American Urological Association

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2021 AUA Annual Meeting Highlights: Genitourinary Cancer

Features highlights from the following AUA 2021 Annual Meeting sessions:

- AUA Guidelines: Advanced Prostate Cancer
- Prostate Cancer Update 2021
- AUA Guideline Amendment: Muscle Invasive Bladder Cancer/Non-Muscle Invasive Bladder Cancer
- First and Second Line Therapy in Advanced and Metastatic Bladder Cancer: A Changing Paradigm
- Management of Non Muscle Invasive Bladder Cancer: Practical Solutions for Common Problems
- Renal Cell Carcinoma: Surgical and Medical Management of High-Risk Renal Cell Carcinoma
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- Integrating Care for Oncology Patients: Establishing a Multidisciplinary Oncology Clinic with Advanced Therapeutics
- Chemotherapy and Immunotherapy for the Urologist and Advanced Practice Provider

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AUA2021 PLENARY

2021 Advanced Prostate Cancer Guideline Plenary

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Learning Objective

At the conclusion of the activity, participants will be able to:

- *Discuss the 2020 AUA/ASTRO/SUO Guideline for the management of advanced prostate cancer.*

Prostate cancer remains the most commonly diagnosed solid organ malignancy in men in the U.S. and stands as the second leading cause of cancer deaths in this population. Nearly 250,000 new diagnoses of prostate cancer and over 34,000 deaths are estimated in the U.S. for 2021.[1] As the diagnostic and therapeutic options available to advanced prostate cancer patients continue to rapidly evolve, clinicians are challenged to remain current with respect to the array of options available for disease prognosis and management. The increasing complexity of advanced prostate cancer treatment highlights the need for the current clinical practice guideline, developed to provide a logical basis for treatment of patients with advanced disease based on a systematic review of the highest quality published data available. The 2020 AUA Advanced Prostate Cancer Guideline expands on the Castration-Resistant Prostate Cancer (CRPC) Guideline, originally published in 2013, and now includes a number of advanced disease states, including nonmetastatic biochemically recurrent prostate cancer, metastatic hormone-sensitive prostate cancer, and nonmetastatic and metastatic CRPC. Following additional U.S. Food and Drug Administration (FDA) approvals since the 2020 publication of the guideline, the document was updated in 2021 to reflect new availabilities in the areas of androgen deprivation therapy and advanced imaging.

> "Multimodality approaches and integration of care are critical to improving the care for men with advanced prostate cancer."

The Advanced Prostate Cancer Guideline explores the currently available prognostic and treatment modalities available for each disease state while acknowledging ongoing research in the field and current unmet needs. Treatments evaluated in the guideline include conventional androgen deprivation therapy alone and in combination with first and second line antiandrogens, chemotherapy, radiation therapy, surgery, radiopharmaceuticals, immunotherapy, and surveillance strategies. Outcomes of interest include overall survival, prostate cancer mortality, progression-free survival, prostate specific antigen progression-free survival, failure-free survival, metastases-free survival, time to metastases, time to progression, skeletal events, and adverse events.

Multidisciplinary Approach to Patient Care

Central to this guideline is the understanding that multimodality approaches and integration of care are critical to improving the care for men with advanced prostate cancer. Multidisciplinary clinics and the resulting multimodality treatment approaches can optimize treatment selection, maximize results, and minimize overtreatment and side effects. As the therapeutic landscape evolves to include further combinations of systemic therapies with or without local therapies, advances in imaging, and genetic testing, treatment of advanced prostate cancer increasingly requires that clinicians embrace such management approaches. Team members should include urologists, medical oncologists, and radiation oncologists at a minimum when supporting treatment decisions for advanced disease. While focusing on disease treatment, patient care must also address issues related to patient quality of life and symptom management; as such, additional specialists may also include genitourinary pathology, genetic counseling, palliative care, and holistic specialists in addition to primary care. Further, clinicians should inform patients about suitable clinical trials and encourage patients to consider participation in such trials based on eligibility and access. In appropriate patients, clinical trial options should be considered, and trial options should be discussed with patients as part of the shared decision making process.

Guideline Updates

Advanced Imaging

It is important for the practicing clinician to note that the studies underpinning this guideline's recommendations were largely predicated upon the use of conventional imaging including computerized tomography, magnetic resonance imaging, and bone scan. As the medical evidence evolves to more consistently incorporate next generation imaging, the definition of "nonmetastatic" and "metastatic" will evolve owing to the significant differences in sensitivity to detect metastatic disease between conventional and advanced imaging modalities. The guideline further explores appropriate use of such modalities to direct the conversation on disease prognosis.

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The prostate cancer community has witnessed considerable developments in the detection of disease with next generation prostate cancer imaging. Positron emission tomography (PET)-computerized tomography has emerged as a sensitive and specific imaging test to detect prostate cancer metastases, particularly among men with biochemical recurrence after primary therapy.[2,3] Multiple PET tracers have demonstrated promise in the evaluation of extent of prostate cancer including ^{18}F-fluciclovine, ^{18}F-sodium fluoride, ^{11}C-choline, and various tagged prostate-specific membrane antigen (PSMA) isoforms. Since the initial publication of this guideline, the FDA has approved 2 new PET agents for the management of advanced prostate cancer, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyl.[4,5] Both are indicated for patients with suspected prostate cancer metastasis considering surgery or radiation therapy and also indicated for patients with suspected prostate cancer recurrence based on elevated serum prostate specific antigen levels. Additional PSMA agents are currently under investigation. While there remains uncertainty about how image-directed therapies will impact oncologic outcomes, there is an emerging literature detailing the use of next generation imaging to guide management decisions in recurrent prostate cancer.[6,7]

Androgen Deprivation Therapy

The use of primary androgen deprivation therapy for the management of certain advanced prostate cancer disease states has been the standard of care since its discovery in the 1940s.[8] At the time of initial publication of this guideline, the methods for achieving castrate levels of testosterone (<50 ng/dL) were either surgical or injectable. In 2020, the FDA approved relugolix as the first oral gonadotropin-releasing hormone receptor antagonist for adult patients with advanced prostate cancer.[9] Additional non-oral options include luteinizing hormone-releasing hormone analogues, other gonadotropin-releasing hormone antagonists, or orchiectomy. These treatments have been considered equivalent in cancer control, although they weren't compared in large randomized controlled trials.

> "PET-computerized tomography has emerged as a sensitive and specific imaging test to detect prostate cancer metastases, particularly among men with biochemical recurrence after primary therapy."

Unmet Needs

While dramatic recent advances have been made, many unmet needs remain in prostate cancer management. Personalized care with predictive markers for treatment selection based on tumor and host biology has not yet been achieved. There has been movement toward identification of prognostic markers and identification of molecular markers based on immunohistochemistry and use of genomic signatures, but these have yet to yield predictive results. As we move forward as a field, we need to focus on the biological make-up of tumors and how these can be better leveraged to identify treatment options for patients. Further, advanced imaging technologies using novel tracers have emerged as sensitive and specific tools to detect metastatic disease at an earlier point in the progression timeline.

Several key areas of future research need emphasis to improve clinical care and provide a path to better patient outcomes with advanced prostate cancer. Historically, the median survival for men with metastatic CRPC was less than 2 years,[10] but due to several factors including standardized definitions, the impact of new therapies, and the sequencing of therapies, the median survival has now more than doubled. It is against this backdrop that the Panel provides evidence-based guidance for the management of advanced prostate cancer and looks to the future with cautious optimism. ■

1. Siegel RL, Miller KD, Fuchs HE et al: Cancer statistics, 2021. CA Cancer J Clin 2021; **71:** 7.
2. Giovacchini G, Incerti E, Mapelli P et al: [^{11}C] Choline PET/CT predicts survival in hormone-naive prostate cancer patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging 2015; **42:** 877.
3. Calais J, Fendler WP, Eiber M et al: Impact of ^{68}Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. J Nucl Med 2018; **59:** 434.
4. U.S. Food and Drug Administration: FDA Approves First PSMA-targeted PET Imaging Drug for Men with Prostate Cancer. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-psma-targeted-pet-imaging-drug-men-prostate-cancer. Accessed June 2021.
5. U.S. Food and Drug Administration: FDA Approves Second PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-second-psma-targeted-pet-imaging-drug-men-prostate-cancer. Accessed June 2021.
6. Akin-Akintayo OO, Jani AB, Odewole O et al: Change in salvage radiotherapy management based on guidance with FACBC (fluciclovine) PET/CT in postprostatectomy recurrent prostate cancer. Clin Nucl Med 2017; **42:** e22.
7. Emmett L, van Leeuwen PJ, Nandurkar R et al: Treatment outcomes from ^{68}Ga-PSMA PET/CT-informed salvage radiation treatment in men with rising PSA after radical prostatectomy: prognostic value of a negative PSMA PET. J Nucl Med 2017; **58:** 1972.
8. Huggins C and Hodges CV: Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941; **1:** 293.
9. U.S. Food & Drug Administration: FDA Approves Relugolix for Advanced Prostate Cancer. Available at https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-relugolix-advanced-prostate-cancer. Accessed February 8, 2021.
10. Moreira DM, Howard LE, Sourbeer KN et al: Predicting time from metastasis to overall survival in castration-resistant prostate cancer: results from SEARCH. Clin Genitourin Cancer 2017; **15:** 60.

AUA2021 COURSE

Prostate Cancer Update 2021

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Learning Objectives

At the conclusion of the activity, participants will be able to:

- *Cite important new publications in this field during the past year.*
- *Identify the relative strengths and weaknesses of the reports.*
- *Appraise how new studies relate to the existing state-of-the-art in clinical practice.*
- *Analyze whether they and their colleagues should consider changing their practice based on the new information.*

Several important new publications addressed major prostate cancer (PC) topics in 2020–2021.

