



### 2019 ANNUAL MEETING HIGHLIGHTS Genitourinary Cancer

#### Course #010IC

Renal Cell Carcinoma: Surgical & Medical Management of High-Risk Renal Cell Carcinoma: New Paradigms for Treatment

#### Course #023IC

Chemotherapy and Immunotherapy Options for Genitourinary Malignancies: A Primer for Urologists and Advanced Practice Providers

#### Course #038IC

Case-Based Discussion of AUA Non-Muscle Invasive Bladder Cancer Guidelines

#### Course #077IC

Integrating Care for Oncology Patients: Establishing a Multidisciplinary Oncology Clinic with Advanced Therapeutics

#### Urologic Care for the Advanced Practice Provider

The Emerging Role of Genetic Counseling and Testing in Urologic Cancers

## Second Opinion Cases (Ask the Guidelines!)

Castrate Resistant Prostate Cancer

Take Home Messages Prostate Cancer Kidney Cancer Bladder Cancer

AUANews Editor John D. Denstedt, MD, FRCSC, FACS, FCAHS

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## AUA2019 ANNUAL MEETING HIGHLIGHTS

## **Genitourinary Cancer**

CME Credit

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### CME INFORMATION

## 2019 AUA Annual Meeting Highlights: Genitourinary Cancer

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#### Statement of Need

To better meet the educational needs of urologists and advanced practice providers (APPs), in 2017 the AUA gathered data from a variety of sources, including a comprehensive literature search, as well as membership surveys to determine where gaps exist in knowledge, proficiency and practice in regard to genitourinary (GU) cancer. The needs assessment findings for urologists and APPs with regard to treating patients with bladder cancer center on immunotherapy and use of checkpoint inhibitor treatments, sequencing of agents/therapies, managing side effects of treatments/therapies and management of comorbid conditions. Additionally, urologists indicated an educational need in the areas of identifying potential interactions between immunosuppressive agents and other medications, appropriate use of biomarker testing to risk stratify patients and a thorough review course of the AUA Clinical Guidelines on Bladder Cancer.

In November 2018 the AUA administered a survey to assess the educational needs of U.S. based urologists treating patients with renal cell carcinoma (RCC). Of 1,001 surveys completed 74% of respondents indicated they manage RCC. Based on the results of the needs assessment, the top 3 greatest educational needs of urologists in the areas of managing RCC include the sequencing of agents, use of emerging treatment options and management of immune related adverse events.

#### **Target Audience**

Urologists, urologists in training and nonphysician providers involved in urology.

#### Course 010IC: Renal Cell Carcinoma: Surgical & Medical Management of High-Risk Renal Cell Carcinoma: New Paradigms for Treatment

#### **Learning Objectives**

At the conclusion of this CME activity, participants should be able to:

- Manage complications of robotic partial nephrectomy to optimize outcomes through videotape analysis
- Manage advanced renal cell carcinoma with new FDA (U.S. Food and Drug Administration) approved treatment options
- Utilize transperitoneal and/or retroperitoneal robotic partial nephrectomy approaches to minimize ischemia time and optimize renal function

#### Faculty

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#### A. Oliver Sartor, MD

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#### Course 023IC: Chemotherapy and Immunotherapy Options for Genitourinary Malignancies: A Primer for Urologists and Advanced Practice Providers

#### **Learning Objectives**

At the conclusion of this CME activity, participants should be able to:

- Describe the standard-of-care chemotherapy regimens for genitourinary malignancies
- Recall historic and newer immunotherapy options for the treatment of genitourinary malignancies, including

### AUA NEWS

#### **CME Information**

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recently approved checkpoint inhibitors and antibody-drug conjugates

- Outline the mechanism of action of common chemotherapy and immunotherapy regimens for genitourinary malignancies
- Recognize and manage the adverse events related to these agents
- Identify the survivorship issues surrounding patients on systemic treatments for genitourinary malignancies
- List completed and accruing clinical trials that are defining the paradigms of chemotherapy and immunotherapy use in genitourinary malignancies

#### Faculty

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#### Meeting Participant or Lecturer Course 038IC: Case-Based Discussion of AUA Non-Muscle Invasive Bladder Cancer Guidelines

#### **Learning Objectives**

At the conclusion of this CME activity, participants should be able to:

- Analyze the latest evidence on the management of nonmuscle invasive bladder cancer as outlined in the AUA guidelines
- Apply the guidelines in urological practice to improve the therapeutic decision making processes
- Summarize the process by which evidence is used to develop scientifically rigorous, yet actionable, guidelines

#### Faculty

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#### Course 077IC: Integrating Care for Oncology Patients: Establishing a Multidisciplinary Oncology Clinic with Advanced Therapeutics

#### **Learning Objectives**

At the conclusion of this CME activity, participants should be able to:

- Describe the components of a multidisciplinary urological cancer practice and identify the best structure for the practice
- Utilize advanced therapeutics based on current and emerging best evidence including immunotherapy in urologic oncology patients
- Identify opportunities for shared care and team-based approaches to patients with urologic cancers including advanced prostate, bladder and kidney cancer
- Explain advances in genomic testing and personalized medicine for urologic cancers
- Differentiate among new therapeutics that expand the treatment options for

patients with urologic cancers and alter the definitions of cancer treatment

#### Faculty

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### COURSE #010IC

## Renal Cell Carcinoma: Surgical and Medical Management of High Risk Renal Cell Carcinoma: New Paradigms for Treatment

Benjamin Lee, MD, Course Director; A. Oliver Sartor, MD and Chandru Sundaram, MD, Faculty

Investigation into renal cell subtypes and ongoing genetic studies have revealed the underlying germline changes that occur with this disease. The most common pathogenic variants seen in germline mutations in 16.5% of patients with advanced renal cancer were CHEK2, FH and APC.<sup>1</sup>

The role of cytoreductive nephrectomy in metastatic disease remains somewhat controversial. Results of the CAR-MENA phase III trial of nephrectomy in patients treated with sunitinib were negative for survival benefit.<sup>2</sup> However, other data indicate that patients with favorable and intermediate risk, but not high risk, metastatic disease may benefit from this therapy.<sup>3</sup>

Immunotherapy doublets and combinations of immunotherapy with axitinib represent the most important recent advances in metastatic renal cancer.<sup>4,5</sup> Adjuvant therapy with tyrosine kinase inhibitors remains controversial at best and most oncologists do not endorse this approach.

In one of the most influential new trials, CheckMate 214, a combination of nivolumab and ipilimumab was compared to sunitinib as initial treatment for metastatic clear cell renal cancer.<sup>6</sup> Overall survival was clearly positive

and favored the combination immunotherapy. When examining subsets of low, intermediate and high risk disease, low risk disease did not preferentially benefit from combination immunotherapy, whereas combination therapy did preferentially benefit those with intermediate and high risk disease. Patients 75 years old or older did not appear to benefit in the subset analysis. Toxicity of the combination immunotherapy was clearly distinct and in some cases greater than sunitinib but health related quality of life was better with immunotherapy.

Two immunotherapy studies of combination axitinib with pembrolizumab4 and axitinib with avelumab5 are now complete. The pembrolizumab trial clearly was positive for survival compared to sunitinib. Analysis of subsets indicated little benefit of combination therapy in those with low risk metastatic disease.

In the second line setting after conventional tyrosine kinase inhibitors nivolumab and cabozantinib were superior to everolimus (in separate trials).<sup>7,8</sup>

Immunotherapy is now known to be active in a subset of advanced nonclear cell cancer cases.<sup>9</sup> Sarcomatoid variants are clearly susceptible to checkpoint inhibitors and chromophobe cancers appear less so.

Taken together, progress in renal cell carcinoma treatments is substantive with immunotherapy and checkpoint inhibitors assuming an increasingly greater role. Genetics and biomarkers continue to evolve but to date, practice changing studies have yet to be presented.

