2023 AUA Annual Meeting Highlights: Prostate Cancer

Features highlights from the following AUA 2023 Annual Meeting sessions:

- Crossfire: Controversies in Urology: Impact of PSMA-PET on Treatment Decision-making
- The Changing Face of Advanced Prostate Cancer 2023
- Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection and Management of Localized and Advanced Disease
- AUA Guidelines on Advanced Prostate Cancer
- Prostate Cancer Diagnostics: AUA Guidelines on use of PSA Biomarkers, MRI and Biopsy Techniques
- Evidence-based Update on Prostate Cancer Detection and Management
- Managing Toxicities of Checkpoint Inhibitors: A Urologist’s Guide

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Controversies in Urology: Impact of PSMA-PET on Treatment Decision-making

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Learning Objective
At the conclusion of this activity, participants will be able to define clinical scenarios where prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging can be applied in prostate cancer, and characterize clinical action from results of PSMA PET imaging in newly diagnosed unfavorable-intermediate and high-risk localized prostate cancer, recurrent disease, and metastatic hormone-sensitive prostate cancer (mHSPC).

Since its initial approval in 2020, PSMA PET imaging utilization has increased in utilization and brought a new era of advanced imaging for prostate cancer. Prostate cancer clinical guidelines have now added recommendations suggesting that PSMA PET can be an alternative to conventional imaging (eg, standard CT and bone scan). However, how to utilize the information from PSMA PET to guide treatment decisions is less well defined. At AUA2023, a plenary panel of experts addressed the issues surrounding the impact of PSMA PET on the clinical management of common prostate cancer scenarios. Panelists Dr Anthony D’Amico, Dr Nathan Lawrentschuk, and Dr Evan Yu provided experienced recommendations and insight with the goal to provide attendees with practical guidance on when to use these newer molecular imaging agents and what to do with the results of advanced imaging, specifically focusing on newly diagnosed unfavorable intermediate- and high-risk localized prostate cancer, recurrent disease, and mHSPC.

PSMA PET imaging was initially approved in the setting of recurrent prostate cancer after primary curative therapy, such as radiation (RT) or surgery, usually triggered by a rising PSA. The case for the use of PSMA PET imaging is strengthened by multiple studies that show changes in treatment decision-making at the time of biochemical recurrence. The goals of PSMA PET imaging for recurrent prostate cancer are different, depending on initial primary therapy.

If surgery was the initial therapy, the goal of imaging would be not only to identify prostate bed or pelvic disease for RT planning, but also to identify extrapelvic disease that would not be encompassed in standard salvage pelvic RT. The use of imaging after surgery is hampered by the limits of detection at low PSA levels. Although there is no established PSA cut point to recommend molecular imaging, higher PSA levels are associated with increasing sensitivity and specificity of detecting recurrent disease. Most experts would not recommend imaging until the PSA reaches at least 0.2 ng/mL. The advantages of waiting for a higher PSA (eg, above 0.2) should be balanced with data that show earlier salvage RT yields improved results. For example, in RADICALS RT patients were randomized to adjuvant RT or early salvage RT at a PSA of 0.1 ng/mL and could not establish superiority for the use of adjuvant RT as compared to early salvage RT; however, there were very few patients with 2 high-risk factors (prostatectomy Gleason score 8, 9, 10 or prostatectomy T3 or T4). These data support the findings of a recent study that suggests if salvage RT is initiated prior to a PSA level of 0.25 ng/mL, then there is no increased risk of all-cause mortality in men with 1 high-risk factor. However, there are other data that suggest in men with 2 high-risk factors, adjuvant RT should be delivered prior to the PSA reaching 0.10 ng/mL to avoid an increase all-cause mortality risk. It is well recognized that the sensitivity of PSMA PET is relatively low at this proposed threshold PSA, and clinicians must weigh the benefits of waiting longer for higher PSA levels and associated improved performance of PSMA imaging vs potentially losing a window of curability.

