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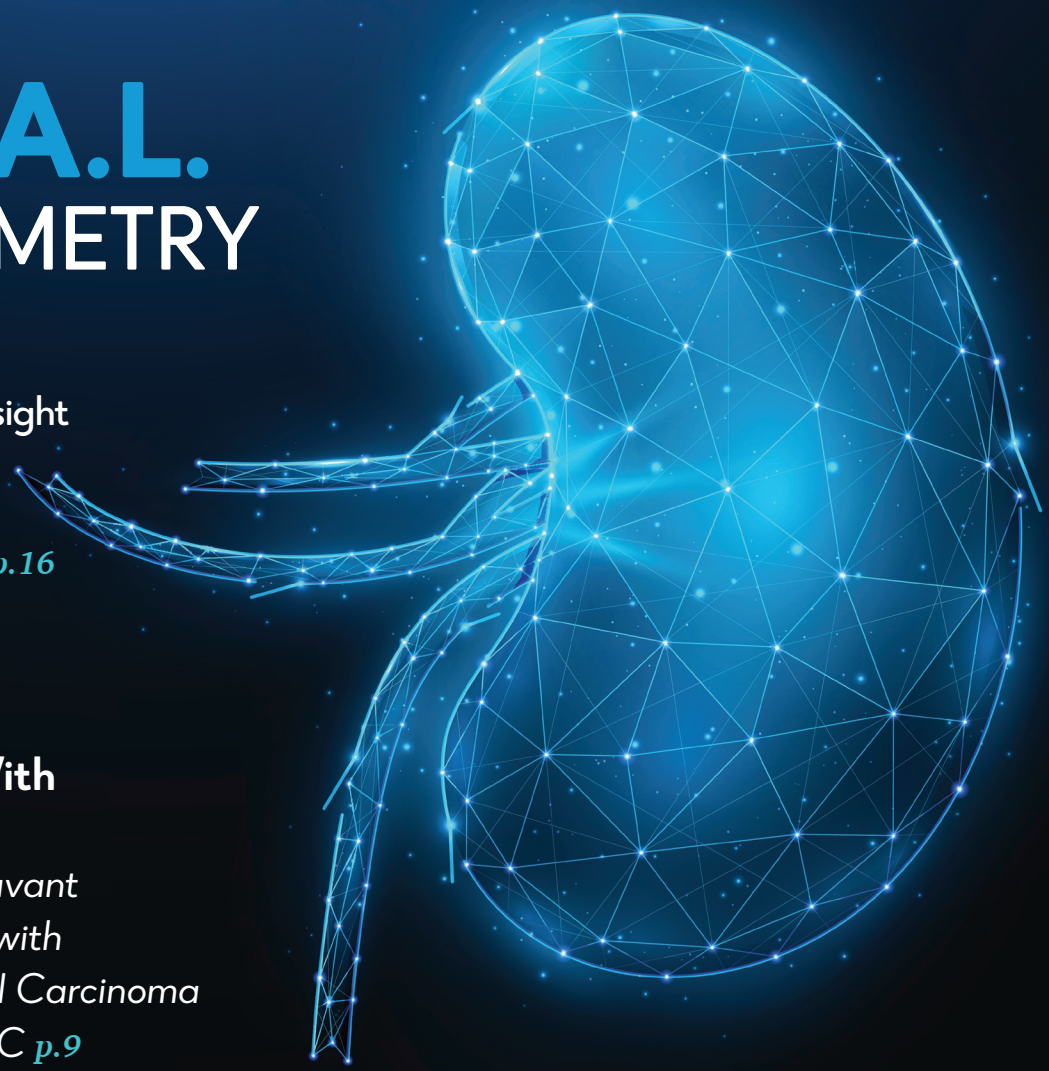
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THE R.E.N.A.L. NEPHROMETRY SCORE:

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PROFILES IN GU ONCOLOGY

Bradley A. McGregor, MD



Dr McGregor relates how his years practicing general oncology in military hospitals led to his current position as clinical trial leader specializing in genitourinary oncology at the Dana-Farber Cancer Institute. p.6

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(kit for the preparation of gallium Ga 68 gozetotide Injection)

Illuccix is now separately reimbursed in the hospital outpatient setting!

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^{68}Ga-PSMA-11 (also known as gallium Ga 68 gozetotide) is a widely accessible radioisotope for PSMA PET imaging with:

- Nationwide distribution network of generators and cyclotrons, including those within major academic centers and community health systems[2]
- Capability for either high-volume production or on-site, on-demand production[2,3]
- Flexibility to image patients throughout the day, even on short notice[3]

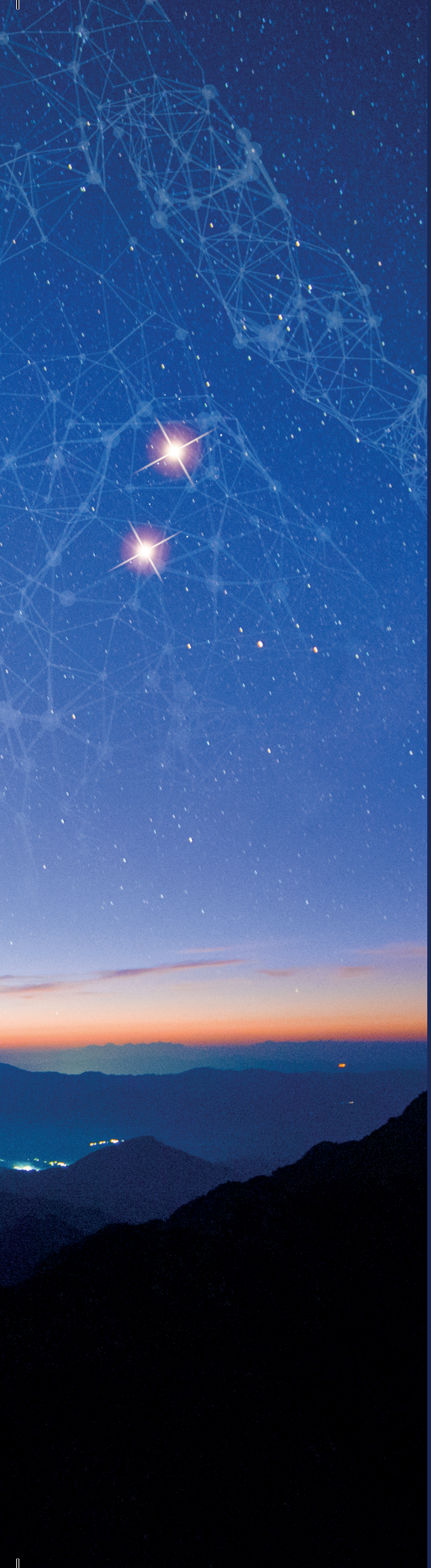
Illuccix® for the preparation of ^{68}Ga-PSMA-11 is poised to expand the potential of PSMA PET imaging and help guide more informed management decisions in prostate cancer.[1-4]



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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INDICATIONS AND USAGE

Illuccix®, after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer:

- with suspected metastasis who are candidates for initial definitive therapy
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level

Important Safety Information

WARNINGS AND PRECAUTIONS

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

Risk for Misdiagnosis
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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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Chemotherapy in Advanced Prostate Cancer

Catherine H. Marshall, MD, MPH



Catherine H. Marshall, MD, MpH

PROSTATE CANCER CONTINUES to be the second leading cause of cancer mortality in American men[1] with an estimated 35,000 anticipated deaths in 2022. The treatment of advanced prostate cancer has evolved dramatically in the past decade with the introduction of several novel anti-androgen pathway inhibitors as well as further defining the role of chemotherapy and even newer modalities such as PSMA directed theranostic radiation therapy. In this interview, Dr Akhil Saji, MD talks with Dr Catherine H. Marshall about the current state of chemotherapy in advanced prostate cancer and how she uses the available modalities in her practice.

Akhil Saji, MD: Let's start by talking about chemotherapy in general. Which ones do you use in the treatment of advanced prostate cancer?

Catherine H. Marshall, MD, MPH: So there are two that we use primarily. One is docetaxel and the other is cabazitaxel. They both work by interfering with microtubules in the tumor cells leading to cell death. Both are approved for use in advanced prostate cancer, but cabazitaxel is only approved for use after docetaxel or for patients who are ineligible for docetaxel. I also use carboplatin sometimes in combination with docetaxel or cabazitaxel, but that is used less commonly.

Could we talk about when you would recommend chemotherapy for a patient with prostate cancer? We



can start by first talking about the metastatic castration naïve setting and then talk about your thoughts on where chemotherapy fits into the setting of men with castration resistant disease.

First, in the castration naïve setting, I consider adding chemotherapy in patients with high volume disease. This is defined by people who either have visceral disease or people with significant bony disease. For example, patients who present with disease that has spread to the liver, I will almost always recommend, or at least discuss adding chemotherapy to the treatment regimen. For patients with bony disease, the threshold for defining high volume in many trials was 4 bony lesions with at least one outside of the axial skeleton. For patients who just meet that criteria or are close to it, it is usually more of a discussion. For patients who are way behind the 4 bony lesions, I almost always am discussing chemotherapy with those patients. For patients with lymph node only disease, I usually do not recommend chemotherapy.





...And in the castration resistant setting?

In the metastatic castration resistant prostate cancer setting, data from the CARD trial supports using chemotherapy in between the oral androgen axis targeting drugs. So I talk to patients about those data. For patients who have rapidly progressing disease, or symptomatic disease, I also usually recommend chemotherapy over other agents in that setting too. If they've never received chemotherapy, then I usually do docetaxel. If they've received prior docetaxel, now actually they may be candidates for lutetium PSMA treatment, or I would recommend cabazitaxel.

In terms of the patients who do get the upfront chemotherapy, do you find that they all complete their full six courses, or do a lot of people have unacceptable toxicities earlier than the 6 doses?

