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Closing another year of tracking advances in urologic cancer care

MIKE HENNESSY SR / chairman and founder of Urologists in Cancer Care™’s parent company, MJH Life Sciences™.

Paging through the 4 issues of Urologists in Cancer Care™ from 2020 prompts several observations. One is the sheer breadth of topics covered throughout the year, including the effects of systemic intravesical therapies for the treatment of non-muscle-invasive bladder cancer, the use of immune checkpoint inhibitors for advanced prostate cancer, implementation of an Enhanced Recovery After Surgery pathway for patients undergoing radical cystectomy, and transurethral resection of the bladder tumor, to name just a few.

The other observation to be made is how fortunate we are to have such great physician contributors writing timely, relevant, and practical articles. We are very grateful to all of our contributors who help make this publication the resource that it is.

The final issue of Urologists in Cancer Care™ in 2020 certainly finishes off the year strong. The lead article examines poly (ADP-ribose) polymerase (PARP) inhibitors for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Jacob et al concisely summarize key trials of these treatments and outline their mechanisms of action.

“The time has now come to think about and treat mCRPC from a genetic basis, especially in the case of patients with earlier carcinogenesis and more aggressive disease...PARP inhibitors truly offer the solution needed to combat germline mutation-driven mCRPC,” the authors write.

This issue’s prostate cancer content continues with a timely piece from Olson et al examining the urologic implications of Lynch syndrome, which is associated with prostate and other urologic cancers. In addition, look for an overview of adjuvant radiotherapy post radical prostatectomy from Daniel E. Spratt, MD.

In bladder cancer, Daniel D. Joyce, MD, describes his institution’s standard technique for transurethral resection of the bladder tumor and outlines key advances in the procedure. Finally, Andrew M. McIntosh, MD, contributes an excellent piece regarding radical nephrectomy before or after systemic therapy for metastatic renal cell carcinoma in the context of the recent CARMENA and SURTIME trials.

As always, thanks for reading, and stay safe.

Have a comment about our content? Contact Concepcion c/o Urologists in Cancer Care™ at urology_times@mmhgroup.com.
The promise of precision medicine

RAOUL S. CONCEPCION, MD, FACS

As we move into the last quarter of 2020, although much of the news has been dominated by the challenges of adapting to the ongoing coronavirus disease 2019 (COVID-19) pandemic and associated lockdown, as well as the most recent election, there have been some real breakthroughs as we continue our march toward precision medicine in cancer care. When I brought this term up the other day in conversation with a friend in the music industry, his comment was, “I hear this all the time from acquaintances and in the press, but what does this mean and what is its effect in benefiting patients?”

It is my hunch that most people, in and out of the health care world, have this basic question without true clarity as to its importance and profound impact on the treatment of patients with benign or malignant conditions. For urologists, there is no question that the global work in prostate cancer has led the way, primarily due to the sheer number of patients across the spectrum of disease that are available to study. All urologists understand the importance of the Gleason grading system and the association of aggressiveness and possible disease progression for those with higher Gleason scores. In fact, current National Comprehensive Cancer Network risk stratification is based, for the most part, on this parameter—basic histopathology, cellular architecture and appearance under the microscope, which our anatomic pathologists are skillfully trained to identify. For car aficionados, it is akin to the ability on inspection to differentiate between a Ferrari versus a Lamborghini versus a Ford Mustang.

But keeping with the car analogy, what makes these cars (prostate cancer) so vastly different in performance and value (currently measured by Gleason)? They all have engines, drive trains, tires, exhaust, etc (androgen receptors), but with rare exceptions, the price of 1 Italian supercar is equivalent to a minimum of 4 or 5 iconic American ponies. Thus, to really understand why certain individuals spend vast sums of money for, in its most simplistic definition, a transportation vehicle, it behooves one to have a complete working knowledge of what it takes to build and design the components that make these high-priced motorcars so unique and desired.

We are finally gaining on our understanding of the major molecular drivers that are responsible for the progression of the disease beyond Gleason. Poly (ADP-ribose) polymerase (PARP) inhibitors in the management of heavily treated metastatic castrate-resistant prostate cancer (mCRPC) received FDA approval in 2020. However, for our patients to receive these agents, it mandates that the physician order genomic testing for mutations in DNA damage repair genes involved in homologous recombination. In a similar fashion, testing for variants in mismatch repair genes might allow the use of specific immunotherapies/checkpoint inhibitors, just as an identified splice variant mutation of the androgen receptor, measured by circulating tumor cells, could point us down the therapeutic pathway of who might respond to taxane chemotherapy. In less than 10 years, we have progressed a long way from the days we initiated therapy solely based on the presence of a metastatic lesion and rising prostate-specific antigen.

A highly anticipated new line of precision medicine–based treatment for mCRPC, which we hope will be approved soon, is radioligand PSMA targeted therapy. The use of radiopharmaceuticals for both palliation and prolonged survival in the management of bone metastasis has been readily available for more than 2 decades. However, the development of a “theranostic” approach, based on the patient’s expression of PSMA detected on molecular imaging, represents yet another therapeutic option that is predicated not just on the presence of abnormalities based on traditional nonspecific bone scans but also on actual tumor activity that requires advanced imaging technique. It’s worth noting that on December 1, the FDA approved Gallium 68 PSMA-11 for PET imaging of PSMA-positive lesions.
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New data for nadofaragene firadenovec show efficacy in BCG-unresponsive NMIBC

JASON M. BRODERICK / Associate Editorial Director, Urologists in Cancer Care™

Nadofaragene firadenovec induced complete responses (CRs) in over half of patients with high-grade, BCG-unresponsive non-muscle invasive bladder cancer (NMIBC), according to phase 3 data published in the Lancet Oncology.1,2

In patients with carcinoma in situ with or without concomitant high-grade Ta or T1 disease (CIS ± Ta/T1), the CR rate with nadofaragene firadenovec was 53.4% at 3 months. The 12-month CR rate was 24.3% and the median duration of CR was 9.69 months.

“Once patients with high-grade, non-muscle invasive bladder cancer no longer benefit from their initial BCG treatments, patients often make an informed decision to decline cystectomy—a highly complex and life-altering bladder removal surgery—or are often medically ineligible for this complex operation, leaving them with limited options,” senior author Colin P. N. Dinney, MD, chair of urology at the University of Texas MD Anderson Cancer Center, Houston, said in a press release.

“These data published in the Lancet Oncology show that nadofaragene firadenovec, a first-of-its-kind therapy, may be an effective treatment option for BCG-unresponsive non-muscle invasive bladder cancer patients,” added Dinney.

The multicenter, open-label, repeat-dose phase 3 study (NCT02773849) accrued patients with BCG-unresponsive NMIBC at 33 clinical sites in the United States. Among 157 treated patients, there were 107 patients with CIS ± Ta/T1 tumors. The median patient age in this group was 72 years (range, 66-77), 89% were male, 93% were Caucasian, and the median time from initial bladder cancer diagnosis was 20 months (range, 13-35).