Screening

Up to age 76, prostate specific antigen (PSA) screening was associated with a lower all-cause mortality rate, except for men with cognitive dysfunction.[1]

Genetics/Genomics

Categories of genetic-based biomarkers include common germline single-nucleotide polymorphisms, rare germline genetic mutations (eg *BRCA1/2, HOXB13)*, and somatic (tumor) gene expression panels (eg Oncotype Dx®, Decipher®). For PC risk assessment, a polygenic risk score incorporating 269 PC risk single-nucleotide polymorphisms is more accurate for assessing risk for PC than is the family history, which is recommended by National Comprehensive Cancer Network® guidelines.[2,3] Most of the single-nucleotide polymorphisms work across races, and 50% of aggressive tumors occur in men in the top 20th percentile of the polygenic risk score.[2] A study reported that polygenic risk score is associated with conversion from active surveillance (AS) to treatment.[4] Rare highly penetrant germline variants (eg *BRCA2*, *ATM*) also are associated with risk, and together the common and rare variants lead to more precise estimates of the lifetime risk of PC.[2,3,5] Plasma cell-free DNA may become important for managing patients with advanced PC, as it is prognostic for overall survival, selecting therapy, and response to therapy.[6] It may be more helpful than repeated biopsies.

Health Disparities

Outside the equal-access Veterans Administration (VA) system, Black men were more likely to present with metastatic disease and had correspondingly higher PC mortality rates, but these differences were not observed in the VA system.[7] However, VA studies of men who were potential candidates for AS reported that Black patients were more likely to have intermediate risk disease, less likely to receive conservative management, and more likely to receive definitive therapy within 5 years.[8] Most of the racial disparities appear to be due to sociodemographic factors.[7] Among those managed with AS, Black men were reported to have more frequent disease reclassification and/or progression and definitive treatment but not more metastasis or higher PC-specific mortality.[9] A multi-institutional AS study outside the VA system found no association of race with conversion to treatment.[10] Thus, AS appears comparably safe for Black and White men.[11] PSA velocity was reported to be associated with Gleason grade progression and metastases, but the thresholds were lower for Black men.[12]

Biopsy

Transperineal prostate biopsy is being increasingly adopted (in a third of urologists recently polled) to reduce the risk of sepsis (even without antibiotics) and, with fusion guidance, to provide an improved sampling of the apical and anterior regions of the prostate.[13] The challenges of transperineal biopsy are patient comfort, the need for a template, increased time, overhead and difficulties with insurance coverage. Transperineal biopsy involves a substantial learning curve for where and how to achieve local anesthesia, which takes practice and experience. Currently, about half are performed under intravenous sedation.

Lymph Node Metastases

Several studies failed to find clear benefits from extended pelvic lymph node dissection, while others demonstrated a benefit associated with radiotherapy to involved pelvic nodes (see Radiotherapy section below).[14-16] With the emergence of prostate-specific membrane antigen (PSMA)-positron emission tomography (PET) imaging, the management of nodal metastases may become an increasingly important issue.

Imaging

Magnetic Resonance Imaging (MRI): MRI increases the accuracy of diagnosing PC but does not identify which men need treatment, and serial prostate MRI alone in patients on AS is not sufficiently accurate to reliably rule out or rule in tumor reclassification or progression.[17] Biparametric MRI protocols are quicker, less expensive and more accurate than those using ultrasound plus PSA alone.[18] A study of men who never had a biopsy compared standard systematic

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ultrasound versus MRI-targeted biopsy taking only 2–3 cores from the MRI region of concern and found that the targeted biopsy alone was noninferior to systematic biopsies.[19] Over a third of MRI patients avoided a biopsy, and there were 50% fewer low-grade diagnoses. Other studies have shown that adding systematic biopsies is of value and should remain part of the process. It is not unusual to find significant cancers in the systematic cores even in areas that have a normal MRI appearance. MRI is not sufficiently accurate to substitute for surveillance biopsies but is helpful overall.[20,21] Patients with high Prostate Imaging–Reporting and Data System (PI-RADS™) lesions and negative initial biopsies should have repeat MRI scans, and if the high PI-RADS abnormalities persist undergo a repeat biopsy (including peri-lesion biopsies), as nearly two-thirds of these may reveal cancer.[22,23] Positive target biopsies should be counted as being only 1 positive core (ie the most extensively involved core).

PSMA PET: The PSMA PET scans (gallium and fluorine) may have a large impact on patient management because of their high sensitivity and specificity.[24–28] One study reported that half of the patients with positive PSMA PET scans had a serum PSA <0.2 ng/uL.[26] The most accurate platform would include the PSMA PET with MRI (rather than computerized tomography) that increases the sensitivity for high-risk tumors.[28]

Radiation Therapy

In the FLAME trial, men receiving higher doses to MRI-defined tumor nodules had a twofold reduction in biochemical failure and no additional toxicity.[29] In the POP-RT study, the treatment of pelvic lymph nodes improved biochemical control and distant-metastasis-free survival at the cost of a mild increase in late genitourinary toxicity.[30] In the PROSINT trial, men receiving treatment in a single fraction or 5 fractions had similar biochemical outcomes and toxicity.[31] In the postoperative setting, 3 randomized studies evaluated the role of adjuvant radiation in men with high-risk disease after prostatectomy.[32–34] The largest of these (RADICALS), as well as a meta-analysis, showed that early salvage therapy when needed did not compromise outcomes and spared a significant proportion of men from unnecessary treatment.[32,35] The SAKK 09/10 study demonstrated that dose escalation from 64 to 70 Gy did not improve biochemical outcomes and added toxicity.[33] The EMPIRE-1 study suggested that using fluciclovine PET improved biochemical outcomes compared to conventional imaging when used to select men and to plan postoperative radiation.[34] In the setting of oligo-recurrence in regional lymph nodes, the GETUG07 study demonstrated ~50% biochemical control at 3 years' followup with pelvic radiation and 6 months of hormonal therapy (ADT).[36] In the setting of metastatic disease, a secondary analysis of the STAMPEDE trial suggested that survival is improved after prostate radiation, particularly in men with lymph node only or 3 or fewer bony metastases.[37]

Advanced Disease

Men with locally advanced disease account for ~15% of patients with newly diagnosed PC and have a relatively poor cancer-specific mortality. In a prospective neo-adjuvant trial for patients with high-risk disease given either 6 months of ADT with apalutamide + abiraterone/prednisone + leuprolide vs abiraterone/prednisone + leuprolide, adding the third agent didn't make a difference, but there was a remarkable 20% complete response or minimal residual disease rate.[38] A meta-analysis of neo-adjuvant trials found that 60% of patients were without biochemical recurrence after 3 years.[39] In patients who achieve a complete response/minimal residual disease, there is a large difference in the recurrence rate (8% vs 50%). Thus, in the neoadjuvant setting a robust response to ADT is a good indicator of outcomes. Oral relugolix is a luteinizing hormone-releasing hormone antagonist.[40] A trial of relugolix vs leuprolide showed that relugolix achieved superior testosterone suppression and it occurred faster, whereas the cardiovascular side effects were lower. A meta-analysis also showed that cardiovascular events are more frequent with the luteinizing hormone-releasing hormone agonists than with the antagonists.[41] The high cost of relugolix limits its adoption. Enzalutamide is superior to bicalutamide in Black patients, but bicalutamide can be safely used to prevent testosterone flare-ups in Black patients.[42] For castrate-sensitive PC, abiraterone and apalutamide have the best results for survival, and these agents do not seem to cause a cognitive decline.[43] Zoledronic acid and denosumab are approved for preventing or delaying skeletal-related events.[44] Zoledronic acid may compromise renal function, whereas, denosumab may cause hypocalcemia. Osteonecrosis of the jaw occurs at approximately the same rate with both agents. Denosumab is far more expensive. In patients with castrate-resistant disease, these agents improve overall survival in addition to reducing skeletal-related events and should be used in all patients with bone metastases who are castration-resistant.[45] In a study of olaparib (a PARP inhibitor used in patients with homologous DNA repair deficiency mutations such as *BRCA1/2*) vs abiraterone/enzalutamide (crossover), in which 30% of patients had some type of pathogenic mutation, there was a significant improvement in overall survival, especially in patients with *BRCA* mutations.[46] Another study reported that for patients with a mutation other than *BRCA*, cabazitaxel had an advantage.[47] A trial comparing lutetium-177-PSMA-617 (a radioligand therapy targeting PSMA) with standard care using ADT in patients who had PSMA highly expressed on their metastases, there was a highly significant survival advantage for the lutetium arm.[27] This radioligand treatment is not yet U.S. Food and Drug Administration-approved. Immunotherapy has been disappointing for PC. However, a study of nivolumab plus ipilimumab for metastatic castrate-resistant PC showed a 25% response rate in the pre-chemotherapy setting with a better response rate in patients whose tumors had a high mutational burden.[48] This regimen was quite toxic. ■

1. Schoenborn NL, Sheehan OC, Roth DL et al: Association between receipt of cancer screening and all-cause mortality in older adults. JAMA Netw Open 2021; **4:** e2112062.

2. Darst BF, Sheng X, Eeles RA et al: Combined effect of a polygenic risk score and rare genetic variants on prostate cancer risk. Eur Urol 2021; **80:** 134.

