ESMO22: Updated Results from the Phase 3 PROpel Trial p18

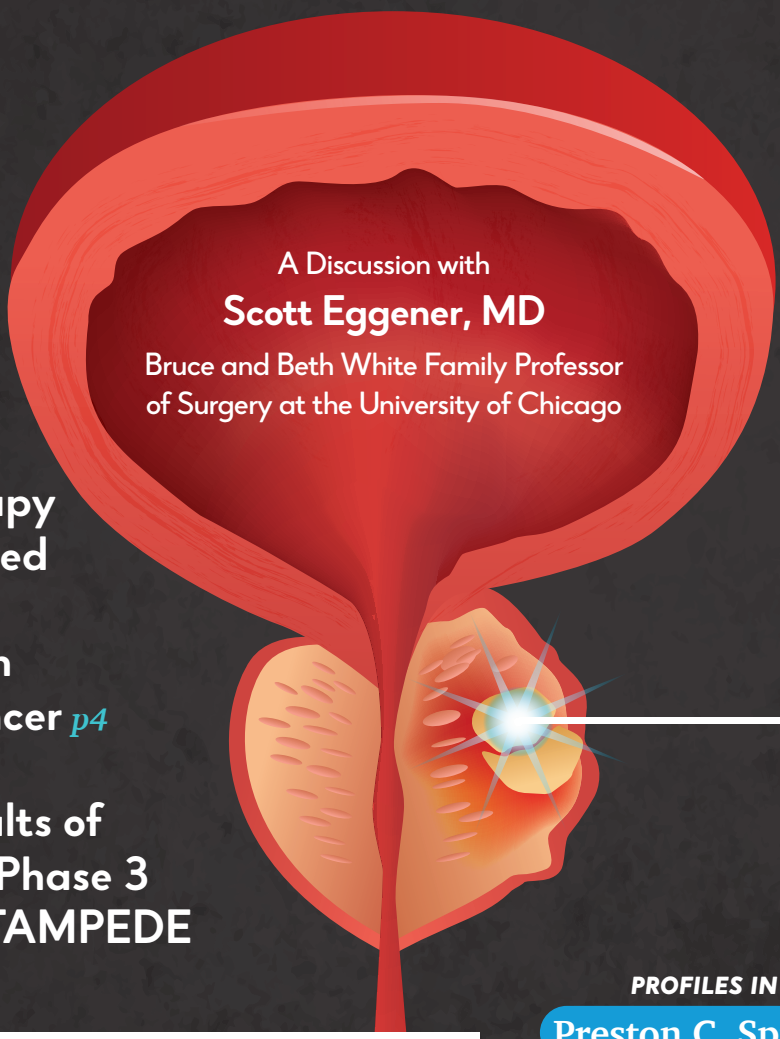
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FOCAL THERAPY:

How it Started, Where We Are Now, Where We Are Going



A Discussion with

Scott Eggener, MD

Bruce and Beth White Family Professor of Surgery at the University of Chicago

ALSO...

Immunotherapy and Cell-Based Therapies for Patients With Prostate Cancer *p4*

Survival Results of Randomized Phase 3 Trials from STAMPEDE Protocol *p20*

PROFILES IN GU ONCOLOGY

Preston C. Sprenkle, MD



Dr Preston Sprenkle describes how his career path led to Yale, his practice in the surgical management of prostate cancer, research into new technology, and his commitment to patient education. *p9*

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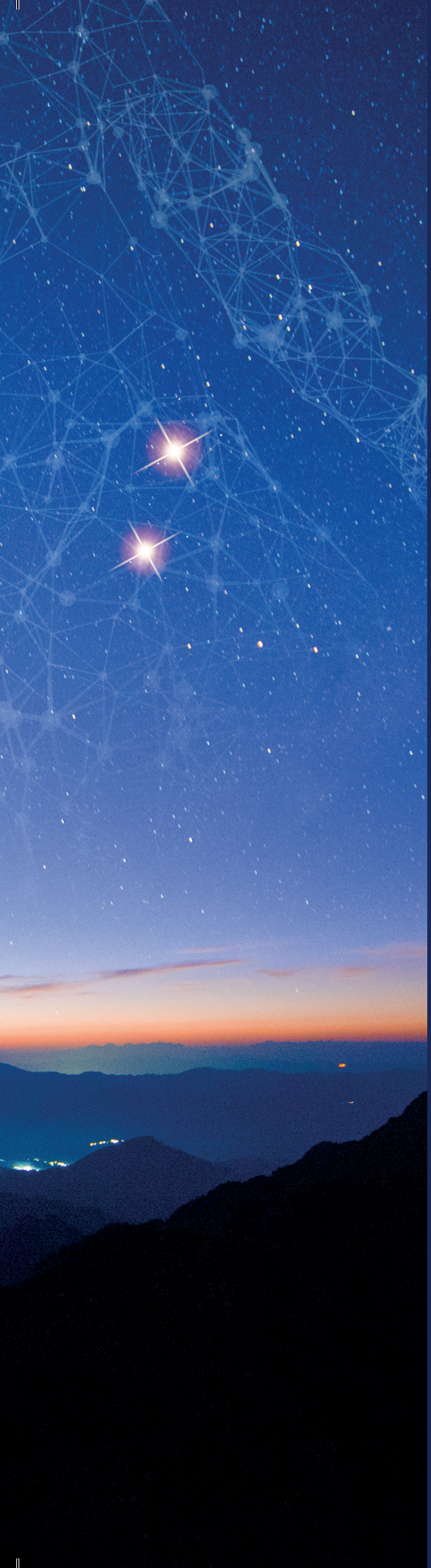
Illuccix® for the preparation of ^{68}Ga-PSMA-11 is poised to expand the potential of PSMA PET imaging and help guide more informed management decisions in prostate cancer.[1-4]



References: 1. Illuccix (kit for the preparation of gallium Ga 68 gozetotide injection) prescribing information. **2.** Massat MB. Nuclear medicine prepares for greater 68Ga demand. *Appl Radiol.* 2021;50(2):30-31. https://appliedradiology.com/articles/nuclear-medicine-prepares-for-greater-ga-68-demand. Accessed July 13, 2021. 3. Velikyan I. 68Ga-based radiopharmaceuticals: production and application relationship. *Molecules.* 2015;20(7):12913-12943. 4. ARTMS and Telix Pharmaceuticals announce successful production of PSMA-11 with cyclotron produced 68Ga from a solid target [news release]. Telix Pharmaceuticals; January 12, 2021. https://telixpharma.com/news-media/artms-and-telix-pharmaceuticals-announce-successful-production-of-68ga-psma-11-with-cyclotron-produced-68ga-from-a-solid-target/.

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Risk for Misdiagnosis
Image interpretation errors can occur with gallium Ga 68 gozetotide PET. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer. The performance of gallium Ga 68 gozetotide for imaging of biochemically recurrent prostate cancer seems to be affected by serum PSA levels and by site of disease. The performance of gallium Ga 68 gozetotide for imaging of metastatic pelvic lymph nodes prior to initial definitive therapy seems to be affected by Gleason score. Gallium Ga 68 gozetotide uptake is not specific for prostate cancer and may occur with other types of cancer as well as non-malignant processes such as Paget's disease, fibrous dysplasia, and osteophytosis. Clinical correlation, which may include histopathological evaluation of the suspected prostate cancer site, is recommended.

Radiation Risks
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.

Please note this information is not comprehensive. Please see brief summary of the full prescribing information on the next page, or visit illuccixhcp.com for full prescribing information.

Illuccix (kit for the preparation of gallium Ga 68 gozetotide Injection)
BRIEF SUMMARY: Consult the full prescribing information for complete product information

WARNINGS AND PRECAUTIONS

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ADVERSE REACTIONS

Clinical Trials 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 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.

Lactation

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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CONTENTS



PROFILES IN GU ONCOLOGY

Preston C. Sprenkle, MD:

Dr Preston describes how his career path led to Yale, his practice in the surgical management of prostate cancer, research into new technology, and his commitment to patient education.

EDITOR'S TALK

Immunotherapy and Cell-Based Therapies for Patients With Prostate Cancer 4

CONVERSATIONS WITH THE UROMIGOS

Active Surveillance in Low-Risk Prostate Cancer: Is Treatment Ever Necessary? 6

COVER STORY

Focal Therapy: How it Started, Where We Are Now, Where We Are Going 14

FEATURES

Intravesical Immunotherapy in the Management of Non-Muscle-Invasive Bladder Cancer: What Role Does it Play? 12

Biomarker Analysis and Updated Results from the Phase 3 PROpel Trial 18

Overall Survival Results of 2 Randomized Phase 3 Trials from STAMPEDE Protocol 20

Role of PET/CT in Metastatic Renal Cell Carcinoma 22

Hereditary Renal Cell Carcinoma: Presentations and Approaches to Treatment 25

Review of A Comparison of Percutaneous Ablation Therapy to Partial Nephrectomy for cT1a Renal Cancers 28

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Immunotherapy and Cell-Based Therapies for Patients With Prostate Cancer–

Challenges and the Potential for Hope in the Future



Catherine Handy Marshall, MD, MPH

THE EXPANSION OF available therapies, including options for individualization of therapy, represents an exciting space in the field of oncology. Cell-based therapies specifically have demonstrated efficacy in several disease settings, but in the case of solid tumors, the progress and promise of research has proceeded at a slower pace. We spoke with Catherine Handy Marshall, MD, MPH, to get her perspective on outlook for use of these therapies in patients with prostate cancer. Dr. Marshall is an Assistant Professor of Oncology in the Department of Oncology, Division of Genitourinary Cancer, 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, Future Oncology,* and *Prostate Cancer and Prostatic Diseases.*

GU Oncology Now: **The expansion of available therapies, including options for individualization of therapy, represents an exciting space in the field of oncology. Along with checkpoint inhibitor and cytokine inhibitor therapies, cell-based therapies—such as CAR-T and T-cell redirector therapies—have shown promise in patients with certain types of cancer, including melanoma, head and neck, lung, bladder, and kidney cancers. Yet immunotherapy has not been as successful in prostate cancer. Why is that? Is there something about the tumor microenvironment that makes prostate cancer more challenging to address with these treatments?**

Catherine Handy Marshall, MD: The reasons are multi-factorial and include the tumor microenvironment. Some of the known biomarkers that predict response to immunotherapies that have been explored before—especially regarding checkpoint inhibitors—like tumor mutational load, are low in the majority of prostate cancers. Programmed death 1, or PD-1 expression is also low and there are few T-cell infiltrates in most prostate cancers. Only about 2% of prostate cancers are mismatch repair deficient, another predictive biomarker for immunotherapy. Additionally, the tumor microenvironment does have immunosuppressive cell populations, so I think that all of these things contribute to why, within the drugs that have been approved so far to treat other cancers, we have not seen a lot of striking disease responses in prostate cancer.

Are there no cell-based therapies with a specific indication for prostate cancer that are approved right now?
The only immunotherapy drug that is approved for prostate cancer is sipuleucel-T, or Provenge®.It is an autologous cell-based therapy where patients have their own white blood cells taken out and activated outside of the body and reinfused back into them.

There are small subsets of patients who can get immunotherapy under US Food and Drug Administration (FDA) approvals. Pembrolizumab is approved under a tumor-agnostic – meaning regardless of the tissue of origin – - setting for patients with microsatellite instability (MSI)-high tumors, but fewer than about 5% of men with prostate cancer have an MSI-high type prostate cancer. However, if they do, then immunotherapy with checkpoint inhibitors would be approved for that indication. Pembrolizumab is also FDA approved for the treatment of cancers with a high tumor mutational burden—at least 10 mutations per megabase—would also be another FDA-approved indication. However, only a low percentage of men with prostate cancer would qualify for that.