Overall, 90.7% of patients had an ECOG performance score of 0, and 3.7% had prior radiotherapy. The number of prior BCG courses included 1 (0.9%), 2 (42.1%), 3-8 (53.3%), and 9 or more (3.7%).

The novel intravesical gene-mediated therapy nadofaragene firadenovec was administered by catheter as a single dose into the bladder. Those patients without recurrence received repeat doses at 3, 6, and 9 months. The primary end point was the CR rate in patients with CIS ± Ta/T1 tumors.

Of the 107 patients with CIS ± Ta/T1 disease, 103 were included in the efficacy analysis (4 patients were excluded because they did not meet the study definition of BCG-unresponsive NMIBC). Among these 103 patients, 55 (53.4%) had a CR at month 3, and 25 (24.3%) were in CR at 12 months.

“As a practicing urologist, I’m encouraged by these efficacy and safety data which demonstrate the potential for a novel treatment option that fits within the urology practice and gives patients the choice of receiving treatment once every 3 months—which may be a particularly important consideration in this evolving healthcare environment,” Gennady Bratslavsky, MD, president of Urologists in Cancer Care.”

FROM THE EDITOR

Continued from page 6

sions in men with prostate cancer.

As previously mentioned, this quest to identify key genetic mutations, and ultimately targeted therapies, is not strictly confined to oncology and malignant transformation. Amyotrophic lateral sclerosis (Lou Gehrig disease) is a devastating progressive neurogenerative disorder, uniformly fatal. However, identification of subtypes, based in part on newly identified genetic mutations, hopefully will result in therapies that can delay progression.1

As we slowly move toward the promise of precision medicine, it is important to understand fully this concept and the importance of testing and how it is to be used for diagnosis, management, and risk assessment for the family. We will have to get comfortable in the vast lexicon associated with genomic classification and begin to think in terms of mechanistic pathways, not just the disease. After all, who would not want the chance to drive and hear the roar of an Italian racing machine?●

REFERENCE

FDA grants fast track designation to novel peptide-based vaccine in prostate cancer

JASON M. BRODERICK / Associate Editorial Director, Urologists in Cancer Care™

The FDA has granted fast track designation to RV001, an investigational synthetic long peptide vaccine that targets RhoC, for the treatment of patients with prostate cancer.1

RhoC is a small GTPase that is overexpressed in advanced solid tumors. Results from a phase 1/2 first-in-human study published in the Journal for ImmunoTherapy of Cancer showed that 18 of 21 evaluable patients had an immunological response to RV001.2 Safety data showed that the vaccine was tolerable, with no grade 3 or higher treatment-related adverse events reported.

The phase 1/2 study (NCT03199872) included 22 patients 18 years or older who had previously received radical prostatectomy. Patients had histologically confirmed adenocarcinoma of the prostate gland and were not receiving anticancer therapy at the time of enrollment. Prior androgen-deprivation therapy was not allowed. Patients had an ECOG performance status of 0 or 1.

RV001 was administered subcutaneously every 2 weeks for 6 injections, then 5 times every 4 weeks for a total treatment regimen duration of 30 weeks. Safety was the primary outcome measure, with immunological response as a secondary outcome measure.

Overall, 18 of 21 evaluable patients developed a strong CD4 T-cell response against the vaccine. The response durations all lasted at least 10 months after the patient received the last injection of RV001. The investigators identified 3 promiscuously presented HLA-class II epitopes. “Vaccine-specific CD4 T cells were polyfunctional and effector memory T cells that stably expressed PD-1 (CD279) and OX-40 (CD134), but not LAG-3 (CD223),” the study authors explained.2 Additionally, there was 1 detected CD8 T-cell response. “Targeting of RhoC induced a potent and long-lasting T-cell immunity in the majority of the patients. The study demonstrates an excellent safety and tolerability profile,” the authors wrote.3 RV001 is currently being evaluated in the double-blind phase 2 BRaVac trial in men with biochemical failure following curatively intended therapy for localized prostate cancer. Patients enrolled on the trial will be randomized to RV001 or placebo. The primary outcome measure is time to PSA progression, and the estimated primary completion date is September 2021.

REFERENCES

NADOFARAGENE

Continued from page 8

Society of Urologic Oncology Clinical Trials Consortium, and professor and chair of urology at SUNY Upstate Medical University, Syracuse, New York, said in the press release. “Our organization is proud to have played a key role in the mid- and late-stage clinical studies for nadofaragene firadenovec.”

The safety analysis included all 157 patients enrolled on the trial who received at least 1 dose of nadofaragene firadenovec. The most common grade 3 treatment-related adverse event (TRAE) was micturition urgency, which occurred in 2 patients. There were 4 other grade 3 TRAEs occurring in 1 patient each: bladder spasm, syncope, hypertension, and urinary incontinence. No grade 4 TRAEs were reported and there were no treatment-related deaths.

The trial remains ongoing with the study design set up for a 4-year treatment and monitoring phase.

REFERENCES
A s the complexity of cancer management continues to mount, clinicians frequently face difficult therapeutic decisions that mandate the input from colleagues and various specialties critical for optimizing patient care. To this end, *Urology Times*, in partnership with LUGPA, has launched Around the Practice, a monthly urologic virtual tumor board featuring live case review from multidisciplinary experts.

In the most recent installment, a panel convened to discuss cases involving de novo metastatic renal cell carcinoma, metastatic castration-sensitive prostate cancer, and nonmetastatic castration-resistant prostate cancer. What follows is an edited portion of the panel's conversation regarding the metastatic case.

The panelists included moderator Raoul S. Concepcion, MD, FACS; Jorge Garcia, MD; Kenneth M. Kernen, MD; and J. Travis Mendel, MD.

CONCEPCION: The case we’re going to discuss is of de novo metastatic castration-sensitive prostate cancer. In December 2019, a 79-year-old Caucasian man presents to urology with acute urinary retention and a PSA of 4.6 ng/mL from his local primary care office. He has a history of cerebrovascular accident (CVA).

The patient undergoes minimally invasive therapy for his acute urinary retention, but 8 months later returns to the office with worsening lower urinary tract symptoms as well as gross hematuria. He undergoes a cystoscopy in the office, which shows an obstructing prostate, a questionable mass effect of a left hemitrigone at the left orifice, and a PSA of 8.1 ng/mL.

He undergoes transurethral resection of the prostate (TURP) to relieve the worsening obstruction, as well as biopsy of the trigonal mass. Now, he has Gleason grade group 5, Gleason 4+5 prostate cancer in all the tissue that is submitted. He has no visceral metastases and on bone scan, he has multiple areas to the axial skeleton, femur, and pelvis that are all suggestive of metastatic disease.

Dr Kernen, given what I’ve outlined, please share your thoughts on how you would manage this patient.

KERNEN: Dr Garcia and I actually did a tumor board like this one recently that included discussion of data collected for 1400 patients with de novo metastatic renal cell carcinoma, metastatic castration-sensitive prostate cancer, and nonmetastatic castration-resistant prostate cancer. What follows is an edited portion of the panel’s conversation regarding the metastatic castration-sensitive prostate cancer case.

The panelists included moderator Raoul S. Concepcion, MD, FACS; Jorge Garcia, MD; Kenneth M. Kernen, MD; and J. Travis Mendel, MD.