→ Continued on page 7

3. Xu J and Isaacs WB: Incorporation of polygenic risk score into guidelines for inherited risk assessment for prostate cancer. Eur Urol 2021; **80:** 139.
4. Jiang Y, Meyers TJ, Emeka AA et al: Genetic factors associated with prostate cancer conversion from active surveillance to treatment. Preprint at medRxiv 2021: https://doi.org/10.1101/2021.08.30.21262305. Accessed October 18, 2021.
5. Plym A, Penney KL, Kalia S et al: Evaluation of a multiethnic polygenic risk score model for prostate cancer. J Natl Cancer Inst 2021; http://doi.org/10.1093/jnci/djab058.
6. Sumanasuriya S, Seed G, Parr H et al: Elucidating prostate cancer behaviour during treatment via low-pass whole-genome sequencing of circulating tumour DNA. Eur Urol 2021; **80:** 243.
7. Klebaner D, Travis Courtney P, Garraway IP et al: Association of health-care system with prostate cancer-specific mortality in African American and Non-Hispanic White men. J Natl Cancer Inst 2021; **113:** 1343.
8. Parikh RB, Robinson KW, Chhatre S et al: Comparison by race of conservative management for low-risk and intermediate-risk prostate cancers in veterans from 2004 to 2018. JAMA Network Open 2020; **3:** e2018318.
9. Deka R, Courtney PT, Parsons JK et al: Association between African American race and clinical outcomes in men treated for low-risk prostate cancer with active surveillance. JAMA 2020; **324:** 1747.
10. Cooley LF, Emeka AA, Meyers TJ et al: Factors associated with time to conversion from active surveillance to treatment for prostate cancer in a multi-institutional cohort. J Urol 2021; **206:** 1147.
11. Shen X, Pettaway CA and Chen RC: Active surveillance for Black men with low-risk prostate cancer. JAMA 2020; 3**24:** 1733.
12. Nelson TJ, Javier-DesLoges J, Deka R et al: Association of prostate-specific antigen velocity with clinical progression among African American and Non-Hispanic White men treated for low-risk prostate cancer with active surveillance. JAMA Netw Open 2021; **4:** e219452.
13. Bajeot AS, Covin B, Meyrignac O et al: Managing discordant findings between multiparametric magnetic resonance imaging and transrectal magnetic resonance imaging-directed prostate biopsy–the key role of magnetic resonance imaging-directed transperineal biopsy. Eur Urol Oncol 2021; http://doi.org/10.1016/j.euo.2021.06.001.
14. Cacciamani GE, Maas M, Nassiri N et al: Impact of pelvic lymph node dissection and its extent on perioperative morbidity in patients undergoing radical prostatectomy for prostate cancer: a comprehensive systematic review and meta-analysis. Eur Urol Oncol 2021; **4:** 134.
15. Lestingi JFP, Guglielmetti GB, Trinh QD et al: Extended versus limited pelvic lymph node dissection during radical prostatectomy for intermediate- and high-risk prostate cancer: early oncological outcomes from a randomized phase 3 trial. Eur Urol 2021; **79:** 595.
16. Touijer KA, Sjoberg DD, Benfante N et al: Limited versus extended pelvic lymph node dissection for prostate cancer: a randomized clinical trial. Eur Urol Oncol 2021; **4:** 532.
17. Borre M: Prostate Cancer screening–the need for and clinical relevance of decision analytical models. JAMA Netw Open 2021; **4:** e212182.
18. Eldred-Evans D, Burak P, Connor MJ et al: Population-based prostate cancer screening with magnetic resonance imaging or ultrasonography: the IP1-PROSTAGRAM study. JAMA Oncol 2021; **7:** 395.
19. Klotz L, Chin J, Black PC et al: Comparison of multiparametric magnetic resonance imaging-targeted biopsy with systematic transrectal ultrasonography biopsy for biopsy-naive men at risk for prostate cancer: a phase 3 randomized clinical trial. JAMA Oncol 2021; **7:** 534.
20. Rajwa P, Pradere B, Quhal F et al: Reliability of serial prostate magnetic resonance imaging to detect prostate cancer progression during active surveillance: a systematic review and meta-analysis. Eur Urol 2021; http://doi.org/10.1016/j.eururo.2021.05.001.
21. Zhou Z, Zhou Y, Yan W et al: Unilateral lesion detected on preoperative multiparametric magnetic resonance imaging and MRI/US fusion-guided prostate biopsy is not an appropriate indication for focal therapy in prostate cancer. Urol Oncol 2021; **39:** 730 e717.
22. Meng X, Chao B, Chen F et al: Followup of men with PI-RADS 4 or 5 abnormality on prostate magnetic resonance imaging and nonmalignant pathological findings on initial targeted prostate biopsy. J Urol 2021; **205:** 748.
23. Lahoud J, Doan P, Kim Let al: Perilesional biopsies increase detection of significant prostate cancer in men with PI-RADS 4/5 lesions: validation of the PI-RADS Steering Committee recommendation. Eur Urol 2021; **80:** 260.
24. Calais J, Ceci F, Eiber M et al: ^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 2019; **20:** 1286.
25. Pienta KJ, Gorin MA, Rowe SP et al: A Phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with ^{18}F-DCFPyL in prostate cancer patients (OSPREY). J Urol 2021; **206:** 52.
26. Cerci JJ, Fanti S, Lobato EE et al: Diagnostic performance and clinical impact of ^{68}Ga-PSMA-11 imaging in early relapsed prostate cancer after radical therapy: a prospective multicenter study (IAEA-PSMA study). J Nucl Med 2021; http://doi.org/10.2967/jnumed.120.261886.
27. Sartor O, de Bono J, Chi KN et al: Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021; **385:** 1091.
28. Kalapara AA, Ballok ZE, Ramdave S et al: Combined utility of ^{68}Ga-prostate-specific membrane antigen positron emission tomography/computed tomography and multiparametric magnetic resonance imaging in predicting prostate biopsy pathology. Eur Urol Oncol 2021; http://doi.org/10.1016/j.euo.2021.02.006.
29. Kerkmeijer LGW, Groen VH, Pos FJ et al: Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: results from the FLAME randomized phase III trial. J Clin Oncol 2021; **39:** 787.
30. Murthy V, Maitre P, Kannan S et al: Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): outcomes from Phase III randomized controlled trial. J Clin Oncol 2021; **39:** 1234.
31. Greco C, Pares O, Pimentel N et al: Safety and efficacy of virtual prostatectomy with single-dose radiotherapy in patients with intermediate-risk prostate cancer: results from the PROSINT phase 2 randomized clinical trial. JAMA Oncol 2021; **7:** 700.
32. Parker CC, Clarke NW, Cook AD et al: Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. Lancet 2020; **396:** 1413.
33. Ghadjar P, Hayoz S, Bernhard J et al: Dose-intensified versus conventional-dose salvage radiotherapy for biochemically recurrent prostate cancer after prostatectomy: the SAKK 09/10 randomized phase 3 trial. Eur Urol 2021; **80:** 306.
34. Jani AB, Schreibmann E, Goyal S et al: ^{18}F-Fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial. Lancet 2021; **397:** 1895.
35. Vale CL, Fisher D, Kneebone A et al: Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet 2020; **396:** 1422.
36. Supiot S, Vaugier L, Pasquier D et al: OLIGOPELVIS GETUG P07, a multicenter phase II trial of combined high-dose salvage radiotherapy and hormone therapy in oligorecurrent pelvic node relapses in prostate cancer. Eur Urol 2021; **80:** 405.
37. Ali A, Hoyle A, Haran AM et al: Association of bone metastatic burden with survival benefit from prostate radiotherapy in patients with newly diagnosed metastatic prostate cancer: a secondary analysis of a randomized clinical trial. JAMA Oncol 2021; **7:** 555.
38. McKay RR, Xie W, Ye H et al: Results of a randomized phase II trial of intense androgen deprivation therapy prior to radical prostatectomy in men with high-risk localized prostate cancer. J Urol 2021; **206:** 80.
39. McKay RR, Berchuck J, Kwak L et al: Outcomes of post-neoadjuvant intense hormone therapy and surgery for high risk localized prostate cancer: results of a pooled analysis of contemporary clinical trials. J Urol 2021; **205:** 1689.
40. Shore ND, Saad F, Cookson MS et al: Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med 2020; **382:** 2187.
41. Abufaraj M, Iwata T, Kimura S et al: Differential impact of gonadotropin-releasing hormone antagonist versus agonist on clinical safety and oncologic outcomes on patients with metastatic prostate cancer: a meta-analysis of randomized controlled trials. Eur Urol 2021; **79:** 44.
42. Vaishampayan UN, Heilbrun LK, Monk P 3rd et al: Clinical efficacy of enzalutamide vs bicalutamide combined with androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a randomized clinical trial. JAMA Netw Open 2021; **4:** e2034633.
43. Alibhai SMH, Breunis H, Feng G et al: Association of chemotherapy, enzalutamide, abiraterone, and radium 223 with cognitive function in older men with metastatic castration-resistant prostate cancer. JAMA Netw Open 2021; **4:** e2114694.
44. Takvorian SU and Haas NB: Use of bone resorption inhibitors in metastatic castration-resistant prostate cancer–20 years later, and the answer is still yes. JAMA Netw Open 2021; **4:** e2117159.
45. Francini E, Montagnani F, Nuzzo PV et al: Association of concomitant bone resorption inhibitors with overall survival among patients with metastatic castration-resistant prostate cancer and bone metastases receiving abiraterone acetate with prednisone as first-line therapy. JAMA Netw Open 2021; **4:** e2116536.
46. Hussain M, Mateo J, Fizazi K et al: Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 2020; **383:** 2345.
47. Wallis CJD, Klaassen Z, Jackson WC et al: Olaparib vs cabazitaxel in metastatic castration-resistant prostate cancer. JAMA Netw Open 2021; **4:** e2110950.
48. Sharma P, Pachynski RK, Narayan V et al: Nivolumab plus ipilimumab for metastatic castration-resistant prostate cancer: preliminary analysis of patients in the CheckMate 650 trial. Cancer Cell 2020; **38:** 489.

AUA2021 PLENARY

AUA Guideline Amendment: Muscle-Invasive Bladder Cancer/Non-Muscle-Invasive Bladder Cancer

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Learning Objective

At the conclusion of the activity, participants will be able to:

- *Explain the 2020 amendments to the SUO/AUA Non-Muscle-Invasive Bladder Cancer and Muscle-Invasive Bladder Cancer Guidelines, including what to do if bacillus Calmette-Guérin (BCG) is unavailable.*

At the 2021 American Urological Association annual meeting the AUA/SUO non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) guidelines were reviewed in a plenary session.[1] In 2020, based on the rapid pace of change in the field of bladder cancer, the AUA had each of these guidelines reviewed for relevant content updates. Working with the Agency for Health Research Quality (AHRQ), a group of experts reviewed the most recent literature in the field of NMIBC and MIBC and updated each guideline accordingly. These updates were presented and several existing guidelines were emphasized in the plenary session.

For the NMIBC guideline, the updated AHRQ search identified 1,626 relevant new publications, of which 76 met inclusion criteria for review by the committee. The committee recommended a significant guideline change for the management of bacillus Calmette-Guérin (BCG) unresponsive bladder cancer. In early 2020 the U.S. Food and Drug Administration (FDA) approved systemic pembrolizumab for the treatment of BCG unresponsive carcinoma in situ (CIS) for patients who refuse or are ineligible for radical cystectomy.[2] Since that time the KEYNOTE-057 trial, a multicenter, open-label, single-arm, phase II trial of pembrolizumab for BCG unresponsive CIS, was published in *The Lancet Oncology*.[3] This trial demonstrated an initial response rate of 41%, a durable response rate of 21% at 1 year, with 11% remaining disease-free beyond 2 years. The NMIBC guidelines now include the option to use systemic pembrolizumab for BCG unresponsive CIS in patients who are ineligible or refuse radical cystectomy. The efficacy seen in this trial led the committee to suggest that there remains a significant unmet need for more effective agents in this area. NonFDA approved but commonly utilized salvage chemotherapy regimens were also listed as options for the management of BCG unresponsive disease, including gemcitabine, docetaxel and combinations of these agents.