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### COURSE #023IC

## Chemotherapy and Immunotherapy Options for Genitourinary Malignancies: A Primer for Urologists and Advanced Practice Providers

Costas D. Lallas, MD, FACS, Course Director; Anne E. Calvaresi, DNP, CRNP and Edouard J. Trabulsi, MD, FACS, Faculty

The next generation of management of advanced genitourinary (GU) malignancies is marked by multidisciplinary care, interdisciplinary conferences and collaborative efforts. Long gone are the days when these patients were treated

by clinicians operating out of separate silos with outcomes often determined by one person making the majority of the

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decisions surrounding care. Often these patients were starting in a urology office before they were referred for management of advanced or metastatic disease. This field continued to change rapidly during the last decade. In order to stay relevant and to maintain a relationship with the patient, urologists must be familiar with the newest agents and guidelines, including specific indications and side effects. This issue is highlighted in the exciting field of immunotherapy oncology agents.

The concept of immunotherapy for bladder cancer is not new. Bacillus Calmette-Guérin (BCG) was approved by the FDA (U.S. Food and Drug Administration) for the treatment of superficial bladder cancer in 1990 and is still considered standard of care for noninvasive, high grade urothelial carcinoma of the bladder (nonmuscle invasive bladder cancer).<sup>1</sup>

BCG is generally believed to elicit an immune response much like native tuberculosis, for which it was first created as a potential vaccine. Additionally, the relatively muted response of BCG in an immune deficient state suggests its foundation in immunotherapy. Finally, although BCG is associated with ease of administration and tolerability, it can cause particularly toxic side effects including dysuria, fevers, arthralgia and (thankfully rarely) BCG induced sepsis. Therefore, it should never be administered in the setting of active infection or gross hematuria. Unfortunately, for reasons out of control of the urology community, gaps in production and resultant availability of BCG have recently led to a national shortage of this medication, and have forced urologists to seek alternative intravesical treatments for nonmuscle invasive bladder cancer.

Most of the recent excitement surrounding immunotherapy and bladder cancer lies in the introduction of checkpoint inhibitors (CPIs). The astounding efficacy of this class of medications against urothelial cancer prompted a well-known and established genitourinary oncologist to state at an international meeting that he had "not seen such dramatic responses in my 30 years of treating these cancers."

The checkpoint proteins are molecules that impede immune function (namely T-cell immunity). In a normal individual this immune regulation helps the body recognize self and prevent autoimmunity and immune overactivity. However, malignant cells can hijack this mechanism and mimic the signals released by healthy cells. In so doing, the immune system remains inactive against the malignant cells, allowing them to grow and proliferate unregulated. A checkpoint inhibitor takes the proverbial foot off the brake and activates the cellular response, allowing the immune system to attack the malignant cells.

The 3 checkpoint targets PD-1 and CTLA-4 (on the T-cell) and PD-L1 (on the tumor cell) are currently the focus of investigation. Atezolizumab is a monoclonal antibody, the first described PD-L1 inhibitor found to be active in bladder cancer. It received accelerated approval by the FDA for the treatment of urothelial cancer after failed platinum based chemotherapy, the first such agent in this disease space in more than 2 decades. The phase 2 IMvigor trial was the basis for the FDA approval as it demonstrated an objective response rate of 16% in 310 patients with platinum treated inoperable, locally advanced or metastatic urothelial carcinoma.<sup>2</sup>

Pembrolizumab is a humanized monoclonal antibody against PD-1 that was studied in KEYNOTE-045, a large, open label, international, phase III trial evaluating its efficacy in the platinum refractory setting.3 The positive results of this trial led to FDA approval of pembrolizumab for platinum refractory advanced urothelial carcinoma. Additional checkpoint inhibitors that are FDA approved in this disease space are nivolumab (anti-PD-1), durvalumab and avelumab (both anti-PD-L1). The objective response rate for these agents ranges from 15% to 25%, with a higher response in PD-L1 expressing tumors.

Furthermore, atezolizumab and pembrolizumab have gained approval in the first line cisplatin ineligible population. Also exciting is the FDA approval of erdafitinib for patients with locally advanced or metastatic bladder cancer with an FGFR3 or FGFR2 alteration and in whom platinum based therapy has failed. In addition, the antibody-drug conjugate enfortumab has shown significant activity in patients with advanced bladder cancer in whom checkpoint inhibitors have failed.<sup>4,5</sup>

Like bladder cancer, renal cell carcinoma (RCC) is not a stranger to immunotherapy, particularly for the treatment of metastatic disease. From the 1990s to the early 2000s the only agents considered effective for patients with advanced RCC were high dose interleukin-2 and interferon. In fact, much of the data concerning cytoreductive nephrectomy was based on patients receiving adjuvant interferon.6 However, harsh toxicities and relatively poor response rates associated with these older immunotherapy agents in part led to the quick conversion to the targeted therapy era in advanced RCC. These medications (eg sunitinib) were considered standard of care for approximately 10 to 15 years.

With the arrival of the CPIs came a new immunotherapy era for RCC. CheckMate 214 results were published in 2018 and demonstrated improved overall survival in the intermediate to poor risk metastatic RCC group treated with ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) combination vs sunitinib monotherapy.7 Additionally, the combination CPI regimen was better tolerated. These results led to FDA approval of this regimen as first line treatment for intermediate to poor risk metastatic RCC. Moreover, this year 2 separate trials evaluating a combination regimen of a CPI and targeted agent for the first line treatment of advanced clear cell renal cell carcinoma were published in the same issue of The New England Journal of Medicine.8,9 Both trials were positive and led to the recent FDA approval of pembrolizumab plus

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axitinib and avelumab plus axitinib in this disease space. Other trials are actively accruing and awaiting data maturation that will also impact management of advanced and metastatic RCC.

Unlike other GU malignancies prostate cancer has not demonstrated a clear benefit from CPIs and most of the recent strides for advanced prostate cancer surround the androgen receptor targeted agents. However, unlike with androgen receptor targeted therapies, where there are a plethora of new data, the only immunotherapy currently FDA approved for prostate cancer remains sipuleucel-T, which is used in nonvisceral, asymptomatic or minimally symptomatic M1 castration resistant prostate cancer.<sup>10</sup> It involves 3 separate cycles of leukapheresis, ex vivo cell activation and reinfusion of the activated immune cells into the patient. Each cycle occurs during 1 week. Counterintuitively, efficacy does not necessarily correlate with a biochemical response and prostate

specific antigen is not a reliable surrogate marker in patients being treated with this immunotherapy. Also, the labor-intensive mechanism of sipuleucel-T administration has limited its use in many outpatient settings, particularly that of the urologic oncologist.

Immunotherapy in GU oncology, although not necessarily novel, has certainly had a resurgence with the introduction of newer classes of medications. Patients with advanced disease are more functional because of better survival and tolerability and, thus, are more often being seen in the outpatient setting. Because of increased collaboration of care for these patients, they are being evaluated more frequently in the clinic of a urologic oncologist, who must stay abreast of the exciting and rapidly changing landscape.

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### COURSE #038IC

## Case-Based Discussion of AUA Non-Muscle Invasive Bladder Cancer Guidelines

Sam S. Chang, MD, MBA, Course Director; James M. McKiernan, MD and Chad R. Ritch, MD, Faculty

This course provided an overview of the current AUA guideline for the management of nonmuscle invasive bladder cancer (NMIBC),<sup>1</sup> and targeted health care providers who manage NMIBC as well as those urologists preparing for board certification/recertification. By reviewing the guidelines and then focusing on real-world cases, participants were able to review and then see how the guidelines can offer helpful algorithm based information. In addition, this year's course devoted a significant section to bacillus Calmette-Guérin (BCG) alternative regimens.

