervention. The weighted mean operative time for R-CT was 282 minutes. Mean estimated blood loss ranged from 150 to 2000 mL, and 38% of patients required a perioperative blood transfusion. It is worth noting that only 1.2% of cases (n=4) were converted to open surgery. A total of 6 cases (1.8%) reported an intraoperative complication,

including 3 vascular injuries, 2 bowel injuries, and 1 liver laceration. The overall perioperative complication rate was 30%, with a major complication rate (Clavien-Dindo grade rIII) of 8.5%.

In perhaps the most, meaningful analysis of their study, Garg et al identified 4 studies comparing R-CT to O-CT.[5,6,7,8] In these studies, 110 patients underwent R-CT and 936 patients underwent O-CT. No definitive statement could be made about the operative time of R-CT versus O-CT. One study used a matched cohort analysis to match 31 patient pairs by age, ASA score, and tumor characteristics, and found median operative time was significantly shorter for patients undergoing R-CT than O-CT. However, 2 other studies found median operative time for R-CT to be significantly longer than for O-CT, while the fourth study did not demonstrate a significant difference. However, all 4 studies reported significantly less median blood loss and a significantly lower transfusion rate in patients undergoing R-CT compared with O-CT. Notably, the overall complication rate was significantly lower in the R-CT group than in the O-CT group, but there was no significant difference between the groups regarding serious complications (Clavien-Dindo grade rIII). There also was no difference identified between the groups in 30-day mortality, unplanned readmission, progression-free survival, or overall survival. The median follow-up time was 27 months for patients receiving R-CT and 44.8 months for those receiving O-CT.

At more than 10 years since the first reports on R-CT, the findings of Garg et al help provide a contemporary understanding of the safety and feasibility of using R-CT, compared with standard O-CT, in patients with RCC and tumor extension into the IVC. Their systematic analysis of the relevant literature establishes that R-CT's safety and perioperative outcomes are acceptable compared with O-CT. Moreover, some aspects of R-CT are potentially safer, with patients experiencing significantly less blood loss after robot-assisted versus open surgery. However, the authors acknowledged the frequent use of perioperative angioembolization with R-CT to help decompress venous collaterals and assist in robotic efficacy compared with the rare (given a lack of evidence) use of the procedure for O-CT as a primary difference between the approaches. They also noted that despite using the best available evidence in the current literature, the data collected may be skewed by selection bias, as well as by the varied methodologies for of reporting complications. While they commented that their promising data appear to support the use of R-CT in patients who have RCC with an IVC tumor thrombus, a prospective randomized clinical trial is needed make a thorough assessment of the 2 procedures.



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Daniel Tennenbaum is a urology resident at Maimonides Medical Center in Brooklyn, NY. His interests include surgical education and GU oncology with a focus on pediatric malignancies.





Review:

Association of Family History of Cancer With Clinical and Pathological Outcomes for Prostate Cancer Patients on Active Surveillance

David Ambinder

SHOULD A FAMILY HISTORY of prostate cancer influence consideration of a patient's candidacy for active surveillance? Researchers at Memorial Sloan Kettering Cancer Center in New York attempted to answer this question in their retrospective investigation of patients in a large active surveillance database.[1] Their goal was to examine the association between a family history of prostate cancer, or other cancers with disease progression or adverse pathology in patients whose prostate cancer was managed through active surveillance.

Despite the documented association between a family history of prostate cancer and the risk of developing the disease, there are fewer data available for prostate cancer compared with other well-known hereditary syndromes. In recent years, however, emerging genetic data—including data on the *BRCA2* germline mutation that is associated with development of earlier-onset and more aggressive prostate cancer[2,3]—have shown a correlation between family history and worse pathological and oncologic outcomes.[4] The authors noted a 2019 study that found the presence of a *BRCA1* or *BRCA2* mutation was associated with upstaging in patients on active surveillance protocols[5] and a study published in early 2022 that found other germline variants associated with prostate cancer were positively correlated with risk for conversion of patients on active surveillance to treatment with definitive therapies.[6]

Although current recommendations differ slightly in their definitions of patient populations most likely to benefit from testing, they agree that testing typically benefits the patient with a family history of disease or high-risk disease stage. However, identifying family history criteria for germline testing may be important for patients with low-risk disease or on active surveillance.