Guideline Statement 15 was amended to include gemcitabine as an option for immediate postoperative chemotherapy. In 2018, a randomized trial of an immediate postoperative dose of gemcitabine (2 gm/100 cc saline) compared to saline for patients with suspected low grade NMIBC demonstrated a relative risk reduction in recurrence of 35% with gemcitabine.[4] Given the favorable toxicity profile, the committee recommended consideration of gemcitabine for patients being given an immediate postoperative dose of chemotherapy.

The topic of urinary biomarkers was discussed, and additional review and discussion of the new urinary biomarker panel known as Cxbladder™ Monitor and its role in NMIBC surveillance. Cxbladder Monitor has been shown to have a 93% sensitivity and 97% negative predictive value for recurrent NMIBC. Although it was found to outperform several commonly used biomarkers, it did not meet recommendations for use in lieu of standard cystoscopic surveillance in patients capable of undergoing cystoscopy. The notable limitations of Cxbladder Monitor are its poor sensitivity to detect low-risk recurrences and the concern for low specificity.

The session also discussed the ongoing international BCG shortage and reviewed the 2019 AUA statement on guidance during the BCG crisis. This statement includes several management strategies to maintain high-quality care for patients with NMIBC. These recommendations supersede several of the NMIBC guidelines statements that apply to intravesical BCG.

In addition, the guideline statements stressing pathological review in the setting of variant histology, definition of BCG unresponsive state, the surveillance schedule for low risk patients, and the use of fluorescent cystoscopy were all discussed. No changes were made in these guidelines.

In the area of MIBC, the updated literature search from 2016 to 2020 identified 2,005 relevant publications, of which 38 met inclusion criteria for consideration by the committee.

There were several minor modifications made to this guideline, including the recommended extent of surgical resection during a female radical cystectomy. The indications for resection of the anterior vaginal wall, uterus and ovaries were discussed in order to emphasize that preservation of these organs may be considered in well-selected patients if negative surgical margins can be ensured. This updated content is based on retrospective cohort studies, and surgeons must ultimately decide whether gynecologic organ-preserving cystectomy is safe in

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each individual patient. In regards to the management of patients following neoadjuvant chemotherapy, the modified guideline now states that radical cystectomy should ideally be performed within 12 weeks of completion of neoadjuvant chemotherapy.

Several existing guidelines that did not undergo revision were reviewed during the plenary session. The recommendation that cisplatin based multiagent chemotherapy is the standard of care in the neoadjuvant setting and the specific recommendation that carboplatin should not be used as a neoadjuvant therapy were stressed. In addition, the guideline covering organ preservation stresses that maximal debulking transurethral resection of bladder tumor be performed and that radiotherapy alone in the absence of systemic therapy is not supported by the guidelines.

The review of these 2 critical guidelines reinforced that the majority of existing guideline recommendations were confirmed to be correct, as only minor modifications were made for each guideline. The committee identified several areas of research to improve care in the future, including the role of biomarkers, more effective options for BCG unresponsive disease in NMIBC, integration of systemic immunotherapy in the treatment of MIBC, and improved protocols for bladder preservation in MIBC. ■

1. Chang SS, Boorjian SA, Chou R et al: Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol 2016; **196:** 1021.
2. U.S. Food and Drug Administration: FDA approves pembrolizumab for BCG unresponsive, high-risk non-muscle invasive bladder cancer [news release]. U.S. Food and Drug Administration 2020. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-bcg-unresponsive-high-risk-non-muscle-invasive-bladder-cancer. Accessed March 8, 2020.
3. Balar AV, Kamat AM, Kulkarni GS et al: Pembrolizumab monotherapy for the treatment of high risk non-muscle invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open label, single-arm, multicentre, phase 2 study. Lancet Oncol 2021; **22:** 919.
4. Messing EM, Tangen CM, Lerner SP et al: Effect of intravesical instillation of gemcitabine vs saline immediately following resection of suspected low-grade non-muscle-invasive bladder cancer on tumor recurrence: SWOG S0337 randomized clinical trial. JAMA 2018; **319:** 1880.

AUA2021 PLENARY

First and Second Line Therapy in Advanced and Metastatic Bladder Cancer: A Changing Paradigm

Cora N. Sternberg, MD, FACP
Author, Course Director/Moderator, Faculty

Learning Objective

At the conclusion of the activity, participants will be able to:

- *Analyze recent studies on first and second line therapies for treatment for advanced urothelial cancer.*

Urothelial cancer (UC) is the sixth most common cancer in the U.S. and will be responsible for an estimated 164,000 new cases in 2021 and 31,940 deaths.[1]

Most patients with advanced UC have disease control in 65% to 85%, with first line platinum-based chemotherapy, but progression-free survival (PFS) and overall survival (OS) are most often limited due to the emergence of chemotherapy resistance. Since methotrexate, vinblastine, adriamycin and cisplatin (M-VAC) chemotherapy in 1989,[2] there have been few achievements in the past 30 years aside from gemcitabine and cisplatin and high-dose M-VAC (HD-M-VAC).[3,4] Until recently, only 25% to 55% of patients received second line treatment with suboptimal outcomes due to rapid disease progression. This has changed considerably with the advent of immunotherapy and novel therapies.

UC has a high mutational burden, making it particularly responsive to immunotherapy.[5]

Five checkpoint inhibitors–atezolizumab, pembrolizumab, nivolumab, durvalumab and avelumab–have been approved in the U.S. in the second line setting based on phase I to phase III trials. No head-to-head studies have been conducted and direct comparisons cannot be made between these studies.

Keynote 45 is the only randomized phase III trial of pembrolizumab vs investigator's choice of chemotherapy; paclitaxel, docetaxel or vinflunine in patients who had progressed after 1–2 lines of platinum-based chemotherapy. This trial has consistently shown an improvement in OS irrespective of PDL-1 status. The first data showed a 27% reduction in the risk of death in patients treated with pembrolizumab, irrespective of CPS score.[6] Five-year data were consistent and updated at ASCO (American Society of Clinical Oncology) 2021. Immune checkpoint blockade with pembrolizumab and atezolizumab have also been approved as first line therapeutic options in either platinum ineligible patients or carboplatin eligible patients whose tumors also express PD-L1.

The SAUL study was designed to assess atezolizumab in a broader population of patients, including patients typically excluded from phase III trials because of comorbidities, autoimmune disease, poor performance, poor creatinine clearance etc. We often see these patients in our clinical practice but there is little or no information on outcomes in these patients.

The primary endpoint of SAUL was safety. Secondary endpoints included overall survival, response rate and duration of response. We enrolled 1,004 patients from 32 countries and found that it was possible to safely give immunotherapy to many of these patients who would otherwise have been excluded from this therapy.[7]

A number of first line phase III trials of checkpoint inhibitors alone or in combination with chemotherapy in UC have been reported. The U.S. Food and Drug

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Administration (FDA) and European Medical Associations stopped accrual of patients on single-agent immunotherapy without positive PDL-1 status in the atezolizumab and pembrolizumab phase III trials. The results of these combination studies unfortunately have for the most part been largely disappointing. The trials are listed in the figure.

IMVIGOR 130 evaluated gemcitabine and cisplatin or carboplatin ± atezolizumab vs atezolizumab. There was an improvement in progression-free survival with the combination,[8] as first reported, but ultimately no improvement in OS, as last reported at the American Association for Cancer Research meeting in 2021.

Keynote 361 was a global randomized open label phase 3 trial of pembrolizumab alone or combined with platinum-based chemotherapy versus chemotherapy as first line treatment in advanced UC.[9] Patients were randomized 1:1:1 to pembrolizumab and chemotherapy (351) or pembrolizumab alone (307) or chemotherapy alone (352). Keynote 361 was a negative trial in terms of both end points of progression-free survival and OS. The results of this trial were unexpected as pembrolizumab is approved in several settings including high-risk non-muscle-invasive bladder cancer after bacillus Calmette-Guérin failure.

The Danube trial was a phase III randomized open label first line study of durvalumab ± an anti-CTLA-4 inhibitor, tremelimumab, vs chemotherapy in unresectable, locally advanced or metastatic UC.[10] Patients were randomized 1:1:1 to durvalumab (346) or durvalumab plus tremelimumab for up to 4 doses (342) or gemcitabine + cisplatin or carboplatin (344.) The co-primary end points were OS between durvalumab and chemotherapy in patients with high PD-L1 expression in their tumors and OS between durvalumab + tremelimumab and chemotherapy in the entire intention-to-treat population. DANUBE did not meet either of these co-primary end points of OS. Secondary analyses suggested that the combination of durvalumab + tremelimumab had activity that was enhanced in the subset of patients with tumors that had high PD-L1 expression, a suggestion that a biomarker strategy to enrich for patients likely to receive benefit may still be important.

Results have not yet been presented for Checkmate 901 with nivolumab and ipilimumab vs nivolumab and chemotherapy or standard platinum-based chemotherapy.

The JAVELIN Bladder 100 trial of switch maintenance evaluated 700 patients with locally advanced or metastatic UC not progressed following first line, platinum-based chemotherapy.[11] Patients had 4–6 cycles of chemotherapy, and those who had complete response (CR), partial response (PR) or stable disease (SD), were randomized to every 2-week avelumab vs best supportive care. The primary end point was OS (in all randomized patients and in patients with PD-L1+ tumors). The median OS was 21.4 months vs 11.3 months with HR 0.69, with 61% vs 44% alive at 18 months in favor of avelumab switch maintenance therapy. OS in the PD-L1+ population was not reached vs 17.1 months and HR 0.56 with 70% vs 48% at 18 months in favor of avelumab switch maintenance therapy.

This is a landmark study that has changed clinical practice and has been incorporated into most practice guidelines.