Most patients are able to complete the six doses, especially early on in the disease course. Ability to withstand the toxicities is also something I consider when deciding when to give chemotherapy. Sometimes, if patients have certain disease-based risk factors that suggest a particularly aggressive prostate cancer, I think they will need chemotherapy at some point soon. I will try and use chemotherapy earlier rather than later when performance status is better. But most patients are able to get through six cycles of docetaxel.

Is that the case in castration resistant setting too?

For the castration resistant setting, I still only do about six to 10 cycles. I don't usually go beyond 10 cycles of chemotherapy, and try and get through at least four cycles of chemotherapy before determining disease response. So I do tell patients that they will have at least four and a maximum of 10 cycles of chemotherapy when we do that.

Looking to the future, what is on the horizon?

There are some newer chemotherapy agents that are being tested, so it'll be interesting to see how those trials turn out and whether or not new strategies in terms of chemotherapy are effective in prostate cancer. And then with the agents that we have, docetaxel and cabazitaxel, there are some interesting combination trials with non-chemotherapy agents and also some other chemotherapy agents that might also be beneficial.

I think in general, we're going to get to a place where we are becoming more refined, especially later on, and we will be able to identify more biomarkers as well determine who has disease most likely to respond to chemotherapy, or less likely to respond to the oral agents, so then would benefit from chemotherapy.

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Taking a Different Road Toward Clinical Research

–Bradley A. McGregor, MD

Linda Brookes, MSc

BRADLEY ("BRAD") MCGREGOR, MD, is currently Director of Clinical Research at the Lank Center for Genitourinary Oncology and Senior Physician, specializing in genitourinary (GU) malignancies at the Dana-Farber Cancer Institute, as well as Instructor in Medicine at Harvard Medical School. At first glance, his career path appears to have been similar to that of many other GU oncologists in academic medicine –- early ambition to become a physician followed by graduation from a prestigious medical school –- but his commitment to the US Air Force ensured that his postgraduate training and clinical practice were different from the usual track. "I've had a very unusual path for academic medicine compared to most," Dr McGregor acknowledges.

Dr McGregor's view of the military – and the medical profession – was formed as he was growing up the son of a navigator in the US Air Force. Born in California, he and his family moved around the US with his father's work. When he was 10 years old, his father was diagnosed with acute lymphoblastic leukemia (ALL) and the care he received from the military greatly impressed the youngster. "I remember very clearly, we were in Nebraska, and he was air-evac'd out to San Antonio, where he got treated, He was actually cured of ALL, which to this day is still amazing," Dr McGregor recalls. "So from a young age I wanted to be a doctor and to be able to do the same things those doctors did for my dad," he says.

After his father recovered and was medically retired from the Air Force, the family moved to New England. When it was time for college, Dr McGregor was accepted by Tufts University School of Medicine into the MD Early Assurance Program. "My dad being in the military, with the financial implications of medical school, I joined the Air Force under the Air Force Health Professions Scholarship Program (HPSP)," he explains.

After graduating in 2004, he envisaged himself staying in Boston, "but the military had other ideas" and he ended up going to the San Antonio Uniformed Services Health Education Consortium (SAUSHEC) to do his residency (internal medicine) and fellowship (hematology/oncology). SAUSHEC is one of two major Department of Defense multi-service graduate health education platforms in the US (the other is National Capital Consortium at Walter Reed National Military Medical Center). "I actually did my training at the same hospital, Wilford Hall Medical Center, where my dad received his treatment for ALL," he notes. During this time, he obtained board certification in internal medicine (2007), hematology (2010), and medical oncology (2010)

After his postgraduate training, he began his service in the Air Force, providing oncologic care to active-duty members, their families, and retirees. He remained in San Antonio as staff for one additional year and then with his wife, whom he had met and married in San Antonio, he moved to California, to work at the David Grant USAF Medical Center at Travis Air Force Base in Fairfield, CA. While in the 60th Medical Operations Squadron, he provided oncologic care across the spectrum of malignant

and benign hematology and medical oncology. “While I was in California, I saw everything – I was constantly learning,” he recollects. “There were 4 to 5 of us in the department at any given time and so you would get comfortable with everything, including the really rare cancers,” he adds.

Since he signed on to Air Force, however, the military had been changing. “Before 2004, deploymerntsdeployments of physicians were infrequent, but then it became a much different experience overall, starting with people going out to Iraq,” Dr McGregor explains. So in September 2012, shortly after he found out his wife was pregnant with their first child, he found out that he would be deploying to Afghanistan as an advisor to the Afghan national army. He spent the next 6 months training for deployment, including basic and weapons skills. (“I did OK, but I’m still nervous holding a weapon,” he admits.) He was deployed in January 2013. Luckily, he kept in touch with his wife via FaceTime and he was there for virtually for the birth of his daughter in March 2013, while he was overseas.

At the time of his deployment, the NATO-led International Security Assistance Force (ISAF) in Afghanistan was in the process of transferring command of combat missions to the Afghan forces and moving to advising and training. Dr McGregor served as Deputy Commander of the Medical Training Advisory group in Kabul. His role was advisor to the Afghan National Army, working with military physicians to help improve their health care system, “Every morning I would put on my body armor and helmet, take up my assault rifle, and leave the US compound and walk over to the Afghan compound,” he recollects. He mentored physicians, both men and women, at the Afghan Military Hospital the largest military medical facility in Afghanistan, “I mentored in different aspects of medicine and running a hospital, from things like how to park the ambulances next to each other and not behind each other so you don’t have to wait for each driver to leave to providing lectures on ICU care,” he says. It gave him a lot of experience, “but I think about the doctors I mentored and what might have happened to them since then,” he admits. He reached the rank of Lieutenant Colonel and received the Meritorious Service medal.

In July 2016, Dr McGregor left the Air Force. “My time in the military was up and I wanted to do more,” he explains. “I wanted to be an expert in oncology, which is challenging when practicing all hematology and oncology, and we wanted to live on the East Coast. Dana-Farber had an option for a GU clinical oncologist to see patients, and I thought, that sounds perfect. So I applied and said to them, ‘I want to do this. I’ve no specific GU background, but I’m an excellent doctor and I will excvelexcel in this role.’ In many ways, though, I think I was a risk, because I’m not the classical path” he acknowledges. “But the military taught me that there are things under my control and things that are not





Top: With patient Lamar Valentina, at the Jimmy Fund Radiotelethon (fundraiser for Dana-Farber)
Above: In military uniform at the Red Sox game being honored as part of their “Hats off to Heroes”

under my control, and I have to seize opportunities when I can. So I would seek out opportunities, but I wouldn’t try to make opportunities that weren’t there.” It worked well. His goal was to be a clinical trialist within 2 or 3 years, and within 2 years, he was leading clinical trial enrollment for his group. “I evolved quite quickly from a clinician to a clinical trialist,” he says. “It’s given me amazing opportunities, and now I am at a point where I can be more selective and I can choose my path a little more.”

Nowadays he spends one day a week at each of

Dana-Farber's two locations, at Boston (Longwood) and Chestnut Hill, seeing patients with adrenocortical carcinoma, bladder cancer, kidney cancer, penile cancer, prostate cancer, or testicular cancer. The rest of his week is taken up with a range of institute responsibilities. He also serves as the Dana Farber GU Network Liaison with other hospitals within the New England area.

"I was recently very heavily involved in the EV-201 trial, which led to the regulatory approval of enfortumab vedotin in bladder cancer." –Dr Brad McGregor

From a research perspective, Dr McGregor is currently focused on kidney cancer and bladder cancer. "I was recently very heavily involved in the EV-201 trial, which led to the regulatory approval of enfortumab vedotin in bladder cancer," he notes.[1-4] He also co-authored the report of the COSMIC-021 trial results in patients with advanced clear cell and non-clear cell renal cell carcinoma who received combination cabozantinib plus atezolizumab as well as first data on VEGF/IO combinations in RCC with variant hisotlogy with atezo-bev (McGgregor et al, JCO).[5]

The ongoing trials that he is most excited about for the near future include a phase 2 study of nivolumab combined with ipilimumab in rare GU tumors (NCT03333616). It already showed a 37% response rate in bladder and upper tract carcinoma of variant histology,[6] which led to an expansion cohort of an additional 24 patients. "That trial just completed accrual, so I'm hoping that we will have results to publish or present in the near future," he says. "If we can show that that response rate is maintained in a large patient population, it may be a new option for these patients." The CaNI (cabozantinib in combination with nivolumab and ipilimumab) trial, (NCT04413123) is a phase 2 study in advanced non-clear cell renal cell carcinoma.[7]

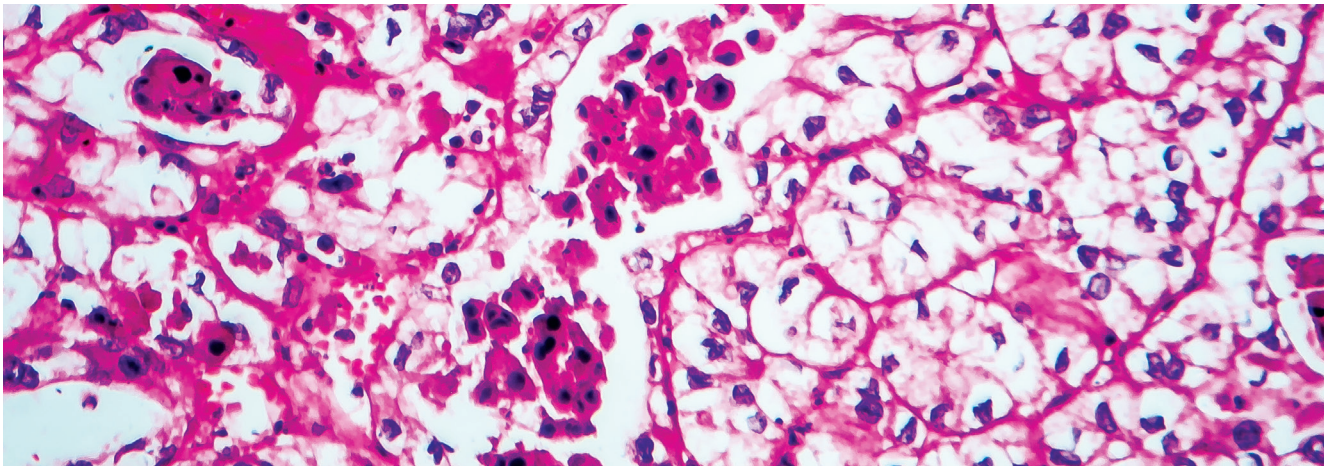
"We have an accrual of 40 patients. We've seen data for the triplet in clear cell disease and I hope we can add data for the variant histology," he says. He anticipates that those data will be ready in the next 6 months. Another trial of particular interest is the DAD (Double Antibody Drug conjugate) trial (NCT04724018), a single-center, open-label, nonrandomized phase I trial looking at sacituzumab govitecan plus enfortumab vedotin for metastatic urothelial carcinoma progressing on platinum-based chemotherapy and PD-1/L1 inhibitors.[8] "We have enrolled over 16 patients and will enroll 8 more. We expect to complete the trial in 2023 and are already discussing expansion of the trial," he predicts.