Are there any clinical trials that are currently enrolling patients to explore cell-based therapies or other types of immunotherapy for prostate cancer?
There are many across the country. For patients and

providers who are interested in enrolling in trials of immunotherapy for prostate cancer, it is important to consider enrollment any time a change of therapy is being considered. A lot of times, these clinical trials are testing in patients before chemotherapy, others are testing in patients after they have received chemotherapy, but what is important to consider is that the prior therapy or therapies are written into the exclusion and inclusion criteria for the studies. So, it is not necessary to wait until all other treatment options are exhausted to start looking at these trials.

There is often the problem in medicine where we have studies that are not inclusive of diverse ethnic populations and we are trying to extrapolate the results to everyone. Do you know if any of these trials are written to include a diverse population as part of the enrollment criteria?
Clinical trials should all be written to include a diverse population as part of the enrollment criteria. There are many barriers to enrolling diverse populations of people. One issue is the accessibility of trials and if they are being offered, another is the inclusion and exclusion criteria of trials, and another is the logistics of clinical trials and facilitating participation for diverse populations. If there is a trial that would be a good fit for a particular patient, and the patient is interested, there may be resources, within the clinical trial site or even outside, like through the American Cancer Society, that can help with some of these barriers to clinical trial enrollment and participation. If there are trials in the area that you think might be a good fit, I would recommend reaching out to the trial team to see if they are able to help with other perceived barriers for patients. Clinical trials should be on the list of treatment options being considered for all patients who are changing therapies.

Today, so many individuals are conducting their own lay research and coming to the clinic asking their physicians to offer them certain treatments. How do you explain to them why, with their specific disease or comorbidities, cell-based therapies might not be effective for them?
Typically, patients come in with questions about immunotherapy in general, so I usually start with the types of treatment that they might have heard about – approved for prostate cancer and then those approved for other cancers. Most patients with advanced prostate cancer do not have the type of cancer that would be predicted to respond to treatment with FDA- approved immunotherapy. I use that as the lead-in to talk about clinical trials and options for clinical trials, and treatment strategies for how we think we might be able to help patients with prostate cancer. In general, other strategies that are being tested include combination treatments (ie immunotherapy + standard treatments in prostate cancer) or novel treatments that are being tested.

The goal for all these treatments would be an improvement in overall survival, but there have been FDA-approved trials whose endpoint is metastasis-free survival.

What are some of the combinations that might be considered?
People are looking at number of different combinations. Different combinations of checkpoint inhibitors, new targets for checkpoint inhibitors. For example, LAG-3 inhibitors, recently approved for use in melanoma, are being studied in prostate cancer. B7-H3 is another target being tested in prostate cancer. Cell based therapies – like PSMA CAR-T cells are being tested, BiTEs (bispecific T cell engagers) are being tested as well. Researchers are also looking at the use of radiation or cancer vaccines in combination with immunotherapy. Some are looking at cytokine inhibitors, like inhibitors of interleukin-8 in combination with immunotherapy. Those are some of the newer ones that, again, are all under study. The side effects can really vary. One thing that is important to note, is that some of these trials require the patient to be in the hospital to receive the therapy. The range of potential toxicities from these treatments for patients with prostate cancer is very, very broad, from some that are likely to have minimal toxicities, to some that require being in the hospital to be monitored for the side effects.

The goal for all these treatments would be an improvement in overall survival, but there have been FDA-approved trials whose endpoint is metastasis-free survival, so it is likely that some will be tested, and maybe even more will be approved if they achieve that outcome.

What does the treatment horizon look like for the use of these therapies in patients with prostate cancer? Do you see the potential for some success in 5, 10, 20 years?
The pace of drug discovery and development in oncology is very rapid right now. So, this is a total guess, but I would say it is likely that along the line of 5 to 10 years, rather than 20 years, we might see more of these treatments start to work or that we discover some that work.



Active Surveillance in Low-Risk Prostate Cancer

Is Treatment Ever Necessary?

Linda Brookes, MSc

For a recent *Uromigos* podcast, Dr Thomas Powles and Dr Brian Rini invited Dr Matthew R. Cooperberg and Dr Declan Murphy to discuss how guideline-recommended active surveillance is being implemented for patients with low-risk prostate cancer, and whether treatment trials should be conducted in this population.

ACTIVE SURVEILLANCE (AS) was established as standard of care for low-risk prostate cancer in the late 2000s and is now endorsed by all the relevant professional organizations. Implementation of AS remains variable, however, and is especially low in the US. Despite having been studied as a management strategy in large cohort studies, questions are still raised about the safety of AS, well as the risk of progression. Treatment alternatives to AS had already been investigated in clinical trials like REDEEM,[1] MAPPED,[2] and CLIN1001 PCM301.[3] However the recent publication of the ENACT (Enzalutamide in Patients With Localized Prostate Cancer Undergoing Active Surveillance) trial (NCT02799745),[4] which suggested enzalutamide as an alternative to AS, was met with a wave of criticism in print[5,6] and on social media, and suggestions that the trial should never have been carried out at all.

This controversy was discussed by Matthew R. Cooperberg, MD, MPH, professor of urology, epidemiology, and biostatistics and Helen Diller Family Chair in Urology at the University of California, San Francisco (UCSF), who was one of the ENACT investigators, and Declan Murphy, MB BCh, BAO, Consultant Urologist and Director of Genito-Urinary Oncology at Peter MacCallum Cancer Centre, Melbourne, and Honorary Clinical Professor, the University of Melbourne, Australia, who is one of the trial's critics. Thomas Powles, MBBS, MD, (Barts Cancer Centre, London, UK) and Brian Rini, MD (Vanderbilt University, Nashville, TN) moderated their discussion.

Dr Cooperberg related how AS has been a major

focus of both clinical practice and research at UCSF since the mid-1990s. In the early days, surveillance was reserved for men with small volume, low grade cancers, and involved an intensive schedule of follow up prostate-specific antigen (PSA) tests, biopsies, and imaging, he recalled. As more became known about the natural history of untreated prostate cancer, this evolved to anyone with low-risk disease, i.e., Gleason Grade Group 1, clinical stage cT1-CT2a, and PSA <10 ng/mL being a candidate for AS, which is now consistent across all the major guidelines. There are exceptions, including young men with high volume tumors, Dr Cooperberg noted.

What Dr Cooperberg referred to as "the frontier" in AS is men with intermediate-risk disease who are suitable for AS. These tend to be men with Gleason Grade Group 2 tumors, with a relatively low volume of Gleason pattern 4, especially where that pattern is fused gland type or poorly formed glands, or patients who have a high PSA level because they have a big prostate. These are the two most obvious cases for expanding AS into the so-called intermediate-risk group, he said.

In the US, the rate of AS is evolving very quickly, Dr Cooperberg observed. At UCSF, a study of the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) registry, a longitudinal, observational database of approximately 15,000 men with all stages of biopsy-proven prostate cancer enrolled at over 40 practices, showed that throughout the 1990s and 2000s, the rate of AS was consistently under 10%.[7] By 2013-14, however, the rate had risen to about 40%. Recent data from the newer AQUA (AUA Quality) registry, a much bigger database including about 26,000 men with low-risk disease at over 250 urology practices, showed that AS use had risen linearly to about 60% by 2020.[8] "That's rapid progress in the right direction, but it's still not where we should be," Dr Cooperberg commented. "If you look in countries like Sweden, their national data show rates around 80%, which is probably at least where we should be in the US."[9]

A "massive" problem is variation, he pointed out. "Depending on which individual urologist's door you happen to knock on with your low-risk diagnosis, your likelihood of getting surveillance ranges from fully zero to 100%," he said. Although this variation is not unique to AS for prostate cancers, it is more evident in prostate cancer because it is only in the past few years that the guidelines have all consistently recommended AS, he maintained. In the absence of very clear guidelines, there will be many non-clinical factors driving this variation, such as physician comfort, physician preferences, patient preferences, financial incentives, legal concerns, and local culture, he believes.

Dr Murphy described how overtreatment of patients with low-risk disease is avoided in countries like Australia and the UK, which use magnetic resonance imaging (MRI) for early detection in men with a raised PSA instead of a prostate biopsy. That has not been widely adopted in the US outside academic centers like UCSF, he noted. Dr Cooperberg pointed out that although MRI has not been adopted universally, liquid biomarker testing is being done with the same goal of not biopsying men who don't have clinically relevant cancer. So although the proportion of men with low-risk disease in the days when it was heavily overtreated was over half of all diagnoses, it is now down to about one third of all diagnoses in the US.

"Depending on which individual urologist's door you happen to knock on with your low-risk diagnosis, your likelihood of getting surveillance ranges from fully zero to 100%." –Dr Cooperberg

The number of men who will die because they chose AS and the cancer progressed is extremely low, Dr Cooperberg asserted. The likelihood of a patient on AS progressing to treatment or tumor reclassifying to higher risk within the first 3-5 years is 30-50%. "In most of those cases, the higher grade cancer was always there, and we happened to find it on the second or third biopsy," he said. The proportion of cases where the cancer worsens over 2-3 years or progresses to an incurable stage within the first 3-5 years is also extremely low, he added.

Dr Murphy had no qualms about his opposition to treatment trials in AS patients. "When the ENACT trial was published in *JAMA Oncology,* there was genuine shock among most of the urology community around the world," he declared. The Phase 2 trial, conducted between June 2016 and August 2020 at 66 US and Canadian sites, randomized a total of 227 patients with low- or intermediate-risk prostate cancer to enzalutamide 160 mg monotherapy for 1 year or continued AS. The primary endpoint was time to progression (r1 increase in primary or secondary Gleason pattern or r15% increased cancer-positive cores or earliest occurrence of primary therapy). Treatment with enzalutamide was reported to significantly reduce the risk of prostate cancer progression by 46% vs AS (hazard ratio, 0.54; 95%CI, 0.33-0.89; *P*=0.02). The conclusion of the trial upset many people because it suggested that enzalutamide monotherapy was well tolerated, which it wasn't, Dr Murphy complained. "Most of us find that completely lacking in equipoise," he said. He pointed out that fatigue was reported in 55.4% and gynecomastia in 36.3% of patients.

"Most of us involved in this area do not like this messaging that we need trials and that we need to consider enzalutamide or even sipuleucel-T [autologous vaccine], which is currently in a trial in AS patients [ProVent, NCT03686683]," he continued. "It's sowing the seeds of doubt in the clinical community to say, 'we need to give them hundreds of thousands of dollars' worth of drugs, because we have a problem with active surveillance' when we don't." The problem is not that we're worried about the terrible oncological outcomes when you select a patient for AS, we just need to do more surveillance, he stressed. "But remember, it is literally, do nothing; just keep an eye on your patient, and maybe do so with smart tools."

"But it's early days...To my knowledge, to this point, no one has thought of running a Phase-3 trial or going to regulatory agencies with any sort of intervention or low-risk, otherwise AS-eligible disease." –Dr Cooperberg

"Every guideline recommends that men at low-risk or favorable intermediate-risk who it's not clear will benefit from treatment, should be put on AS," he pointed out. Many in the field have pushed very hard to try and educate physicians and patients about this to try and reduce the overtreatment that has "polluted the arena for the past couple of decades," so why should these men be put on "a super powerful" systemic oncology drug like enzalutamide, he questioned. Asked by Dr Rini whether there might be a subset of the AS population that could be treated in a trial with a different type of therapy, Dr Murphy was adamant: "There is absolutely zero, nothing," he said emphatically.

Dr Cooperberg acknowledged that there is "definitely" industry interest in treatments for low-risk AS patients, "But it's early days," he said. "To my knowledge, to this point, no one has thought of running a Phase-3 trial or going to regulatory agencies with any sort of intervention for low-risk, otherwise AS-eligible disease."