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Dr Kernen, given what I’ve outlined, please share your thoughts on how you would manage this patient.

KERNEN: Dr Garcia and I actually did a tumor board like this one recently that included discussion of data collected for 1400 patients with de novo metastatic CSPC between April 2019 and March 2020. Seventy-four percent of all patients were treated with androgen deprivation therapy (ADT) alone or with just a first-generation anti-androgen. Basically, in 2019-2020, we’re treating patients with 1980s-era standards. That’s the wrong answer. ADT alone plus or minus first-generation anti-androgen, such as bicalutamide, is clearly the wrong therapy.

If you look at the National Comprehensive Cancer Network guidelines, basically, these patients need ADT plus either chemotherapy or novel hormonal therapy.

We tend to use degarelix (Firmagon) first. It lowers the testosterone almost immediately. That’s our starting point. Then you have to decide on a novel hormonal agent versus chemotherapy. This patient has had a stroke. That eliminates enzalutamide (Xtandi), so then you would consider apalutamide (Erleada) or abiraterone acetate (Zytiga) versus chemotherapy.

This patient has high-volume disease. In the TITAN trial [evaluating the addition of apalutamide to ADT], both patients with low-volume and high-volume disease did very well.

For this patient, I would probably lean more towards apalutamide as opposed to standard chemotherapy. I think he would tolerate it pretty well.

CONCEPCION: Dr Garcia, could you give us an overview of disease volume and how it might play a role in what agent you would prescribe up front for this particular patient?
GARCIA: I think that a year or 2 ago, I would have put more emphasis on disease volume. But I think the data right now would suggest, as Dr Kernen mentioned, that regardless of volume, what you need is treatment intensification.

I think many have shifted away from chemotherapy to abiraterone, just for simplicity’s sake, and from abiraterone to the androgen receptor inhibitors just by virtue of the lack of prednisone and the lack of fasting. My agents of choice right now for the most part are apalutamide or enzalutamide. I agree with Dr Kernen that CVA may push me away from enzalutamide a little bit because of the issue of increasing the risk for seizure activity, which I still don’t buy fully.

I think the issue with volume is that this man has high-volume disease for 2 reasons. No. 1, he has grade group 5 disease and No. 2, he has more than 3 bone metastases. That is the definition that we use based on the LATITUDE trial. Based on the CHAARTED criteria, which defined high volume as presence of visceral metastases or 4 or more bone lesions with 1 or more outside the spine and pelvis, more bone lesions with 1 or more outside the spine and pelvis, more than likely he would have been considered high volume as well.

I think the STAMPEDE data challenged the notion that volume really matters when you make these selections because the heterogeneity data of the follow-up from that analysis would suggest, in fact, that regardless of volume, men with metastatic castration-naïve or castration-sensitive disease will derive a benefit regardless of the agent selected.

But I do want to remind the group that if you look at median survival, which is getting into Dr Kernen’s very important point as to single-agent monotherapy with an LHRH agonist- or antagonist-based therapy, the median survival for someone with high-volume metastatic disease today is approximately 33 to 34 months.

With intensifying the treatment regardless of the agent used, you can double that survival improvement to almost 60-plus months, thus reducing the relative risk of mortality by almost 40%, something that is clearly unheard of in the history of prostate cancer.

I think many in the US would probably use one of the novel androgen receptor inhibitors for this patient and probably just by virtue of the CVA, apalutamide would be the agent of choice, at least in my opinion.

CONCEPCION: Dr Mendel, let’s say the patient in the case we’re discussing is 60 years old. What are your thoughts on treating the primary tumor with radiation?

MENDEL: We’ve had a lot of back and forth in my practice about cases like this. I use data from STAMPEDE and 2 other trials to guide me. STAMPEDE was published in 2018 and looked at definitive treatment essentially of the primary tumor with radiation versus just standard systemic therapy. This was a randomized trial that included hundreds of patients.

Initially, there didn’t seem to be an overall survival signal with treatment of this. But then they stratified the patients to low-volume and high-volume disease, and they found that patients who have low-volume disease actually benefited from treatment of their prostate. I think their definition was 3 or less lesions, but the term “oligometastatic” is starting to be thrown around a lot in radiation oncology, especially in prostate cancer.

I use 5 lesions. If they have 5 or fewer lesions, then I’ll treat the primary tumor and treat those lesions. The second trial I refer to is called STOMP, which found that metastasis-directed therapy was associated with increased ADT-free survival compared with surveillance alone. The other trial is SABR-COMET, and that study evaluated multiple cancer types, including prostate. The investigators treated oligometastatic lesions and were able to detect an overall survival benefit that was statistically significant within the design of the trial. STAMPEDE, STOMP, and SABR-COMET are the 3 trials I use to rationalize treating patients with low-volume disease.

This patient does not have low-volume disease. It sounds like he’s riddled with metastasis. In these patients, I would reserve external beam radiation for palliative purposes. He might be a candidate for possibly Xofigo [radium-223 dichloride] in the future once he becomes castrate resistant.

For references, please go to bit.ly/ucccasereview

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In recent years, prostate cancer has grown to become the most common carcinoma affecting men in terms of incidence and the second most common in terms of mortality. The American Cancer Society estimates that in 2020, there will be 191,930 new cases and 33,330 deaths from prostate cancer. It was well known for many years that approximately a quarter of men who develop metastatic castration-resistant prostate cancer (mCRPC) have a mutation in DNA repair genes, with the most common mutated genes being BRCA2 (44%), ATM (13%), CHEK2 (12%), and BRCA1 (7%). It was previously thought that these patients harbored somatic mutations that could develop at any time in a patient’s life, with the frequency of these DNA repair aberrancies increasing with continued disease progression. However, recent discoveries in the last 5 years have indicated that up to 12% of all men with mCRPC have germ-line/inherited defects in DNA repair genes. This distinction is important because new data suggest that patients with prostate cancer with BRCA2 mutations have earlier onset of disease, lower overall survival rates, and shorter progression-free survival rates.

The discovery of germline DNA repair gene mutations is significant in that it changes the entire paradigm of family history investigation algorithms that occur during the first clinical encounter with a patient with a new diagnosis of prostate cancer. The increased risk is specifically correlated to the BRCA1 and BRCA2 DNA repair genes, which have been well established as genes whose mutations confer an increased chance of breast and ovarian cancer development in women. Now clinical investigation on the part of physicians must include the consideration that just as having a father or brother with prostate cancer can double a man’s risk of developing prostate cancer, having a mother or sister with breast or ovarian cancer can increase this same man’s risk of developing prostate cancer. This rationale has been reflected in the most recent National Comprehensive Cancer Network (NCCN) guidelines for 2020, while only 2 years ago genetic testing was not widely promoted. Now, germline genetic testing is recommended for every patient with prostate cancer with high-risk disease, regional spread, and metastases. In addition to these disease statuses, patients with a family history of high-risk germline mutations (BRCA1/BRCA2, etc), a family history of cancer, and Ashkenazi Jewish ancestry are also candidates for genetic testing. Somatic tumor testing is recommended in prostate cancer with both regional and metastatic spread. Thus, it is strongly encouraged that almost every patient with prostate cancer, except for the very low-risk patients, undergo genetic testing according to the new NCCN guidelines.