"A lot of people have helped me find my niche and helped me be where I am today." Dr McGregor acknowledges. At Dana-Farber, he is particularly grateful to Toni Choueiri, MD, Director of the Lank Center for Genitourinary Oncology, and to medical oncologists Mary-Ellen Taplin, MD and Christopher Sweeney, MB, BS who have provided mentorship in the past 6 years. Going back to his time in the military, he recalls Michael B. Osswald, MD, hematologist at the Brooke Army Medical Center, as "an amazing mentor who helped me become a clinical oncologist, without a doubt."

Outside of his office and time spent with his family (he and his wife now have three children), Dr McGregor spends a good deal of his time cycling. " I have a Peloton, I'm a Peloton junkie," he confesses. He combines his love of cycling with raising money for cancer research and treatment. He regularly rides the Pan-Mass Challenge, an annual Massachusetts-based bike-a-thon that raises funds for the Dana-Farber Cancer Institute. He also loves to bake and cook. In addition, he loves to cook, and while baking is his passion, he relishes the opportunity to cook for his family on the weekends. And he hasn't completely cut his ties to the US military; in his spare time he serves in the Air Force Reserve, still giving back for the care his father received and for the training that enabled him to reach his career goal.

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Outlook for Neoadjuvant Therapy in Patients with High-Risk Renal Cell Carcinoma After PROSPER RCC

Linda Brookes, MSc

THE 2022 ANNUAL CONGRESS of the European Society of Medical Oncology (ESMO), held September 9-13, featured the results of three eagerly anticipated Phase 3 trials of adjuvant immunotherapy in renal cell carcinoma (RCC). All three trials failed to meet their primary endpoint, most disappointingly PROSPER RCC,*[1] which took the novel approach of adding neoadjuvant therapy on one arm. Shortly after presentation of PROSPER RCC, Thomas Powles, MBBS, MD, (Barts Cancer Centre, London, UK) and Brian Rini, MD (Vanderbilt University, Nashville, TN) met up with the presenter, Mohamad E. Allaf, MD, Urologist-in-Chief of the Johns Hopkins Hospital, Baltimore and Professor of Urology and Oncology, to review the trial and discuss its implications for clinical practice (Uromigos podcast episode 191).

The Phase III RandOmized Study Comparing PERioperative nivolumab versus observation in patients with Renal Cell Carcinoma (PROSPER RCC trial, also known as ECOG-ACRIN EA8143 (NCT03055013), was a randomized open-label trial that compared neoadjuvant nivolumab prior to nephrectomy followed by adjuvant nivolumab versus surgery alone in patients with high-risk RCC.[2,3] The premise of the trial, Dr Allaf explained, was to leverage neoadjuvant therapy and the promise of potentially eliciting a better and stronger immune response by priming the immune system, while also maximizing the immune effect by continuing immune engagement with the adjuvant doses. The study was conducted by the ECOG-ACRIN Cancer Research Group and funded by the National Cancer Institute and the Canadian Cancer Society. Expectations for PROSPER RCC were high following the positive results with pembrolizumab in the adjuvant setting in the KEYNOTE-564 trial.[4]

Between February 2017 and June 2021, 404 patients were randomized to perioperative nivolumab 480 mg IV administered every 4 weeks with 1 dose prior to surgery (partial or radical nephrectomy) followed by 9 adjuvant doses and 415 to surgery alone followed by surveillance without a placebo. Clinical stage at enrollment was 53% cT2, 47% cT3-4, 17% cN1, and 4% cM1; 83% of patients

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had clear cell RCC. Select oligometastatic disease was permitted if the patient could be rendered "no evidence of disease" within 12 weeks of surgery. Baseline tumor biopsy was required only in patients on the nivolumab arm.

The trial was stopped early by the Data and Safety Monitoring Committee (DSMC) due to futility. After a median follow-up of 16 months, the primary endpoint, recurrence free survival (RFS), was similar on the two study arms (HR 0.97; 95% CI: [0.74 – 1.28]; P1-sided = 0.43). Median RFS was not reached. Data for overall survival (OS), a secondary endpoint, were not mature at the time of analysis but showed no statistical difference between the two arms. Withdrawal rates were about 12% with the nivolumab and surgery-alone arms and 20% of patients treated with nivolumab experienced at least one Grade 3-4 drug-related adverse event.

"Had we done it differently with different methods, and I'm not sure what they would be, could we get a positive study that way? Do you think we've answered that question definitively? Is this the end of neoadjuvant studies?" –Dr Powles

During his presentation, Dr Allaf expressed pride in the involvement of patient advocates in the trial design. Initially, the patients were not enthusiastic about a placebo arm. Their other major concern was that they did not want to get nivolumab if they did not have RCC. Enrolling patients into PROSPER RCC was a *tour de force,* Dr Allaf said. "It took multiple years and there were a lot of logistical hurdles," he admitted. "Initially we were a little slow. It was a unique trial design, urology-centered, and we needed urologists who would usually put patients on surgery within a week or two after seeing them to pause, think about a trial, and change their thought process and decision making," he explained. Some patients were also concerned about delaying their treatment. "But with the help of urologists, teamed with oncologists and the Society of Urologic Oncology Clinical Trials Consortium (SUO-CTC), we were able to accrue fully," he said.

Dr Rini wondered about the rationale for including patients' non-clear cell RCC (nccRCC), observing that since half the patients did not have a biopsy before surgery, there was no choice but to include these patients. Dr Allaf explained that the number of nccRCC patients was capped, but that the threshold for stopping accrual of these patients was never reached. It will be an interesting subset analysis to look at that population alone, he suggested.

Dr Rini noted that on the nivolumab arm of the trial, as many as 47 patients did not receive the allocated intervention, including 20 who were ineligible and, surprisingly, 22 who refused before starting protocol therapies. "You would have thought that if they were randomized to nivolumab arm, they would be happy," he remarked. "This was an early interim analysis and we need to go and look at these ineligible patients and dropouts, to see exactly what happened," Dr Allaf replied. There were also 45 patients who did not receive surgery on the nivolumab arm compared with 28 on the observation arm, and 51 on the nivolumab arm who did not get the neoadjuvant dose and then, "surprisingly to me," 90 who did not receive any adjuvant therapy, he recalled. "It's not known whether these were patients who had a T1 low-grade tumor and were told by someone to get out of the trial and not take a toxic drug if they were cured, or people with high-grade disease who really needed it," Dr Allaf said. Dr Powles wondered how much that influenced the results, because they were "a bit disappointing," he said. Many people were expecting positive results, similar to those of the melanoma trial, SWOG S1801, presented earlier at the ESMO congress, in which neoadjuvant therapy with pembrolizumab in patients with high-risk resectable disease was found to improve event-free survival compared with adjuvant pembroliumab.[5]

Dr Powles wondered why the neoadjuvant approach was not effective in this disease. "Had we done it differently with different methods, and I'm not sure what they would be, could we get a positive study that way? Do you think we've answered that question definitively? Is this the end of neoadjuvant studies?" he asked. Dr Allaf hopes that "we are at the beginning of more investigations in the neoadjuvant space." He pointed out that when PROSPER RCC was designed, much less was known about neoadjuvant therapy, particularly about the toxicity of PD-1 inhibitors. He cited the ASSURE trial ((ECOG-ACRIN E2805), which started in 2006 and in which over 55% of patients treated with a VEGF receptor tyrosine kinase inhibitor (sunitinib or sorafenib) had grade r3 adverse effects.[6] "Now we know how to take care of those," he noted. He also suggested that the dosing of nivolumab in PROSPER RCC might have been too low. Initially he had favored a trial with three doses of nivolumab on the neoadjuvant arm, but that design had been rejected. "It may be difficult to achieve CR with one neoadjuvant cycle," Dr Powles agreed. There are also issues of the study's being open label and not having a placebo arm, he added. Dr Allaf defended the trial as a real world experience. "Unlike a well-curated adjuvant trial where everybody gets surgery and then you pick the ones to get it, in a neoadjuvant trial, how many aren't going to

get the surgery? How many are going to refuse therapy or for whatever reason? I think we're going to learn a lot from this," he predicted.

Dr Powles was concerned that the trial definition of an event was a progression event, which is standard, but also not having surgery. "That is obviously challenging, because many of those patients who didn't have surgery did not have it because their cancer was getting worse; it was the reverse," he noted. "How do you address that bias and do you think that this is a robust surrogate for OS?" Dr Allaf replied that they don't know what happened to the patients who did not have surgery. "I doubt that the patients who responded dropped off because they were doing well, They may have enrolled in the trial and had surgery locally and it's not recorded. We need to look into that further," he commented. He added that they had re-examined the data "and our statisticians are very comfortable saying that it met futility, at least as designed," he said. "The question is, where do we go from here?"