The course began with a review of guideline methodology and described the process of data collection involved in guideline creation. To develop the NMIBC guidelines a systematic review of more than 200 NMIBC studies was undertaken by the AHRQ (Agency for Healthcare Research and Quality).<sup>2</sup>

The AHRQ group assessed these studies for risk of bias and whether they were fit for inclusion in the guideline. Strict criteria for level of evidence (A, B, C) and strengths of recommendation, as defined by the AUA, were then applied. In addition, if study data were limited the statement was graded as "clinical principle" (ie general agreement among most urologists) or "expert opinion" (general consensus among guideline panel members).

Next, key epidemiological characteristics of bladder cancer were presented, as it is the 4th most common solid malignancy in men and approximately 75% of the 74,000 new cases of bladder cancer each year are NMIBC.<sup>3</sup> Etiologic factors were described including tobacco smoking and exposure to chemical carcinogens. Genetic mutations in tumor suppressor genes such as p53 and RB-1 were discussed as well. Staging and grading based on the most recent version of the American Joint Committee on Cancer TNM classification and the WHO/International Society of Urological Pathology grading system were presented.

The survival prognosis for patients with NMIBC (stages Ta, Tis and T1) is relatively favorable, with cancer specific survival in high grade disease ranging from approximately 70% to 85% at 10

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years. The heterogeneous spectrum of NMIBC was described, specifically with respect to prognosis as defined by recurrence and progression. While some tumors are more likely to recur, others are more likely to progress despite subtle differences in stage and grade. To this end, the AUA guidelines panel decided to incorporate a risk stratification system as a part of the new algorithm for the management of NMIBC.

The AUA risk stratification system was derived from data used to develop the EORTC (European Organisation for Research and Treatment of Cancer)<sup>4</sup> and CUETO (Club Urológico Español de Tratamiento Oncologico) models,5 and expands on these tools to include the prognostic impact of BCG treatment failure, as well as adverse pathological features such as the presence of lymphovascular involvement, prostatic urethral involvement and variant histology. A point of emphasis was that at each instance of occurrence or recurrence, the risk stratification tool should be applied to the patient algorithm to ensure adherence to the guidelines.

The course faculty then presented and discussed each guideline statement and supporting evidence, in depth, with relevant background data. A detailed listing of the statements and references can be found at https://www.auanet.org/ guidelines/non-muscle-invasive-bladdercancer-(aua/suo-joint-guideline-2016). The first 4 statements are essential clinical principles for documenting and diagnosing NMIBC (cystoscopy, transurethral resection and tumor description in operative/procedural notes).

Statement 5 is unique to the current guidelines as it specifically recommends that risk stratification be performed, using the AUA risk groupings of low, intermediate and high, at each occurrence/recurrence of NMIBC. The emphasis on risk stratification is to aid in a more personalized approach to decision making as opposed to the one size fits all method.

Statements 6 to 8 highlight that variant histology is a rare but worrisome patho-

logical finding and should be confirmed by an expert genitourinary pathologist. In addition, due to the limited data demonstrating a high rate of up staging, these variant histologies should be managed aggressively with repeat resection in the cases for which bladder sparing is being considered, or preferably, with radical cystectomy.

Statements 9 to 11 address the issue of urinary biomarkers and their use in diagnosis and surveillance. While some urinary biomarkers may have improved sensitivity and specificity compared to cytology, none of the available evidence supports their use in replacing cystoscopic surveillance. Furthermore, specifically for low risk patients, urinary biomarkers should not be used during routine surveillance. However, urinary biomarkers may help in cases of equivocal cytology or assessing response to intravesical BCG.

Statements 12 to 14 discuss repeat resection, and advocate its use in patients with incomplete resection, high risk, high grade Ta disease and T1 disease.

Statements 15 to 21 provide an overview of intravesical therapy. Key elements include the use of single agent intravesical chemotherapy within 24 hours for patients with low or intermediate risk disease, without perforation or extensive resection, 6-week induction intravesical therapy (chemotherapy or immunotherapy) for intermediate risk disease and 6-week induction BCG for high risk disease (CIS, HG T1, high risk Ta).

It was emphasized that maintenance therapy may be offered for up to 1 year in intermediate risk patients who respond to BCG and should be administered for up to 3 years in high risk patients based on the results of EORTC 30962.<sup>6</sup>

Statements 22 to 26 address BCG relapse and salvage regimens. Patients with persistent or recurrent disease, or positive cytology after intravesical therapy, should undergo workup including upper tract evaluation and prostatic urethral biopsy to identify occult sites

of disease. A second course of BCG can be offered to patients with persistent or recurrent CIS or Ta disease after induction BCG and this second course may be 3 or 6 weeks in duration. However, patients with HG T1 disease who do not respond to induction BCG should be offered radical cystectomy due to worse prognosis and increased risk of death from disease in patients with delayed vs early cystectomy. Additional BCG should not be used in cases of BCG intolerance or recurrence/persistence within 6 months following 2 induction courses or induction plus maintenance.

In discussing the BCG shortage, the update from Merck indicated a hopeful 2020 date of meeting all needs. In the meantime, guidance from the AUA included several points. Intravesical chemotherapy should be used as the first line option for patients with intermediate risk NMIBC. Patients with recurrent/multifocal low grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy. If BCG would be administered as second line therapy for patients with intermediate risk NMIBC, an alternative intravesical chemotherapy should be used instead. For patients with high risk NMIBC, high grade T1 and CIS disease, those receiving induction therapy should be prioritized for use of full strength BCG. If that is not available, these patients and other high risk patients should be given a reduced one-half to one-third dose if feasible, and with T1 cases, radical cystectomy being an important option. If supply exists for maintenance therapy for patients with NMIBC, every attempt should be made to use one-third dose BCG and limit dose to 1 year. In addition, BCG should not be given to patients with low risk disease.

A comprehensive overview was then given of currently available clinical trials in NMIBC for patients in whom intravesical therapy failed and for those who are not willing or suited for radical cystectomy. Statements 27 to 29 further emphasize the role of radical cystectomy for select, high risk patients

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and those who experience BCG failure. Statements 30 to 31 are new to the current guideline and recommend the use of enhanced cystoscopy (blue light, narrow band imaging), when available, to increase detection and decrease recurrence.

Final statements 32 to 38 address the issue of NMIBC surveillance frequency and intensity. The guideline recommends a risk based approach to surveillance with shorter intervals between cystoscopic evaluations for intermediate and high risk patients. In addition, upper tract evaluation should be considered at 1 to 2-year intervals for intermediate and high risk patients. However, it was pointed out that these statements represent expert opinion and that there is limited available evidence to support any particular surveillance regimen.

Importantly, throughout the course the faculty and attendees had an interactive experience discussing specific patient scenarios that highlighted important aspects of the guidelines. The cases that were discussed allowed extensive interaction with audience members who also raised specific questions in regard to specific patients.

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### COURSE #0771C Integrating Care for Oncology Patients: Establishing a Multidisciplinary Oncology Clinic with Advanced Therapeutics

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#### The Multidisciplinary Oncology Clinic

The delivery of care for patients with cancer has become increasingly complex given the pressures to see increasing numbers of patients, with mounting administrative burden and personalized treatment plans with new targeted therapies. The urologist is a central figure in the expanding treatment team of patients with urological cancers. The multidisciplinary oncology clinic (MDC) is a way that urologists can work with other cancer care providers to create advanced multi-modality treatment plans. Governing bodies and professional groups have identified multidisciplinary care as a marker for quality and improved outcomes.1 In some countries national guidelines have been established supporting the use of MDC teams to coordinate treatment of patients with cancer.<sup>2</sup> However, even when required, use of MDCs remains low for urologists.<sup>3</sup> Patents may be missing the benefit of input from other cancer specialties such

as radiation oncology or medical oncology and from supportive services such as nutrition or pain management.

Several models have been proposed for urologists interested in establishing a MDC. They can be either all-in-one in which all providers meet a patient in the same clinic space, or virtual clinics in which patients move from one member's clinic to another (see figure).<sup>4</sup> Both clinic types generally include a time to review case history, pathology and radiographic studies in a tumor board setting. The MDC can also provide an opportunity to share patient care with advanced practice providers (APPs) under the direction of a supervising physician. The ASCO (American Society of Clinical Oncology) Oncology Practice Census indicated that a majority of oncology practices have APPs. The role of APPs in the MDC can range from shared clinic visits with patient education on treatment dosing, side



Figure. Oncology multidisciplinary clinic.