The answer to the question of how one can account for germline mutations in DNA repair genes for the treatment of mCRPC lies in the mechanism of action of poly (ADP-ribose) polymerase (PARP) inhibitors (Figure 1). When a single strand break in DNA occurs, PARP1 proteins repair the break in a mechanism called base excision repair. With a double-strand DNA break, DNA repair genes (the most recognizable being BRCA1 and BRCA2) initiate repair through a mechanism known as homologous recombination. When there is a knockout mutation in DNA repair genes (somatic or inherited germline), aberrant DNA with breaks that cannot be repaired begin to accumulate. This is the catalyst for carcinogenesis. PARP inhibition works through a rationale called synthetic lethality, which essentially is a mechanism of cell death that occurs when
both the single-strand and double-strand DNA repair pathways are inhibited. In the case of a germline mutation of DNA repair genes, the double-strand DNA repair pathway (homologous recombination) is already knocked out. Therefore, the last step for synthetic lethality of cancer cells to work would be to impair the single-strand repair pathway (base excision repair) through the inhibition of PARP1. This can be achieved through PARP inhibitors and lead to a cascade of cell death in tumor cells.

Before discussing the available PARP inhibitors that physicians can employ in targeting prostate cancer, it is important to distinguish that there are 2 main mechanisms of action by which PARP inhibitors work. One method of inhibition is through the direct blockade of the enzymatic activity of PARP1 and PARP2, and the second is through “PARP trapping” on the DNA and preventing its release. There are many PARP inhibitors available, but the most important for the field of prostate cancer treatment are olaparib (Lynparza), rucaparib (Rubraca), niraparib (Zejula), and talazoparib (Talzenna) (Figure 2).

The PROfound Study (NCT02987543) was a trial that studied 387 patients with mCRPC who had progressed on a hormonal agent such as enzalutamide (Xtandi) or abiraterone (Zytiga) and had 1 or more homologous gene repair mutations in a 15-gene panel that was utilized for this study. Cohort A consisted of 245 patients with BRCA1, BRCA2, or ATM gene mutations, and cohort B consisted of 142 patients with 1 or more of the other 12-gene panel aberrations. Patients were randomized 2:1 to receive 300 mg of olaparib orally twice daily or physician’s choice of either 160 mg of enzalutamide orally once daily or 1000 mg of abiraterone acetate orally once daily with 5 mg of prednisone twice daily. Median progression-free survival (PFS) in cohort A in the patients who received olaparib was 7.39 months compared with a PFS of 3.55 months in the patients who received enzalutamide or abiraterone (HR, 0.34; 95% CI, 0.25-0.47; P < .001). Overall survival in cohort A with the patients receiving olaparib was 18.5 months versus 15.1 months in the patients receiving the physician’s choice of treatment (HR, 0.64; 95% CI, 0.43-0.97; P = .02). Common adverse events (AEs) of olaparib that physicians must be aware of are anemia, fatigue, nausea, anorexia, diarrhea, thrombocytopenia, creatinine elevation, cough, and dyspnea. Very rare but serious complications of olaparib are myelodysplastic syndrome development, acute myeloid leukemia development, pneumonitis, and deep vein thrombosis or pulmonary embolism. The groundbreaking PROfound Study led the FDA, on May 19, 2020, to approve olaparib for the treatment of patients with mCRPC who have pathogenic germline or somatic homologous DNA gene repair mutations, and who have progressed following prior treatment on enzalutamide or abiraterone.

The TRITON2 study (NCT02952534) was a phase 2 trial that examined the efficacy of rucaparib in patients with metastatic castration-resistant prostate cancer who had 1 or more somatic or germline mutations in homologous DNA repair genes and who had progressed following prior androgen receptor (AR)–directed therapy and 1 prior taxane-based chemotherapy. Patients were randomized to receive 600 mg of rucaparib twice daily in 28-day cycles every 8 weeks for 24 weeks then every 12 weeks. Primary end points that were measured were objective response rates (ORRs) and prostate-specific antigen (PSA) rates among each homologous DNA repair genes and who had progressed on prior androgen receptor (AR)–directed therapy and prior taxane-based chemotherapy. Patients were randomized to receive 600 mg of rucaparib twice daily in 28-day cycles every 8 weeks for 24 weeks then every 12 weeks. Primary end points that were measured were objective response rates (ORRs) and prostate-specific antigen (PSA) rates among each homologous DNA repair gene mutation. The most notable responses were among the 57 patients that had a BRCA1/BRCA2 mutation; 44% of these patients had an ORR, and there was a PSA response rate in 52% of these same patients. Among
**BRCA1/BRCA2** mutations, the median time to PSA progression was 6.5 months (95% CI, 5.7-7.5). The AE profile associated with rucaparib that physicians must be aware of includes anemia, fatigue, nausea, anorexia, diarrhea, constipation, thrombocytopenia, abnormal liver function tests, creatinine elevation, and rash. Extremely rare but very serious complications include myelodysplastic syndrome development, acute myeloid leukemia development, and teratogenic effects to the fetus if taken while pregnant. The ongoing TRITON3 study (NCT02975934) is studying efficacy of rucaparib in patients with mCRPC who had progressed on prior AR-directed therapy but are chemotherapy naïve. The TRITON2 study led to accelerated approval of rucaparib on May 15, 2020, for patients with mCRPC with **BRCA1/BRCA2** knockout mutations who have been previously treated with AR-antagonist therapy or taxane-based chemotherapy.

The time has now come to think about and treat mCRPC from a genetic basis, especially in the case of patients with earlier carcinogenesis and more aggressive disease. Though the vast majority of mCRPC cases will be acquired in a patient’s lifetime, thousands of patients with inherited germline mutations will benefit from a thorough family history screening and genetic testing. Clinicians can interpret the new prostate cancer NCCN guidelines regarding genetic panel testing as essentially applying to all patients with prostate cancer, as low-risk disease is rarely present at the time of presentation in an oncology new patient visit. PARP inhibitors truly offer the solution needed to combat germline mutation-driven mCRPC. When choosing between the 2 current FDA-approved PARP inhibitors it is important for clinicians to consider that olaparib has shown efficacy against a wide range of homologous DNA repair gene mutations and rucaparib is mainly indicated to combat **BRCA1/BRCA2** mutations at this time. There are several ongoing trials studying the efficacy of combinations of PARP inhibitors with other novel agents, and we believe the future is truly exciting in terms of the expansion of the number of patients that will benefit from treatment and the number of therapeutic options that will become available to physicians in the coming decade.

**REFERENCES**


For author bios, please go to bit.ly/uccparp
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Lynch syndrome (LS) is one of the most common hereditary cancer disorders and includes multiple urologic cancers within its spectrum. This autosomal dominant syndrome was one of the first hereditary cancer disorders to be identified and affects approximately 1 in 279 people. LS is historically known as hereditary nonpolyposis colorectal cancer but is also associated with urothelial, prostate, testicular, and adrenal malignancies (Figure).