Dr Cooperberg believes that where there is legitimate discussion and room for different opinions is not the fundamental question of whether lower risk prostate cancer is a problem, but what we do about it over the next 5-10 years across the different healthcare systems. "I think the jury is still out, and we need to continue to advance science along all these different directions, with different types of interventions, be they psychological or medical, as long as the impact of the intervention, the side effects, and the risks are low enough," he said. "We need to continue to make progress in how we do surveillance, and how we improve the outcomes for all men with low-risk disease."

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

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Preston C. Sprenkle, MD–

A Focus on Surgical Oncology and Patient Education

Linda Brookes, MSc

PRESTON C. SPRENKLE, MD, is associate Professor, Urology, at the Yale School of Medicine in New Haven, CT. He also serves as Director of the Urology Research Fellowship and Urologic Oncology Clinical Fellowship Programs at Yale, as well as Chief of the Division of Urology at the associated VA Connecticut Healthcare System in West Haven, CT. "I'm a urologist who focuses on surgical oncology," Dr Sprenkle explains. "I see patients clinically, then operate on them and manage them both medically and surgically."

Dr Sprenkle's clinical practice and research are focused on prostate cancer, although he also manages patients with kidney cancer, testicular cancer, and bladder cancer. He is well known for his interest in new imaging technologies to improve the diagnosis and treatment of prostate cancer and for pioneering focal ablation therapy, in which the prostate lesion is treated rather than the whole organ, avoiding treatment-related adverse effects such as urinary incontinence and erectile dysfunction associated with radical prostatectomy and toxicities from radiation therapy.

Although Dr Sprenkle decided to specialize in surgery quite early during medical school, that was not his original preference when he was considering his career options. Growing up in Seattle, WA, he was interested in medicine, influenced by his father who was an allergist/immunologist, and he did his prerequisites for medical school. His major at Stanford University was evolutionary biology and ecology, however. "My general interests were in how we co-evolve with our environment and the environmental factors that influence human development and evolution," he admits.

So after graduating from Stanford in 1998 with a BA in human biology, Dr Sprenkle did not immediately enter medical school. After reviewing a variety of possible career paths, he joined a health care management consulting firm in San Francisco. He recalls how his boss, health systems expert Molly Coye, MD, MPH, was influential in showing him how to integrate a medical education with solving problems by being involved in trying to improve the quality of people's lives.

"I didn't think I would ever leave California, but in 2004 I had the opportunity to go to Columbia University and it seemed like a great opportunity to jump coasts for a little while," he says. He planned to return to the West Coast after four years, but he met his future wife in medical school, and they have been together in the Northeast ever since. (His wife practices as a gynecologist.)

Before he decided on his specialty, Dr Sprenkle was not inclined toward urology or surgery. "I thought that given my interest in the environment and travel, I would probably go into something like international health, so potentially tropical medicine or infectious diseases," he says. ("I was very young," he adds, laughing at the recollection.) "But we had a great semester-long anatomy lab, and once I got into that and started learning about the human body and more about surgery, it became very clear that surgery was what I wanted to do," he recalls. "I thought that pelvic anatomy was especially intriguing, and obstetrics/gynecology and urology both seemed very

challenging, the anatomy was complex, and the surgeries were difficult but rewarding. We were able to achieve a lot of benefit for patients with the surgical interventions."

"Having a single test for any man over the age of 40 can really help stratify who should be followed more closely versus who doesn't need that." –Dr Sprenkle

After medical school and opting for urology, Dr Sprenkle stayed at Columbia for his residency, where he had "great training" with many internationally recognized urologists, including Carl Olsson, MD, Chief Emeritus, Mitchell Benson, MD, then Chief of Urology at New York Presbyterian Hospital Columbia Campus, and James McKiernan, MD, who is the current Chief of Urology at Columbia. "Dr McKiernan is still a fantastic mentor and role model," Dr Sprenkle enthuses. "He was very supportive in helping me understand which subspecialties and what areas of urology I wanted to be in."

During his fellowship in urologic oncology at Memorial Sloan Kettering Cancer Center, Dr Sprenkle did bench research for a year. "It was a great experience, because I worked in the lab of James P. Allison, PhD, then director of the Ludwig Center for Cancer Immunotherapy," Dr Sprenkle recalls. Dr Allison subsequently moved to The University of Texas MD Anderson Cancer Center in Houston, where he shared the 2018 Nobel Prize in Physiology or Medicine "for the discovery of cancer therapy by inhibition of negative immune regulation."

"When I was working in his lab, I was investigating immunological markers to identify prostate and other cancers and their response to immunologic manipulation." Dr Sprenkle recalls fondly the awe-inspiring discussions of his lab partners during the lab meetings and the continued relevance of the work for current practice. Following his year in the lab, Dr. Sprenkle was fortunate to train under many of the current thought leaders in urologic oncology, whose instruction and approach to oncology continue to guide much of his practice.

Dr Sprenkle has been at Yale School of Medicine since 2012. A typical week now consists of two days spent at Yale, and 3 days a week at the VA hospital. "My time is probably 90% clinical, with patients in clinic and in the operating room," he explains. He uses about one day every other week for research and administrative work, which includes working with residents and fellows to ask and answer clinical research questions in urology, acting as Oncology co-chair of the Cancer Liaison Committee of the VA Connecticut Healthcare System, and as vice-chair of the National Comprehensive Cancer Network (NCCN) Panel that issues its clinical practice guideline on early detection of prostate cancer (most recently version 1.2022, issued February 16).[1]

"The panel tries very hard to bring forward published evidence to support any changes in the guideline or recommendations," he remarks. "One that we recently shepherded through was the use of multiparametric magnetic resonance imaging (mpMRI) prior to biopsy, which is now considered standard of care where available," he notes.

The panel has not yet reached consensus about screening, he admits. "I'm not going to mince any words there; I think it's appropriate, but not for everyone," he states. "Having a single test for any man over the age of 40 can really help stratify who should be followed more closely versus who doesn't need that."

Dr Sprenkle also believes that the current guideline cutoff age for screening, 75 years, is inappropriate. Realistically, men who were over 75 years in studies done 10 or 15 years ago were not as healthy as men who are over 75 today, who currently have an average life expectancy approaching 15 years, he points out. "I think one of the points we'll be discussing at our next meeting will be whether we should get rid of age-cutoff altogether and really emphasize the concept of a 10-year life expectancy," he predicts. That is what really matters, he says, because prostate cancer is very unlikely to lead to death or morbidity within 10 years after diagnosis.



With me are my sons Wyatt and Gabriel, and wife Linda Fan MD at Snowbird, Utah.

Most prostate cancer guidelines, including those of NCCN and the American Urological Association (AUA), stress the importance of shared decision making, he notes. "I think it's appropriate for prostate cancer screening and prostate-specific antigen (PSA) testing, because it's very important that patients understand the risks and benefits before 'getting on the PSA train,'" he says. Primary care providers could explain this, "but they don't, because they don't have the time or the detailed understanding of what's going on," and not even many urologists do it, he maintains. "One of the projects at Yale that I'm proud to be participating in is the development of care pathways and guidelines for primary care physicians about who should be having a PSA test and the type of language they should use with patients when discussing PSA testing," he says. "I am interested in trying to make more patient-facing content for education about the complex decisions regarding PSA screening."

"I am very interested in how we can utilize technology to improve the patient experience and maximize their quality of life while maintaining appropriate cancer care..." –Dr Sprenkle

His main current clinical interest, and topic for patient education, is prostate ablation therapy. It is a relatively new technology and not a lot of urologists are aware of the latest developments and the options available, he believes. "I am very interested in how we can utilize technology to improve the patient experience and maximize their quality of life while maintaining appropriate cancer care. Getting rid of all of the cancer is our goal, but that's very hard to do, and even when we give it our best try with conventional treatments, we're not always successful," he says.

The appeal of many ablation technologies is that it is possible to treat the cancer area in a more precise manner: so with minimal damage to the nerves related to sexual function, preservation of the urethra and surrounding structures, and with minimal changes in urinary continence. "A drawback is that if you are not doing it as radical a treatment, you're probably not going to have as good cancer control," Dr Sprenkle admits. "But many men don't need to have their cancer controlled so well. If it's a small improvement in cancer control, with a big improvement in treatment-related side effects, we can repeat those treatments if the cancer recurs with a similar side effect profile," he points out.

Ablative therapy is not for everyone, he stresses. "but for some patients, it is a great option and an increasing numbers of patients and physicians and urologists are embracing it." The biggest impediment has been an acceptance of the importance of the quality of life and the balance between quality of life and cancer control, he notes. "For the longest time, we accepted that we had to do the big cancer control and that to compromise this was doing the patient a disservice. [Ablation therapy] is changing the playing field, because we can get 80% cancer control or higher and have minimal impact on quality of life."

As evidence of patients' attitudes to this, Dr Sprenkle cites the COMPARE (COMparing treatment options for ProstAte cancer) study (NCT01177865), which surveyed patients with localized prostate cancer in 34 urology departments in the UK, and found that patients at all risk levels were willing to trade cancer-specific survival for a better chance of retaining urinary continence and erectile function.[2] "That was an interesting study that really drives home the point that this is what patients want and that having these options is very important to them," he says. "I spend most of my clinic days having long talks with patients about all their options, and I am trying to put some of the talking points and information on our web site, because I think the education component for patients is largely missing."

Research in ablation therapy is a very exciting area to be involved in, he adds. New technologies are being evaluated at Yale, including, currently the TULSA (Transurethral Ultrasound Ablation) procedure (Profound Medical), which combines real-time MRI with robotically driven directional thermal ultrasound to deliver precise, customized ablation of whole-gland or partial prostate tissue. It is being compared with radical prostatectomy in the CAPTAIN trial (NCT05027477). Dr Sprenkle is looking forward to additional clinical trials with other new technologies starting in the next few years.

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

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Intravesical Immunotherapy in the Management of Non-Muscle-Invasive Bladder Cancer:

What Role Does it Play?

David Ambinder, MD

DOES INTRAVESICAL IMMUNOTHERAPY have a role in the management of non-muscle-invasive bladder cancer (NMIBC)? According to a recent study, there is much to be excited about regarding use of immunotherapy when patients do not respond to bacillus Calmette-Guérin (BCG). Researchers in Chicago evaluated the safety and potential efficacy of intravesical pembrolizumab when administered in conjunction with intravesical BCG.[1]

Currently, management for NMIBC revolves around optimal endoscopic resection and subsequent administration of intravesical BCG and, in certain situations, intravesical chemotherapy (eg, mitomycin-C). Unfortunately, many patients will not respond to BCG, and many recent studies have investigated the treatment of these patients. In 2021, intravenous pembrolizumab—a checkpoint immunotherapeutic agent that targets programmed death 1—was shown to be effective and was approved for use in BCG-unresponsive NMIBC, based on a study showing a response.[2] The authors commented that "although the 3-month response was 41% (39/96), the median duration of a complete response (CR) was 16 months with 19% (18/96) complete response at 12 months. While pembrolizumab was well tolerated, 66% of patients reported an adverse event (AE), with a total of 11 serious AEs in 8 patients." The authors noted that even though a response was seen, >80% of patients did not respond, and 2 of 3 experienced an AE.

This is what led the researchers to evaluate whether changing the route of administration would reduce the rate and severity of AEs while maintaining antitumor activity. To that point, a recent preclinical study published in the *Journal of Urology* using mouse models showed an increase in lymphocytic activity after the administration of intravesical immunotherapy.[3] This was the backbone for this study, namely to conduct a phase 1 dose-escalation trial using increasing doses of intravesical pembrolizumab with BCG in patients unresponsive to BCG and to "report safety, toxicity, and clinical response from the first in-human clinical trial of intravesical administration of an immune checkpoint inhibitor."