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effects and costs to independent visits and treatment monitoring.

#### Multidisciplinary Prostate Cancer Treatment

The evolution of treatment for advanced prostate cancer was jumpstarted by the results of the CHAARTED trial for men with metastatic hormone sensitive prostate cancer (mHSPC).5 Six cycles of docetaxel with androgen deprivation therapy (ADT) were compared to ADT alone in men with mHSPC, and significant improvement was noted in the primary outcome of overall survival in the combination therapy group. Importantly, a followup study revealed that the benefit occurred specifically in men with high volume metastatic disease.6 This finding provides an opportunity for urologists to participate in MDC care for patients with high volume disease at presentation. The results of these studies were further supported by the STAMPEDE trial.7

The management of mHSPC with advanced androgen axis agents such as abiraterone was supported by the Latitude trial.8 The results of that trial increased the complexity of the treatment landscape for patients with advanced prostate cancer. STAMPEDE also established a benefit for patients receiving abiraterone for mHSPC. However, there are no data to support use of chemotherapy over abiraterone in the high risk population, although there is some insight from the STAM-PEDE trial when overlapping groups received either abiraterone or docetaxel. However, in a post-hoc analysis there was no advantage of one treatment over the other. The ARCHES trial similarly evaluated enzalutamide in patients with mHSPC.

Radiation therapy to the primary represents another opportunity for MDC care in patients with mHSPC. The STAMPEDE trial evaluated radiation therapy in patients treated with docetaxel plus ADT. For the entire population, there was no benefit to radiation of the primary but when stratifying low vs high volume disease, there was significant improvement in survival of patients who received radiation therapy to the primary. Patients with mHSPC represent a unique opportunity for treatment by a MDC team.

Patients with metastatic castration resistant prostate cancer (mCRPC) also provide an opportunity for MDC care. For asymptomatic mCRPC treatment options include abiraterone, enzalutamide, sipuleucel-T and docetaxel.9 Sipuleucel-T is a patient derived immunotherapy for those who have no or minimal symptoms defined by the absence of pain requiring narcotics. The treatment results in an upregulation of the immune system that responds to prostate cancer cells, which improved overall survival without a prostate specific antigen (PSA) or radiographic response. Abiraterone and enzalutamide are oral agents that can be managed by either a medical oncologist or urologist. The inhibitory action of abiraterone on the CYP enzymes may result in disturbances in potassium levels, edema or liver enzyme elevations. Frequent monitoring at initiation is required and can be co-managed by an APP familiar with the side effects of abiraterone. Docetaxel chemotherapy is also available as a first line agent for mCRPC, and may be preferred over other agents in patients with widespread or visceral metastases. For patients with symptomatic mCRPC, particularly bone metastases in the absence of visceral metastases, radium-223 can be offered as a bone seeking isotope that targets areas of bone metastases.

#### Multidisciplinary Kidney Cancer Treatment

Until recently, the primary role of surgical management for advanced kidney cancer was removal of the primary tumor with the hope that disease did not recur. However, many patients are at high risk for recurrence. Several agents have been tested as adjuvant therapies to prevent recurrence, although most of the studies on adjuvant therapy have been negative. Sunitinib remains the sole adjuvant therapy with potential benefit based on results of the S-TRAC study.<sup>10</sup> In that study disease-free survival improved but not overall survival. Although the use of adjuvant therapy has not become widespread for high risk kidney cancer, there are several situations when additional therapy in a MDC setting may be beneficial.

Neoadjuvant therapy has been proposed to downstage tumors before surgical intervention with recent reports of tumor shrinkage with preoperative pazopanib and axitinib.11,12 The expansion of treatment options for metastatic kidney cancer has resulted in a reevaluation of the benefit of cytoreductive nephrectomy for those who present with metastases. In the CAR-MENA trial treatment naïve patients with biopsy proven metastatic clear cell renal cell carcinoma were randomized to receive sunitinib alone vs cytoreductive nephrectomy plus sunitinib in a non-inferiority study.13 Results indicated that sunitinib alone was not inferior to cytoreductive nephrectomy followed by sunitinib. However, the study was enriched with high risk patients who may have been poor surgical candidates. The results suggest that a nuanced approach to patients with metastatic kidney cancer may be most beneficial. The opportunity for MDC management is further complicated by the superiority of immunotherapy agents such as ipilimumab and nivolumab over tyrosine kinase inhibitors such as sunitinib.

#### Multidisciplinary Bladder Cancer Treatment

The benefits of multidisciplinary management, including neoadjuvant chemotherapy before radical cystectomy, and the importance of surgical quality as measured by lymph node count were shown in the SWOG 8710 trial.<sup>14</sup> A followup meta-analysis provided evidence of a 5% overall survival benefit at 5 years with neoadjuvant chemotherapy.<sup>15</sup> These findings support the recommendation in the AUA guidelines for a MDC approach to muscle invasive bladder cancer.<sup>16</sup> Conversely, support for adjuvant chemotherapy following radical cystectomy has been limited by

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clinical trials with poor patient accrual and inadequate sample size. Although routine adjuvant chemotherapy is not recommended, the AUA guidelines support the use of adjuvant chemotherapy in chemotherapy naïve patients who have undergone radical cystectomy with non-organ confined or lymph node positive pathology. For patients with metastatic disease, cisplatin based chemotherapy remains the first line treatment of choice. However, immunotherapy including pembrolizumab and other PD-1/PD-L1 agents has recently been approved for second line and cisplatin ineligible patients. For some treatments, PD-L1 expression testing may be required to confirm treatment eligibility. For these patients with an intact bladder, urologists can provide a potential source of tissue.

#### Conclusion

As advanced therapeutics become a growing part of the management of urological cancer, the urologist will be required to coordinate care among a growing number of oncology specialists. The creation of a MDC can provide the infrastructure to manage these cases along with the growing demands of clinical practice. New agents and expanded indications provide patients an opportunity to receive targeted treatments and immunotherapy with fewer side effects and the hope of long-term response.

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## UROLOGIC CARE FOR THE ADVANCED PRACTICE PROVIDER The Emerging Role of Genetic Counseling and Testing in Urologic Cancers

#### Ashlynn Messmore, CGC

Germline genetic testing in patients with prostate cancer can provide crucial information that can influence the treatment, prognosis and overall health management. Knowledge of germline mutations can clarify which surveillance and treatment options are indicated, such as more frequent tumor assessment, targeted chemotherapies and/or surgical removal before metastasis (as germline variants can predispose to a higher likelihood of metastatic disease). Additionally, germline mutation findings can promote cascade testing in family members, allowing them to engage in risk reduction strategies and receive increased surveillance for early detection.

Current National Comprehensive Cancer Network<sup>®</sup> (NCCN<sup>®</sup>) guidelines regarding germline genetic testing of prostate cancer are inconsistent, complicated and limiting.<sup>1,2</sup> Their qualifications for genetic testing require patients to have biopsy proven metastatic prostate cancer or high grade (Gleason score 7 or greater) prostate cancer with specific features in the family history. Such requirements prevent testing in a significant number of individuals who do not meet these criteria but may still carry mutations. Current guidelines also only address testing and screening implications of BRCA1 and BRCA2, and exclude other genes known to increase prostate cancer risk, such as ATM,

CHEK2 and HOXB13, and DNA mismatch repair genes.<sup>2,3</sup>

Pritchard et al attempted to characterize the frequency of mutations in DNA repair genes found in patients with prostate cancer.<sup>3</sup> In 82 men (11.8%) with pathogenic variants mutations were found in a total of 16 genes. The most frequently found mutated gene was BRCA2, followed by ATM, CHEK2 and BRCA1.<sup>2,3</sup> Family history or age at diagnosis had no influence on pathogenic variant presence.