Patients included in the study were in Gleason grade group 1 or 2 over a 20-year period from 2000 to 2019. Family history of cancer and family history of prostate cancer were defined by criteria from the 2019 National Comprehensive Cancer Network® (NCCN®) guidelines for prostate cancer and other commonly used guidelines. Family history of prostate cancer was self-reported and defined as r1 first-degree relative with prostate cancer or r2 first- or second-degree relatives with prostate cancer. Family history of cancer was also defined by the NCCN guidelines as r3 family members on the same side of the family diagnosed with melanoma or bile duct, breast, colorectal, endometrial, gastric, kidney, ovarian, pancreatic, prostate, small bowel, or urothelial cancer.

The authors considered that ascertainment bias may be introduced when patients have a family history of cancer or prostate cancer. Therefore, part of their analysis was designed to evaluate if patients in these populations underwent more surveillance while on active surveillance, compared with those who had no family history. They focused on whether a strong family history of cancer or prostate cancer was associated with time to progression (ie, upgrading Gleason grade group on biopsy) while on active surveillance. Patients who initiated surgical, radiation-based, focal, or chemotherapy/hormonal therapy without having shown progression on biopsy were censored on the date of commencing treatment.

After eligibility and exclusion criteria were met, 3211 patients on active surveillance were included in the study: of these 21% (n=669) met the criteria for a family history of prostate cancer, 1.1% (n=34) had a family history of other cancer, and 3% (n=95) fit the criteria for a family history of cancer and prostate cancer. A total of 23.5% of patients progressed on active surveillance. The authors found that patients with a family history of cancer or prostate cancer were not more frequently followed while on active surveillance and did not undergo a statistically significant increase in the frequency of prostate biopsy or magnetic resonance imaging (MRI) compared to patients with no family history.

The authors reported that there was a statistically significant association between a strong family history of prostate cancer and risk of progression on active surveillance (hazard ratio, 1.31; 95% CI, 1.11-1.55; P=0.002). This was not true for patients with a family history of other cancer or patients with a family history of both cancer and prostate cancer. After adjusting for age, Gleason grade group, and prostate-specific antigen level at the time of diagnosis, patients with a family history of prostate cancer had a 48% risk of progression over 10 years on active surveillance (95% CI, 42-53) compared to a 39% risk for patients with no family history of cancer or prostate cancer (95% CI, 36-42). In patients who had undergone a radical prostatectomy, a family history of cancer or prostate cancer was not associated with a higher risk for adverse pathology.

In their discussion, the authors stated that they found a slight statistically significant increase in the risk of progression for patients on active surveillance who had a family history of prostate cancer. However, they cautioned that, given the small difference between the study groups and the wide confidence intervals in their findings, the clinical importance of these results remains unclear. They also noted that while having a family history of cancer or prostate cancer was not associated with undergoing more frequent MRI study or more frequent biopsies, they did not assess whether patients were more likely to undergo surgical treatment. Their findings of no association between family history of prostate cancer and pathological upgrading or adverse pathology are consistent with previous studies,[7] as are their similar findings regarding patients with a family history of other cancer.[8]

Based on their results, the authors suggest that "patients with a family history of cancer per the authoritative guidelines may be suitable for active surveillance due to the low risk of progression to curative treatment and adverse pathology on definitive radical prostatectomy…in the absence of a known genetically defined hereditary cancer syndrome, family history of prostate cancer and or cancer should not be used as a sole trigger to preclude patients with low risk disease to active surveillance protocols." There remains a significant need, however, for further research evaluating the association of germline mutations with disease outcome in patients treated with active surveillance.

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A Prospective Randomized Trial Comparing the Outcomes of Open Vs Laparoscopic Partial Nephrectomy

David Ambinder, MD

IS LAPAROSCOPIC SURGERY equivalent to open surgery when it comes to partial nephrectomies? According to a recent study published in *The Journal of Urology,* it may even be superior in certain respects.[1] The use of partial nephrectomy has increased largely because it has been shown to reduce the risk of developing kidney failure, cardiovascular disease, and mortality while having equivalent oncologic outcomes and impact on quality of life when compared to radical nephrectomy.[2] Tumor characteristics, including size and location within the kidney, largely determine whether the disease would be best managed with a partial nephrectomy instead of a radical nephrectomy. Minimally invasive approaches, including laparoscopic/robotic surgery are also becoming more frequently utilized, although there is little high-level evidence to support their use. The authors of the article conducted a prospective, randomized study design at a single institution to compare the complications and oncologic/functional outcomes of open and laparoscopic partial nephrectomy.