The study was conducted at a single institution. It included patients with high-grade NMIBC who had previously been treated with 5 induction courses and 2 maintenance courses of BCG or had undergone r3 doses of a salvage alternative (gemcitabine and/or docetaxel). Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. The authors describe the induction course for patients in the study as a single dose of intravesical pembrolizumab at a specified dose level of 1 to 2 mg/kg at the second week before induction. This was followed by BCG 50 mg BCG from weeks 0 to 5 and intravesical pembrolizumab at weeks 0, 2, and 4. The maintenance regimen consisted only of pembrolizumab every 2 weeks until the 17th week of treatment and then every 4 weeks for the remainder of the year.

The study included 9 patients (3 treated with a starting dose of 1 mg/kg and 6 treated with a starting dose of 2 mg/kg) who were enrolled from 2016 to 2020 and followed until May 2021. The trial was closed prematurely due to the COVID-19 pandemic. Patients were evaluated at each visit and underwent endoscopic evaluation with biopsy if indicated at week 17 and then every 8 weeks from then until the end of the trial at 1 year. Recurrence was evaluated by cystoscopy with bladder biopsy, if indicated, and urine cytology. The finding of high-grade recurrence ended the treatment. After the end of the trial year, patients were followed every 3 months for 2 years.

All patients experienced a grade 1-2 AE. In total, 21 grade 1-2 AEs due to BCG and/or pembrolizumab were reported, with the most common being gross hematuria (55.6%), followed by diarrhea, fatigue, and urinary tract infection (each 22%). One patient had a grade 2 dose-limiting toxicity of prolonged diarrhea. The only reported grade r3 or higher event reported was 1 patient who had died due to treatment-related myasthenia gravis. The authors describe the timing of symptoms as well as the management of this patient. This patient had a very high number of CD45+ cells (highest in the cohort) in the urine before treatment initiation, and the count increased over the course of the treatment.

A total of 5 patients were alive at the end of the study; the median follow-up time for those patients was 35 months. All patients ultimately experienced a recurrence, with recurrence-free survival (RFS) rates of 100%, 67%, and 22% at 3, 6, and 12 months, respectively. Median RFS was approximately 6 months. Additionally, there were 5 patients who had progression of disease. Median progression-free survival (PFS) was 36 months, and the PFS rates at 6 and 12 months were 100% and 56%, respectively. Development of locally advanced disease was seen in 4 of 9 patients, and 6 of 9 patients developed recurrence outside of the bladder. Two patients underwent radical cystectomy, 1 patient underwent nephroureterectomy, and 1 underwent a partial cystectomy with a distal ureterectomy. A total of 4 patients died during the study period.

To evaluate whether intravesical pembrolizumab remained in the urinary tract, or had systemic absorption urine and plasma pembrolizumab levels, were checked. No detectable levels of pembrolizumab were found in the bloodstream of any patient, whereas detectable pembrolizumab levels were found in the urine after week 4.

The researchers found that when comparing the local immune environment 2 weeks before and 2 weeks after treatment with a single dose of intravesical pembrolizumab, there was a significant decrease in granulocytes and a significant increase in CD4+ and CD8+ T cells. They concluded that this "reflects at least transient changes to the microenvironment."

Urinary cytokine profiling showed levels of BCG-regulated inflammatory chemokines, including macrophage inflammatory protein-1β and monocyte chemoattractant protein-1, and cytokines, including tumor necrosis factor-α and interleukin-8 increased over the course of BCG induction.

When comparing urinary immune profiles between patients with early versus late recurrence, the researchers found that there was a difference in the immune profile between the time points when patients were being administered intravesical pembrolizumab plus BCG versus BCG alone, and that in the patients with late recurrence (4 patients with a median recurrence of 12 months) compared to early recurrence (5 patients with a median recurrence of 5.3 months), there was a lower fraction of granulocytes and higher fraction of lymphocytes, including a higher count of CD4+ and CD8+ T cells.

The researchers also looked at complex spatial transcriptomic analysis and found that the "differences in clinical endpoints of BCG unresponsive tumor may be secondary to distinct pathways of the tumor or tumor microenvironment (TME), with responsive tumors showing greater T-cell infiltration with less exhaustion, while resistant tumors have increased neutrophils and a stroma-rich microenvironment."

Although closed prematurely, this trial aimed to evaluate if intravesical BCG potentially avoiding systemic toxic and serum and plasma pembrolizumab was undetected. The authors noted that there still were significant AEs seen in 2 patients and it remains unclear if lowering the dose would reduce the risk of AEs. The patient who developed myasthenia gravis had the highest number of CD45+ cells in the urine, and the number continued to increase over the treatment period. The authors note that although this patient had a late recurrence, this enhanced immune activation may have contributed to the development of myasthenia gravis. The association of the development of BCG in older patients has been described,[4] but only a handful of case reports describe the development of myasthenia gravis in patients being treated with intravenous immunotherapy.[5]

The study was limited by its small sample size. Nevertheless, intravesical delivery of pembrolizumab may be a safe and viable treatment option for patients with BCG-unresponsive NMIBC, and further research should include validation in a large cohort and investigation of the correct dosage and patient selection.

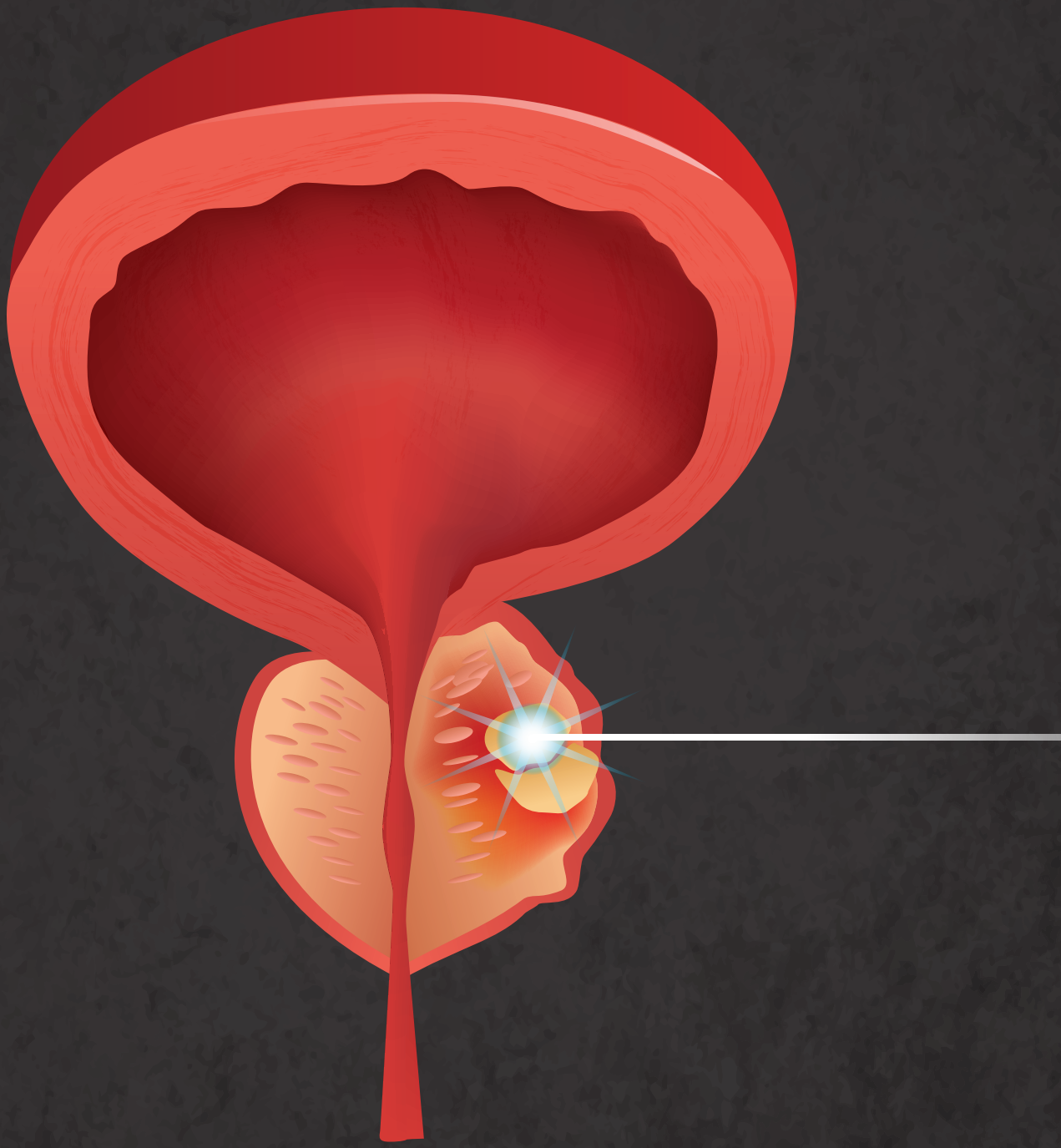
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FOCAL THERAPY:

How it Started, Where We Are Now, Where We Are Going

A Discussion with Scott Eggener, MD



by David Ambinder, MD



Scott Eggener, MD

SCOTT EGGENER, MD, *is a professor of radiology and urologic oncology and the Bruce and Beth White Family Professor of Surgery at the University of Chicago. He is also vice chair of the Section of Urology at University of Chicago Medicine, where he serves as director of the UChicago High-Risk and Advanced Prostate Cancer Clinic (UCHAP). In addition to many other interests and contributions to the field of urologic oncology, he has been a strong leader in the development of focal therapy, including acting as the principal investigator (PI) for several clinical trials, and presenting on the topic globally.*

David Ambinder, MD: For more than 15 years, you have been involved in the use of focal therapy in the treatment of patients with prostate cancer. Would you give us a brief history of how it started and developed, and where we are today?

Scott Eggener, MD: The brief overview of this long story must begin by recalling that before the development of focal therapy, radical surgery was the standard of care. However, it eventually became apparent that more isn't necessarily better. The breast cancer setting is held up as the best example of success with focal therapy for treatment of patients. Initially, localized breast cancer was managed with radical therapy, but, over time, performing a lumpectomy has become a standard of care. Today roughly 60%-70% of women receive focal therapy for breast cancer. This experience laid the groundwork for pioneers in the use of focal therapy for prostate cancer, although, unfortunately, we are about 40 or 50 years behind in properly evaluating it in prostate cancer.

The parallels from initial reports to case series to randomized trials are quite similar between breast and prostate cancer. Gary Onik, MD, started investigating the use of focal cryotherapy in the 1990s. At that time, it was not very popular, and focal therapy was initially met with significant resistance. However, about 15 years ago, support for focal therapy began to grow. There was a group of well-known academic prostate cancer specialists who started entertaining the idea that maybe we should consider it. That is how I got involved, as a fellow working with Peter Scardino, MD, at Memorial Sloan Kettering Cancer Center. Over the past 15 years, there has been a lot of innovation and much work has been done to improve the quality of the data and our understanding of the technology. In 2022,

Continued on next page

we're finally in an era where there are several developed and ongoing randomized trials of focal therapy for prostate cancer that we hope will add to our knowledge.

Many people are unclear about what is included in the category of focal therapy and its various aspects. Would you define and describe the different modalities of focal therapy and how they work?
Focal therapy is defined as treating prostate cancer by any modality short of treating the entire prostate. This includes many different templates, including just treating the lesion itself, a hemiablation, hockey-stick ablation, etc. Currently, there are more than 15 different modalities available. The most common and oldest forms that are still being used include cryotherapy or high-intensity focused ultrasound (HIFU), but focal therapy also includes focal brachytherapy or focal external beam radiation therapy. Irreversible electroporation, or IRE, other forms of ultrasound energy, and laser ablation are also modalities available. In summary, there are numerous ways to destroy or ablate certain areas of the prostate.