Enfortumab vedotin (EV) is an antibody drug conjugate that targets Nectin-4, a protein highly expressed on the surface of most UC. This antibody is conjugated to the anti-microtubule agent monomethyl auristatin E. Once the antibody binds the Nectin-4 expressing cell, the agent is internalized and the payload is released. EV can be considered both in advanced disease after immunotherapy and chemotherapy. The EV-301 phase III study demonstrated for the first time that a novel targeted agent improved survival in the refractory setting beyond immunotherapy and chemotherapy when compared to chemotherapy.[12] EV was granted accelerated FDA approval in 2019, prior to this phase III study. The multi-cohort EV-103 study evaluates the safety/activity of enfortumab vedotin and pembrolizumab; 93% of cisplatin-ineligible patients with locally advanced or mUC had tumor reduction.[13] Combination trials with immunotherapy are promising and ongoing.

Sacituzumab Govitecan is another antibody drug conjugate directed against Trop-2, a cell surface antigen highly expressed UC. Its payload is SN-38, the active metabolite of irinotecan, a topoisomerase I inhibitor that blocks DNA replication. The linker is hydrolysable, which helps to ensure that an active concentration of SN-38 is maintained in the tumor, while hydrolysis of the linker releases the cytotoxic payload intracellularly and in the tumor microenvironment to kill cells. The response rate with Sacituzumab Govitecan after platinum-based chemotherapy and immunotherapy was 27%.[14] In April 2021, the FDA granted accelerated approval to Sacituzumab Govitecan for patients with locally advanced or metastatic UC who previously received platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor.

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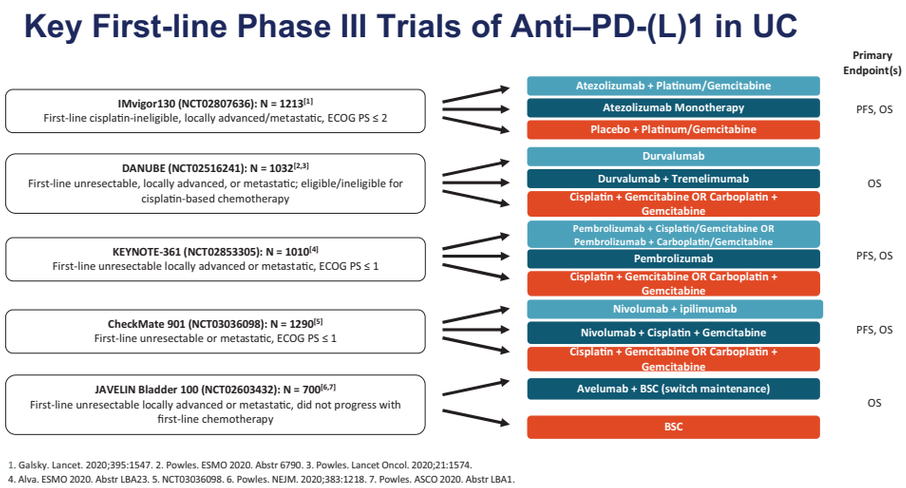

1. Galsky. Lancet. 2020;395:1547. 2. Powles. ESMO 2020. Abstr 6790. 3. Powles. Lancet Oncol. 2020;21:1574.
4. Alva. ESMO 2020. Abstr LBA23. 5. NCT03036098. 6. Powles. NEJM. 2020;383:1218. 7. Powles. ASCO 2020. Abstr LBA1.

Figure. Combination studies with immunotherapy and chemotherapy.

In 2019, the FDA granted accelerated approval to erdafitinib for patients with locally advanced or metastatic UC, with susceptible FGFR3 or FGFR2 genetic alterations, that have progressed during or following platinum-containing chemotherapy. This occurred after the results of a multicenter, open-label, single-arm phase II trial in mUC in 99 patients with FGFR3 mutations or FGFR2/3 fusions.[15] These molecular alterations are more often found in upper tact tumors. Molecularly targeted therapy is an important breakthrough and hopefully many more targeted therapies will be discovered. ■

1. Siegel RL, Miller KD, Fuchs HE et al: Cancer statistics, 2021. CA Cancer J Clin 2021; **71:** 7.
2. Sternberg CN, Yagoda A, Scher HI et al: M-VAC for advanced transitional cell carcinoma of the urothelium: efficacy and patterns of response. Cancer 1989; **64:** 2448.
3. Sternberg CN, de Mulder P, Schornagel HS et al: Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 2006; **42:** 50.
4. Von der Maase H, Hansen SW, Roberts JT et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000; **18:** 30688.
5. Lawrence MS, Stojanov P, Polak P et al: Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 2013; **499:** 214.
6. Bellmunt J, de Wit R, Vaughn DJ et al: Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017; **376:** 1015.
7. Sternberg CN, Loriot Y, James N et al: Primary results from SAUL, a multinational single-arm safety study of atezolizumab therapy for locally advanced or metastatic urothelial or nonurothelial carcinoma of the urinary tract. Eur Urol 2019; **76:** 73.
8. Galsky MD, Arranz Arija JÁ, Bamias A et al: Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2020; **395:** 1547.
9. Powles T, Csőszi T, Özgüroğlu M et al: Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol 2021; **22:** 931.
10. Powles T, van der Heijden MS, Castellano D et al: Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2020; **21:** 1574.
11. Powles T, Park SH, Voog E et al: Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 2020; **383:** 1218.
12. Powles T, Rosenberg JE, Sonpavde GP et al: Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021; **384:** 1125.
13. Friedlander TW, Milowsky MI, Bilen MA et al: Study EV-103: update on durability results and long term outcome of enfortumab vedotin + pembrolizumab in first line locally advanced or metastatic urothelial carcinoma (la/mUC). J Clin Oncol, suppl., 2021; **39:** abstract 4528.
14. Tagawa S, Balar AV, Petrylak DP et al: TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. J Clin Oncol 2021; **39:** 2474.
15. Loriot Y, Neeki A, Park SH et al: Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med 2019; **381:** 338.

AUA2021 COURSE

Management of Non-Muscle-Invasive Bladder Cancer: Practical Solutions for Common Problems

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Author, Course Moderator/Director

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Faculty

Cheryl T. Lee, MD
Faculty

Fred Witjes, MD, PhD
Faculty

Learning Objectives

At the conclusion of the activity, participants will be able to:

- *Implement current practice guidelines into the office setting.*
- *Identify the best intravesical agent and duration of therapy for low, intermediate, and high-risk settings and what to do during a BCG shortage.*
- *Identify methods to treat significant toxicities from various intravesical therapies.*
- *Define high risk scenarios that necessitate cystectomy and options for BCG-unresponsive disease.*
- *Discuss the scientific rationale for investigating immune oncology agents for BCG unresponsive disease and become familiar with current clinical trial designs.*

Transurethral resection of a bladder tumor (TURBT) is the first step in bladder cancer management for both new and recurrent tumors. For urologists, it a highly rewarding procedure as it cures most patients with non-muscle-invasive bladder cancer (NMIBC) and provides valuable prognostic information. Detailed characterization of the cystoscopic findings and a complete visual TURBT is imperative to outcomes and this cannot be overemphasized. Studies confirm implementing a surgical checklist during the performance of a TURBT as well as surgeons receiving serial feedback on key quality indicators, such as the presence of muscularis propria in the pathology specimen, are strategies that can lead to better quality TURBT. A procedure checklist that includes recording number of tumors, largest tumor size, tumor configuration, presence of carcinoma in situ (CIS), direct visualization of including muscularis propria in the resection and confirming complete TURBT led to better quality care and the desired result of lower tumor recurrence rates.[1]

After the initial TURBT, knowing which patients benefit from a repeat TURBT within 6 weeks adds to the overall quality of the completeness of TURBT improves staging and very likely reduces tumor recurrence. A visually incomplete initial TURBT

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is an indication for repeat complete TURBT, if feasible. Other indications for repeat TURBT include T1 bladder cancer, high-grade Ta bladder cancer of large volume or if muscularis propria was not present and if bladder preservation in a patient with variant histology is planned. If the equipment is available, use of enhanced cystoscopy, such as blue light, during TURBT also improves quality of TURBT and reduces recurrence rates.

A visually complete TURBT provides greatest confidence in assigning NMIBC patients as low, intermediate or high risk of disease recurrence and progression. The AUA NMIBC guideline places emphasis on tumor grade and stage, tumor size, presence of CIS, whether the tumor is recurrent, variant histology, lymphovascular invasion, prostatic urethral involvement and response to bacillus Calmette-Guérin (BCG) as criteria needed to assign NMIBC risk group. By assigning a risk group decisions whether to administer single-dose perioperative intravescial chemotherapy (SPI), induction and maintenance intravesical therapy become clear and evidence based. All low risk (low grade, <3 cm, solitary Ta tumor) and some intermediate risk NMIBC patients benefit from SPI (EORTC [European Organization for the Treatment of Cancer] risk score <5). Intravesical gemcitabine is becoming the standard of care for SPI because of less toxicity and lower cost but mitomycin remains an option and importantly in the low-risk group no further intravesical therapy is recommended following SPI.[2]

Intermediate risk (low grade Ta tumor >3 cm or multifocal or recurrent) patients represent a heterogeneous population and is the largest group of NMIBC. Almost all patients in this category benefit from a 6-week course of induction chemotherapy (ie mitomycin or gemcitabine) or BCG. For intermediate risk patients, maintenance intravesical therapy should be considered for up to 1 year especially if BCG was used for induction. Maintenance chemotherapy is administered once monthly and BCG thrice weekly at 3, 6 and 12 months. Intravesical chemotherapy is best for patients with a lower probability of tumor recurrence because of similar efficacy, lower toxicity and greater drug availability when compared to BCG. In the intermediate risk category, 4 factors including only 1 tumor, tumor size <3 cm, no recurrence in the past year and low frequency of recurrence over time help select patients for chemotherapy with a lower probability of tumor recurrence.[3] However, if a patient received prior induction chemotherapy and develops a tumor recurrence these recurrences should be treated with intravesical BCG and vice versa regardless of prognostic factors for tumor recurrence.

> "At the present time we do not have the ability to determine which cancers are likely to respond to BCG from those that are resistant to the treatment."