Many of the DNA repair genes found with pathogenic mutations are also related to increased risks of other cancer types, including breast, ovarian, pancreatic, colon and melanoma ▼ Continued on page 11

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as well as other inherited conditions, such as ataxia telangiectasia. Identification of germline variants in these genes can have significant implications for health management. Importantly, mutation specific therapy options can be added to treatment plans. Patients with prostate cancer and mutations in DNA repair genes may respond well to poly-ADP ribose polymerase inhibitors and platinum based therapies.<sup>2,3</sup> Those with mutations in mismatch repair genes and high microsatellite instability may respond well to immunotherapies.1

The study by Pritchard et al provided important evidence that germline genetic testing in patients with prostate cancer can reveal actionable mutations in several genes.3 They concluded that it would be of interest to perform broader testing of all patients, regardless of family history, as that would likely increase detection of actionable mutations (similar to the case of epithelial ovarian cancers).

Despite the findings of the study, guidelines were not updated to reflect the new information. A consensus statement issued by the Philadelphia Prostate Cancer Consensus Conference in 2017 addressed some of the gaps in the current guidelines.1 A panel of 71 experts and key stakeholders agreed that current criteria for genetic testing should be expanded to include patients with broad family histories indicative of the 3 syndromes of hereditary breast and ovarian cancer (BRCA1/2), hereditary prostate cancer (HOXB13) and Lynch syndrome (MSH2, MSH6, MLH1, PMS2 and EPCAM).

The panelists agreed that BRCA2 and HOXB13 mutations should be factored into screening discussions, and recommended that mutation carriers should begin screening at age 40 years or 10 years prior to the diagnosis of the youngest family member. It was also agreed that men with tumor profiling showing mutations in BRCA1/2, mismatch repair genes, HOXB13 and ATM should undergo confirmatory germline testing. Most importantly, the

panelists acknowledged the usefulness of multigene panels for prostate cancer and called for more comprehensive guidelines regarding multigene panel application. While the panelists did not recommend testing of all men with prostate cancer, they noted that more evidence needs to be collected and analyzed for future revisions of criteria because at that point, most studies of germline testing for prostate cancer only selected for metastatic or high grade forms.

Most recently, in a cross-sectional study Nicolosi et al assessed 3,607 men diagnosed with prostate cancer, unselected for disease stage, family history or age of diagnosis.2 The men were clinically tested between 2013 and 2018. Mean patient age at diagnosis was 60 years, while mean age at testing was 65 years, indicating a notable lag between initial diagnosis and genetics referral. Pathogenic variants were found in 17.2% of the men, of whom 37% would not have qualified for testing based on existing guidelines.

Gleason score information was available for 1,539 of the 3,607 men studied. Based on this subset, the percentages of individuals with pathogenic variants were almost equal to those with low and high Gleason scores (15.1% low scores, 16.3% high scores). Thus, a high Gleason score was not a determinant of pathogenic variant presence. Findings of mutated genes in this study were similar to those found by Pritchard et al in men with metastatic prostate cancer.3 This finding indicates that patients with low grade and less aggressive prostate cancer can also benefit from germline genetic testing.

Overall, multigene germline testing for prostate cancer has a significant yield, including high locus heterogeneity with each gene having unique implications for the patient and family. The factors currently used to delineate which patients qualify for testing are not associated with pathogenic variant presence. It is recommended that patients with prostate cancer be referred to a genetics

team when appropriate for evaluation, regardless of age, cancer stage, Gleason score and race/ethnicity. While it is true that prostate cancer is more prevalent in the African American population, most of the pathogenic mutations identified in previously mentioned studies were found in Ashkenazi Jewish and Caucasian individuals with study populations limited in demographic coverage.1-3 There is an urgent need to conduct focused studies of germline genetic testing for African American males. The panelists at the Philadelphia conference reached strong consensus that African American men should be treated based on the same criteria for germline testing as males of any other race or ethnicity, at least until more studies are performed and adequate genetic data are analyzed.1

In our own multidisciplinary urology clinic at the University of North Carolina we initiated a pilot study incorporating myself, a genetic counselor, into clinic weekly to help decrease barriers to care. The small pilot study included 51 men with metastatic prostate cancer. The same genetic test was ordered for each patient, a multigene prostate cancer panel including sequencing and deletion duplication of ATM, BRCA1, BRCA2, BRIP1, CHEK2, EPCAM (deletion/ duplication only), FANCA, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D and TP53. The results of this pilot study indicated a 10% pathogenic mutation rate, 12% variant of unknown significance rate and 78% negative rate. One pathogenic variant each was identified in BRCA2, HOXB13, NBN, PALB2 and MSH2.

These results directly impacted the treatment for the individual with the BRCA2 mutation as well as the MSH2 mutation, beginning with a poly-ADP ribose polymerase inhibitor and checkpoint inhibitor, respectively. The patient with the MSH2 mutation also had a history of colon cancer and liver lesions were recently identified. He was scheduled to have a liver biopsy to understand if the lesions were of colon or prostate origin but due to his germline test result

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treatment with checkpoint inhibition was initiated and no liver biopsy was performed. For all 5 individuals who had pathogenic variants cascade testing was performed for their adult family members including children, siblings etc, allowing more appropriate cancer screening for those at increased risk.

Genetic counselors are also in the unique position to understand insurance coverage and criteria for germline genetic testing. In our small pilot study 58% of patients did not meet the insurance criteria for having this test performed. Of the individuals who tested positive for a pathogenic variant 40% did not meet the insurance criteria for this testing based on their personal and family history of cancer. This denial in coverage is a reflection of insurers not updating their criteria for germline testing for men with prostate cancer based on the changing landscape of what is now known about germline mutations in prostate cancer as well as the updated NCCN guidelines.

A broad and more inclusive approach of genetic evaluation and testing for prostate cancer may prove to be economically beneficial in the long run for patients and providers. Comparing the cost of a genetic test to the financial and emotional costs of late stage cancer detection and treatment, the benefits of testing far outweigh the risks.<sup>2</sup> Going forward, it is reasonable to expect germline genetic testing to be fully incorporated as an integral part of prostate cancer management.

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## SECOND OPINION CASES (ASK THE GUIDELINES!) Advanced and Castration Resistant Prostate Cancer

David F. Jarrard, MD, Moderator; Michael S. Cookson, MD, MMHC, William T. Lowrance, MD, MPH and William K. Oh, MD, Panelists

The field of advanced and castration resistant prostate cancer (CRPC) is rapidly changing due to a number of recent clinical trials that have impacted the care that urologists provide. Recent phase III trials of agents in combination with standard androgen deprivation therapy (ADT) have changed our approach to newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC). In addition, with the advent of 8 new drugs for the management of CRPC, we now have a menu of options that we can offer to patients. An important theme of these new approaches is the earlier use of these agents in the course of the disease. Sequencing these drugs also becomes an important component of patient care. To highlight these changes, a case based format was used for this presentation involving several experts including urological oncologists Drs. Michael Cookson, David Jarrard and William Lowrance, and medical oncologist Dr. William Oh.