"We need to use a proper evidence-based approach to be sure which patients would benefit from focal therapy and how to counsel them appropriately. That requires collecting long-term data, ideally via randomized controlled trials." –Dr Eggener

Ultrasound-based focal therapy seems to be gaining the most in popularity. HIFU has been approved by the US Food and Drug Administration (FDA) for a number of years, and there are several companies that use its technology. Many centers use HIFU primarily for focal therapy, sometimes whole gland therapy, and occasionally for salvage therapy following radiation therapy. There also are a number of centers that still use some form of cryotherapy.

This is a busy space, and there are a lot of well-funded, commercially driven, scientifically backed delivery systems for focal therapy. However, it is critical that we don't "put the cart ahead of the horse." We need to use a proper evidence-based approach to be sure which patients would benefit from focal therapy and how to counsel them appropriately. That requires collecting long-term data, ideally via randomized controlled trials.

To that point, who is the ideal candidate to consider focal therapy?
Unfortunately, it is not easy to define the right patient and often depends on whom you ask. To quote former Supreme Court Justice Potter Stewart, "You know it when you see it." Determination is based on biopsy, multiparametric magnetic resonance imaging (MRI), and the patients themselves. When I counsel patients, I try to explain what we know about focal therapy in numbers and percentages while staying even-handed about discussing what we don't know. I would summarize by saying I've rarely, if ever, met a patient to whom I've said I absolutely recommend focal therapy because it is the best thing for you. However, it is always one option among other options, and as long as patients are well-informed and they choose to do it, I'm very comfortable with it.

If I had to describe the characteristics of an ideal candidate, they would include some degree of Gleason pattern 4 disease as well as 1 or 2 lesions visible on MRI in an area of the prostate that could be thoroughly ablated with minimal toxicity. The patient should also be compliant with the requirements for follow-up, and there are a lot of other potential indications.

A motivation for pursuing focal therapy is the reduction in treatment-related effects compared with whole-gland therapy, be it surgery or radiation. Of course, no treatment is without side effects. What are the common treatment-related toxicities and side-effect profiles seen with the more common forms of focal therapy?
It depends on the area and amount of the prostate being treated. Like the familiar phrase in real estate, it's about "location, location, location." There are parts of the prostate that you can treat very aggressively, like the anterior prostate, where there is low to no risk of meaningful side effects as long as the treatment is not near the urethra. It's very different if the lesion is sitting on the capsule, right near the nerves posterolaterally, or if it's at the apex of the prostate.

I try my best to estimate the likelihood of erectile dysfunction based on how much we're going to treat and where the lesion is located. Urinary incontinence is rare. I can't think of a single patient who developed meaningful stress incontinence afterwards, although some patients can experience short-term urgency. In one of the trials done with transurethral ultrasound ablation (TULSA) there was ~2% chance of new meaningful incontinence. However, I haven't encountered this in my own experience. Certainly, there is a risk of fistulas with very aggressive ablation, but that risk should be extremely low to zero, although it has been reported in some cases.

What are some technical challenges that should be considered while performing focal therapy?
This is an important question. We make the decision to offer focal therapy based on digital rectal exam (DRE) findings, biopsy, prostate-specific antigen (PSA), and, importantly, MRI. However, MRIs are good, but far from great, and tend to underestimate tumor volume. Its use is important for administering the energy and covering the intended lesion or lobe of the prostate, but it's imperfect. Many studies looking at biopsies following focal therapy suggest approximately 80% eradication of the area targeted for treatment. I tend to like systems that give feedback. At our center, we have had experience with magnetic resonance-based therapies, where there is thermometry feedback, and we get a sense of when we have reached certain temperatures throughout the prostate. However, even that is aspirational, not perfect.

What are the relevant and important studies that focus on the oncologic and functional outcomes after focal therapy?
The only randomized trial in this space in urology evaluated the photodynamic therapy trial.1 Unfortunately, it was designed to include only patients with low-risk disease and never met the bar for FDA approval, and is not available in the United States.

Regarding, HIFU, the best long-term data come from the United Kingdom, single centers, and nationwide data with 10-year follow-up on overall survival, disease-free survival, development of metastatic disease, and the need for further therapy. Excitingly, there are now a handful of randomized trials either accruing or being planned as well as discussions with the FDA for registration of controlled trials to develop high levels of evidence of cancer-specific and functional outcomes.

What are some published clinical trials in which you have been involved?
We've published 2 separate MRI-guided laser ablation studies. The University of Chicago was a treatment site, and I was the PI for the TULSA phase 2 study, which involved roughly 110 patients who underwent transurethral MRI-guided ultrasound ablation—a procedure that is now available for focal therapy. We also took part in a randomized trial where there was injection of immunotherapy. That's not focal therapy per se, but it falls within the category of minimally invasive, novel techniques.

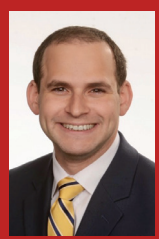
Focal therapy has a lot of potential. I think people are coming around to that. What motivated you to get involved early on with it and to stick with it?
For me, it was being at the right place at the right time and having good mentors. I was a fellow at Memorial Sloan Kettering, and one of my heroes and most influential people in my career was Dr. Scardino. He approached me and said, "We've been having these meetings and discussions on focal therapy with other folks. Would you mind writing it up and being involved with this consensus statement?" It sounded like a crazy idea, but something worth learning more about, and I subsequently dove in. In my first faculty position I partnered with our current chair of radiology, Aytekin Oto, MD, MBA, wrote some grants and worked with small companies on focal therapy and laser ablation. I really took an interest in the research and clinical space.

"There is potential for combining focal therapy with other medications such as immunotherapy. However, this idea is still in the conceptual phase and is a long way from being realized." –Dr Eggener

What do you foresee changing in the landscape of focal therapy over the next 10 years?
In this era of marketing, many companies are working in this space and financially motivated, which is why the trials are so important. There is potential for combining focal therapy with other medications such as immunotherapy. However, this idea is still in the conceptual phase and is a long way from being realized.

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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.

Biomarker Analysis and Updated Results from the Phase 3 PROpel Trial – Abiraterone Plus Olaparib vs Abiraterone Plus Placebo as First-line Therapy in Patients With Metastatic Castration-resistant Prostate Cancer

Akhil A. Saji, MD

THE PROSTATE-FOCUSED SESSION at the European Society for Medical Oncology Congress (ESMO) 2022 meeting in September offered presentations on several interesting trial results and analyses. Below, we highlight findings from the biomarker analysis, as well as updated results of the PROpel trial (NCT03732820)[1] investigating the role of olaparib in addition to abiraterone acetate plus prednisolone (AAP) in first-line treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). The presentation was delivered by Fred Saad, MD, FRCS, the Raymond Garneau Chair in Prostate Cancer, and professor and chair of urology and director of genitourinary oncology at University of Montreal Hospital Center in Canada.

Poly (ADP-ribose) polymerase, or PARP, is a family of proteins involved in DNA repair pathways.[2] Annually, an estimated 270,0003 new cases of prostate cancer are diagnosed in the United States alone, and nearly 35,000[3] men will experience prostate-cancer related mortality. Many of these individuals have metastatic castration-resistant prostate cancer (mCRPC) at the time of death. The concept of PARP inhibition as a therapeutic modality in this setting stems from the fact that an estimated 1 of 4 patients with mCRPC has a germline mutation in *BRCA2, BRCA1, ATM,* or *CHEK2,* with BRCA2 mutation being the most common.[4] The good news is that the treatment armamentarium for mCRPC has expanded significantly in the past decade. Median overall survival (OS) has also significantly increased over prior historical averages of 18 to 24 months.[5] However, there is a growing number of patients presenting with de novo metastatic disease at diagnosis,[6] emphasizing the importance of continuing to expand treatment modalities.

PROpel is a phase 3 clinical trial investigating the role of olaparib in addition to AAP (olaparib+AAP) versus AAP alone as primary therapy for patients with mCRPC who have received no prior cytotoxic chemotherapy or hormonal therapy. Dr Saad began his presentation by explaining the impetus for the PROpel. Patients with mCRPC, even in the clinical trial setting, have a median OS of only ~36 months. Therefore, further investigation and trials of new therapies are needed to improve patient outcomes. Additionally, prior trials involving olaparib have demonstrated improvements in radiographic progression-free survival (rPFS) and OS in mCRPC patients with germline mutations who had disease progression despite treatment with next-generation hormonal agents.[7] In a report published earlier this year in *The New England Journal of Medicine,* the results of the PROpel trial demonstrated significant improvement in rPFS in patients in the olaparib+AAP arm compared with the placebo+AAP arm regardless of their *HRR* (homologous recombination repair gene) mutational status.[8]

It is important to remember that PARP inhibition works via the concept of synthetic lethality. That is, the PARP protein complex is involved in single-stranded DNA repair; therefore inhibiting the PARP complex renders prostate cancer cells unable to repair single-stranded DNA damage.[9] Cells with persistent single-stranded DNA damage will undergo replication, which results in double-stranded DNA damage that requires repair via double-strand repair mechanisms, such as homologous recombination repair and nonhomologous end joining.[9] Both of these repair mechanisms rely on peptide products encoded in the *ATM, CHK2, BRCA1, PALB2,* and *BRCA2* genes to correctly repair double-stranded DNA damage. However, in patients with germline mutations, 1 or more of these genes may be damaged.[9] Consequently, we can understand that PARP inhibition via synthetic lethality will result in cell death,

as both single-stranded and double-stranded DNA repair mechanisms are unable to function.

Dr Saad briefly reviewed the PROpel trial design. He explained that patients were enrolled for primary treatment with olaparib+AAP (n=399) compared with placebo+AAP (n=397). Patients with prior AAP exposure were excluded, but patients with exposure to other hormonal agents were included if exposure occurred >12 months before enrollment. The baseline characteristics of patients in the 2 arms were well balanced. In both the olaparib+AAP and placebo+AAP arms, most patients had an Eastern Cooperative Oncology Group performance status score of 0 (71.7% and 68.5%. respectively), and median ages were 69 and 70 years, respectively. Dr Saad remarked that, like prior trials of olaparib in patients with mCRPC, about 30% of patients had detectable *HRR* mutations (27.8% and 29%, respectively).

Dr Saad explained that, compared to placebo olaparib+AAP as primary therapy for mCRPC yielded a substantial improvement in rPFS (8.6 months; HR, 0.66; P<0.0001).

The primary endpoint for the trial was rPFS. Dr Saad explained that the olaparib+AAP arm saw an 8.2-month improvement in rPFS compared with the control arm (24.8 vs 16.6 months; hazard ratio [HR], 0.66; *P*<0.001), correlating to a 34% reduction. Based on updated results, Dr Saad explained that rPFS had improved to 8.6 months at the time of the ESMO presentation (25.0 vs 16.4 months; HR, 0.67; *P*<0.0001). When patients were stratified by *HRR* mutation status, subgroup analysis demonstrated benefit regardless of *HRR* mutation status (HR 0.50 for the HRRm and HR 0.76 for non-HRRm). The investigators also stratified patients by *BRCA* mutation status and found patients had benefit regardless of their status (HR for cohorts with vs without the mutation: 0.23 and 0.76). Dr Saad further remarked that in all subgroup analyses, including stratification by age at randomization and site of distant metastasis, patients in the olaparib+AAP arm experienced an rPFS benefit.