Patients diagnosed with high-risk NMIBC (high-grade tumors, CIS or T1) benefit little from SPI but they should receive induction and maintenance BCG for 3 years as it known to reduce cancer recurrence and progression. Unfortunately this is not always possible as there is a national BCG shortage, so risk-adapted strategies are needed to conserve the drug for those who need it most. Guidance of what to do during a BCG shortage has been provided by various organizations and authors and an important consideration when comparing patients who received 1 year vs 3 years of maintenance BCG was no difference in cancer progression or cancer-specific mortality. The only benefit was lower cancer recurrence rates in patients receiving 3 years of maintenance.[4] This finding along with other findings is applicable during a BCG shortage as 1 year of maintenance, receiving 2 instead of 3 doses of BCG and receiving a half to a third dose BCG if 1 vial can be shared amongst patients need to be strongly considered to conserve a highly valuable resource in short supply. These recommendations are unlikely to lead to higher rates of tumor progression but are certainly associated with higher rates of tumor recurrence. During a BCG shortage, intermediate risk patients should only be treated with intravesical chemotherapy.

BCG is a great story of success in the field of urology and has cured or preserved the bladders of millions of people worldwide. Nevertheless, BCG is not an effective therapy for all patients diagnosed with high-risk NMIBC and these individuals are better managed by up-front radical cystectomy before disease progression. Individuals at greatest risk for progression to muscle-invasive bladder cancer include T1 bladder cancer with concurrent multifocal CIS or lymphovascular invasion or variant histology (ie sarcomatoid, plasmacytoid, micropapillary, neuroendocrine). The presence of multifocal T1 bladder cancer, concurrent prostatic urethral involvement and T1 disease on repeat TURBT are other indications to consider up-front radical cystectomy for NMIBC. Radical cystectomy in a surgically fit patient is always appropriate for high-risk NMIBC if not removing the bladder would present a loss of an opportunity to cure the patient.

Maintenance BCG is highly effective at reducing cancer recurrence rates as well as disease progression in high-risk NMIBC. However, up to 20% of patients at high risk will develop muscle-invasive bladder cancer during followup, and the majority of these patients were expected to respond well to BCG and not offered up-front radical cystectomy. At the present time we do not have the ability to determine which cancers are likely to respond to BCG from those that are resistant to the treatment. Nevertheless, based on our current knowledge it is vitally important to develop an understanding of when continuing to administer further intravesical BCG is not in the best interest of the patient. This state of disease has been recently characterized as BCG-unresponsive and evolved from a collaborative effort between clinicians with expertise in the field of bladder cancer and the FDA (U.S. Food and Drug Administration; FDA-guidance document 2018). Following exposure to an adequate course of intravesical

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BCG and dependent upon whether a complete response was achieved or if the cancer recurred after a disease-free state various states of high-risk NMIBC have been defined including BCG-refractory, BCG early or late relapsing and BCG intolerant. These newly accepted definitions are dependent upon patients receiving an adequate course of BCG defined as 5 of 6 doses of induction BCG plus at least 2 additional doses of BCG (as part of re-induction or maintenance) within 6 months of starting treatment. BCG-refractory disease (presence of T1 bladder cancer at 3 months after induction BCG or persistent high-grade disease at 6 months despite adequate BCG) or BCG-early relapsing disease (recurrence of high-grade disease within 6–12 months after achieving a disease-free state after adequate BCG) are included in the category of BCG-unresponsive disease. This denotes a subgroup of patients at highest risk of disease recurrence and progression for whom additional BCG is not a feasible option. If the patient is deemed ineligible or refuses radical cystectomy for BCG-unresponsive disease they should be considered for a number of single-arm clinical trials currently enrolling patients in this disease space. A recently closed trial, KEYNOTE 057, led to the approval of intravenous pembrolizumab for BCG-unresponsive CIS with or without papillary tumors with an overall 1-year response rate of about 20%.[5] Other options to consider for BCG-unresponsive disease include the more favored combination (gemcitabine and docetaxol) as opposed to single agent (ie gemcitabine, docetaxol, mitomycin) intravesical chemotherapies and possibly, if approval is granted, other investigational agents currently under review by the FDA (ie nadofaragene firadenovec and oportuzumab monatox). ■

1. Anderson C, Weber R, Patel D et al: A 10-item checklist improves reporting of critical procedural elements during transurethral resection of bladder tumor. J Urol 2016; **196:** 1014.
2. Messing EM, Tangen CM, Lerner SP et al: Effect of intravesical instillation of gemcitabine versus saline immediately following resection of suspected low-grade non-muscle invasive bladder cancer on tumor recurrence. SWOG S0337 randomized clinical trial. JAMA 2018; **319:** 1880.
3. Kamat AM, Witjes JA, Brausi M et al: Defining and treating the spectrum of intermediate risk non-muscle invasive bladder cancer. J Urol 2014; **192:** 305.
4. Oddens J, Brausi M, Sylvester R et al: Final results of an EORTC-GU cancers group randomized study of maintenance BCG in intermediate and high risk Ta/T1 papillary carcinoma of the urinary bladder: one third dose versus full dose and one year versus three years of maintenance. Eur Urol 2013; **63:** 462.
5. Balar AV, Kamat AM, Kulkarni GS et al: Pembrolizumab monotherapy for the treatment of high risk non-muscle invasive bladder cancer unresponsive to BCG (KEYNOTE 057): An open-label, single arm, multicenter, phase II study. Lancet Oncol 2021; **22:** 919.

AUA2021 COURSE

Advanced Renal Cell Carcinoma and Surgical Management of T1b and Hilar Renal Masses

A. Oliver Sartor, MD
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Benjamin R. Lee, MD
Course Director/Panelist

Learning Objectives

At the conclusion of the activity, participants will be able to:

- *Manage bleeding complications of robotic partial nephrectomy.*
- *Describe the algorithm of immunotherapy treatment of advanced renal cell carcinoma.*
- *Minimize positive margin rates of robotic partial nephrectomy.*

Recent Advances in Systemic Therapy for Renal Cancer

Medical management of renal cell carcinoma continues to be a rapidly evolving area. As of August 2021, a new anti-HIF-2alpha approach is now U.S. Food and Drug Administration (FDA) approved for nonmetastatic von Hippel-Lindau-associated tumors not requiring immediate surgery.[1] This agent (belzutifan) is a new class of agent and will be assessed in future clinical trials as well.

> "Medical management of renal cell carcinoma continues to be a rapidly evolving area."

New FDA approvals in 2021 have also occurred in treatment of metastatic clear cell renal cell carcinoma. Nivolumab + cabozantinib has shown improvements in survival as compared to sunitinib,[2] and the FDA has now approved this regimen. In addition, lenvantinib + pembrolizumab is now FDA approved, again with a clear survival improvement relative to sunitinib.[3]

Clinical trials in advanced papillary renal cell carcinoma demonstrated cabozantinib is a relatively active agent in the setting.[4] This agent either alone or plus nivolumab has clear activity in advanced papillary renal cell patients.

In the adjuvant space there is a new trial that likely will result in a new FDA approval. This trial examined adjuvant pembrolizumab after nephrectomy in clear cell renal cell carcinoma. Patients were included if they were determined to have (after nephrectomy) pathological stage T3 or higher tumors (or node positive tumors) or pathological T2 tumors with nuclear grade 4, or T2 tumors with sarcomatoid differentiation. The adjuvant use of pembrolizumab clearly improved disease-free survival[5] and likely this will be FDA approved during the year ahead.

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Partial Nephrectomy for T1b and Hilar Renal Masses

Nephron-sparing surgery is recommended when surgery is indicated in T1a renal masses. For T1b renal masses, partial nephrectomy results in improved postoperative renal function with equivalent oncologic outcomes, though the complication rate and blood loss are expected to be greater.[6] Overall survival of patients with T1b tumors may also be better when compared to radical nephrectomy based on data from the National Cancer Database.[7] Hence partial nephrectomy may be performed in these patients after considering tumor location and complexity, patient factors such as comorbidities, and renal function and surgeon experience. The robotic and open approach for partial nephrectomy is based on surgeon experience and can have equivalent oncologic outcomes. Partial nephrectomy for T1b tumors is expected to be complex and must have good preoperative imaging to determine the location of the mass in relation to the hilar vessels. The collecting system in most of these patients will be entered and will need to be closed. We prefer a 2-layer renorrhaphy in these patients. Segmental venous involvement with tumor thrombus on preoperative imaging as well as during surgery must be looked for and managed appropriately, if present for T1b and T2 neoplasms.

> "Nephron-sparing surgery is recommended when surgery is indicated in T1a renal masses."

> "Overall survival of patients with T1b tumors may also be better when compared to radical nephrectomy."

Hilar masses can also present surgical challenges that must be managed. The relationship of the mass to adjacent blood vessels must be determined. Endophytic masses will need a preoperative ultrasound to determine its echogenicity to enable optimal intraoperative imaging. The vessels will need to be dissected to include the branches as they enter the renal sinus and branches that are close to the mass. Often the dissection will have to be on the capsule of the mass to prevent vascular injury. Selective clipping or diathermy of branches as they enter the mass may be required. Enucleation of hilar masses may also be considered to prevent vascular injury. After excision of the hilar mass, renal reconstruction will have to be individualized based on the configuration of the defect. A traditional 2-layer renorrhaphy may not be possible or recommended. When the collecting system is not violated, a horseshoe defect can be managed with a single-layer renorraphy. Double pigtail indwelling ureteral stents are not recommended even in complex partial nephrectomies. Drains and tissue sealants are not required in the vast majority of partial nephrectomies but may be considered in complex scenarios. ■

1. U.S. Food and Drug Administration: FDA approves belzutifan for cancers associated with von Hippel-Lindau disease. U.S. Food and Drug Administration 2021. Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-belzutifan-cancers-associated-von-hippel-lindau-disease.
2. Choueiri TK, Powles T, Burotto M et al: Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2021; **384:** 829.
3. Motzer R, Alekseev B, Rha SY et al: Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 2021; **384:** 1289.
4. Pal SK, Tangen C, Thompson IM Jr et al: A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. Lancet 2021; **397:** 695.
5. Choueiri TK, Tomczak P, Park SH et al: Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. N Engl J Med 2021; **385:** 683.
6. Mir MC, Derweesh I, Porpiglia F et al: Partial nephrectomy versus radical nephrectomy for clinical T1b and T2 renal tumors: a systematic review and meta-analysis of comparative studies. Eur Urol 2017; **71:** 606.
7. Venkatramani V, Koru-Sengul T, Miao F et al: A comparison of overall survival and perioperative outcomes between partial and radical nephrectomy for cT1b and cT2 renal cell carcinoma–analysis of a national cancer registry. Urol Oncol 2018; **36:** 90.e9.