The carcinogenic mechanism of LS is caused by a mutation within the mismatch repair (MMR) genes, with the most common mutations being in mutL homolog 1 (MLH1), mutS homolog 2 and 6 (MSH2, MSH6), and postmeiotic segregation increased 2 (PMS2). Mutations in the epithelial cellular adhesion molecule can also lead to silencing of MSH2. MMR genes work together to identify and excise DNA mismatches during DNA synthesis, and mutation of a single protein in this pathway can lead to dysfunction of the entire repair system. The inherited germline mutation alone is not enough to lead to disruption of the MMR system. The second normal allele must be inactivated as well, typically through epigenetic silencing, somatic mutation, or loss of heterozygosity.

**Urothelial cancer**

UPPER TRACT UROTHELIAL CANCER: The most common urologic cancer associated with LS is upper tract urothelial cancer (UTUC). It is rare, with an incidence of 2 in 100,000 people per year. However, MMR deficiency is seen in 5% to 11% of all patients with UTUC. The MMR genes most commonly associated with UTUC are MSH2 and MSH6. Urologists evaluating patients with UTUC who display certain characteristics should suspect an underlying genetic syndrome. Young patients, bilateral tumors, abnormal pathologic analysis, and family history compatible with LS all warrant further evaluation for LS.

The risk of developing UTUC in a patient with LS is about 22 times higher than that of the general population and is estimated at between 0.4% and 20%. A review of 288 patients with LS in Denmark showed that 22% developed UTUC and 17% developed urothelial carcinoma of the bladder. The mean age at diagnosis was 61, and MSH2 mutations were seen in 73% of cases. In addition, men and women appear equally affected in those with LS. Tumor stage and development of subsequent bladder cancer do not appear to differ in patients with LS versus sporadic patients. Bilateral tumors are more common in LS, and previous studies have observed bilateral tumors in 46% of patients.

Due to increased risk of UTUC among patients with LS, screening for urothelial cancer is recommended, though there is no consensus on screening approach. Many groups use annual urinalysis with subsequent microscopic hematuria evaluation because this is relatively low cost and minimally invasive. Other groups suggest addition of urogram phase to surveillance scans in those patients who had previous colorectal cancer (CRC). Annual computed tomography urogram or renal ultrasound may be particularly beneficial in patients with known MSH2 mutation, because this is the MMR gene most commonly associated with UTUC. The National...
Comprehensive Cancer Network (NCCN) specifically recommends starting yearly urinalysis in patients with MSH2 mutations who are aged 30 to 35 years.8 Genetic testing for MMR mutations should be performed in certain patients with UTUC. Metcalfe et al screened patients without prior history of LS and with UTUC for risk of LS using the Amsterdam II criteria (Table) and immunohistochemical (IHC) testing. This identified 13.9% of patients who were considered at risk for LS. Subsequent genetic testing confirmed that 5.2% of patients had LS.9 Therefore, those with positive screen using Amsterdam II criteria as well as those with positive IHC testing for MMR mutation should undergo genetic testing.

UROTHELIAL CANCER OF THE BLADDER: Bladder cancer occurring in multiple members of a family is still more likely to be a result of shared environmental risk factors than of heredity. However, emerging data demonstrate increased risk of bladder cancer in patients with LS, especially in men and those with MSH2 mutations. In the previously cited article from Denmark, 17% of patients with LS may develop urothelial cancer of the bladder.3 A second study, from Canada, showed a lower percentage (6.21%) of patients with LS and MSH2 mutations with bladder cancer; however, this was still significantly higher than the general Canadian population.10 These observations are likely high enough to justify a yearly urinalysis staring at age 30 in patients with known LS and MSH2 mutation.

PROSTATE CANCER: Inclusion of prostate cancer as an LS-associated cancer remains controversial despite being clearly defined by Ryan et al in 2014.11 This meta-analysis and systematic review showed that there is a 3.67-fold relative risk for developing prostate cancer in patients with MMR mutations, especially MSH2 (95% CI, 2.32-6.67). Other studies have shown comparable results confirming increased prostate cancer risk in patients with LS.2,13

Men with prostate cancer meeting certain criteria should be tested for LS. Based on the 2017 Philadelphia Prostate Cancer Consensus Conference, the recommendation is to screen for MMR gene mutations in men with family history of LS or with 2 or more blood relatives with an LS-associated cancer.11,13 These recommendations are similar to those for UTUC, though they do not specifically recommend use of the Amsterdam II criteria.

There are no data to suggest earlier onset of prostate cancer or higher stage at diagnosis. Some have proposed PSA screening starting at age 40; however, studies have shown a median age at diagnosis ranging from age 59 to 69 years.12 Therefore, men with LS should be strongly encouraged to undergo yearly PSA and physical exam testing. However, screening starting earlier than age 55 years is not supported by the literature.

Emerging data demonstrate increased risk of bladder cancer in patients with Lynch syndrome, especially in men and those with MSH2 mutations.

Other urologic cancers
The relationship between LS and testicular cancer is not well established. Current literature is conflicting, with some data showing up to 33% of testicular germ cell tumors containing microsatellite instability (MSI) compared with other studies showing no MSI and no MMR deficiency on histopathologic analysis.2,12
Because of the rarity of adrenocortical carcinoma (ACC), association with LS is difficult to establish. ACC is associated with poor prognosis and affects only about 1 to 2 patients per million each year. Various case studies have reported incidence of ACC within patients with LS and MSH2 mutations, and, in a combined prospective and retrospective study, MMR mutations were found in 1.5% to 3.2% of patients with ACC. These data are not adequate to encourage screening for ACC in patients with LS; however, they do suggest that ACC should be considered when evaluating patients with LS with adrenal masses.

Conclusions
Lynch syndrome is one of the most common hereditary malignancy syndromes and is associated with multiple urologic cancers. To apply this knowledge of LS to daily practice, we should keep in mind the following:

- UTUC is the third most common LS-associated cancer.
- Patients with known LS and MSH2 mutations should undergo yearly urinalysis and microhematuria work-up as indicated; they may also benefit from yearly renal ultrasound or CT urogram.
- Patients with UTUC or prostate cancer meeting the Amsterdam II criteria or having abnormal immunohistochemical testing on pathology should undergo genetic screening for LS.
- In patients with LS presenting with adrenal mass, ACC should be considered.

Beyond treating patients for urologic cancers, it is our role as urologists to identify patients at risk for undiagnosed Lynch syndrome and provide appropriate screening in this population.

**REFERENCES**

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Our randomized trials have established that adjuvant radiotherapy (ART) post radical prostatectomy (RP) for men with a positive margin and/or pathologic stage T3 (pT3) disease reduces biochemical recurrence compared with men managed with observation post RP.\(^1\)\(^-\)\(^4\) One of these 4 trials demonstrated improvements in metastasis rates and in overall survival (OS).\(^2\) These results led to most guidelines recommending the use, or at least discussion of the benefits, of ART for men with adverse pathology post RP. However, ART did result in a small increase in grade 3 toxicity by 1% to 3% in most trials, and more than 30% of men in all trials never recurred post RP without ART. Thus, despite guideline recommendations, use of ART has decreased, with only 5% to 10% of men with adverse pathology receiving ART in the United States given the fear of overtreatment and unnecessary toxicity. Although this may seem troubling, it is not necessarily a problem given that salvage radiotherapy (SRT) can be used in the subset of patients who do develop a recurrence post RP. This will avoid unnecessary radiotherapy in men who may be cured by RP alone, and potentially reduce toxicity by treating men months to years after RP when more complete functional recovery has occurred.