Dr Saad also discussed some other key secondary endpoints of interest, including time to first secondary therapy (TFST) and time to second progression (PFS2). TFST improved substantially in the combination arm compared with the placebo arm (25.4 vs 19.5 months; HR, 0.76; *P*=0.0032). Regarding PFS2, Dr Saad mentioned that the endpoints were not reached in either group, but preliminary data appear to favor the combination arm (HR, 0.71; *P*=0.019). Finally, although the final OS endpoint was not reached, the data continue to show high promise with significant improvement in OS, noted specifically after ~22 months of combination therapy. Safety endpoints were also explored in both arms. Dr Saad explained that there was no significant increase in toxicity noted in the combination arm despite a longer duration of therapy at the second analysis. An overall difference of ~12% in grade r3 adverse events was noted between the 2 therapeutic arms. Dr Saad remarked that this was primarily driven by the higher rate of anemia in the combination arm compared with the placebo arm (15.8% vs 3.3%).

In concluding remarks, Dr Saad explained that, compared to placebo +AAP, the combination of olaparib+AAP as primary therapy for mCRPC yielded a substantial improvement in rPFS (8.6 months; HR, 0.66; *P*<0.0001). Moreover, at the time of this analysis, data continued to demonstrate developing improvement in OS. Dr Saad also emphasized that the safety profile of combination therapy remained consistent with the original publication data. Thus, the data presented in this trial provide substantial support for the use of olaparib+AAP in the mCRPC setting. We look forward to the final results for OS and other secondary endpoints.

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Overall Survival Results of 2 Randomized Phase 3 Trials from STAMPEDE Protocol:

Comparison of Abiraterone Acetate and Prednisolone (AAP) or Combination Enzalutamide + AAP for mHSPC Cancer Starting Androgen-deprivation Therapy

Akhil A. Saji, MD

DURING THE PROFFERED paper session focusing on prostate genitourinary malignancy at the European Society for Medical Oncology (ESMO) 2022 congress, Gerhardt Attard, MD, PhD, FRCP, the John Black Charitable Foundation Endowed Chair in Urological Cancer Research at University College London, offered results of a phase 3 trial as a component of the STAMPEDE platform trial. The presentation focused on comparing patients with newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC) undergoing initiation of androgen-deprivation therapy (ADT) with either abiraterone acetate plus prednisolone (AAP) or enzalutamide (ENZ) plus AAP.

Current treatment options for patients with mHSPC include cytotoxic docetaxel[1] chemotherapy regimens and use of androgen synthesis inhibitors such as AAP[2] or androgen-receptor antagonists such as apalutamide[3] and ENZ.[4,5] At ESMO 2021, a presentation of updated results from the ARCHES trial (ADT+placebo vs ADT+ENZ), which provided support for using ENZ in the mHSPC setting, included findings on overall survival (OS), time to subsequent antineoplastic therapy, and safety outcomes. Patients enrolled in the original ARCHES[5] trial all had mHSPC confirmed by bone scan, cross-sectional computed tomography/magnetic resonance imaging, and histologic confirmation. Patients were stratified by disease volume (low vs high) and prior docetaxel exposure (0, 1-5, or 6 cycles) before the trial was initiated. Patients in the ADT+ENZ arm of ARCHES enjoyed a significant OS improvement of 34% at 48 months compared with those in the placebo arm (71% vs 57%). Further subgroup analyses also demonstrated that patients, regardless of prior docetaxel exposure, received benefit. However, patients with visceral metastatic disease had worse outcomes. ARCHES also demonstrated that ADT+ENZ was relatively safe, with the only major safety issues being a higher rate of hypertension and some concerns about cognitive impairment. Cardiovascular risks appeared to be low.

Professor Attard began his presentation by noting that addition of AAP or ENZ to standard ADT for mHSPC has been shown to improve outcomes. He cited data demonstrating that treatment with AAP+ENZ[6] in the metastatic castration-resistant prostate cancer (mCRPC) setting did little to demonstrate any improvement in OS despite a higher rate of adverse events (AEs) compared to use of ENZ alone. However, the AAP+ENZ combination did yield improvement in radiographic progression-free survival (rPFS). Despite these findings, the role of such a combination in the mHSPC setting remains unknown. Prof Attard briefly reviewed the STAMPEDE platform patient population by explaining that those enrolled in the trial are stratified into 2 groups: the M1 group (mHSPC) based on imaging, or the M0 group based on high-risk localized disease. Patients with significant cardiovascular disease are excluded. (A full description is available at stampedetrial.org.)

To further underscore the importance of the STAMPEDE platform, Prof Attard referred to the investigators' presentation at ESMO 2021,[7] which demonstrated the utility of combining AAP with ENZ in the high-risk M0 setting. The primary endpoint of that analysis was metastasis-free survival (MFS), which improved by 47% with AAP with or without ENZ compared with standard ADT (hazard ratio [HR], 0.53; 95% CI, 0.44-0.64). Further substratification comparing patients who received AAP+ENZ with those given AAP alone demonstrated no discernible clinical benefit.

Moving forward, Prof Attard explained the layout of the two phase 3 trials being compared in his group's

analysis. Standard of care (SOC) was defined as standard ADT with or without addition of docetaxel. A total of 501 participants in the AAP-alone trial were enrolled and treated between 2011-2013. In comparison, the AAP+ENZ trial enrolled and treated 462 participants between 2014-2016. Prof Attard emphasized the lack of an overlapping control group between the 2 arms. The primary outcome of the analysis was OS. Characteristics of patients in both trials were well balanced. The median age was 68 years (interquartile range [IQR], 63-72) and the median prostate-specific antigen value was and 96 ng/mL (IQR, 26-346). Most patients had de novo mHSPC at diagnosis (94%), with a minority of patients (6%) diagnosed with disease after initial therapy. Prof Attard also explained that both trials had robust data at follow-up (AAP, 95.8 months; AAP+ENZ, 71.7 months).

The data from this analysis provide conclusive evidence that there is no discernible clinical benefit when using AAP+ENZ in the mHSPC setting, as the OS improvements mentioned above are durable with just AAP (in addition to SOC) at >7 years after treatment.

Prof Attard next reviewed the results of the trials. Both demonstrated significant OS benefit (HR, 0.62 for AAP and 0.65 for AAP+ENZ), but there was no significant difference in benefit between them. The subgroup analysis in each trial also demonstrated some interesting findings. In the AAP-only trial, there was a significant difference in OS between patients aged <70 compared with those >70 (HR, 0.52 vs 0.83; *P*=0.002); however, no such difference was seen in the AAP+ENZ trial. A similar difference was seen in patients using nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin. In the AAP-only trial, patients taking aspirin or NSAIDs on a regular basis had a lower OS than those that who did not use these medications (0.78 vs 0.56; *P*=0.037); however, similar to the subgroup analysis for age, no difference was seen in the AAP+ENZ trial (0.63 vs 0.68; *P*=0.576). Prof Attard mentioned that, despite these findings, there is currently no biological explanation for this interaction between NSAIDs or aspirin and AAP or ENZ.

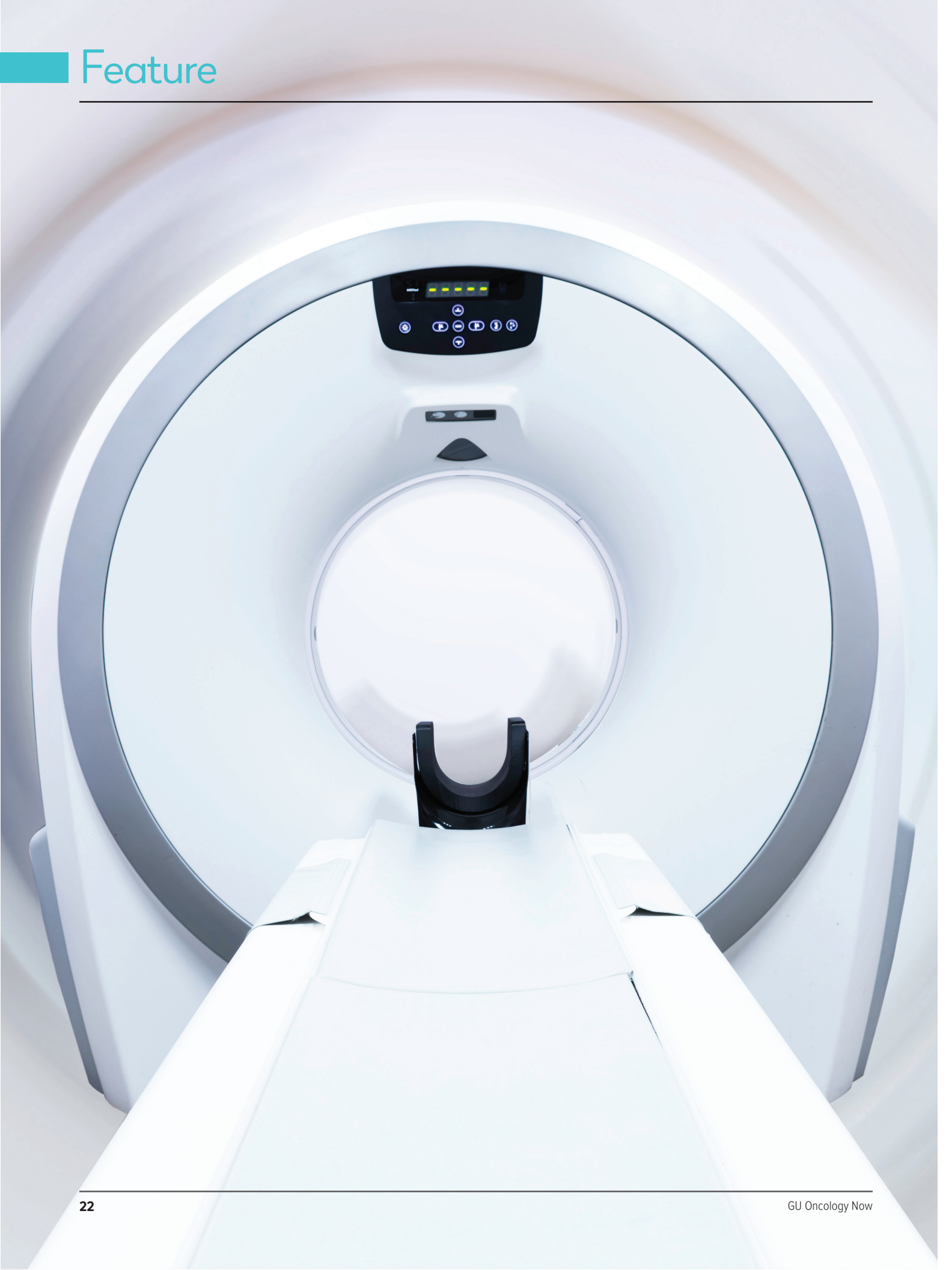
The final OS-related subgroup analysis that Prof Attard discussed concerned the utility of docetaxel. Specifically, later in the AAP+ENZ trial, investigators had the option of co-administering docetaxel with AAP+ENZ to investigate the potential for any significant drug to drug interactions between cytotoxic chemotherapy and AAP+ENZ. The current data suggest there are no significant interactions.

Regarding secondary outcomes, Prof Attard remarked that MFS was similar between the AAP (HR, 0.50) and AAP+ENZ trials (HR, 0.52), suggesting no significant treatment effect differences. He also discussed the findings on AEs with the medication combinations. Briefly, he explained that although AEs were similar between the AAP and AAP+ENZ trials, patients in the latter trial experienced them more frequently. Fatigue, transaminitis, and hypertension were noted in both groups, but hypertension occurred more frequently in the AAP+ENZ trial.

In concluding remarks, Prof Attard reviewed several key data points. Comparison of patients in the original SOC vs SOC+AAP trial, showed that the addition of AAP in these patients resulted in an 18% survival benefit at 84 months of follow-up (48% vs 30%, as demonstrated by event-free survival). The data from this analysis provide conclusive evidence that there is no discernible clinical benefit when using AAP+ENZ in the mHSPC setting, as the OS improvements mentioned above are durable with just AAP (in addition to SOC) at >7 years after treatment.