Dr Rini observed that four studies with adjuvant immune checkpoint inhibitor therapy in RCC have now reported, three negative (CheckMate-914,[7] IMmotion010,[8] and PROSPER RCC[1]) and one positive (KEYNOTE-564[5]). Dr Powles would now like to see a biomarker study examine whether it would be possible to identify patients who would benefit from therapy. "I feel that we are reaching a plateau with immune therapy," he stated. "I'm not sure that pursuing it any further in this disease is necessarily the right thing to do " He noted that the results of the LITESPARK022 trial (NCT05239728) with the hypoxia-inducible factor (HIF)-2α inhibitor belzutifan added to pembrolizumab,[9] and RAMPART (NCT03288532), comparing durvalumab (a PD-L1 inhibitor) plus tremelimumab (a CTLA-4 inhibitor) with durvalumab monotherapy,[10] are pending. "I suspect the PROSPER RCC study had some flaws and that under those circumstances, there is scope for a second, really clean PD-1 inhibitor study. But I don't think that would move the field forward," he said. "I would like to see a randomized phase 2 of three cycles of neoadjuvant therapy rather than one, but that wouldn't be top priority," he added. "I think we should move the field forward with new-generation drugs and new-generation biomarkers. Now that we have hit this plateau, I don't think we can go much further with VEGF-targeted therapy or with single agent immune checkpoint inhibition.

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

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*PROSPER RCC" to avoid confusion with the PROSPER trial (A multinational, phase 3, randomized, double-blind, placebo-controlled, efficacy and safety study of enzalutamide in patients with nonmetastatic castration-resistant prostate cancer; NCT02003924).



Thomas Powles, MBBS, MRCP, MD

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Brian Rini, MD

Review of Study on Phase 1/2 Trial Results of a Large Surface Area Microparticle Docetaxel for the Treatment of High-Risk NMIBC

By David Ambinder, MD

MIGHT THERE BE A NEW delivery mechanism available to administer intravesical docetaxel? According to a recently published study in the *Journal of Urology* by Dr. Max Kates et al from the James Buchanan Brady Urological Institute at Johns Hopkins, there is reason to be excited.[1] The standard of care for treatment of patients with non-muscle-invasive bladder cancer (NMIBC) is transurethral resection of bladder tumor (TURBT) followed by intravesical bacille Calmette-Guérin (BCG), but 50% of patients will experience a recurrence in 2 years.[2] Additionally, there is a need for optimization of intravesical chemotherapy for patients who are not responsive to BCG. Kates et al explain large surface area microparticle docetaxel (LSAM-DTX) as "docetaxel microparticles formulated for tissue entrapment and sustained local drug release" that "is engineered using a precipitation with compressed antisolvent process that employs fluid state carbon dioxide held at or above its critical temperature and pressure (supercritical) and acetone to generate pure docetaxel microparticles with well-characterized particle size distribution and large surface area."[3] An earlier report investigating the potential benefit of higher concentrations of docetaxel for a longer time with a significant immune reaction and intratumoral injection of LSAM-DTX demonstrated significant tumor reduction.[5] Additionally, investigators using a mouse model to study intratumoral LSAM-DTX in combination with systemic anti-cytotoxic T lymphocyte antigen-4 for metastatic breast cancer reported a reduction in tumor progression and metastatic disease with detection of significant changes to effector immune cells[4]. This led Kates et al to investigate the safety and tolerability of LSAM-DTX for the management of high-risk NMIBC.

Eligibility criteria included high-grade T1, recurrent high-grade Ta, high-grade Ta >3 cm, high-grade Ta multifocal disease, carcinoma in situ, variant histology, and lymphovascular invasion, including high-grade prostatic urethral involvement. Enrolled patients also had a life expectancy of >6 months and adequate marrow, liver, and renal function. Patients were excluded if they had evidence of metastatic disease, a history of other malignancies besides nonmelanoma skin cancer within 12 months, intravesical therapy within 4 weeks prior to consent, a resection surface >8 cm^2, bladder perforation during TURBT, or upper tract and urethral disease within 18 months.

The authors note that LSAM-DTX has not yet been approved by the US Food and Drug Administration. LSAM-DTX was prepared as a saline suspension and was administered via injection into the tumor resection bed immediately following TURBT. Within 2 hours of injection, patients underwent intravesical instillation of LSAM-DTX for 30 minutes. After r4 weeks, patients underwent a weekly intravesical induction course for 6 weeks, followed by 6 weeks of rest, and 3 weeks of maintenance. Cytology and cystoscopic surveillance were conducted before induction, and then at 12 and 24 weeks after induction initiation.

A total of 19 patients were enrolled between 2019 and 2020; the population comprised mostly white men with a median age of 72 years. The median time from diagnosis to the start of treatment was 17 months. A total of 74% of patients had received BCG, and 84% had undergone multiple TURBTs in the past. All tumors were high grade and included 37% Ta, 42% Tis, and 21% T1. The researchers administered 4 different concentrations (3-15 mg) of LSAM-DTX as the direct injection, and there was a dose escalation for the intravesical instillation. Both direct injection and intravesical instillation of LSAM-DTX were well tolerated, and there were no drug-related systemic or local serious adverse events (AEs) observed. There were 31 grade 1 or 2 local AEs reported (including hematuria, dysuria, or urinary tract infection). There also were 5 grade 1 systemic AEs in 1 patient (including diarrhea, fatigue, and elevated liver enzymes).

In the 3 lowest dose cohorts, follow-up was 8.6 months and 90% of patients developed recurrence (median time to recurrence, 5.4 months). The estimated recurrence-free survival (RFS) rate was 90% at 3 months and 40% at 6 months. For the high-dose and expansion cohorts, median follow-up was logged at 12.2 months, and 56% of patients developed recurrence. Estimated RFS was 100% at 3 months, 78% at 6 months, and 50% at 12 months. After univariate analysis, there was a significant increase in RFS for the high-dose escalation and expansion cohorts compared with those that received lower doses. Multiplex immunofluorescence analysis was performed on 5 tissue samples from biopsies performed before and after LSAM-DTX treatment. The researchers found important increases in immune cellular profiles and concluded that "although these results are limited due to sample availability, they demonstrated favorable antitumor immune cell changes."

The outcomes support the need for further research to identify the optimal patient and therapeutic regimen to improve RFS in patients with high-risk NMIBC.

The authors began their discussion by highlighting that intratumoral treatment may significantly impact disease progression and reduce systemic toxicities associated with systemic therapies. This has been studied conceptually in other malignancies, including pancreatic cancer,[6] and is currently under investigation in phase 1 and phase 2 ongoing clinical trials.[7,8] This is important to consider in patients with high-risk NMIBC, where TURBT and intravesical chemotherapy (gemcitabine/docetaxel) is associated with RFS rates of 89%, 85%, and 82% at 6, 12, and 24 months, respectively.[9] The study reported that individuals who received high doses of LSAM-DTX had RFS rates of 78% at 6 months and 50% at 1 year. On a cellular level, there was an increase in tumor microenvironment immunogenicity, "including increases in adaptive T cells and innate NK effector cells." The authors note that while the immune analysis in this study was limited, "immune checkpoint receptor expression was increased across all cell types evaluated, including T cells, macrophages, and PanCK+ cells." This suggests the possibility that adding an immune checkpoint inhibitor to LSAM-DTX may improve progression-free survival. The authors' findings support the hypothesis that local LSAM-DTX has cytotoxic effects and acts as a stimulant for effector immune cells, leading to tumor cell death.

Limitations of the study included small sample size, heterogenous tumor stage, range of previous TURBT procedures, limited immune analysis, a short maintenance period, and a short follow-up. However, the results lend evidence to support that LSAM-DTX has a positive safety profile and "has the potential to overcome the limitations of conventional intravenous chemotherapy." Further studies addressing the limitations of conventional treatment are warranted.

The authors concluded that the treatment was well tolerated with a seemingly low AE profile and that the "preliminary efficacy data suggesting that post-TURBT direct injection and intravesical therapy of high dose LSAM-DTX may provide therapeutic benefits to patients with high risk NMIBC. Furthermore, findings suggest that LSAM-DTX has the potential for enhanced sensitivity to checkpoint inhibitors." The outcomes support the need for further research to identify the optimal patient and therapeutic regimen to improve RFS in patients with high-risk NMIBC.

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Advancements in Robot-Assisted Radical Prostatectomy

By Akhil A. Saji, MD

EACH YEAR, NEARLY 270,000 new cases of prostate cancer are diagnosed in the United States, and prostate cancer continues to be the second leading cause of cancer-related mortality in American males.[1] Surgical treatment of localized prostate cancer remains a key component in the treatment pathway for these patients. Historically, although laparoscopic radical prostatectomy was investigated, it was not widely adopted for multiple reasons, including a challenging learning curve and no significant difference in operating time.[2] Open radical prostatectomy (ORP) remained the predominant method for treatment of localized prostate cancer until the early 2000s, when the introduction of the da Vinci Surgical platform ushered in the era of robotics.[3] Over the course of the past 20 years, various techniques, outcomes, and continued improvements in robot-assisted laparoscopic radical prostatectomy (RALP) have continued to emerge. More recently, the introduction of the da Vinci Single Port (SP) robot has provided further room for innovation and enhancement of the RALP technique.[3] Concerns about cost, compared with traditional open radical prostatectomy, seem to have dissipated as several reports have consistently reported RALP to be a cost-effective treatment alternative to its open counterpart.[4] In this article, we briefly summarize a history of the RALP, its outcomes, and future directions.