AUA2021 COURSE

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

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Learning Objectives

At the conclusion of the activity, participants will be able to:

- *Describe the components of a multidisciplinary urologic cancer clinic and identify the best structure for the practice.*
- *Deliver advanced therapeutics based on current and emerging best evidence including immunotherapy in urologic oncology patients.*
- *Identify opportunities for shared care and team-based approaches of patients with urologic cancers including advanced prostate, bladder, and kidney cancer.*
- *Demonstrate an understanding of advances in genomic testing and personalized medicine for urologic cancers.*
- *Differentiate between new therapeutics that expand the treatment options for patients with urologic cancers and alter the definitions of cancer treatment.*

The Multidisciplinary Oncology Clinic

The delivery of care for cancer patients 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 Multidisciplinary Oncology Clinic (MDC) is one way that urologists can work with other cancer care providers to create advanced multimodality 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 cancer patients.[2] However, even when required, utilization of MDCs remains low for urologists.[3] For urologists, several MDC models have been proposed including all-in-one, where all providers meet a patient in the same clinic space, or virtual clinics where patients move from one member's clinic to another.[4] The COVID-19 pandemic has necessitated widespread and substantial changes in health care delivery, including the routine use of video visits, teleconsultations and other forms of electronic communication. Virtual MDCs are an attractive option that could potentially surmount the barriers to implementing single-location MDCs, such as patient travel time, transportation costs, access to transport, and physician time and space limitations

Multidisciplinary Approach to Prostate Cancer Care

The evolution of treatment for advanced prostate cancer was jumpstarted by the results of the CHARRTED trial for men with metastatic hormone-sensitive prostate cancer (mHSPC).[5] The study found a significant improvement in the primary outcomes of overall survival in patients receiving docetaxel with androgen deprivation (ADT) compared to ADT alone. Importantly, in a follow-up to the study it was found that the benefit was specifically in the group of men with de novo and high-volume metastatic disease.[6] This provides an opportunity for urologists to participate in MDC care for patients with high-volume disease at presentation. These findings were further supported by the STAMPEDE trial.[7] The management of mHSPC with advanced androgen axis agents, such as abiraterone, apalutamide, and enzalutamide, is supported by the Latitude, TITAN and both the ENZAMET and ARCHES trials, respectively.[8–11] The results of these trials have increased the complexity of the treatment landscape for patients with advanced prostate cancer and provide another opportunity for urologists to integrate these therapies into their advanced prostate cancer practice. 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 + ADT. For the entire population, there was no benefit to radiation to the primary, but when stratifying as low- vs high-volume disease, there was a significant improvement in survival in low volume patients who received radiation therapy to the primary.

> "Governing bodies and professional groups have identified multidisciplinary care as a marker for quality and improved outcomes."

Patients with nonmetastatic (M0), castration resistant prostate cancer (M0CRPC) are an important group of patients to consider given the worse overall survival with disease progression to metastasis. Treatment options now include the use of apalutamide,[12] enzalutamide[13] and darolutamide,[14] which have been shown to increase

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both time to metastasis and overall survival. Ideally treatment would be given at a low prostate specific antigen (PSA) doubling time (<10 months), providing another opportunity for multidisciplinary treatment coordination to ensure patients with M0CRPC receive systemic therapy more efficiently to prevent disease progression.

Patients with metastatic castration resistant prostate cancer (mCRPC) also provide an opportunity for MDC care. For patients with asymptomatic mCRPC treatment options traditionally include abiraterone, enzalutamide, sipuleucel-T and docetaxel.[14] Fortunately, patients with mCRPC have several treatment options though optimal sequence of treatments has yet to be determined.

Sipuleucel-T is a patient-derived immunotherapy for patients who have no or minimal symptoms. This was found to improve overall survival without a PSA or radiographic response, especially in African American men. Both abiraterone and enzalutamide are oral agents that can be managed by either a medical oncologist or urologist. The inhibitory action of abiraterone on the cytochrome (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 advanced practice provider 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 for bone metastases in the absence of visceral metastases, radium-223 can be offered as a bone-seeking isotope that targets areas of bone metastases.

Genetic testing is recommended in patients with advanced prostate cancer with up to 30% of men with mCRPC harboring a deleterious DNA repair gene mutation.[15,16] Selective patients with deleterious germline or somatic mutations in 2 poly (ADP-ribose) polymerase (PARP) are eligible for directed therapies with PARP inhibitors (PARPi). The PARPi olaparib is approved for patients with mCRPC with a known PARP mutation who have progressed following androgen receptor directed therapy or taxane based chemotherapy.[15] Likewise, patients with mCRPC found to have a BRCA1 or BRC2 gene mutation who have disease progression following traditional therapy are eligible for use of the PARPi rucaparib.[17] PARPi use in both these populations is noted to significantly improve progression-free survival

> "For urologists, several MDC models have been proposed including all-in-one, where all providers meet a patient in the same clinic space, or virtual clinics where patients move from one member's clinic to another."

Pembrolizumab has also been recently approved for those patients with microsatellite instability-high or mismatch repair-deficient mCRPC following docetaxel and targeted endocrine therapy with favorable progression-free and overall survival.[16,18] Given the new targeted therapies for patients with mCRPC incorporating genetics and genetic counselors will likely become an important component of MDC.

Multidisciplinary Kidney Cancer Treatment

Until recently, the primary role of surgical management for advanced kidney cancer was the removal of the primary tumor with the hope that patients do not have disease recurrence. However, many patients are at high risk for recurrence. Several agents have been tested as adjuvant therapies to prevent recurrence. Most of the studies of adjuvant therapy have been negative. Sunitinib is currently the sole adjuvant therapy with potential benefit in the adjuvant setting based on results of the S-TRAC study.[19] The study showed an improvement in disease-free survival, but no improvement in overall survival in these patients. However, in the recent KEYNOTE-564, patients with locoregional clear cell renal cell carcinoma (RCC) with high risk of recurrence following nephrectomy were randomized to receive pembrolizumab vs placebo.[20] This cohort of patients included those patients with M1 disease with completely resected metastasis at or shortly following nephrectomy. In this study patients who received pembrolizumab experienced a significant improvement in disease-free survival following nephrectomy compared with placebo.

Although adjuvant therapy has not become widespread in high-risk kidney cancer, there are several areas where additional therapy in an MDC setting may be beneficial. Neoadjuvant therapy has been proposed to downstage tumors prior to surgical intervention. Recent reports have included preoperative pazopanib and axitinib, both of which can produce tumor shrinkage.[21,22] In a recent advancement patients with von-Hippel Lindau (VHL)-associated RCC are eligible for use of the HIF2a inhibitor, MK-6482 or belzutifan. This medication has been approved by the U.S. Food and Drug Administration (FDA) to slow tumor growth with significant improvements noted in tumor volume, treatment durations, relapse rates and progression-free survival.[23]

The expansion of treatment options for metastatic kidney cancer has resulted in a re-evaluation of the benefit of cytoreductive nephrectomy. The CARMENA trial evaluated treatment-naïve patients with biopsy proven metastatic clear cell renal cell carcinoma randomized to sunitinib alone vs cytoreductive nephrectomy plus sunitinib in a non-inferiority study.[24] The study showed that sunitinib alone was not inferior to cytoreductive nephrectomy followed by sunitinib. However, the study was enriched with patients at high risk who may have been poor surgical candidates. The results suggest that a nuanced approach to patients with metastatic kidney cancer may be most beneficial. Several next generation cytoreductive nephrectomy and radiation trials are ongoing.

Multidisciplinary Bladder Cancer Treatment

There are several opportunities for multidisciplinary care within the realm

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"Virtual MDCs are an attractive option that could potentially surmount the barriers to implementing single-location MDCs"

of bladder cancer. Bacillus Calmette–Guérin (BCG)-unresponsive high-risk non-muscle-invasive bladder cancer (NMIBC) patients who decline or are ineligible for radical cystectomy are an especially challenging population. Treatment with the immunotherapeutic pembrolizumab is FDA approved for use in this population based on the KEYNOTE-057 trial with a 41% complete response rate and a median duration of complete response of 16.2 months.[25]

Additionally, ongoing phase II trials investigating atezolizumab, a similar immuno-oncologic to pembrolizumab, in this patient cohort have reported encouraging complete responses at 3 and 6 months.[26] A novel intravesical gene-mediated therapy, adstiladrin, is also currently being investigated in this patient cohort with noted durable high-grade free recurrences up to 12 months.[27] With the advancement in both systemic and surgical treatments of NMIBC, multidisciplinary care is key to treatment of this population.

The benefits of multidisciplinary management including neoadjuvant chemotherapy prior to radical cystectomy and the importance of surgical quality as measured by lymph node count were shown in the SWOG 8710 trial.[28] A followup meta-analysis provided evidence of a 5% overall survival benefit at 5 years with neoadjuvant chemotherapy.[29] These findings support the recommendation in the AUA guidelines for an MDC approach to the patient with muscle-invasive bladder cancer.[30] For patients with metastatic disease, the cisplatin-based chemotherapy remains the first-line therapy of choice. However, immunotherapy including pembrolizumab and other PD-1/PD-L1 agents has recently been approved for second-line and cisplatin ineligible patients.