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Role of PET/CT in Metastatic Renal Cell Carcinoma

Akhil A. Saji, MD

RENAL CELL CARCINOMA (RCC) is the eighth most commonly diagnosed malignancy in the United States and the third most commonly diagnosed genitourinary malignancy (following prostate and bladder cancer).[1] According to 2019 data, more than 68,000 new cases of RCC were diagnosed and more than 14,000 individuals died of an RCC-related mortality. Estimates for 2022 show a linear growth in new cases to 79,000; however, a lower death rate of 13,920 is also modeled.[2] Rates of RCC diagnoses are not evenly distributed across the United States; people living in southern states such as Oklahoma, Texas, Arkansas, Louisiana, Mississippi, and Alabama are diagnosed at markedly higher rates compared with the rest of the country (median, 21 per 100,000 persons for southern states vs a national median of 17 per 100,000 persons).[3] To make matters worse, most cases of RCC-related mortality occur in patients with metastatic RCC,[4, 5, 6, 7, 8] with common sites of spread including the lung, bone, liver, and brain.

The management of metastatic RCC has continued to evolve rapidly as immunotherapy has become mainstream as a treatment strategy compared to the historical resistance to cytotoxic chemotherapy and radiation therapy that has plagued the management of RCC. Several phase 3 clinical trials have investigated different combinations of immunotherapy aiming for either dual immune checkpoint inhibition targeting PD-1 (programmed death 1) or targeting PD-L1 (programmed death ligand 1) in conjunction with CTLA-4 (cytotoxic T-lymphocyte associated protein 4). Alternatively, checkpoint inhibition plus tyrosine kinase inhibition (TKI) via the VEGF (vascular endothelial growth factor) or its receptor, VEGF-R, have been trialed. A recent meta-analysis9 comparing four phase 3 clinical trials with different regimens—CheckMate 214,[9] CheckMate 9ER,[10] KEYNOTE-426,[11] and KEYNOTE-58112 — demonstrated interesting results. The authors noted that the combination of checkpoint inhibition and TKI (CheckMate 9ER; cabozantinib plus nivolumab) provided maximal overall survival (OS) benefit.[9] Despite not being a direct noninferiority trial, these types of meta-analyses further emphasize that the therapeutic development of combination therapies for treatment of metastatic RCC will continue to evolve.

The advent of integrated imaging with positron emission tomography and computed tomography (PET/CT) has allowed clinicians to garner significant anatomical and oncologic information about a given tumor. However, traditional ^{18}F-fluoro-2-deoxy-2-d-glucose (FDG)- PET imaging for RCC has had several limitations. Under normal circumstances, the accumulation of FDG-6-phosphate within the cancer cells occurs because of the higher expression of glucose transporters and low intracellular glucose-6-phosphatase.13 However, in renal cancer, due to excretion of FDG via normal renal parenchyma, the utility of FDG-based PET imaging has been limited. Several authors have reported sensitivities in the range of 50-60 in the primary diagnostic setting.[13,14] Despite its limited role in that setting, FDG-PET can be useful for cross-sectional imaging evaluation of patients with suspected advanced or metastatic disease. In a series of 23 patients, Lee et al demonstrated that the median maximum standardized uptake value (SUV_{max}) was 2.6 in patients without metastatic disease and significantly higher in those with metastatic disease (5.0), supporting the contention that FDG-PET may be useful in evaluating patients for locally advanced or metastatic disease.[15]

Cases supporting other uses for FDG-PET also exist. For example, when evaluating patients suspected to have RCC-related thrombosis, FDG-PET imaging may assist in identifying malignant thrombosis of the inferior vena cava (IVC). In a series of 60 RCC patients, FDG-PET imaging detected 7 of 7 cases of IVC tumor invasion.[7] Further adding to the evidence, other studies have shown that FDG-PET can help delineate benign from malignant venous thromboembolism. In patients who have undergone primary treatment, and in whom there is concern for new recurrence or new sites of metastatic disease, a large pooled meta-analysis demonstrated that FDG-PET imaging has a sensitivity of 86% and specificity of 88%.[16] As targeted therapy for metastatic RCC continues to evolve, the ability to monitor disease progression has grown equivalently in importance. In a phase 2 series of 44 patients with

metastatic clear cell RCC receiving sunitinib treatment, FDG-PET imaging demonstrated on multivariate analysis that high SUVmax and greater PET-positive lesions correlated to a shorter OS.[17]

What about imaging based on prostate membrane-specific antigen (PSMA)? Despite its name, PSMA is highly expressed in a variety of solid tumors, including RCC.[18] This has allowed various authors to investigate the utility of PSMA-based PET imaging in an attempt to overcome the limitations of FDG-PET. In a limited series of 5 patients[19] with preexisting metastatic RCC, investigators used imaging with ^{18}F-DCFLPyL (Pylarify®); approved by the US Food and Drug Administration in 2021 for use in the prostate cancer setting. The authors reported that, for cross-sectional imaging, the sensitivity for detecting metastatic RCC with ^{18}F-DCFLPyL was 94.7% compared to 78.9% based on conventional imaging alone. Scans based on gallium-68 have also been investigated. Most recently, at the 2022 meeting of the American Urological Association (AUA), authors from the department of urology at Ludwig Maximilian University in Germany reported on their experience with 68Ga-EMP-100, a novel ligand targeting tumoral c-MET expression which is commonly elevated in clear cell RCC.[3] In a series of 12 patients, the authors demonstrated identification of 87 individual tumor lesions with a median c-MET–positive SUV_{max} of 4.4, with further positivity at the primary site (SUV_{max}, ~9). Such tools could improve patient selection, especially for patients undergoing consideration for treatment with cabozantinib, a TKI targeting the MET receptor.

Despite a growing volume of evidence and trials documenting the utility of PET and integrated PET/CT imaging in RCC, the AUA guidelines still do not advise clinicians to use PET-based imaging in the routine evaluation or staging of RCC. Furthermore, the role of PET in routine surveillance of RCC also remains unclear; however, the guidelines do advocate for considering PET-based imaging if traditional imaging is equivocal. Future prospective studies such as the ZIRCON (NCT03849118) phase 3 study evaluating the role of ^{89}Zr-TLX250 may provide further data to elucidate the specific role of PET/CT imaging in care of patients with RCC.[20]

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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.



Hereditary Renal Cell Carcinoma:

Presentations and Approaches to Treatment

By Daniel Tennenbaum, MD

THE PATHOGENESIS OF renal cell carcinoma (RCC) is multifactorial, and is often associated with obesity, hypertension, and smoking.[1] Moreover, ~5% of cases are thought to be associated with a family history of RCC. Familial RCC is often inherited in an autosomal dominant fashion, with varying degrees of penetrance. It is critical to discern familial RCC from RCC associated with a specific genetic mutation. Not all patients with a mutation of a predisposing gene for RCC will have a family history, as there can be de novo mutations that lead to the pathogenesis of the disease. Even when there is no family history, however, hereditary RCC may still be suspected in the presence of bilateral or multicentric tumors, or early development of RCC, at which point molecular genetic analysis may be performed. Additionally, in the presence of familial RCC, there often are syndromic multisystem findings, such as hemangioblastomas along with clear-cell RCC in von Hippel-Lindau (VHL) disease or pulmonary cysts along with chromophobe RCC in Birt-Hogg-Dubé syndrome (BHD).

In this article, we review some of the most important information about hereditary RCCs and the syndromes with which they present, as well as the relevant recommended guidelines for diagnosis and management.

Common Hereditary RCCs

VHL Disease

VHL disease is a rare autosomal dominant disorder, caused by mutation of the VHL tumor suppressor gene, with an incidence of ~1 in 30,000 persons. This mutation puts the lifetime risk of hemangioblastoma of either the retina or central nervous system, or clear-cell RCC at >70%.[2] These individuals are also at risk of developing pheochromocytoma, with a lifetime risk of development of 20%, or pancreatic neuroendocrine tumors (risk of 10%). On diagnostic imaging, these patients will often have multiple cysts within the kidney and/or the pancreas, which can assist with diagnosis. The *VHL* gene has a critical role in regulating hypoxic response within the cell. This has provided the rationale for the use of antiangiogenic tyrosine kinase inhibitors in the treatment of patients with RCC, as most clear-cell RCCs have mutations in the tumor-suppressing *VHL* gene.

Patients with confirmed VHL disease and their family members may or may not be symptomatic. Those who are found to carry the familial mutation must be screened annually to detect asymptomatic tumors. This screening is performed via cross sectional imaging—magnetic resonance imaging (MRI) is preferred to computed

tomography—starting at age 15 years and continuing every 2 years thereafter.[3] Because of their known risk, these patients are offered early intervention, as small RCCs are usually removed via nephron-sparing partial nephrectomy when they reach 3 cm in diameter.

Birt–Hogg–Dubé syndrome

BHD syndrome is characterized by an autosomal dominantly inherited predisposition to fibrofolliculomas (most often on the face), lung cysts with risk of developing spontaneous pneumothorax, RCC, and possibly colorectal tumors.[4] The risk of RCC in BHD syndrome is significantly less than that in VHL disease (approximately 25%), but annual renal surveillance cross-sectional imaging should be offered to patients and mutation carriers beginning at age 20 years and performed every 3 years thereafter. Although the characteristic RCC histology is considered to be chromophobe RCC with oncocytic elements, other more malignant subtypes have been described, including clear-cell RCC. The mutations that can cause BHD are germline-inactivating mutations in *FLCN*, the folliculin tumor-suppressor gene. They have also been found to cause nonsyndromic familial pneumothorax. The function of the *FLCN* gene product has not been fully elucidated; however, inactivation leads to activation of the mTOR (mammalian target of rapamycin) pathway, which has previously been used as a pharmacologic target for patients with poor-risk RCC treated with drugs such as combination everolimus/tacrolimus.

Hereditary Leiomyomatosis RCC

The presence of multiple cutaneous leiomyomas in a patient with RCC suggests a diagnosis of hereditary leiomyomatosis renal cell cancer (HLRCC). This very rare disorder—with an incidence of ~1 in 200,000—is caused by inactivating mutations in the *FH* gene that encodes fumarate hydratase, a key component of the tricarboxylic acid cycle. Women with this mutation may present with early-onset uterine fibroids. *FH* gene mutations are also a rare cause of inherited pheochromocytoma. RCC in HLRCC classically presents as papillary type II RCC or collecting duct RCC, both of which carry poor prognoses.5 Although the lifetime risk of RCC for patients with this condition is ~15%, it is typically an aggressive early metastatic tumor that can occur at a young age, with recommend annual surveillance beginning at 8 to 10 years of age. Therefore, practicing surveillance on an identified small tumor is not recommended. The recommended treatment is early radical nephrectomy.

Hereditary Papillary RCC

Activating mutations in the mesenchymal-epithelial transition (MET) proto-oncogene predispose patients to type I hereditary papillary RCC (HPRC). This is an extremely rare disorder that is inherited as an autosomal dominant trait with incomplete penetrance. Surveillance is recommended to begin at 30 years of age, with cross-sectional imaging conducted every 1 to 2 years. Type I papillary disease is often considered a less malignant disease than other RCC histologies, but if the patient presents with metastatic RCC, then treatment with a MET-inhibitor can be considered.

Bilateral or multicentric tumors, or early age of onset are classic features of inherited RCC, and are indications for genetic evaluation.