Although randomized controlled trials in surgical care are difficult to perform due to their invasive nature, there is some high-level evidence showing an overall favorable profile for RALP compared with ORP. In a phase 3 randomized clinical trial comparing RALP with ORP in Australia, investigators randomized men with localized prostate cancer in a 1:1 ratio to RALP or ORP respectively.[5] Primary outcomes included sexual function measured by the International Index of Erectile Function (IIEF), urinary function measured by the Expanded Prostate Cancer Index (EPIC), and oncologic outcomes including biochemical recurrence (BCR). Although RALP and ORP were found to have equivalent urinary and sexual function outcomes, there was a significant difference in rates of BCR in favor of the RALP cohort as compared with ORP despite the RALP cohort having a higher rate of positive surgical margins. Other benefits favoring RALP over ORP include decreased blood loss, shorter length of hospital stay, and an improved postoperative pain profile.[2]

Various techniques for performing RALP have been described. The most frequently utilized technique for the RALP is the transperitoneal technique described by Menon et al in 2004.[6] This technique is a derivative of the laparoscopic technique described by the Department of Urology at the Institut Mutaliste Montsouris, Université Pierre et Marie Curie, Paris, France.[7] Limitations of the traditional transperitoneal technique include the need for steep Trendelenburg positioning, which can pose adverse physiologic challenges, including increased cardiopulmonary stress and increased intracranial pressure.[2] Additionally, entry into the peritoneal cavity can lead to bleeding and inflammation from urinary contamination during the procedure. In response to these issues, several authors have described a purely extraperitoneal RALP approach to the procedure; however, the extraperitoneal approach is limited by difficulty in developing the working space and subsequent limited mobility. Both the transperitoneal and extraperitoneal approaches have been shown to be safe and appear to have similar perioperative and oncologic outcomes.[8] Since the widespread dissemination of these techniques, there have been a variety of modifications posed by various authors to improve patient outcomes with regard to erectile dysfunction, urinary continence, and oncologic outcomes.

An estimated 21% of patients will experience urinary incontinence requiring at least 1 pad per day after prostatectomy[2]; therefore, urinary continence is component of RALP that many surgeons have sought to improve. One of the most common techniques is referred to as the Rocco stitch,[9] which is used to reconstruct the posterior aspect of the rhabdosphincter. In the original report, the authors proposed the reconstruction of the "musculofascial plate," suturing the rhabdosphincter and Denonvilliers fascia to the posterior wall of the bladder prior to performing the vesicourethral anastomosis. The authors reported a 49.2% improvement in urinary continence when performing this modification.[9] Another modification to improve continence

is the retropubic suspension stitch proposed by Patel et al, who reported a 7% improvement in early return to continence (3 months) compared to not applying the stitch.[10]

No discussion of postprostatectomy continence could be complete without mentioning the "Retzius-sparing" RALP (RS-RALP) approach as described by Galfano et al.[11] In RS-RALP, surgeons do not violate the space of Retzius; instead, the dissection is carried out posterior to anterior, starting by identifying the seminal vesicles and ending with the separation of the dorsal venous complex.[11] The primary proposed benefit is a faster return of urinary continence compared to traditional RALP; however, rates of continence are similar between the techniques after >-3 months. Compared with traditional RALP, there is still concern about the oncologic efficacy of RS-RALP as some authors reported higher rates of positive surgical margins. However, a recent large-scale meta-analysis has proposed no significant difference and no difference in rates of BCR between the 2 techniques.[12]

As surgeons continue to push the boundaries of robotic surgery, the invasiveness of RALP will decrease, while patient outcomes will continue to improve while simultaneously increasing the number of techniques available in the treatment armamentarium.

Erectile dysfunction is a complication of RALP, affecting an estimated 50% to 70% of postprostatectomy patients.[2] One of the earliest techniques described is preservation of the accessory pudendal artery[13] during RALP, which the authors reported may assist with return of erectile function in patients with arterial insufficiency. Other modifications, such as preservation of the "Veil of Aphrodite," have been described and shown to improve erectile dysfunction outcomes, and continue to play a role in modern RALP.[14]

More recently, novel techniques for RALP have been described with the introduction of the SP robotic surgery platform. The 3 primary methods reported are extraperitoneal, perineal, and transvesical. Kaouk et al described the perineal approach using a 3-cm perineal incision that showed promising results, including early urinary continence, in a series of 4 patients.[15] The perineal approach may be a useful option for patients with an extensive history of prior abdominal surgery. Desai et al described the feasibility of transvesical RALP in the late 2000s using cadaveric models; however, it took the evolution of the SP platform to bring it to fruition.[16] Kaouk et al reported on a series of 10 patients undergoing SP transvesical RALP with same-day discharge, early return of urinary continence, and a minimal rate of complications.[17] As surgeons continue to push the boundaries of robotic surgery, the invasiveness of RALP will decrease while patient outcomes will continue to improve while simultaneously increasing the number of techniques available in the treatment armamentarium.

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THE R.E.N.A.L. NEPHROMETRY SCORE:

A Brief History and Insight Into Its Use in Practice

An Interview with Robert Uzzo, MD, MBA

By David Ambinder, MD



Robert Uzzo, MD, MBA

ROBERT UZZO, MD, MBA, is president and CEO of Fox Chase Cancer Center in Philadelphia and serves as the G. Willing "Wing" Pepper Chair in Cancer Research, Professor of surgery at Temple University Health System, Senior Associate Dean and EVP of Cancer Services. He is a nationally recognized urologic oncologist and has been a leading investigator in many clinical trials with over 500 publications. His research primarily focuses on renal cell carcinoma (RCC). He is well known for developing the RENAL nephrometry score, used to delineate the complexity of renal tumor.

Dr David Ambinder: You have worked on many things in your career, including significant research into the management of the small renal mass, adjuvant therapy and the role of cytoreductive nephrectomy in RCC. Early in your career, you researched and developed the RENAL nephrometry score, which is not only helpful clinically to assist in surgical planning but also gives us a language to use in defining renal masses, discussing them in research, and communicating with other urologists and patients. Can you give us a brief history of the early development of the RENAL nephrometry score and how you first started to think about it?
Dr Robert Uzzo: The RENAL nephrometry score was designed to be a framework. During my training, I realized that there was a great deal of variation in medical decision making. That is why patients get so many

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opinions. In my reading outside of medicine, I decided two important concepts improve both education and care in medicine. The first is developing heuristics or frameworks and the second is standardizing those frameworks so care can be validated and generalized under various clinical scenarios.

When I was a resident, and then later a fellow, I tried to understand what goes into the decision to pursue a radical versus a partial nephrectomy since you could ask three excellent surgeons and get three different answers. How do urologists evaluate risks and benefits? How do they objectify and defend their clinical decisions? While understanding that care is complex with many nuances, we all realize that it is an issue if Dr. A recommends a partial nephrectomy while Dr. B might look at the same case and conclude "that can't or shouldn't be done!".

"When I was a resident, and then later a fellow, I tried to understand what goes into the decision to pursue a radical versus a partial nephrectomy since you could ask three excellent surgeons and get three different answers." –Dr Robert Uzzo

There were many clinical factors being discussed in terms of whether they should have an impact on management, including pathology (i.e, multifocal disease), tumor location (i.e, proximity to vessels or collecting system), and other practical questions, including whether the kidney would maintain functionality after resecting a significant portion. At the time, all these clinical questions seemed like they went into every surgeon's individual mental blender to come upon an answer. As a trainee, this created a struggle for me to understand how people were developing their recommendations.

Much of the decision making at that time was based on anecdotal reports, key opinion leaders and other publications; but there was no standard, in other words it mainly depended on where one trained, their skill set and how they viewed the oncologic disease. This led me to try to understand how to standardize and create an objective framework to evaluate renal masses. At the time, there was nothing out there. I looked at the literature to ask if other surgeons had a framework and realized that I might be able to learn from the liver surgeons who used the segmental anatomy of the liver. Their vocabulary for the various segments of the liver transmitted meaning into the difficulty of performing a partial hepatectomy. I spent a lot of time thinking about the anatomical considerations and thought, "Is there a way to do this that is equivalent to the segmental anatomy of liver?"

Like others, when I became an attending physician, I starting to struggle directly with those questions surrounding candidacy for a partial nephrectomy. At the time, there weren't a lot of partial nephrectomies being done in the country outside of Cleveland and a select few other centers. So, while beginning to increase my volume of partial nephrectomies performed, I started to try to communicate how I made the decision. Then I started to develop and entertain different systems and adjusted accordingly.

Can you briefly tell us how you evaluated and ultimately chose to incorporate the components of the RENAL nephrometry score, and how you came up with the acronym?

I thought about factors that were important in my own decision making. Size was important, that's where the "R"—for radius—comes in. "E" is for endophytic versus exophytic because people were deciding on whether to pursue a partial nephrectomy based on whether the tumor was endophytic or exophytic. There were a number of publications at the time suggesting the purely central or endophytic tumors were more aggressive. I thought, "Is that biologically true, or just convenient for those who want to do a radical?" Then, we thought about how close it was to the vasculature, collecting system, and renal sinus because this has staging implications, and that makes up the nearness or "N" component. This was when laparoscopy nephrectomies were becoming popular, which is why we added the "A" component for anterior or posterior since flipping the kidney might prevent people from an MIS partial in the pre-robot days. We thought this might be useful—i.e, if it is posterior, maybe a retroperitoneal approach would be ideal, or in some case,s potentially one would not attempt a laparoscopic approach. "L" is to aid in describing the tumor "real estate"—or location—in the kidney using the polar lines of the kidney since polar partials seemed to be easier, especially the lower pole.

So, I had all these elements without the acronym and was struggling with how to frame it. I thought, it's really about the "geometry of the kidney," so I called it "nephrometry". Dr. Alex Kutikov, who was a fellow at the time, was very instrumental with thinking some of this through with me and he came in one day and credited his wife for the acronym "RENAL". We chose it out of poetic license even though it really should have been DENAL, with a *D* for diameter.