Among the inclusion criteria for patients enrolled into the study were a localized single renal mass <7 cm with no evidence of nodal or distant metastasis and evaluation by a urologist to determine the appropriateness of undergoing a partial nephrectomy. Exclusion criteria were based on kidney function, previous renal masses, contraindication for surgical extirpation, other kidney conditions (such as horseshoe kidney), history of nephrolithiasis, or an ectopic kidney. Patients were randomized and underwent an open or a laparoscopic partial nephrectomy over approximately 8 years, between 2012 and 2020, at a single institution with 4 experienced surgeons.

The authors describe that open partial nephrectomy was performed via a subcostal incision while laparoscopic partial nephrectomy was performed via a transperitoneal approach. In both the open and laparoscopic cohorts, the choice to use vascular clamping, ureteral stent placement, or application of glue was based on surgeon preference.

The researchers accounted for multiple variables, including preoperative demographics and tumor characteristics; operative and postoperative data, including perioperative and postoperative complications; postoperative kidney function; and oncologic outcomes. The primary endpoint was the incidence of postoperative surgical complications. Secondary outcomes included oncologic and functional outcomes at 3 and 12 months after surgery.

After determination of patient eligibility for partial nephrectomy, 84 patients were randomized to the laparoscopic arm and 96 patients were randomized to the open arm. Patient characteristics in the 2 cohorts were similar regarding age, body mass index, sex, comorbidities, baseline kidney function, preoperative EDTA function, history of previous abdominal surgeries, tumor size and R.E.N.A.L. nephrometry score (R=radius of the tumor; E=exophytic/endophytic properties; N=nearness of tumor's deepest portion to the collecting system or sinus; A=anterior/posterior ; L=location). Importantly, 79 (94%) patients randomized to the laparoscopic arm underwent transperitoneal laparoscopic surgery while 1 underwent retroperitoneoscopy and 4 underwent open surgery (3 subcostal and 1 lumbotomy). Of the patients randomized to the open partial nephrectomy arm, 77 (80%) underwent the study standard subcostal approach while 16 underwent an open lumbotomy approach and 3 underwent a laparoscopic transperitoneal approach. The intention-to-treat analysis during the perioperative period found no differences between the arms in terms of time, bleeding, or intraoperative complications. No difference in ischemia time was found when renal hilum clamping was used, and there was no difference in the incidence of surgical complications, need for blood transfusion, or the length of hospital stay (3 days regardless of approach). However, during their post-crossover analysis, the authors found a significant difference in blood loss (317 vs 530 mL) and

need for blood transfusion (0% vs 6.2%) that favored the laparoscopic over the open approach.

A total of 22.6% of patients in the laparoscopic cohort developed a Clavien-Dindo grade 2 or higher complication compared to 13.5% in the open partial nephrectomy cohort (P=0.1). The incidence of abdominal wall complications, including incisional hernia, abdominal wall bulging, seroma, keloid, surgical site infection, or abdominal pain necessitating an emergency room visit was significantly better in the patients in the laparoscopic cohort with the open cohort (13.1% vs 31.2%; P=0.004).

In terms of adverse events, the authors noted 1 death reported in the laparoscopic cohort after the patient presented with a urinary fistula. The patient was treated with a ureteral stent but developed a neurologic condition and subsequent sepsis and death. In the open cohort, 16 patients developed abdominal muscle atrophy with symptomatic incision bulging; 5 patients developed a urinary leak fistula, which was managed by urinary diversion, and 1 patient required a radical nephrectomy. Additionally, 3 patients developed massive hematuria owing to intrarenal pseudoaneurysms; 1 of these patients had spontaneous resolution while the other 2 required intravascular embolization.

A secondary analysis of this study will be done to assess whether volume of residual renal parenchyma has an impact on glomerular filtration rate.

At the 12-month follow-up there was consistently greater loss of renal function and higher incidence of worsening chronic kidney disease (CKD) classification among patients in the open cohort compared with the laparoscopic cohort. Regarding oncologic outcomes in the laparoscopic versus open cohorts, median tumor size (3.3 vs 3.7 cm), histological subtype, and rates of positive surgical margins (8.3% vs 6.2%) were not significantly different between the groups, and at the 4-year (48 months) follow-up, the rates of recurrence were similar.