For the last 70 years the management of advanced hormone sensitive prostate cancer (HSPC) was based primarily on ADT either in the form of chemical castration or orchiectomy. The treatment of mHSPC with ADT leads to initial disease regression and stabilization but results in the clonal selection of cells capable of surviving testosterone withdrawal. Targeting this susceptible niche after ADT initiation with docetaxel has been successfully demonstrated in 3 randomized trials (CHAARTED, GETUG-ARU15 and STAMPEDE) encompassing roughly 3,000 patients.<sup>13</sup>

In the CHAARTED trial the median overall survival was 5,7.6 months in the chemohormonal arm vs 44 months in the ADT only arm, conferring an improvement of 13.6 months in overall survival (HR 0.61, 95% CI 0.47-0.80, p <0.001). Patient selection is important for ADT-docetaxel, and maximal benefit was achieved in patients with high volume disease defined as the presence of visceral metastases and/or at least 4 bone lesions, including at least 1 lesion in any bony structure beyond the spine or pelvis. Importantly, quality of life assessments of the side effects of chemotherapy included neutropenia and neuropathy. These studies show that the shorter term of increased risk of side effects due to chemohormonal therapy is offset by an improved quality of life at

later time points.4

Recently, other phase III clinical trials of mHSPC explored combining ADT with the androgen signaling inhibitors abiraterone or enzalutamide. The LAT-ITUDE trial involved 1,199 patients assigned to receive a combination of ADT plus 1,000 mg abiraterone plus 5 mg prednisolone or ADT plus placebo.5 Abiraterone is an androgen axis inhibitor that decreases androgen biosynthesis by inhibiting the steroidal enzyme 17 α-hydroxylase/C17,20-lyase, causing suppression of androgen synthesis in testicular, adrenal and prostatic tumor tissues. After a median followup of 30 months there was a 38% reduction in the risk of death in the abiraterone group.

Similar results were seen in the abiraterone arm of STAMPEDE.<sup>6</sup> The ARCHES trial tested enzalutamide, a second generation antiandrogen that has multiple sequential actions in the AR pathway, including competitive inhibition of androgen binding to receptors, inhibition of AR nuclear translocation and DNA interaction.<sup>7</sup> The combination of enzalutamide plus ADT significantly improved radiographic progression-free

#### Second Opinion Cases (Ask the Guidelines!)

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survival (HR 0.39, 95% CI 0.30-0.50, p <0.001). Significant improvements were reported in subgroups of patients based on disease volume, pattern of spread and prior docetaxel (HR 0.24 to 0.53). Overall survival data are still maturing.

In light of these published results from the aforementioned clinical trials, combined therapy now represents the standard of care in men with mHSPC. ADT plus docetaxel can be offered to patients with mHSPC who are eligible for chemotherapy, particularly those with a high metastatic burden or a rapid pace of disease. Abiraterone and enzalutamide have different side effect profiles than docetaxel including hyperglycemia and cardiovascular risks. Being oral agents they are easier to administer in the office. For patients with poor cardiac function or other significant comorbid conditions, ADT alone remains an appropriate treatment option and should be discussed in individualized counseling. To date, a direct head-to-head comparison of ADT plus abiraterone, enzalutamide and docetaxel has not been performed, limiting the ability to generate conclusions on superior efficacy.

Another issue discussed was the evolving role of surgical or radiotherapy control of the prostate in patients with limited metastases, known as oligometastatic, and mHSPC. Several recent randomized trials were highlighted including HOR-RAD, which suggested survival might be improved in a subset of patients with fewer than 5 metastases receiving prostate radiation in a secondary analysis (HR 0.68, 95% CI 0.42-1.10, p not significant).8 An arm of the STAMPEDE trial appears to confirm a benefit for ADT and radiation therapy for patients with low volume oligometastatic disease as overall survival improved in 73% to 81% of those patients at 3 years.9 Radiotherapy was well tolerated with 9% experiencing adverse events (grade 3-4). The panel noted a number of ongoing trials for surgery in this metastatic setting which have yet to mature.

A notable trend is the treatment by

urologists and medical oncologists of metastatic CRPC at earlier even asymptomatic time points (M0). Prostate cancer eventually becomes resistant to ADT in most cases, at which time serum prostate specific antigen (PSA) levels begin to rise and/or radiographically detectable metastases emerge. The accepted definition of PSA progression from the Prostate Cancer Working Group 2 is a 25% increase from the nadir, with a minimum rise of 2 ng/ml confirmed with a second value 1 to 3 weeks later in a patient with testosterone less than 50 ng/ml. For patients with negative imaging studies, typically a bone scan as well as computerized tomography of the chest, abdomen and pelvis, this disease state is known as nonmetastatic CRPC (M0). Nonmetastatic CRPC is a heterogeneous disease state with variable progression. For M0 CRPC the rate of change in PSA is the best predictor of progression we have, and patients with a PSA doubling time (PSADT) of greater than 10 months may do best with observation.

Several recent trials have examined the positive impact of enzalutamide and the mechanistically similar apalutamide and darolutamide. In SPAR-TAN men with nonmetastatic CRPC and a PSADT of less than 10 months were randomized to receive placebo or apalutamide.10 The median time from start of treatment to metastases or death (metastasis-free survival) was 16 months in the placebo group and 40 months in the apalutamide group. The interval before symptoms of cancer progression worsened and additional therapy was required was longer in men treated with apalutamide. More patients in the treatment group experienced weight loss, fatigue, rash, falls and bone fractures, and 11% discontinued treatment due to side effects compared with 7% in the placebo group. Survival data are maturing. The PROSPER (enzalutamide)11 and ARAMIS (darolutamide)12 trials demonstrated similar improvements in metastasis-free survival.

Several take home messages from

this discussion were provided, one of which was that administration of more intense hormone therapies (eg ADT plus abiraterone or enzalutamide) sooner in the disease course can improve outcomes of mHSPC. Chemohormonal therapy improves survival compared to ADT alone and is best applied to cases of high volume mHSPC. Offer apalutamide, enzalutamide or darolutamide to patients with higher risk nonmetastatic CRPC with a PSADT of less than 10 months. The panel noted that with the development of newer sensitive positron emission imaging our ability to detect metastatic tumors will increase markedly. This technology may lead to a decrease in the M0 population in the future with more cases of prostate cancer classified as metastatic disease. In conclusion, this rapidly evolving area brings new hope to our patients with advancing prostate cancer. New guidelines on advanced and CRPC are anticipated by May 2020.

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#### Second Opinion Cases (Ask the Guidelines!)

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### TAKE HOME MESSAGES

Following are summaries of Take Home Messages delivered on the final day of this year's AUA meeting. The purpose of these messages is to provide an overview of presentations on select topics. Abstract numbers are in parentheses (J Urol, suppl., 2019; **201**: e1-e1207).

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## **Prostate Cancer**

Sanjay Patel, MD, Oklahoma City, Oklahoma

The educational content of AUA annual meetings is nothing short of drinking from a fire hose and the prostate cancer sessions this year were certainly not an exception. The diagnosis and management of prostate cancer are ever evolving. I have highlighted some of the more salient and clinically relevant aspects of the 2019 AUA prostate cancer sessions.

While the opioid epidemic continues to be a national crisis, the patterns of postoperative opioid use after prostatectomy were highlighted in several presentations. Patterns of opioid consumption after discharge (5 mg tablets of oxycodone) were described for 117 patients who underwent robotic prostatectomy (MP10-02). Only 52% of the patients took 0 tablets and 91% took fewer than 10, suggesting that clinicians should limit post-discharge narcotic quantities and use parameters such as inpatient postoperative pain scores and hospital consumption of narcotics to guide discharge quantities.

In the Michigan statewide experience the MUSIC (Michigan Urological Surgery Improvement Collaborative) and Blue Cross Blue Shield incentivized urologists by allowing a modifier 22 for prostatectomy if they participated in a pain optimization pathway with only 6 tablets of 5 mg oxycodone given after discharge (PD58-02). After implementation of the pathway the average consumption of post-discharge opioids was 3 tablets, again suggesting that with proper implementation a standard opioid limiting pathway is possible after prostatectomy.

There has been an exponential increase in deaths from opioids during the last 4 decades, with more than 75% of opioids coming/stolen from friends and relatives (MP33-03). Presented experience in reducing the number of narcotics prescribed pills from 40 down to 2 after implementation of a formal opioid reduction protocol. Furthermore, "persistent opioid use after prostatectomy is the #1 surgical complication." These studies all demonstrate that urologists can do their part to turn down the spigot of opioid abuse with proper counseling, implementation of postoperative opioid reduction pathways and limitation of post-discharge narcotics.