Thus, the real question is, does ART improve outcomes over SRT? The first 3 trials of ART versus observation used very low rates of SRT in the observation arm. Often only approximately 30% of men who recurred received SRT. Additionally, when SRT was used, it was near uniformly at prostate-specific antigen (PSA) levels higher than 1.0 ng/mL. It is now well established that late SRT at PSAs higher than 0.5 ng/mL has far lower rates of success compared with early SRT when given at time of recurrence, closer to 0.2 ng/mL. Thus, the overall survival benefit observed in the SWOG 8794 randomized trial of adding ART may not be that hard to believe if only 30% of men received SRT, and when they did it was too late.

Three randomized trials reported early results in October 2020 that compared ART with early SRT: GETUG-AFU-17 (NCT00667069), RAVES (NCT00860652), and RADICALS (NCT00541047).\(^5\)\(^-\)\(^7\) Overall, there was no improvement seen with use of ART compared with early SRT in biochemical- or progression-free survival. As expected, there were lower rates of toxicity with SRT, and more than 40% of men in all trials randomized to early SRT have not required SRT because they have not recurred to date.

What this means is that for patients with favorable to moderately aggressive disease post radical prostatectomy, use of early SRT is preferred over ART and, I believe, is now the standard of care. However, there are 3 important take-home points and caveats that must be considered before applying this statement to all prostate cancer post RP.

1. ART = SRT only when early SRT is used. We know from the Finnish randomized trial of RP with or without ART that approximately 85% of men in the trial in the obser-
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viation arm who recurred received SRT. However, it was late SRT at PSAs higher than 0.5 ng/mL. Despite this high rate of SRT in the observation arm, there was still a profound reduction in recurrence in the ART arm. Thus, if a practice does not closely monitor patients and send them for early SRT when their PSA is 0.1 or 0.2 ng/mL, it is likely that ART is superior. A study from MUSIC (Michigan Urological Surgery Improvement Collaborative) showed that only 1 in 6 men who recurred post RP received early SRT. Thus, in the real world, it may be that ART is superior if early SRT is not rapidly adopted.

2. ART = SRT only when all patients who recur post RP receive SRT. As stated, in most of the ART randomized trials, the minority of men who recurred post RP ever received SRT. In SWOG 8794, the trial that demonstrated an overall survival benefit, only 30% of men received SRT who recurred post RP. However, in the Finnish trial, 85% of men who recurred post RP received SRT, and there was no metastasis or survival benefit noted. Despite SRT being the only potential curative treatment option for men who recur post RP, in that same analysis from MUSIC it was shown that only approximately 30% of men who recur post RP in the real world ever receive any SRT (early or late). Thus, if in the real world, only 30% of men who recur post RP ever get SRT, and of those men approximately half are given late SRT, it is highly likely that ART is superior to current real-world use of SRT.

3. ART = SRT only when patients have unfavorable to moderately aggressive prostate cancer. Although it is possible that ART has similar outcomes to early SRT regardless of tumor aggressiveness, this has not yet been shown. All 3 trials that compared ART with early SRT enrolled predominantly patients with Gleason 6 or 7 with either a positive margin or pT3a disease. Only 5% of men on the RADICALS trial, for example, had high-grade disease with seminal vesicle invasion. Thus, there were almost none of these more aggressive patients enrolled in the ART vs early SRT trials. Additionally, almost no men with lymph node–positive disease were enrolled in these trials. Therefore, I would continue to recommend ADT plus delayed ART for men with multiple, very high-risk features or node-positive disease, given that more than 90% of these men are predicted to recur post RP with commonly used nomograms.

It cannot be emphasized enough that SRT is equivalent to ART, but only when SRT is used at time of biochemical recurrence at low PSAs (approximately 0.2 ng/mL), SRT is uniformly used for men who recur post RP, and it is used for men with node-negative disease without multiple high-risk factors (eg, Gleason 8-10 and pT3b). Thus, urology practices must implement methods to closely monitor patients to ensure timely referral for early SRT if they are going to avoid the use of ART. If this is not done, ART should remain the standard of care, because low rates of SRT and late SRT at high PSAs will result in suboptimal outcomes for patients.

REFERENCES

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Since it was first described in 1910, transurethral resection of bladder tumor (TURBT) has evolved into the cornerstone of bladder cancer diagnosis and staging, and it is one of the most common surgeries urologists perform. Following the introduction of video endoscopy in the late 1970s, TURBT has been characterized as a relatively simple procedure, often performed by junior residents in the academic setting. More recent data emphasize the importance of high-quality TURBT by experienced surgeons in order to improve patient outcomes. Significant variation in recurrence rates among urologists has been described, supporting the assumption that experienced technical skill matters. At our institution, junior residents slowly gain more responsibility as their technical skills develop under the close supervision of an experienced surgeon with a low threshold to take over the case when accurate staging may be difficult to obtain. Below, we discuss our standard technique for TURBT and describe new advancements that may help standardize outcomes in a procedure that has experienced little evolution during the past century.

**TURBT technique**

**PREOPERATIVE CONSIDERATIONS.** Before operative intervention, a thorough history and physical should be performed. When possible, slides from prior resections are reviewed by our genitourinary specialized pathologists to ensure accurate staging and identify any variant histology. Routine lab work to assess renal function and rule out infection is obtained at the initial consultation, and imaging studies evaluating the upper urinary tract are performed before or at the time of TURBT. For patients with a history of non-muscle-invasive bladder cancer (NMIBC), we will often utilize blue light cystoscopy given the observed increased cancer detection (especially for carcinoma in situ), decreased recurrence, and possibly decreased progression associated with its use. In addition, for those patients with discordant positive cytology and negative office cystoscopy, we will routinely use blue light technology in accordance with the American Urological Association NMIBC guidelines. Although not yet incorporated into our practice, clinic blue light capabilities may further enhance patient care by increasing detection rates and avoiding unnecessary use of operative resources in patients with negative surveillance cystoscopy.

**PROCEDURE.** Before and following resection, a bimanual exam is performed under sedation to assess clinical staging (fixation of bladder or palpable masses).
a 30° lens, is then introduced into the bladder. When indicated, a urine cytology is obtained. This can be performed by collecting the first emptied urine from the bladder (essentially a voided urine cytology) or as a formal bladder washing using saline. A careful white light cystourethroscopy is performed. In rare cases, a 70° lens may be needed to completely visualize the bladder. If enhanced cystoscopy techniques are planned, a repeat evaluation of the bladder is then performed using this technology. Obtaining photos of tumors can be useful for patient counseling and providing more detailed information for health care providers who are not present during the resection. Assessment of the size, location, grade, and presumed depth of invasion will inform the operative plan.