Diagnosis and Management

Diagnosis of Hereditary RCC

Bilateral or multicentric tumors, or early age of onset are classic features of inherited RCC, and are indications for genetic evaluation.[6] However, testing individuals at low prior risk for a mutation can lead to diagnostic uncertainties, owing to the identification of rare variants of uncertain significance (VUS). In cases of inherited RCC with syndromic features, molecular genetic testing can usually be expected to unequivocally confirm the diagnosis. This is particularly true for well-characterized genes such as *VHL*, in which a wide range of germline mutations have been described, whereas VUS are relatively infrequent. For less well-studied genes, interpretation can be more challenging. To further complicate the matter, there is no clear age at which genetic testing is definitively recommended. The mean diagnostic age of symptomatic RCC in patients with known VHL disease is approximately 45 years, compared with an average age of 60 years in patients with sporadic cases of RCC,[7] but there is no agreed-upon age at which patients with earlier-onset disease should be tested for RCC predisposition mutations.

The current National Comprehensive Cancer Network® guidelines recommend that patients aged R46 years with sporadic RCC should trigger consideration for germline mutation testing, to evaluate for any hereditary RCC syndromes.[3] However, because germline mutation detection rates are typically low, and for patients who test negative the residual risk of an underlying genetic cause is unclear, there are those who recommend consideration of a lower age threshold for testing (eg, 40 years).[8] The low mutation detection rate in familial nonsyndromic RCC suggests that there are more inherited RCC genes to be identified, and achieving a comprehensive picture of the molecular architecture of the disease is necessary to develop optimal evidence-based guidelines for the molecular investigation of potential inherited RCC.

Management and Surveillance of Inherited RCC

Over the past 3 decades, the identification and surveillance of large numbers of *VHL* mutation carriers has afforded the opportunity to achieve a broad consensus on the approach to treating patients with these mutations. In particular, a consensus has developed that small (<3 cm) tumors should be managed by active surveillance, followed by nephron-sparing surgery performed when a solid lesion reaches 3 cm in diameter. As an alternative to partial nephrectomy, percutaneous radiofrequency ablation (RFA) has been used to treat patients with small renal lesions in VHL disease.

Similarly, the approach to the managing RCCs identified through surveillance in VHL disease has been extrapolated to individuals with BHD syndrome with tumors followed by active surveillance. When the tumor reaches 3 cm in diameter, nephron-sparing surgery (or RFA) is performed. However, this "3-cm rule" is not suitable for renal lesions in HLRCC, which are frequently of the higher risk papillary type II variant that can metastasize early. Consequently, individuals with germline *FH* mutations are recommended to undergo annual MRI surveillance even though most will not develop a renal lesion, and surgical intervention is indicated for small screening-detected lesions.

In some patients, particularly those with no previous family history, diagnosis of an inherited RCC is only made after presentation with metastatic disease. Additionally, for individuals with VHL disease, there is the risk of developing multiple central nervous system hemangioblastomas, which often are not amenable to surgical treatment. For these reasons, further efforts are in progress to continue to improve the available medical therapeutics for patients with this disease. Most of the known inherited RCC genes encode tumor-suppressor genes, and biallelic inactivation of the relevant inherited RCC gene is present in all tumor cells. Therefore, in addition to standard therapies for metastatic RCC, use of targeted therapies with agents that exploit the specific molecular pathways represents a rational approach to therapy.

The concept of synthetic lethality-based interventions is particularly interesting for patients with inherited RCC in disorders such as VHL disease, because the kidneys of patients with VHL can harbor hundreds of tiny indolent tumors with biallelic VHL inactivation. This can potentially give rise to malignant RCC many years later.9 However, the development of novel therapeutic approaches to inherited RCC remains slow, with limited recommended regimens. VHL-associated RCC is currently treated with the novel therapeutic belzutifan, while HLRDD is treated with combination erlotinib plus bevacizumab. Further development will require a continued pursuit of deeper knowledge of the function of inherited RCC gene products and the consequences of mutations in the relevant pathways. A likely outcome of such research is the potential for translating the knowledge of the pathogenesis of inherited RCC into novel treatments for sporadic RCC.

Conclusion

A number of familial RCC syndromes and inherited nonsyndromic RCCs have been identified. Genetic evaluation or analysis is typically initiated by early onset of RCC, presence of bilateral or multicentric tumors, or histopathological features consistent with known syndromes. The principal strategy for preventing morbidity and mortality in individuals at risk for inherited RCC is detection of tumors that can be removed at an early stage (eg, HLRCC) or observed until they reach a safe size (eg, 3 cm in VHL disease and BHD syndrome) when removal of the tumor—usually with nephron preservation or ablation—is considered appropriate. Multicenter data sharing of inherited *RCC* gene variant information may facilitate evidence-based improvements in the diagnosis and management of these rare conditions.

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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 of "A Comparison of Percutaneous Ablation Therapy to Partial Nephrectomy for cT1a Renal Cancers

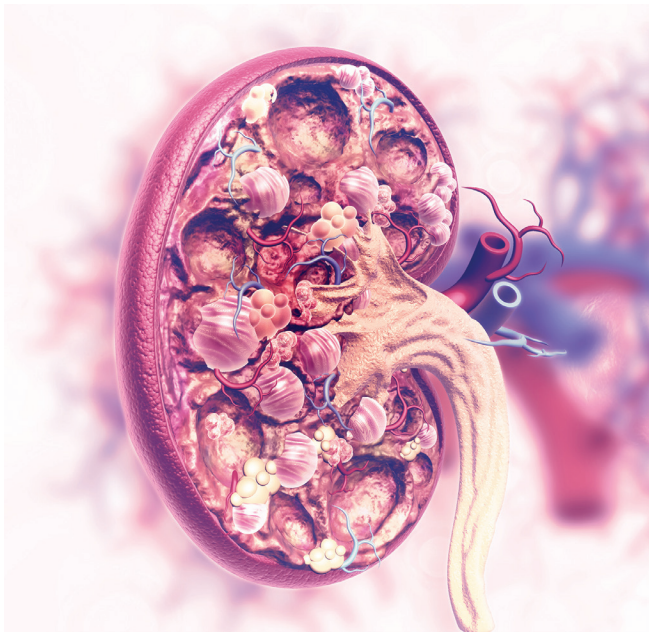
Results from the Canadian Kidney Cancer Information System (CKCis)"

David Ambinder, MD

IS THERE A RIGHT APPROACH to managing cT1a renal masses? In a recent publication in the *Journal of Urology*, researchers from Canada addressed this subject with emphasis on comparing percutaneous ablation with partial nephrectomy.[1] cT1a renal masses are defined as R4 cm in greatest dimension and limited to the kidney.[2] Currently, the gold standard approach, when amenable, is a partial nephrectomy, which has very high rates of disease-specific survival.[3] In recent years, however, these small renal masses have been managed with ablation strategies and active surveillance. Indeed, a systematic review in 2016 showed similar rates of cancer-specific survival and overall survival (OS) when renal masses were managed with ablation compared to partial nephrectomy.[4] The authors noted the strength of their evidence was low, but that past randomized controlled trials exploring use of ablation in this context had failed due to poor recruitment.

In 2019, a large single-institution study comparing partial nephrectomy, radiofrequency ablation (RFA), and cryoablation found no difference between the procedures in local recurrence rates, metastasis-free survival, or mortality.[5] Against this background, the current study was established to "report on the largest multi-institutional comparison of ablation and partial nephrectomy for cT1a renal tumors" using the Canadian Kidney Cancer Information System (CKCis) database, a prospective national cohort collecting data on patients with any renal malignancy from 14 Canadian academic institutions.[6]

Patients included in the study underwent a partial nephrectomy or ablation with either RFA or cryoablation for cT1aN0M0 disease over a 10-year period from 2011 to 2021. Important exclusion criteria were presence of multiple renal masses, benign or missing tumor pathology,



and non–renal cell carcinoma (RCC) histology. Baseline characteristics were collected, and the primary outcomes were defined as recurrence-free survival (RFS) and OS. Recurrence was defined as a new focal enhancement in the ablation or resection bed, enlargement of the ablation defect, or evidence of metastasis on imaging studies. The authors defined OS as survival until death from any cause. Importantly, follow-up imaging was at the discretion of the clinician and not protocoled. The authors analyzed the data with inverse probability of treatment weighting (IPTW) with propensity scores to mitigate against differences in baseline characteristics.

After applying the exclusion criteria, 2276 patients were enrolled in the study, 2001 of whom underwent partial nephrectomy and 275 who underwent ablation with cryoablation (n=129) or RFA (n=146). Patients in the partial nephrectomy cohort tended to be younger (60 vs 67 years) and had fewer comorbidities (Charlson Comorbidity Index [CCI], 4 vs 5). No significant differences were seen when comparing tumor size, sex, race, or smoking history. Median follow-up for patients was longer in the ablation cohort when compared with the partial nephrectomy cohort (2.6 vs 2 years). A total of 24% of patients were lost to follow-up in the partial nephrectomy cohort, compared with 21% in the ablation cohorts. In both cohorts, a higher CCI, larger tumor size, and male sex were associated with a higher risk of recurrence. Similarly, OS was associated with a higher CCI and male sex. Univariate analysis revealed that RFS (hazard ratio [HR], 0.26; 95% confidence interval [CI], 0.17-0.39; $P<0.001$) and OS (HR, 0.46; 95% CI, 0.26-0.81; $P=0.007$) significantly favored partial nephrectomy.

Kaplan-Meier curves presented by the authors indicated that the event rate for disease recurrence at 5 years was seen in 11% of patients who received ablation vs 2.5% who had a partial nephrectomy. Similarly, death from any cause at 5 years was seen in 5.8% versus 2.1% in the ablation versus partial nephrectomy cohorts, respectively. The authors also reported that of the patients who underwent ablation therapy and had recurrence, 12 underwent surgery (3 partial nephrectomies, 9 radical nephrectomies), 13 underwent repeat ablation therapy (9 RFAs, 4 cryoablations), and 3 received systemic therapy. Only 1 patient underwent RFA followed by a partial nephrectomy, and 4 patients underwent no further treatment. Of the patients who initially underwent a partial nephrectomy and had disease recurrence or metastases, 13 required repeat surgery alone (8 second partial nephrectomies, 5 radical nephrectomies); 5 underwent ablation (3 RFAs, 2 cryoablations); 8 underwent surgery (1 partial nephrectomy; 7 radical nephrectomies) plus systemic therapy; 1 underwent ablation followed by radical nephrectomy with subsequent systemic therapy; 20 underwent systemic therapy; and 16 had no further management.

When propensity scoring with IPTW was used to compare ~1500 patients who underwent partial nephrectomy to 164 who underwent ablation therapy – RFS was significantly improved in those who underwent a partial nephrectomy compared to those who underwent ablation (adjusted HR, 0.36; 95% CI, 0.18-0.71; $P=0.003$), however, there was no statistically significant difference in OS between patients who underwent partial nephrectomy and those who underwent ablation therapy.

The authors commented that their large multicenter report using IPTW propensity scoring adjustments adds to the literature by informing on an important treatment-related outcome: There is an increasing number of patients who are treated for small renal masses and, although guidelines include both partial nephrectomy and ablation therapy as options, the studies that support ablation therapy are limited by tumor heterogeneity, only rare biopsy confirmation of RCC, older age of patients, and small retrospective cohorts. In contrast, in addition to using IPTW propensity scoring adjustments, the present study included a multicenter cohort with confirmed RCC, and the patients who underwent ablation therapy were younger than in many other previously published studies.

The authors concluded that "these results emphasize that although these two treatment options are offered to different patient populations, the local cancer control of partial nephrectomy is superior."

After IPTW propensity scoring adjustments, the authors found no statistically significant difference in OS between patients receiving partial nephrectomy versus ablation. A difference favoring partial nephrectomy was seen in RFS at 2 years (97.4% vs 88.1%; HR; 0.36; 95% CI, 0.18-0.71; $P=0.003$). The authors concluded that "these results emphasize that although these two treatment options are offered to different patient populations, the local cancer control of partial nephrectomy is superior."

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