Germline testing has become incorporated into guidelines for ovarian and breast cancer as they can provide important information that can guide decision making, screening for secondary cancers and identification of family members potentially at risk for disease. Exciting data were presented on germline testing in prostate cancer (MP54-12). One in 10 men with metastatic prostate cancer has germline DNA repair mutations, with BRCA1/2, ATM having an association with upgrading on active surveillance, and worse overall and cancer specific survival in patients undergoing localized treatment for prostate cancer.

From an ethical standpoint the Genet-

ic Information Nondiscrimination Act prohibits health insurance and employment discrimination. However, it does not prevent discrimination with regard to life, disability or long-term care insurance. Ultimately germline testing in prostate cancer may become a component in the management paradigm for prostate cancer and urologists should understand the pros and cons of testing as further data emerge.

Molecular imaging of prostate cancer has advanced during the last several years with metabolic agents (fluciclovine, choline etc) as well as agents that target receptors (androgen receptors, prostate cancer specific membrane antigen [PSMA] etc). These agents have laid the groundwork for numerous imaging studies to better characterize extent of disease after biochemical failure after primary treatment for locoregional disease.

High quality data were presented on molecular imaging with Gallium (Ga) PSMA positron emission tomography (PET). In a prospective trial of 635 patients with biochemical recurrence after radical prostatectomy or radiation therapy there were high positive predictive values for Ga PSMA PET of 84% to 92% in a cohort with a 75% overall detection rate in patients with biochemically recurrent prostate cancer and median prostate specific antigen (PSA) 2.1 ng/ml. Notably, there was a high percentage (40%) of patients with ▼Continued on page 15

#### Take Home Messages

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extra pelvic disease across all PSA levels (even at lower PSA levels less than 1 ng/ ml). Furthermore, of the 30% of patients with disease confined to the pelvis, a minority had PSMA positivity in the prostatic bed.

In general, well-designed randomized trials involving surgical management of cancer are few and far between. Results were presented from the CALGB 90203 trial, which randomized 788 men with clinically localized high risk disease to radical prostatectomy vs 6 cycles of neo-adjuvant docetaxel chemotherapy with luteinizing hormone-releasing hormone therapy followed by radical prostatectomy (LBA-12).

## Kidney Cancer

Kara N. Babaian, MD, Shreveport, Louisiana

AUA2019 showcased exciting research in the kidney cancer podium and moderated poster sessions. Common themes of the approximately 180 presentations were renal mass biopsy (RMB), diagnostic imaging, active surveillance (AS), partial nephrectomy (PN) for tumors larger than 4 cm, renal function outcomes, surveillance imaging, predictors of outcome and response to systemic therapy as well as cytoreductive nephrectomy (CN). Some of these outstanding presentations are highlighted in this summary.

Multiple studies demonstrated that RMB decreases treatment for benign histology (PD07-09, MP14-04, MP14-05). Comparing RMB diagnostics to biopsies in other organ sites, RMB performs the same or better (MP31-15). Novel imaging techniques are under investigation to differentiate between benign and malignant tumors and to identify aggressive tumors. Sestamibi SPECT/computerized tomography (CT) can differentiate oncocytoma and hybrid tumors from other histologies with sensitivity and specificity of 87% and 89%, respectively (MP14-02). CT radiomic features can discriminate between sarcomatoid and nonsarcomatoid renal cell carcinoma (RCC) with 93% and 94% sensitivity

The primary end point was 3-year biochemical progression-free survival defined as a PSA greater than 0.2 ng/ ml. While there was no difference in biochemical progression-free survival (0.87 vs 0.82, p=0.13 in neoadjuvant vs prostatectomy, respectively), there was a significant difference in biochemical progression-free survival when expanded to the entire followup period. Of note, a sizeable portion of patients (42%) received additional therapy before reaching the PSA end point of 0.2 ng/ ml, which makes interpretation of the primary end point challenging. Freedom from treatment failure was also improved in the neoadjuvant arm at

and specificity, respectively (MP19-02).

Peak early phase enhancement ratio (PEER), the ratio of signal intensity differences between early and delayed contrast phases for the peak enhancing portion of the tumor compared to the renal cortex, can distinguish between oncocytoma and chromophobe RCC with 95% accuracy. An automated CT measurement has been developed of the PEER value (MP19-01). Of 141 renal masses biopsied 35 CD117 positive oncocytic tumors confirmed to be oncocytoma by PEER were placed on active surveillance. Of all biopsied cases treated surgically, none had benign histology (MP14-06).

The natural history of angiomyolipomas (AMLs) indicates that AMLs can be safely observed. In a retrospective review of 593 AMLs most lesions grew slowly regardless of size (0.25 cm per year) and most patients requiring intervention were symptomatic at presentation (MP14-01). For an AML less than 4 cm and 4 cm or greater, the number needed to treat to prevent 1 intervention/acute event was 82 and 16, respectively.

In patients with germline mutations on AS, tumors with BAP1 and VHL 38% vs 25% in the prostatectomy arm.

Further analysis will be performed to determine the impact of neoadjuvant therapy on the reduction of tumor volume and margin status and molecular tissue analysis will be performed to potentially identify chemohormonal resistance/susceptibly patterns.

Without question there were several other great research findings presented at AUA2019 but not included in this summary. While it is difficult to recap all the findings, it is always exciting to see how they will mature and improve our understanding of the diagnosis and management of prostate cancer.

mutations had the fastest growth rates, whereas FLCN and MET alterations had the slowest (PD07-04). In DIS-SRM, a multi-institutional AS registry, the most common indications for intervention were growth rate (50%) and patient preference (48%), highlighting the importance of counseling to address anxiety in patients who are appropriate candidates for AS (MP14-10).

A retrospective report from a multicenter database showed that robotic PN is feasible for well selected patients with cT3a tumors. The primary outcome of negative margins, warm ischemia time less than 25 minutes and no complications was achieved in 64%, and the optimal renal function outcome of 90% or greater estimated glomerular filtration rate preservation and no chronic kidney disease (CKD) upstaging was achieved in 41% (MP37-08).

Multiple groups reported similar oncologic outcomes between PN and radical nephrectomy (RN) for tumors larger than 4 cm, albeit with more complications after PN and worse functional outcomes after RN (MP42-17, MP37-07, MP42-20, PD41-05).

Functional compensation of the contralateral kidney after RN is due to

#### Take Home Messages

▼ Continued from page 15 an increase in parenchymal volume (10% within 12 months) and filtration efficiency (MP31-05). Urine albuminto-creatinine ratio as a measure of proteinuria can predict for CKD after RN and PN (MP31-12). In an evaluation of the risk of hypertension after RN/PN, RN was associated with a higher rate of new onset hypertension and worsening hypertension compared to PN (HR 1.40 and HR 1.18, respectively, p <0.001, MP42-13).

Among 268 patients with surveillance chest imaging from DISSRM, 12% had an actionable finding at baseline or during followup, which was most commonly lung (63%) or thyroid (25%) nodules (PD07-05). No patient was diagnosed with metastatic RCC, calling into question the usefulness of chest imaging in these patients.

In nonmetastatic locally advanced RCC 1 in 5 patients had recurrence outside the standard imaging template recommended by AUA and NCCN® (National Comprehensive Cancer Network<sup>®</sup>) guidelines (PD46-08). Chest, abdomen and pelvis imaging will identify the majority of recurrences within 2 years after surgery in these patients. Modeling the competing risks of recurrence and nonRCC death in nonmetastatic RCC for any given age, stage, histology and ECOG (Eastern Cooperative Oncology Group) performance status (PS), one group demonstrated when surveillance can be discontinued (MP14-14). For example, for a 50-yearold male with ECOG PS 0 and pT1a clear cell RCC, the risk of nonRCC death surpasses the risk of recurrence at 4.4 years.

Multiple studies investigated the inflammatory marker C-reactive protein (CRP) as a predictor of outcome and response to systemic therapy for localized and metastatic RCC. An elevated CRP was associated with the development of de novo stage III/IV CKD after PN and RN (MP31-16) and worse survival in localized (MP19-10, PD41-11, MP14-16) and metastatic disease (PD03-06).