**TUMOR LOCATION.** When resecting tumors in difficult locations where bladder injury is more likely, we will often use a staccato energy approach, which provides greater control and helps limit thermal injury. Tumors at the bladder dome and anterior wall may require abdominal pressure with the nonresecting hand to bring the mass into view. Occasionally, a long resectoscope may be required to reach the area of interest. The obturator reflex may be invoked when resecting lateral wall tumors, resulting in adduction of the ipsilateral leg and possible bladder perforation. Avoiding overdistention, use of bipolar energy source, resecting with decreased energy settings, and anesthetic paralysis may help limit this occurrence. For posterior wall tumors, bending the resection loop out to assimilate the contour of the bladder wall can provide safer and cleaner resection. For tumors near or overlying the ureteral orifices, pure cutting current should be used to avoid obstruction. The decision to leave a ureteral stent in this setting is surgeon dependent; however, existing data suggest that postresection hydronephrosis is rare regardless of stent use. Diverticular tumor resection carries a greater risk of bladder perforation given the lack of underlying detrusor muscle. When invasion is suspected, bladder perforation may be required in order to obtain adequate staging. In such cases, postoperative indwelling catheter placement should be utilized to allow adequate healing and avoid further complications.

**TUMOR SIZE.** Smaller tumors in patients with thin bladder walls may be managed with cold cup biopsy, thereby mitigating the risk of bladder perforation. Alternatively, cautery loop resection can be performed, often en bloc, with 1 swipe. Larger tumors require a fragmented approach with successive loop resection until the base is exposed.

**When resecting tumors in difficult locations where bladder injury is more likely, we will often use a staccato energy approach, which provides greater control and helps limit thermal injury.**
ollowing intravesical instillation of a lidocaine/bicarbonate solution. For high-grade tumors, obtaining detrusor muscle in the specimen is critical for staging purposes. Loop resection is performed to expose the tumor base. Further loop resection is then performed to obtain muscle. Alternatively, cold cup biopsy of the resection base is used in instances where bladder perforation is a concern.

**BIPOLAR VS MONOPOLAR ENERGY SOURCE.** Bipolar energy, originally developed for transurethral resection of the prostate, is commonly used in TURBT as well, because of several potential advantages. Saline irrigation is used, diminishing the risk of TUR syndrome, which can occur after more extensive resections with water. Monopolar energy travels from the resection electrode through the body to the electrode attached to the patient’s skin, whereas bipolar energy travels between electrodes on the resection device. For lateral tumors where an obturator reflex is likely, bipolar may offer some advantage and limit bladder perforation. The difference in energy propagation may also limit cautery artifact in pathology samples. Finally, bipolar may offer more safety for patients with pacemakers and for pregnant women. Despite these theoretical advantages, comparative data are conflicting. In a recent systematic review of 13 randomized control trials comparing monopolar and bipolar TURBT, there was no observed difference in operative time, recurrence rate, bladder perforation, thermal damage, or overall complications.

**POSTOPERATIVE CONSIDERATIONS.** Perioperative intravesical chemotherapy has been shown to reduce recurrence, especially in low-grade solitary tumors. Although data are more robust for the use of mitomycin C (MMC), we will often instill gemcitabine through an indwelling catheter in the operating room following resection of presumed low-grade tumors given the favorable adverse effect profile and recent phase 3 randomized control trial showing a recurrence rate reduction similar to that of MMC. Intravesical chemotherapy should be avoided following extensive resections or if bladder perforation is suspected.

Although postoperative continuous irrigation has been associated with lower recurrence rates, we typically avoid this in our patients because of concern for inducing or worsening bladder perforation.

For high-grade T1 tumors, repeat resection is planned within 6 weeks to ensure proper staging and complete resection. Repeat resection is also considered for high-grade Ta tumors without muscle in the specimen or if incomplete resection is suspected.

**Advancements in TURBT EN BLOC RESECTION.** En bloc resection (EBR) of bladder tumors has gained interest to avoid theoretical cancer cell circulation and out-of-field recurrences associated with traditional TURBT. Additionally, pathologic evaluation may be more accurate if tumor samples are kept intact. Advantages of this technique include improving muscle sampling and providing better hemostasis. A systematic review of EBR found a 95% rate of detrusor muscle inclusion in the specimen. Interestingly, this higher-quality resection did not lead to decreased complication or recurrence rates. Use of electric energy, water dissection, holmium:YAG laser, thulium laser, and green-light laser have all been described. New endoscopic robotic instruments, such as those being developed by Virtuoso Surgical (Figure), provide a more user-friendly interface for EBR, which may translate into greater consistency in TURBT quality, regardless of skill level. Still, endoscopic removal of intact tumors greater than 3 cm remains a challenge. Various methods have been proposed to address this, including the use of laparoscopic forceps, nephroscopy sheaths, nylon mesh retrieval nets, and Endobags (such as those used in gastrointestinal endoscopy). More data are needed to justify EBR adoption into common practice.

**BLADDER IMAGING.** Improved imaging modalities may offer further consistency and accuracy in clinical staging of bladder cancer. Knowing the depth of invasion before resection
may lead to reducing the observed 50% residual tumor rate and 10% progression rate found at repeat resection through better operative planning and higher-precision resection. Intraoperative use of optical coherence tomography and confocal laser endomicroscopy are emerging technologies that may improve diagnostic accuracy; however, further investigation is required to clarify user variability and its impact on oncologic outcomes. Similarly, preoperative use of multiparametric magnetic resonance imaging (MRI) and development of the Vesical Imaging-Reporting and Data System score appear to improve clinical staging of muscle-invasive disease. Similar to its increasing popularity in prostate cancer diagnosis, MRI may become more common for bladder cancer staging as radiology interpretation becomes more consistent and standardized.

**FUTURE DIRECTIONS.** Artificial intelligence and machine learning offer the promise of standardized diagnostic accuracy and improved cancer detection. Digital bladder mapping software is being developed to reduce cystoscopy interobserver variability. Ultimately, technology that increases detection of bladder cancer and decreases TURBT quality variability may drastically change a procedure that has seen little evolution over the past 100 years.

**REFERENCES**


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Cytoreductive nephrectomy (CN) is a debulking procedure intended to reduce the overall cancer burden in the setting of metastatic disease by extirpating the renal unit containing the primary tumor. This is done without intending to eradicate the disease and is performed with the goal of improving survival outcomes. CN prior to or following up-front systemic therapy has long been considered an important treatment paradigm for metastatic renal cell carcinoma (mRCC). The recent publication of 2 highly anticipated randomized controlled trials, however, has renewed controversy regarding the role of CN for mRCC.

The scientific rationale for performing CN has long been on the basis of level 1 evidence from 2 trials published in 2001. These demonstrated superior overall survival (OS) for mRCC patients undergoing CN plus interferon alfa compared with interferon alfa alone.1-5 However, since the introduction of targeted agents in 2005, the assumption that CN portends a survival benefit has always been extrapolated from these data, which were formed on that basis of inferior and now obsolete systemic therapy. Prior to 2018, multiple retrospective series demonstrated an OS benefit to CN, but no level 1 data existed to support it.5-8 All of this ignores the fact that we have again ushered in a revolution in systemic therapeutics for mRCC with immuno-oncology therapy, further clouding the picture of who should or should not receive CN.