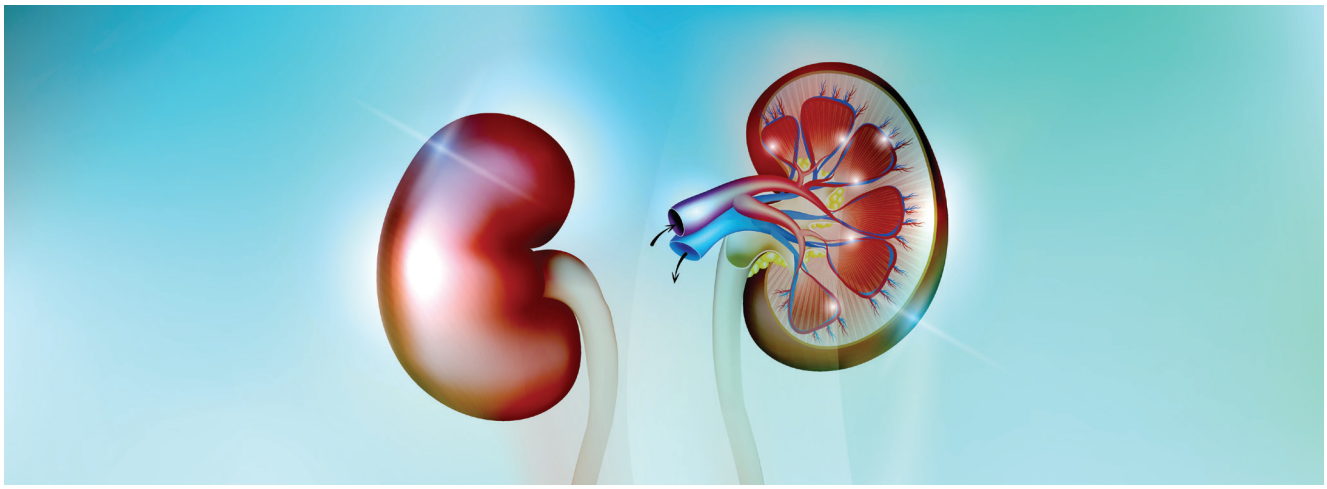
The authors began their discussion by acknowledging that "when the study was designed, robotic surgery was not yet performed in our institution." Furthermore, study enrollment was cut short because of the COVID-19 pandemic. However, this remains an important prospective randomized trial that is consistent with results reported in the literature. The authors note that their per-protocol analysis finding of significantly greater blood loss and need for transfusion in the open versus laparoscopic cohort is consistent with a meta-analysis conducted several years ago that showed less bleeding and shorter hospitalization stays for patients undergoing laparoscopic compared with open partial nephrectomy.[3] However, they acknowledge that data on length of stay are based on hospital-specific protocols regardless of approach and thus are likely not meaningful for analysis.

In regard to the greater decline in renal function and worse CKD classification in the open versus laparoscopic cohort at 12 months, the authors note that a 2010 study found ischemia time to be an important predictor of preserved renal function.[4] However, this finding was called into question in 2019, when Ebbing et al found that ischemia time was an independent risk factor for acute glomerular insufficiency but had no impact on long-term renal function.[5] More recently, preserving renal parenchyma was shown to be associated with preserved renal function.[6] This is consistent with the results of the current study, which found that although patients in the laparoscopic cohort had longer ischemia times, they did not have poorer renal function and in fact had preserved renal function. The authors mention that a secondary analysis of this study will be done to assess whether volume of residual renal parenchyma has an impact on glomerular filtration rate.

The authors concluded that while the open and laparoscopic approaches to a partial nephrectomy showed similar rates of surgical complications and oncologic outcomes, the open approach was associated with higher rates of abdominal wall complications and worse, preservation of renal function.