How does the RENAL nephrometry score differ from other renal nephrometry scoring systems?

Since the development of the RENAL score, many other scores have been developed for similar purposes, some of which are really good. Among these, my favorite is the

contact surface area (CSA) score. The PADUA score was developed after RENAL and is basically the European version of the RENAL score with some minor tweaks.

The RENAL nephrometry score was first developed for surgical planning, but on PubMed there are >600 publications that use the nephrometry score. In a lot of ways, the nephrometry score provided a language for talking about renal cancer.

It is exciting to see how the score has developed and become a commonly used way for colleagues to discuss renal masses and describe them in research, as well to be able to define potentially more difficult masses (e.g., to interpret complication rates based on nephrometry score).

The score is also really helpful in talking with patients and explaining their disease. Some patients are coming in either for a primary evaluation or for a second opinion, and we are able to explain to them why their disease may or may not be best suited for a partial nephrectomy. Many patients want to know the thought process of their urologist, and for those patients, it is a really useful tool to explain it to them.

Many urologists calculate the nephrometry score themselves. Do the radiologists in your hospital system incorporate the RENAL nephrometry score into their imaging reports?

Many of the radiologists here do incorporate it into their readings, especially the radiologists who have been at Fox Chase for a long time. However, not all of them do. At times the attending urologist will input it themselves, and of course we keep a database of all the cases. There are current publications now seeing if AI can calculate the score for you when reading a CT or MRI

What are your thoughts on how we might characterize renal masses in the next 10 years?

The nephrometry score was initially a radiographic tool, but I think radiomics is really much more important. Of course, it would be great to be able to distinguish cancer biology based on cancer radiomics, whether via molecular markers or aggregated data, potentially using artificial intelligence. I think that this is where the field may be headed – the ability to match biology to treatment decision making. Nephrometry is just a very early step in that direction.



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.



"It is exciting to see how the score has developed and become a commonly used way for colleagues to discuss renal masses and describe them in research, as well to be able to define potentially more difficult masses." –Dr Uzzo

A Randomized Trial of PHOTOdynamic Surgery in Non-Muscle-Invasive Bladder Cancer

Review of the PHOTO Trial Publication

David Ambinder, MD

DOES USE OF BLUE LIGHT cystoscopy improve patient outcomes? Researchers from the United Kingdom attempted to investigate this question in a randomized trial recently published online in *NEJM Evidence*.[1] Non-muscle-invasive bladder cancer (NMIBC) is the most common presentation of bladder cancer. The standard of care for its management includes endoscopic resection of the bladder lesions and use of intravesical bacille Calmette-Guérin (BCG) or an immunotherapeutic agent. Many patients will experience recurrence, with greater risk of recurrence associated with tumor burden, previous recurrence, T stage, tumor grade, and—importantly—whether or not there is a component of carcinoma in situ (CIS) disease. The authors note that >50% of patients diagnosed with NMIBC are considered to be at intermediate or high risk at the time of diagnosis, portending a 3-year recurrence rate of >60% with a high rate of progression to muscle-invasive disease.[2] Because the requirement for both routine surveillance and management of bladder cancer makes treatment costly, researchers make significant efforts to optimize and accomplish a complete resection of tumor burden because it may improve recurrence-free survival (RFS).[3] Cystoscopy is generally performed using white light. One strategy has been to enhance the detection of tumor burden to improve endoscopic resection. Photodynamic diagnosis (PDD) using an intravesical photosensitizer can aid in tumor identification and possibly improve recurrence rates by fluorescing the tumor when exposed to blue-light cystoscopy.[4]

The researchers developed a multicenter phase 3 randomized controlled trial (registered as ISRCTN84013636) to explore use of PDD versus white-light treatment in patients >16 years with a suspicion for intermediate- or high-risk NMIBC. Patients with low-risk disease (defined as a solitary tumor <3 cm), muscle-invasive disease on imaging, upper tract involvement, experience of a life-threatening malignancy in the last 2 years, clinical evidence of metastasis, porphyria/known porphyrin hypersensitivity, pregnancy, or other contraindication to use of blue or white light were not included in the study. Patients were randomized to either the white-light arm (WL; control group) or the PDD arm (experimental group). Whether the patient underwent WL or PDD was not blinded but the findings and study personnel were. Patients in the WL cohort underwent a standard transurethral resection of bladder tumor (TURBT) under white light. The patients in the PDD cohort underwent preoperative intravesical instillation of hexaminolevulinate and had a TURBT conducted under blue-light cystoscopy. Fluoresced lesions were resected. All patients received intravesical mitomycin-C within 6 hours after undergoing TURBT or before discharge. Patients diagnosed with high-risk NMIBC (defined as high-grade or histologic stage pT) underwent a repeat TURBT. In accordance with standard guidelines, adjuvant intravesical therapy and white-light cystoscopy were administered at 3-month intervals for the first year, at 6-month intervals for the following year, and had a final cystoscopy 1 year later.

Patients were monitored throughout the study for adverse events (AEs) and health-related quality of life (HRQOL). The primary outcome was time to recurrence from randomization to pathologically proven recurrence, progression, cystectomy, or death from bladder cancer. Secondary outcomes included self-reported HRQOL related to the surgery or cancer treatment, health care utilization costs over the 36-month trial, and estimated quality-adjusted life-years (QUALYs). The researchers also evaluated AEs and complications within 3 months from the initial or

second TURBT, disease progression as evidenced by muscle-invasive disease, development of nodal or distant metastasis or death from bladder cancer, overall survival (OS), and bladder-cancer specific survival.

The authors powered the study based on an assumed 3-year RFS rate of 60% in the control group, supported by the results of previous studies identifying this recurrence rate for patients with intermediate-risk NMIBC.[2] They set a target for PDD to improve the RFS rate to 72% (hazard ratio [HR], 0.64), which they noted "represents a plausible estimate of the minimal clinically important difference in NMIBC that would be sufficient to change practice guidelines."[1]

A total of 538 patients (269 in each cohort) across 22 centers were enrolled over a 4-year period between 2014 and 2018. After application of exclusion criteria, there were 209 patients in the PDD arm and 217 in the WL arm. Cohorts were well balanced with regard to demographics, 80% of patients were male, and the average age was 70 years. Overall, 85% of patients were identified as having intermediate-risk disease and CIS was present in 13%; 93.7% of patients in the PDD group underwent PDD, 68 patients in each cohort underwent a repeat TURBT, and there was a similar rate of postoperative intravesical chemotherapy instillation between the groups (63.2% in the PDD cohort, 65.9% in the WL cohort).

This longer-term PHOTO trial addresses current practice and does not show differences in recurrence over a longer term follow-up.

Patients in both cohorts were observed for nearly 44 months and had similar incidences of bladder recurrence (86 in the PDD cohort, 84 in the WL cohort). The HR for recurrence was 0.94 (95% CI, 0.69-1.28; *P*=0.70). Per-protocol analysis yielded similar findings and was confirmed to "show no evidence that the time ratio differed between groups" using an accelerated failure time model. Similarly, 3-year RFS rates were 57.8% for the PDD cohort versus 61.6% for the WL cohort. In patients who had recurrence, BCG induction with or without maintenance was received by 35% in the PDD cohort versus 21.4% in the WL cohort. No significant difference was appreciated when comparing the number of patients who progressed to invasive disease (PDD cohort, n =19 vs WL cohort, n=12), or with regard to bladder-cancer specific survival (deaths: PDD, n=9 vs WL, n=8) or OS (deaths: PDD, n=27 vs WL, n=30).

There were no significant differences in the rates of AEs; 12 patients (<2%) reported in each cohort accounted for 26 serious AEs. Reported HRQOL outcomes were similar between the 2 cohorts. There also were no significant differences in cost regarding length of stay, health service costs, and staff costs between the 2 groups, but there were additional equipment costs for the PDD cohort. Overall, the authors noted that "there was no evidence of a difference between treatment groups in QALYs gained at 3 years. The probability that PDD was cost-effective was never above 30% over the range of society's cost-effectiveness thresholds considered."[1]

The authors began the discussion by emphasizing that the trial revealed that there was no difference in bladder cancer recurrence at 3 years for patients with intermediate- and high-risk NMIBC, but that PDD was more costly to perform than WL. They noted that the findings of previous studies showing a benefit of PDD to reduce bladder cancer recurrence[4,5,6,7,8] are "difficult to extrapolate" into current practice because they may have used different protocols that did not include immediate postoperative intravesical chemotherapy, repeat resections when indicated, and/or adjuvant intravesical treatments. This longer-term PHOTO trial addresses current practice and does not show differences in recurrence over a longer-term follow-up. Moreover, subgroup analyses considering multiple potential factors, including receipt of BCG or postoperative intravesical chemotherapy, consistently showed no difference in the rates of recurrence.