Interpreting the CARMENA and SURTIME trials
The CARMENA randomized trial (NCT00930033), published by Méjean et al in 2018, compared OS in mRCC patients receiving the tyrosine kinase inhibitor sunitinib (Sutent) alone versus those receiving sunitinib and CN.6 They were able to demonstrate that OS for the sunitinib-alone arm was noninferior to sunitinib plus CN (18.4 vs 13.9 months) in the intention-to-treat (ITT) analysis. Naturally, the publication of this trial raises important questions about the validity of CN as a therapeutic endeavor in the targeted therapy era. However, this trial has significant limitations, and its findings must be interpreted with caution. Patient accrual was slow and the accrual goal was not reached. More significantly, only 0.7 procedures per center were performed. The trial cohort also contained a high proportion of high-risk patients (43%) by Memorial Sloan Kettering Cancer Center (MSK) criteria,7 and the remainder (57%) were intermediate risk. Taken together, this suggests that some exclusion bias likely exists, because more favorable patients were presumably being offered CN outside of the trial.

It is also probable that the inclusion of such a high proportion of MSK...
high-risk patients limited the overall survival (OS) of the study cohort. This is reflected by the truncated median OS experienced by the CN arm. Median OS of 13.9 months is very short and does not reflect most contemporary CN cohorts. Additionally, significant contamination of the study arms occurred, with 7% of the CN arm not undergoing surgery and 17% of the sunitinib-only arm receiving CN.

The SURTIME trial (NCT01099423) was intended to evaluate survival outcomes for patients receiving up-front CN followed by sunitinib versus those receiving sunitinib followed by deferred CN. Because of poor recruitment (n = 99), the authors were forced to revise the primary end point from OS to a 28-week progression-free survival (PFS) rate, which limits the generalizability of the results. The study was not powered to detect an OS difference, so conclusions cannot be drawn from their exploratory analysis.

How should CARMENA and SURTIME alter my practice? These important studies should be viewed as practice confirming rather than practice altering. Appropriate patient selection using objective criteria has always been paramount in managing mRCC with CN. The European Association of Urology updated its guidelines for managing mRCC to reflect the findings of these randomized trials by stating that MSK poor-risk patients should not undergo CN. However, I venture that most urologic oncologists would not have offered an MSK poor-risk patient CN prior to the publication of CARMENA. Importantly, these guidelines also state that MSK intermediate-risk patients should be considered for up-front systemic therapy. This key point highlights the need for objective scoring criteria to evaluate patients suitable for surgical cytoreduction. Any patient suspected to be at high risk for disease progression or perioperative morbidity should be considered for up-front systemic therapy, and this likely includes many intermediate-risk patients. Initial systemic therapy can serve as a litmus test for the clinician—a favorable response may prompt a reevaluation for CN. The goal of CN should be to prolong survival, and therefore clinicians must endeavor to minimize time spent off of systemic therapy.

Risk stratification for CN

Multiple studies and guideline panels utilize the MSK criteria to risk-stratify patients with mRCC. It should be noted that the MSK criteria were initially published to stratify patients receiving interferon. They were never intended to incorporate surgical risk and perioperative morbidity and mortality into their model. The International mRCC Database Consortium has published a risk model, which has been validated in cytoreductive nephrectomy patient cohorts and includes 6 easily measured preoperative variables. These include Karnofsky performance status less than 80%, hemoglobin less than 12 g/dL, corrected serum calcium higher than 10.2 mg/dL, neutrophils higher than 7x10^9/L, and platelets higher than 400k cells/μL. This model was also published during the targeted therapy era, so it likely represents a more generalizable application to modern mRCC.

| TABLE. The University of Texas MD Anderson Cancer Center Criteria for Patient Risk Stratification Prior to Considering CN^2 |
|---------------------------------|------------------|------------------|
| Risk Factor | Hazard ratio (95% CI) | P value |
| Hemoglobin < 14 g/dL (< 16 g/dL if female) | 1.33 (1.08-1.66) | .009 |
| Albumin < 3.5 g/dL | 1.41 (1.07-1.85) | .014 |
| Lactate dehydrogenase > 618 | 1.55 (1.23-1.96) | < .001 |
| Neutrophil/lymphocyte ratio ≥ 4 | 1.46 (1.14-1.86) | .002 |
| Retroperitoneal adenopathy | 1.39 (1.12-1.71) | .002 |
| Supradiaphragmatic adenopathy (does not include hilar adenopathy) | 1.41 (1.07-1.86) | .016 |
| Bone metastasis | 1.42 (1.14-1.77) | .002 |
| cT4 disease | 1.87 (1.18-2.95) | .007 |
| Systemic symptoms at diagnosis (fever, weight loss, and/or night sweats) | 1.24 (1.01-1.52) | .042 |
patients. However, because this model includes “less than 1 year from diagnosis to systemic therapy” as the sixth risk factor, it automatically excludes all patients presenting with de novo mRCC from the favorable risk category. For this reason, these criteria may not be ideally suited for clinical application in surgical candidates.

The University of Texas MD Anderson Cancer Center criteria (MD Anderson), recently published in Cancer (as an update from a prior study11), provides clinicians with 9 objective preoperative clinical variables by which patients with mRCC can be stratified into 3 tiers of risk for increased likelihood of death following CN (Table).12 Patients are considered at low, intermediate, and high risk for poor survival outcomes following CN if they have 0 or 1, 2 or 3, and 4 or more risk factors, respectively. The risk groups not only directly correlate with survival outcomes but also with adverse features on pathology and adverse perioperative outcomes. These findings suggest that the model can predict those patients in whom increased surgical risk may exist outside of their tumor biology. The cohort was derived from consecutive patients undergoing CN in the targeted therapy era and are therefore generalizable to a typical patient with mRCC presenting to a urologist’s office. Notably, median survival in the poor risk group in the MD Anderson cohort was 19 months as compared with 13.9 months in the combined arm (sunitinib + CN) of CARMENA. It seems that when appropriately selected, even poor risk patients receiving CN fare better than those enrolled in CARMENA.

On the basis of the MD Anderson study, patients who fall into a good risk category can be considered for CN and those who are at poor risk should not be offered up-front CN. For intermediate-risk patients, careful patient selection based on these risk factors, individual performance status, and other patient comorbid conditions should be undertaken to individualize recommendations. Those patients who elect to receive up-front systemic therapy should be restaged and risk-stratified for CN once a favorable response is documented. Again, the goal should be to prolong survival and CN should only be undertaken when it can be reasonably expected that the patient can resume/begin systemic therapy in a timely fashion post operatively. As the therapeutic landscape continues to evolve and shift to rely more heavily on immuno-oncology therapy, we must be diligent in continuing to develop tools to appropriately risk-stratify patients with mRCC for CN.

REFERENCES

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