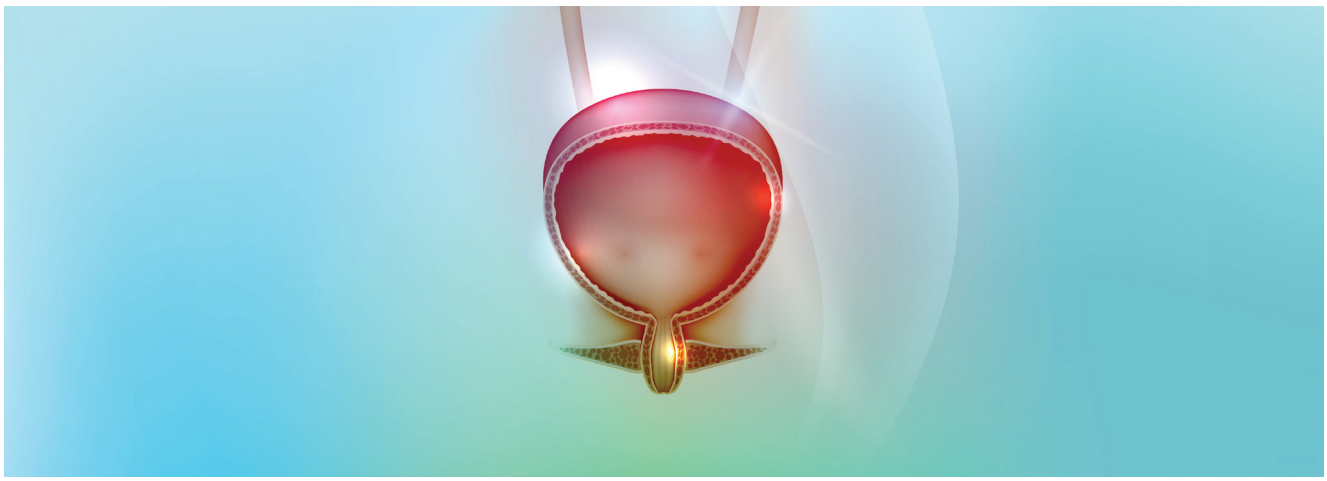
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Health Disparities in Bladder and Kidney Cancer Care

Akhil A. Saji, MD



EQUITABLE ACCESS to cancer care remains a persistent problem in the United States. The National Institutes of Health (NIH) defines differences in health outcomes as measured by incidence, prevalence, mortality, or disease burden variation between population subgroups as health disparities.[1] Among the varied American racial and ethnic groups, African Americans and Hispanics tend to have overall higher mortality rates from cancers compared to their White (non-Hispanic) counterparts.[2] More specifically, patients of Hispanic descent tend to have higher rates of stomach, liver, and cervical cancer, whereas African American patients have a 10% higher incidence rate of cancer, overall, compared to Whites.[2] Moreover, according to the 2019 US cancer statistics, African American patients have a higher rate of cancer-related mortality compared to all other ethnic subgroups (166.3 deaths per 100,000 people).[3] The closest similar results are experienced by Whites, who have a lower rate of 147.1 deaths per 100,000 people, while comprising a much larger proportion of the population.

This disparity between African Americans and Whites is most prominent in prostate cancer, with African Americans having a nearly 2- to 3-fold greater rate of cancer-related mortality than all other ethnic subgroups.[3] One interesting observation, however, is that despite the drastic difference in prostate cancer mortality, Whites continue to have



higher rates of bladder cancer and kidney cancer mortality compared with all minority ethnic groups.[3] In terms of genitourinary cancer, the only exception to these trends is testis cancer, where Hispanic males have a higher rate of mortality compared with all other ethnic groups.[3]

Apart from race and ethnicity, patients in lower socioeconomic classes have been shown to experience higher rates of cancer mortality, overall, compared with the wider population.[2] This finding has been attributed to lack of equitable access to medical care in both preventive and treatment settings.[2] This inequity includes screening for cancer, treatment of eventual diagnoses, and continued follow-up and surveillance to monitor for outcomes. In male patients, 3 of the top 10 cancers related to cancer-related mortality in the overall population are genitourinary (prostate, bladder, and kidney).[2] This highlights the extreme importance of further research into health disparities in urologic cancer care.

Similar to last month, in this article we highlight key recent publications in *Urology* (focused on diversity, equity, and inclusion, and specifically related to both kidney and bladder cancers. Herein, we highlight 2 important articles exploring disparities in kidney and bladder cancer care in the United States.