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Upper Tract Urothelial Carcinoma and Variant Histology–

Review of the Literature

By Akhil A. Saji, MD

UPPER TRACT UROTHELIAL carcinoma (UTUC) is thought to comprise up to 10% of all urothelial carcinoma diagnoses.[1] Risk factors for UTUC include tobacco exposure, occupational exposure to aromatic amines, dietary aristolochic acid and arsenic exposure, and familial inheritance of Lynch syndrome (HNPCC).[1]

Patients with UTUC typically present with symptoms of renal colic including flank pain, gross hematuria, or dysuria, which often prompts urologic evaluation. However, up to 15% of cases can be asymptomatic and ultimately are diagnosed as incidental radiologic findings.[2,3] Among patients diagnosed with UTUC , 1 of 4 will have a component of a variant histologic subtype such as—but not limited to—squamous cell, micropapillary, or neuroendocrine.1 The micropapillary variant is rare, but similar to bladder cancer, has shown poorer oncologic outcomes in terms of progression-free survival (PFS), and cancer-specific survival (CSS) as demonstrated in a series of 418 patients undergoing nephroureterectomy for UTUC.[4] In this issue of *GU Oncology Now,* we review a recently published article by Nogueira et al on the impact of variant histology on UTUC diagnosis.[5]

Currently, the gold standard of care for a new diagnosis of high-risk UTUC is a radical nephroureterectomy (RNU) with bladder cuff excision. Kidney-sparing therapies such as endoscopic (ureteroscopic) ablation are typically reserved for patients with low-risk disease, underlying chronic kidney disease or in the presence of a solitary kidney. Risk categories are defined on the basis of European Association of Urology (EAU) guidelines.[6] The EAU guidelines note that in addition to micropapillary UTUC, squamous and sarcomatoid variants of UTUC have been associated with worse oncologic outcomes.[6] In a large series of 669 patients with UTUC , 13% were noted to have squamous differentiation. On 5-year CSS analysis, this correlated to a 47% rate of CSS for the squamous cohort compared with 63% for the nonsquamous cohort. Regardless of which variant is in question, the presence of variant histology is associated with worse CSS and OS.[6]

Unlike bladder cancer, the role of neoadjuvant therapy for UTUC remains unsettled; however, recent results from a prospective trial offer promise. At the 2022 meeting of the American Society of Clinical Oncology (ASCO), the results of a prospective phase 2 trial investigating the use of gemcitabine and cisplatin (GC) as neoadjuvant therapy for patients with high-grade UTUC were presented.[7] Among the 57 patients enrolled in the trial to receive 4 cycles of GC before surgical therapy, the authors reported a complete response in 19% of patients as well as a 63% pathologic response rate.[7] Furthermore, they reported that 70% of patients were able to complete all 4 cycles of neoadjuvant GC and received surgery, suggesting that the strategy is highly feasible. Also promising were the 5-year overall survival rate of 93% and the PFS rate of 76%.[7]

Unlike bladder cancer, the role of neoadjuvant therapy for UTUC remains unsettled; however, recent results from a prospective trial offer promise.

According to the authors, a primary limitation in the management of UTUC compared with bladder cancer is the "frequent lack of adequate tissue prior to RNU." Furthermore, although instrumentation in ureteroscopy has improved dramatically with the introduction of tools such as the Piranha ureteroscopic biopsy forceps, some drawbacks remain.[8] In a retrospective review comprising 314 patients undergoing pre-RNU ureteroscopic biopsy, the authors noted a significant rate of upgrading (high grade, from 61% to 79%) and pathologic upstaging (cT1, from 21% to 45%) on final pathology.[9] The most likely

culprit is the inability of ureteroscopic biopsy to access deeper layers of the ureter or renal pelvis.[1] Additionally, Nogueira et al remark that the diagnosis of variant histology requires additional tissue that can usually only be acquired on final pathologic sampling after RNU.

As rates of variant histology in UTUC continue to increase, the authors emphasize the importance of understanding the impact of variant histologic patterns. To answer this question, the authors conducted a retrospective search of a clinical research database at Memorial Sloan Kettering Cancer Center (MSKCC) of patients undergoing RNU between January 1995 and December 2018. The authors identified 809 patients who underwent RNU and excluded patients with a final diagnosis of renal cell carcinoma (RCC), or who were negative for malignancy, or who had evidence of metastatic disease. On final analysis, the authors reported that 6.7% (n=47) of the final cohort had variant histology on pathologic analysis. Most of the variants identified were squamous (n=28), followed by sarcomatoid (n=8), and rarer histologies such as pure squamous and small cell. No micropapillary variants were identified. The authors commented that there is wide variation among reports in the literature regarding what percentage of UTUC patients undergoing RNU have variant histology, with ranging from 7.5% of 40% based on cited studies.

Nogueira et al noted that the majority of variant histologic diagnoses were identified after the 2005 creation of the genitourinary pathologist subspecialty, suggesting that the importance of variant histology before that time may not have been fully appreciated. Despite this limitation, the authors were still able to investigate the impact of variant histology on CSS and OS. On Kaplan-Meier analysis, the presence of variant histology portended a worse CSS (hazard ratio [HR], 2.14; P=0.002) and OS (HR, 1.74; P=0.008). However, when the authors adjusted the results for pathological T stage, no relationship was seen, suggesting that "variant histology does not add predictive information to pathologic findings after nephroureterectomy." In other words, patients with a higher stage of disease were more likely to have variant histology, and identification of this relationship prior to RNU would possibly be a predictor of high-risk tumor biology. The authors proposed that their lower reporting percentage could be a result of the inclusion of patients who underwent RNU before the era of genitourinary pathology emphasizing the importance of identifying variant histology.

The authors also discussed several potential limitations presented in the study. As referenced earlier, the phase 2 clinical trial investigating the role of neoadjuvant GC in UTUC is being conducted at MSKCC. The authors commented on the temporal increase in variant diagnoses noted after 2005, and with patients with higher stages of disease receiving neoadjuvant therapy as a part of the clinical trial, the oncologic outcomes presented in the report may have been affected. Other concerns in the literature include the question of variant-specific variability in regard to aggressiveness; however, due to the low number of specific subgroup variants, the authors state they did not perform subgroup analyses.

In conclusion, the results presented by Nogueira et al provide fresh insight into the utility of identifying variant histology. In the presurgical setting, identification of variant histology may be a useful marker for more aggressive tumor biology. However, identification of variant histology after RNU may not provide any further prognostic information. We are grateful to Nogueira et al for presenting this new set of data to advance our understanding of UTUC.

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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.



Radiation for Localized Renal Cell Carcinoma

By Akhil A. Saji, MD



KIDNEY CANCER IS THE THIRD most commonly diagnosed genitourinary malignancy in the United States, and it is estimated that the disease will cause nearly 14,000 cancer-related mortalities in 2022.[1,2] Most of these patients will have renal cell carcinoma (RCC), primarily with either clear cell (80%-85%) or non–clear cell histology (papillary, chromophobe, oncocytoma).[3] Surgery via radical or partial nephrectomy remains the primary treatment modality for patients with localized RCC; however, up to 40% of these patients will ultimately develop metastatic disease even after treatment. Early identification and treatment are essential to reduce this risk. The role of radiation therapy in the management of RCC has traditionally been thought of as minimal due to the inherent radio resistance exhibited by RCC. Several studies have demonstrated this phenomenon, although the exact mechanisms for RCC's molecular resistance to radiation remain unclear. In a study comparing radiation sensitivity of 76 human cell types (in vitro), Deschavanne and Fertil demonstrated that RCC cells are some of the most resistant types of oncologic cells.[4]

According to major guidelines, including those from the American Urological Association (AUA) and the European Association of Urology (EAU), the role for radiation in managing localized RCC is minimal at best. Techniques for primary therapy such as partial nephrectomy and radical nephrectomy provide the best oncologic outcomes, but for patients who are poor surgical candidates, other options are often used. Ablative techniques such as radiofrequency ablation or cryotherapy may be offered to these patients, but such techniques have limitations in the size of lesions that can be treated and result in higher rates of recurrence compared to surgical therapy.[5] Stereotactic body radiotherapy (SBRT), also referred to as stereotactic ablative therapy (SABR), is thought to provide potential benefit for patients who are deemed unfit for surgical therapy and have lesions that cannot be treated with other modalities. Most SBRT protocols deliver 24 to 40 Gy of radiation in 1 to 5 fractions (hypofractionation) in an effort to provide a high, targeted dose of radiation in a noninvasive manner.[6] Because delivery of SBRT requires extreme precision, various techniques, including immobilization devices and placement of fiducial markers, have been developed.[6]

Although there is a paucity of phase 3 randomized trial data on the use of SBRT in the localized RCC setting, several authors have published smaller series of data demonstrating the significant potential for SBRT. In 2015,

Staehler et al demonstrated the use of SBRT for local tumor control in a series of 40 patients.[7] After treatment of 45 total lesions, including 29 RCC lesions, they reported a 98% rate of local tumor control, minimal reduction in renal function, and an overall low rate of treatment-related toxicity. More recently, a meta-analysis conducted by Siva et al comparing single-fraction with multifraction SBRT also demonstrated a favorable therapeutic profile.[8] At 4 years in a total series of 223 patients, the authors reported a local control rate of 97.8%, a cancer-specific survival rate of 91.9%, and a progression-free survival rate of 65.4%.[8]

The toxicity profile of SBRT is also promising. Preservation of renal function is always of paramount concern regardless of the modality used to manage localized RCC. In the series by Staehler et al, patients had a median creatinine clearance of 76.8 mL/min/1.73 m^2 before receiving SBRT that declined only slightly after therapy to a median of 70.3 mL/min/1.73 m^2 7 Siva et al reported a similar result, noting a mean estimated glomerular filtration rate (eGFR) of 59.9 mL/min, which declined by 5.5 mL/min after treatment.[8] SBRT may also be a viable option for patients with preexisting chronic kidney disease at high risk for requiring dialysis after therapy, although the data in this context are limited. In a series of 21 patients with preexisting renal dysfunction, a mean tumor size of 4.8 cm and mean eGFR of 52 mL/min, the authors demonstrated an exponential dose decline curve of renal function.[9] At the end of treatment, all patients remained off dialysis support with an end treatment mean eGFR of 43 mL/min. Although promising, the limited data from small series in this patient population are insufficient to widely recommend SBRT in patients with preexisting renal dysfunction. Adverse effects of SBRT that have been reported include fatigue, gross hematuria, and erythrodermia, all of which were self-limited. In summary, the current role of SBRT in the localized RCC setting will remain investigational until prospective randomized trials are performed, and results become available. At present, SBRT should be reserved as an option for patients who are poor operative candidates and cannot undergo percutaneous ablation.