Patients with metastatic disease treated with nivolumab could be characterized into 3 groups based on their CRP response, namely CRP flare-responder (25%), CRP responder (37.5%) and nonCRP responder (37.5%) (MP25-09). CRP flare-responders had the best response to nivolumab with an average of 35% tumor shrinkage and a 63% objective response rate compared to CRP responders (-8%, 8%) and non-CRP responders (+19%, 0%). CRP could potentially help identify patients for adjuvant treatment, clinical trials or a change in systemic therapy.

A post hoc analysis was performed of neutrophil and platelet-to-lymphocyte ratio (N/PLR) in patients enrolled in S-TRAC,<sup>1</sup> which was the only positive adjuvant trial. A baseline N/PLR less than 3 predicted who would benefit from adjuvant sunitinib and a 25% or greater decrease in N/PLR at 4 weeks predicted who better tolerated therapy (MP25-17).

Inspired by CARMENA,<sup>2</sup> which showed that sunitinib alone was noninferior to nephrectomy followed by sunitinib in the intention to treat analysis, several groups examined CN. Two retrospective studies found no difference or worse survival in patients who underwent CN followed by TKI compared to TKI alone (PD03-04, MP25-05). In a comparison of patients who underwent CN in the National Cancer Database (NCDB) to the CN arm in CARMENA, patients in the NCDB were younger, had fewer metastatic sites and had fewer lung/bone/lymph node metastases than in CARMENA (PD03-07).

A survey of 210 patients with kidney cancer conducted by the Kidney Cancer Research Alliance found that 75% still preferred nephrectomy even after knowing the CARMENA results (MP25-13). When it comes to cytoreductive nephrectomy, patient selection is paramount, and as clinicians we must balance patient preferences and the best available evidence.

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## **Bladder Cancer and the Avant-Garde**

Christopher Koprowski, MD and Amirali Salmasi, MD, MSCR, San Diego, California

Advances in bladder cancer research continue to be full of excitement as we discover more in every aspect of the disease from its basic science to its diagnosis and subsequent management. Where do we stand now?

Advances in genomics and immunology have generated buzz in nearly every urological cancer, of which bladder cancer is no exception. Investigations have been conducted on molecular subtypes of muscle invasive bladder cancer that could have profound treatment implications (MP38-06). Specifically, investigators have identified basal immune signature enriched and basal immune signature suppressed variants. Basal immune signature suppressed variants were found to have chemotherapy resistance and worse survival outcomes in patients who underwent neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC).

Biomarkers continue to be investigated, with an emphasis on extracellular vesicle biomarkers (PD13-07), urinary molecular targets (PD18-05) and urine based methylation targets (PD18-07), all of which may further refine and improve risk stratification in nonmuscle invasive bladder cancer (NMIBC).

In diagnostics, investigators have proposed rethinking how we approach

#### Take Home Messages

▼ Continued from page 16 patients with hematuria by a stratification scheme (hematuria cancer risk score) that seeks to better refine current cancer screening guidelines centered primarily around age and type of hematuria by incorporating patient specific risk factors including gender and smoking status (PD66-06). With excellent discriminatory accuracy (AUC 0.835, 95% CI 0.789-0.880) and a specificity of 30.5% compared to 12.6% (AUA guidelines), hematuria cancer risk score may help to define future screening guidelines.

New active surveillance criteria have been proposed for low risk bladder cancer in a study of 91 patients at the time of recurrence (PD18-08). The majority had a solitary recurrence smaller than 5 mm and were followed with cystoscopy/ cytology biannually. High grade cytology, increased tumor burden or size, hematuria or patient choice prompted formal resection. About a fifth of cases were upstaged but none to muscle invasive disease, suggesting active surveillance may be safely considered with certain criteria.

We saw significant interest and emphasis on bacillus Calmette-Guérin (BCG) unresponsive NMIBC. In an era of national BCG shortage alternative management options are becoming imperative, whether with new targeted therapies, immunotherapies or intravesical chemotherapeutics. Single agent pembrolizumab may have a role in this space. A study of 103 patients (BCG unresponsive carcinoma in situ [CIS] with or without papillary disease) showed a 3-month complete response (CR) rate of 38.8% (95% CI 29.4%-48.9%), although not without a grade 3/4 adverse event rate of 12.6% (MP43-01).

An oncolytic adenovirus (CG0070) was trialed in BCG unresponsive NMIBC in 67 patients with CR of 44%, 30% and 23% at 6, 12 and 18 months, respectively (MP43-02).

CIS subgroups did have worse CR

rates. Retinoblastoma or checkpoint markers may improve patient selection in this setting.

Conductive chemohyperthermia showed promising results as well in BCG unresponsive NMIBC. Postoperative conductive chemohyperthermia (Combat BRS system) was examined in a multicenter retrospective analysis of 87 patients with primary end points of recurrence-free survival and progression-free survival (PD13-10). Recurrence-free survival at 12 months was 55% and at 24 months was 48%. Progression-free survival at 24 months was 95%, with CIS disease substratification demonstrating 6-month rate of 57% with 1 instance of disease progression.

A novel IL-15 based immunostimulatory protein complex (N-803) was investigated in an open label, single arm multicenter phase 2 trial of intravesical BCG plus N-803 in BCG unresponsive NMIBC (LBA-18). Early results are promising, with a CR rate of 89% in 18 patients with CIS pathology after 3 months and 77% in high grade Ta/ T1 disease in 13 patients evaluated at 6 months with a relatively favorable side effect profile.

Another important focus was on the topic of neoadjuvant chemotherapy (NAC) before radical cystectomy for muscle invasive bladder cancer. Patient selection for NAC certainly could be further refined moving forward. This 6-month conditional landmark analysis demonstrated an increased risk of death (HR 1.31, 95% CI 1.23-1.39 and HR 1.22, 95% CI 1.11-1.35, both p < 0.001) and decreased median overall survival (23.5 vs 32.2 months, p < 0.001 and 19.3 vs 22.3 months, p=0.218) in patients treated with NAC+RC compared to RC alone, for pT3 and pT4 disease, respectively (MP32-07). Delay to RC for patients unresponsive to NAC could have serious implications and this patient cohort needs to be better defined.

Squamous cell variant (SCV) specifi-

cally was also studied in the setting of NAC. In 105 SCV cases NAC had a higher rate of pT0 (44% vs 7.5%, p <0.0001), lower SCV persistence at cystectomy (44% vs 65%, p=0.061), fewer positive lymph nodes (28% vs 25.3%, p=0.079), lower mean lymph node density (9.6% vs 26.1%, p=0.001) and fewer recurrences (12% vs 41.3%, p=0.0074) (MP38-02).

In a study of 4,783 patients from the NCDB the proportion with pT0 disease was higher with NAC vs RC alone in both groups, with SCC (7.5% vs 1%, p <0.01) and urothelial carcinoma (14.0% vs 4.0%, p <0.01) (PD52-04). Predictors of pT0 status included SCC (OR 0.42, 95% CI 0.24-0.74, p <0.01) and use of NAC (OR 3.72, 95% CI 3.29-4.22, p <0.01). NAC significantly improved survival (HR 0.81, 95% CI 0.77-0.86, p <0.01) over RC alone for urothelial carcinoma but not SCC (HR 0.93, 95% CI 0.67-1.30, p=0.69).

Finally, the feasibility and safety of prehabilitation before radical cystectomy were highlighted given the high readmission rates following this operation. Fifty-four patients were accrued in a 4-week supervised, escalating preoperative strength and cardiovascular program, which demonstrated improved functional fitness and quality of life outcomes after intervention which were sustained 90 days after surgery (PD52-07). The overall complication rate was 43% with a readmission rate of 20%.

The future of bladder cancer research is promising, and AUA2019 in Chicago certainly delivered exciting new data and future research avenues.



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