Kidney Cancer

According to the latest data from the Centers for Disease Control and Prevention (CDC), in 2019 >68,000 patients were diagnosed with kidney cancer and >14,000 experienced kidney cancer–related mortality.[3] In 2022, the estimated rate of new diagnoses is expected to rise to nearly 79,000 patients, with a similar proportion experiencing cancer-related mortality. In the United States, kidney cancer is the eighth most diagnosed malignancy. Yet, overall, despite a 0.6% year-over-year increase in diagnoses, mortality rates have been declining at a rate of 1.6% annually, suggesting that earlier diagnosis may be crucial to preventing cancer-related mortality.[4]

Meagher et al explored cancer-specific and overall survival (OS) outcomes for African American patients diagnosed with renal cell carcinoma (RCC).[5] Among several important findings, the authors noted an increasing uneven incidence of the disease, with African Americans receiving a greater percentage of RCC diagnoses compared with other ethnic groups. Despite this, they noted that African Americans often receive diagnoses of lower oncologic potential compared with people in other ethnic groups; however, when compared with age-and- stage-matched subgroups, they experience higher rates of cancer-related mortality.[5,6]

Utilizing the INMARC (International Marker Consortium for Renal Cancer) database, Meagher et al analyzed patients undergoing partial or radical nephrectomy from January 2000 to June 2019 with the goal to evaluate all-cause mortality, OS, and certain secondary markers, including cancer-specific mortality and recurrence-free survival. The database contained a total of 3893 patients, with nearly 14.5% identified as ethnic African Americans. Several key demographic findings were of interest. The authors explained that African American patients were younger at time of surgery and had higher body mass indices compared to those in other cohorts. This group also had higher rates of comorbidities, including diabetes mellitus and coronary artery disease.

Apart from race and ethnicity, patients in lower socioeconomic classes have been shown to experience higher rates of cancer mortality, overall, compared with the wider population.

Regarding surgical outcomes, African American patients received radical nephrectomy more frequently (68.4%) while also having lower rates of clear cell histology on final pathology compared with other ethnic groups. Another finding of interest was lower rates of recurrence in the African American cohort compared with the population overall; however, the authors also identified that for those African Americans who did experience recurrence, the time to mortality was shorter. In further analyses, they also identified a difference in 5-year cancer-specific survival for African American patients with stage 3 and stage 4 disease. They suggest that worse outcomes in these patients

may be reflective of lack of access to advanced oncologic care. Overall, despite the retrospective design, the study provided much needed insight into care disparities in RCC among American ethnic groups.

Bladder Cancer

The 2019 US Cancer Statistics from the CDC reported >75,000 new diagnoses of bladder cancer resulting in nearly 16,800 bladder cancer-related deaths.[3] With these numbers in mind, in 2022, an estimated r81,000 patients are expected to be newly diagnosed with bladder cancer, leading to >17,100 estimated deaths.4 Compared with kidney cancer, bladder cancer is an even more frequently diagnosed malignancy, ranked as sixth of the top 10 malignancies most commonly diagnosed.

In another key study, Knorr et al examined socioeconomic disadvantages following radical cystectomy. The authors explain that impact of medical risk factors, including comorbidities and their effect on radical cystectomy outcomes, has been well documented and studied. An area that remains underexplored is the effect of socioeconomics on patient outcomes after radical cystectomy. The authors employed the Area Deprivation Index (ADI), which is calculated using a variety of variables obtained from US Census data (eg, income, education, employment status), and sought to determine the relationship between ADI and patient outcomes. Primary outcomes for the study included complications at 30 and 90 days, 90-day mortality, and OS. In their single-center study of prospectively collected data, the authors identified 906 patients who were eligible for inclusion in the analysis.



Most patients had appreciable levels of follow-up care, with a median follow-up of 48 months for the entire cohort. The authors reported that after accounting for the ADI for all patients, higher ADI scores (indicative of higher inequality) were associated with Black race, smoking history, and other factors such as younger age. In terms of oncologic outcomes, higher ADI scores were associated with higher rates of muscle-invasive disease, node-positive disease, and presence of variant histology. In terms of complications, the authors identified that higher ADI scores were associated with higher rates of 30-day and 90-day mortality; however, complication rates were similar between all ADI quartiles. By contrast, OS, another key indicator of patients with muscle-invasive bladder cancer undergoing radical cystectomy, was noted to decline substantially between ADI quartiles. For example, patients with the lowest ADI scores—indicative of lower levels of sociodemographic disparity—had the highest median OS, 8.25 years, compared with just 4.17 years in those in the quartile with higher levels of disparity. In summary, ADI was shown to be predictive of higher rates of worse cancer-specific outcomes as well as mortality. The authors advocate for using ADI as a metric when conducting postdischarge counseling.

These reports and more highlight how tumor biology is just one component of the multifaceted topic that is cancer care. Issues such as access to care and socioeconomics can significantly affect patient outcomes and should be investigated further.

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