Conclusion

As advanced therapeutics become a growing part of the management of urological cancer patients, the urologist will be required to coordinate care among a growing number of oncology specialists. The creation of an MDC can provide the infrastructure to manage these patients along with the growing demands of clinical practice. ■

1. American Society of Clinical Oncology: The State of Cancer Care in America, 2017: a report by the American Society of Clinical Oncology. J Oncol Pract 2017; **13:** e353.
2. Silbermann M, Pitsillides B, Al-Alfi N et al: Multidisciplinary care team for cancer patients and its implementation in several Middle Eastern countries. Ann Oncol, suppl., 2013; **24:** vii41.
3. Atwell D, Vignarajah DD, Chan BA et al: Referral rates to multidisciplinary team meetings: is there disparity between tumour streams? J Med Imaging Radiat Oncol 2019; **63:** 378.
4. Stratton K, Moeller AM and Cookson MS: Implementation of the AUA Castration Resistant Prostate Cancer Guidelines into practice: establishing a multidisciplinary clinic. Urol Pract 2016; **3:** 203.
5. Sweeney CJ, Chen Y-H, Carducci M et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; **373:** 737.
6. Kyriakopoulos CE, Chen Y-H, Carducci MA et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018; **36:** 1080.
7. James ND, de Bono JS, Spears MR et al: Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017; **377:** 338.
8. Fizazi K, Tran N, Fein L et al: Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017; **377:** 352.
9. Chi KN, Agarwal N, Bjartell A et al: Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019; **381:** 13.
10. Davis ID, Martin AJ, Stockler MR et al: Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019; **38:** 121.
11. Armstrong AJ, Szmulewitz RZ, Petrylak DP et al: ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019; **37:** 2974.
12. Smith MR, Saad F, Chowdhury S et al: apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018; **378:** 1408.
13. Hussain M, Fizazi K, Saad F et al: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018; **378:** 2465.
14. Lowrance WT, Roth BJ, Kirkby E et al: Castration-resistant prostate cancer: AUA Guideline amendment 2015. J Urol 2016; **195:** 1444.
15. de Bono J, Mateo J, Fizazi K et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020; **382:** 2091.
16. Antonarakis ES, Piulats JM, Gross-Goupil M et al: Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol 2020; **38:** 395.
17. Abida W, Patnaik A, Campbell D et al: Rucaparib in men with metastatic castration-resistant prostate cancer harboring a *BRCA1*or *BRCA2* gene alteration. J Clin Oncol 2020; **38:** 3763.
18. Hansen AR, Massard C, Ott PA et al: Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. Ann Oncol 2018; **29:** 1807.
19. Ravaud A, Motzer RJ, Pandha HS et al: Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med 2016; **375:** 2246.
20. Choueiri TK, Tomczak P, Park SH et al: Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. N Engl J Med 2021; **385:** 683.
21. Karam JA, Devine CE, Urbauer DL et al: Phase 2 trial of neoadjuvant axitinib in patients with locally advanced nonmetastatic clear cell renal cell carcinoma. Eur Urol 2014; **66:** 874.
22. Rini BI, Plimack ER, Takagi T et al: A phase II study of pazopanib in patients with localized renal cell carcinoma to optimize preservation of renal parenchyma. J Urol 2015; **194:** 297.
23. Choueiri T, Plimack E, Bauer T et al: Phase I/II study of the oral HIF-2a inbitor MK-6482 in patients with advanced clear cell renal cell carcinoma (RCC). J Clin Oncol, suppl., 2020; **38:** e12624.
24. Méjean A, Ravaud A, Thezenas S et al: Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 2018; **379:** 417.
25. Balar AV, Kamat AM, Kulkarni GS et al: Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. Lancet Oncol 2021; **22:** 919.
26. Black P, Tangen C, Singh P et al: Phase II trial of atezolizumab in BCG-unresponsive non-muscle invasive bladder cancer: SWOG S1605 (NCT #02844816). J Clin Oncol 2020; **38:** 5022.
27. Boojian S, Shore ND, Canter D et al: Intravesical rad-IFNa/Syn3 for patients with high-grade, bacillus Calmette-Guerin (BCG) refractor or relapsed non-muscle invasive bladder cancer: a phase II randomized study. J Clin Oncol 2020; **38:** 442.
28. Grossman HB, Natale RB, Tangen CM et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003; **349:** 859.
29. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration: Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005; **48**: 202.
30. Chang SS, Bochner BH, Chou R et al: Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol 2017; **198:** 552.

AUA2021 COURSE

Chemotherapy and Immunotherapy for the Urologist and Advanced Practice Provider

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Learning Objectives

At the conclusion of the activity, participants will be able to:

- *Describe the standard of care chemotherapy regimens for genitourinary malignancies.*
- *Recall both historic and newer immunotherapy options in the treatment of genitourinary malignancies, including 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 and the survivorship issues surrounding patients on systemic treatments for genitourinary malignancies.*
- *List both completed and accruing clinical trials that are defining the paradigms of chemotherapy and immunotherapy use in genitourinary malignancies.*

The next generation of management of advanced genitourinary 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 1 person making the majority of the decisions surrounding care. Often, these patients are starting in a urology office before they are referred for management of advanced or metastatic disease. 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 is our fourth consecutive year teaching this course, and in looking back at prior years it is very evident how rapidly the landscape for the treatment of advanced and metastatic prostate, bladder and kidney cancer has changed.

In advanced and metastatic prostate cancer, the arrival of the newest generation of androgen receptor-directed therapies and chemotherapy regimens have had the greatest impact. For metastatic castrate-sensitive disease (mCRPC), the newest guidelines include androgen receptor blockers enzalutamide and apalutamide, cytochrome P450 17 alpha-hydroxylase (CYP-17) inhibitor abiraterone, and docetaxel (which up to recently had been reserved for end-of-the-line castrate resistant prostate cancer (CRPC). In the next disease space, nonmetastatic CRPC, add darolutamide to these agents in addition to what had prior been standard of care. Finally, the largest changes in the last decade have been appreciated in the mCRPC disease space. Not only are the aforementioned androgen receptor-directed therapies represented in the guidelines, but also a new chemotherapy, cabazitaxel, and the bone-only metastasis agent radium-223.

For mCRPC, the impact of individualization of therapy and genomic analysis of tumors has been realized with regard to patients with homologous recombination repair gene-mutated disease, in which the poly-ADP ribose polymerase (PARP) inhibitors rucaparib and olaparib are selectively effective. Also in patients with mutations in mismatch repair genes (MMR) and/or microsatellite instability (MSI) in the tumor, the checkpoint inhibitor pembrolizumab has shown benefit, as in patients with other tumor types and these somatic gene mutations. As of now, the only other immunotherapy currently U.S. Food and Drug Administration (FDA)-approved for prostate cancer remains sipuleucel-T, which is used in nonvisceral, asymptomatic or minimally symptomatic M1 castration resistant disease. The labor-intensive mechanism of administration of sipuleucel-T and the lack of a reliable surrogate marker for treatment efficacy has limited its use in many outpatient settings, particularly that of the urologic oncologist.

There have now been 2 Consensus Conferences investigating the role of genetic testing for inherited prostate cancer risk, both taking place in Philadelphia. When reviewing the available literature, it has been determined that in germline testing of men with metastatic prostate cancer, up to 11.8% harbor a mutation compared to 4.6% of patients with localized disease. Over 20 mutations in DNA-repair genes have been identified, with the most common being BRCA2, BRCA1, ATM and CHEK2. Additionally, a consensus recommendation of the conference was to test all men with mCRPC, regardless of family history, to help identify any actionable mutations.[1]

When considering advanced and metastatic urothelial carcinoma of the bladder, cisplatin-based chemotherapy remains the gold standard. However, up to 50% of eligible patients are deemed unfit for cisplatin administration because of poor functional status, chronic kidney disease, hearing loss, neuropathy or heart failure. Up until recently, these patients would either receive suboptimal chemotherapy regimens or no systemic therapy at all, which would severely diminish survival. This has been reversed with the discovery of new immunotherapeutic agents. Although the concept of immunotherapy for bladder cancer is not new, with bacillus Calmette-Guérin being a mainstay of treatment for noninvasive, high-grade urothelial carcinoma of the bladder, the recent excitement surrounding immunotherapy and bladder cancer lies in the introduction of

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the checkpoint inhibitors (CPIs) for the treatment of a variety of disease states. 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 CPI takes the proverbial foot off of 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. 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. The positive results of this trial led to FDA approval of pembrolizumab for platinum refractory advanced urothelial carcinoma of the bladder. Additional CPIs that are FDA approved in this disease space are nivolumab (anti PD-1) and avelumab (anti PD-L1). The ORR for these agents range from 15%–25%, with a higher response in PD-L1 expressing tumors. Furthermore, atezolizumab (anti-PD-L1) and pembrolizumab have gained approval in the first line cisplatin-ineligible population. Also very exciting in the second line post platinum space is a biomarker-driven therapy involving erdafitinib for patients with an FGFR3 or FGFR2 alteration. In the post CPI space, second line and beyond, there is erdafitinib and the antibody-drug conjugates enfortumab and sacituzamab, which have shown significant activity in patients with advanced bladder cancer who have failed CPIs.

Two other areas in which CPIs have entered the guidelines for urothelial carcinoma of the bladder include bacillus Calmette-Guérin-unresponsive noninvasive, high-grade urothelial carcinoma of the bladder, in which pembrolizumab recently gained approval via the Keynote-057 trail; and, as maintenance therapy in patients with advanced or metastatic disease pretreated with chemotherapy, in which avelumab improved overall survival via the JAVELIN trial.

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 were based on patients receiving adjuvant interferon. 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, and new treatment paradigms. CheckMate-214 results were published in 2018 and demonstrated improved overall survival in the intermediate to poor risk metastatic clear cell RCC (ccRCC) cohort treated with ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) combination vs sunitinib monotherapy. 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 ccRCC. The KEYNOTE-426 trial evaluated a novel combination regimen of a CPI and targeted agent (pembrolizumab plus axitinib) for first line treatment of advanced ccRCC. This trial demonstrated a survival advantage regardless of risk stratification and led to the approval of this combination in all risk categories. Through the CheckMate-9ER trial, the combination of cabozatinib and nivolumab gained similar approval, again regardless of risk category. However, this regimen was also indicated for tumors of clear-cell histology. For those patients with advanced or metastatic non-ccRCC, the only preferred regimens remain sunitinib or an available clinical trial.

The new era of treatment for advanced and metastatic prostate, bladder and kidney cancer has been marked by genetic and genomic testing, biomarker-driven therapies, and the continued infiltration of several disease spaces by immunooncologic therapies. Annual review of the newest trials and approvals is absolutely necessary for the urologic oncologist and advanced practice providers alike to stay current. ■

1. Giri VN, Knudsen KE, Kelly WK et al: Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 2020; **38:** 2798.

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