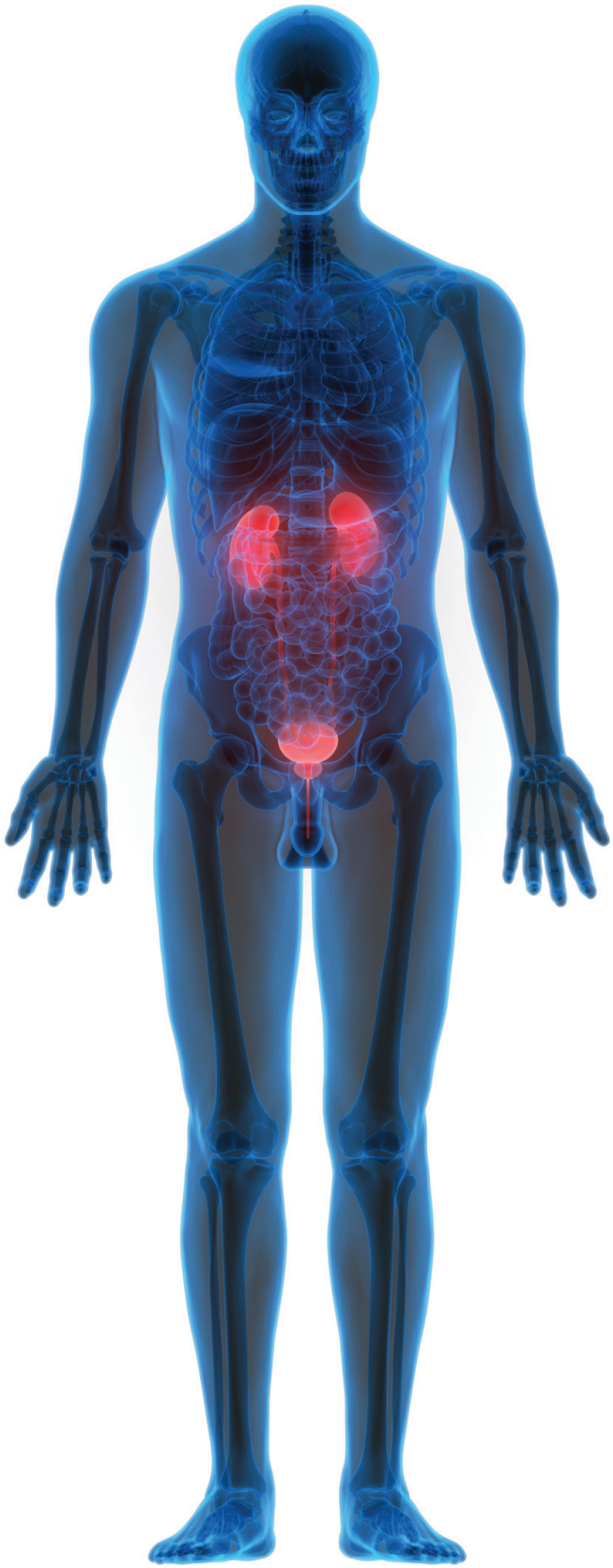
The history of radiation therapy in the adjuvant and neoadjuvant settings of localized RCC has also been explored and is worth reviewing. In the neoadjuvant setting, 2 trials published in the 1970s illustrate the lack of utility of radiation in localized RCC. The first trial, published in 1973 by van der Werf-Messing et al, reported on a series of 126 patients with localized RCC randomized to neoadjuvant radiation followed by nephrectomy or upfront nephrectomy.[10] Patients in the neoadjuvant radiation arm received a total of 30 Gy of radiation prior to nephrectomy, and the results demonstrated no benefit to overall survival at 5 years between the 2 arms.[10] The second major trial demonstrating no significant benefit in the neoadjuvant setting was published in the late 1970s by Juusela et al, in which the authors randomized patients to neoadjuvant radiation of 33 Gy followed by nephrectomy or upfront nephrectomy.[11] They reported that the 5-year survival was superior for patients in the upfront nephrectomy arm at 63% compared with 47% for those in the experimental arm.[11] The results of these trials solidified the lack of a role for radiation in the neoadjuvant setting.

The use of adjuvant therapy has also been explored in historical trials. Kjaer et al published data in 1986 on the role of postnephrectomy adjuvant radiation therapy.[12] They randomized 72 patients after surgical therapy to either radiation therapy (50 Gy in 20 fractions) or observation. In nearly half of the radiation cohort (44%) patients experienced post radiation complications in the stomach, duodenum, and liver, and 19% eventually experienced post radiation complication–related mortality.[12]

As the population continues to age and rates of RCC diagnosis increase with the use of imaging, advancing alternative treatment modalities such as SBRT in the localized setting may be paramount to expanding our treatment repertoire. Until the data surrounding SBRT in the localized setting mature, surgery will remain the primary workhorse approach to managing localized RCC.

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Survival Impact of Variant Histology Diagnosis in Upper Tract Urothelial Carcinoma

By Daniel Tennenbaum, MD

UPPER TRACT UROTHELIAL CARCINOMA (UTUC) is a rare disease, contributing only 10% of all cases of urothelial carcinoma in the United States.[1] However, findings with improved imaging and endoscopic technologies reveal that the incidence of UTUC appears to be rising.[2] Although UTUC is often considered similar to bladder cancer, there are embryologic differences in the development of the bladder compared with the upper tract and genetic differences in their respective oncologic molecular profiles. UTUC appears to have less frequent mutations of *RB1* and *TP53,* and more frequently present with mutations in *FGFR3*. Additionally, there is a significant familial relationship between UTUC and deficiencies in mismatch repair genes that contribute to Lynch syndrome (LS), with UTUC associated with LS in up to 10% of all UTUC cases.[3] However, the genomic profile of UTUC is not the most clinically significant parameter for patients with this disease. Tumor stage and grade remain the most significant prognostic factors in cases of UTUC.[4] Notably, up to one-third of all patients with UTUC present with variant histology, usually with nonstandard differentiation, such as squamous or micropapillary features. Less frequently, pure nonurothelial upper tract disease occurs. These variant histologies have been found to be associated with worse oncologic outcomes in patients with bladder cancer,[5] but have not been evaluated in those with upper tract disease. Instead, the clinical significance of variant histology in upper tract disease has been derived secondhand from our management of bladder cancer, given their histologic similarities. However, the diagnostic pathways by which bladder cancer and UTUC are managed differ greatly, given the technical challenges present with obtaining appropriate staging for UTUC. In upper tract disease, it is often achievable to establish tumor grade via biopsy but difficult to appropriately stage the depth of invasion of the tumor.[6] It is critical to better understand the impact of variant histology

in UTUC on patient outcomes to appropriately tailor the approach to management. For these reasons, Nogueira et al evaluated the survival impact of variant histologies in patients with upper tract disease at their institution and recently published their findings in the Journal of Urology.[7]

The authors reviewed 23 years of consecutive patients who underwent nephroureterectomy for upper tract disease at Memorial Sloan Kettering Cancer Center, finding >700 unique patients. Surgical approach and choice to perform lymph node dissection were at the surgeon's discretion. All patients were offered standardized follow-up postoperative regimens and were monitored for disease recurrence (defined as any disease relapse).

Variant histology was identified in the specimens of 47 patients (6.7%). Squamous differentiation was found in 28 of these patients' specimens; sarcomatoid differentiation was found in 8; glandular differentiation was found in 3 specimens, 2 of which had pure squamous cell carcinoma; and 1 specimen had several other variants. Notably, the prevalence of variant histology significantly increased over time. Patients with variant histology were significantly more likely to have received neoadjuvant chemotherapy prior to their definitive nephroureterectomy, but they were still found to have higher T-staging on final pathology than patients with nonvariant histology.

Importantly, variant histology was found to be associated with a significantly increased risk of worse cancer-specific survival (CSS; hazard ratio [HR], 2.14) as well as overall survival (OS; HR, 1.74). However, there was no significant association found between recurrence-free survival (RFS) and variant histology. The authors then adjusted for T-staging and found no association of variant histology with any difference in survival outcomes. They also found similar results when evaluating for survival outcomes after disease recurrence. Univariate analysis revealed that variant histology was associated with worse CSS and OS after recurrence. However, when the authors performed multivariable analysis, they found that the CSS differences were likely explained by higher pathologic T-staging, whereas the association with OS remained present.

The data and analysis presented by Nogueira et al provide a large retrospective review of patients with nephroureterectomy, ~6.5% of whom had variant histology in their final pathologic specimens. Variant histology was associated with higher stage and greater likelihood of having received neoadjuvant chemotherapy before definitive surgical extirpation. Moreover, variant histology was associated with worse CSS and OS, but no worse RFS after nephroureterectomy. Notably, once the authors controlled for pathologic staging, there were no significant survival differences seen in patients with a variant histology. In other words, *perceived* worse survival associated with variant histology is likely to be related to worse pathologic T-staging, with individuals who have variant histology also happening to be more likely to have higher staging. Multiple prior studies have shown consistent results, with univariate analysis showing survival differences in patients variant histology but loss of this significance, when results are controlled for staging. The authors point out that this finding is also demonstrated in the bladder cancer setting, where variant histology is often diagnosed at a higher stage and greater burden of disease, but analyses demonstrate that stage-matched survival is often similar to that in patients with typical urothelial carcinoma.

As the authors note, their cohort comprised only patients who underwent nephroureterectomy. There may be an inherent selection bias present, as these patients typically are selected because of their advanced disease stage or tumor grade. Smaller or low-grade tumors are often treated with endoscopic management in the effort to ensure renal preservation, and thus would be excluded from the cohort the authors analyzed.

What does this mean for the prognostic significance of variant histology in UTUC? Based on the findings by Nogueira et al, it seems variant histology may be a useful predictor of higher risk disease although it does not add predictive postsurgical prognostic value. The authors note that this is what their data imply, but they are quick to point out that their study was not designed to evaluate such a hypothesis, and such a conclusion cannot be made definitively. Despite the limitations of this study, the presence of UTUC variant histology remains a useful biomarker.

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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.

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