If RT was initial therapy, the goal of imaging would be to understand the site(s) of recurrence, ie, local prostate gland-only vs regional/distant vs both, as site(s) of disease will impact proposed salvage treatment plans. Although practice guidelines support the use of the Phoenix definition for recurrent disease after primary RT, advanced molecular imaging may afford earlier diagnosis of recurrence, an area that deserves further study. Additionally, although change in treatment decision-making is affected by PSMA PET results, the ability to impact long-term outcomes with minimal toxicity will only be determined in ongoing randomized controlled trials.

The role of metastasis-directed therapy (MDT) has been addressed in several small phase 2 clinical trials of treatment to distant metastatic sites (surgery or stereotactic body RT) that were detected by conventional imaging or choline-PET, reporting an improvement in the clinical end points of androgen deprivation therapy (ADT)-free survival or progression-free survival. For example, in the Observation vs Stereotactic Ablative Radiation (SABR) for Oligometastatic Prostate Cancer (ORIOLE) study, 54 men with conventional imaging-detected oligometastatic disease were randomized to SABR or observation with progression at 6 months in 7 of 36 patients (19%) receiving SABR and 11 of 18 patients (61%) undergoing observation (P = .005). The Surveillance

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or Metastasis-directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) trial randomized 62 men with choline-PET oligometastatic disease to either surveillance or MDT, and the median ADT-free survival was 13 months for the surveillance group and 21 months for the MDT group (HR 0.60 [90% CI, 0.40 to 0.90], P = .11).8 The ORIOLE study did address consolidation of PSMA radiotracer-avid disease, while other studies did not, and the role of MDT for sites of disease that are only detected by advanced PET imaging remains unaddressed. Importantly, several large clinical trials are ongoing in biochemical recurrence utilizing PSMA PET, specifically addressing not only MDT to extrapelvic disease, but also the impact of intensified ADT concurrent to salvage radiation delivery (eg, NCT04423211, EA8191).

The other clinical scenario with established indications for PSMA PET imaging is in initial staging of newly diagnosed unfavorable intermediate-risk and high-risk prostate cancer where PSMA PET can be considered as an alternative to standard imaging of bone and soft tissue for initial staging.1 Several studies have examined the utility of PSMA PET imaging in this setting, reporting that advanced imaging is associated with management changes.9–11 One notable study was designed as a randomized clinical trial of PSMA PET imaging vs conventional imaging with CT and bone scan, including a crossover unless 3 or more distant metastases were identified.11 The primary outcome was accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease. Over 300 men were randomized in this unique trial, showing that PSMA PET-CT has contributed to the body of evidence suggesting that conventional imaging is not a necessary prerequisite to PSMA PET and that PSMA PET can serve as an equally effective, if not more effective, front-line imaging tool.1 The purported benefits of advanced imaging in staging have been, in the setting of a positive PSMA PET scan, the earlier identification of mHSPC and, in the setting of negative PSMA PET imaging, increased confidence of localized disease.

Because the established standard of care in mHSPC has been established from several randomized clinical trials using conventional imaging, a major conundrum in prostate cancer involves how to incorporate more advanced imaging technologies in this disease state. For example, trials have separated mHSPC patients into high volume and low volume as defined by conventional imaging parameters, and how to incorporate the burden of disease by molecular imaging is unknown. Perhaps more importantly, it is well established that patients with mHSPC benefit from combination therapies (eg ADT + androgen-receptor signaling inhibitors, ADT + docetaxel), and the question remains if we should treat patients with PSMA PET-detected metastasis and negative conventional imaging similar to patients with conventional imaging-detected metastases. Additionally, whether clinicians should withhold standard local therapy (eg, surgery or RT) from patients with negative conventional imaging but PSMA PET only—detected metastasis is an ongoing controversy; the panel agreed that, at this time, standard of care local therapies should still be offered in this setting. Because of the excellent performance characteristics of PSMA PET imaging, eg, high positive predictive value, clinicians are presented with the challenge of how to translate the findings of advanced imaging to conventional imaging clinical trials.

The panel concluded the session with a message that the future of PSMA PET in prostate cancer looks promising in multiple domains. As the technology advances, perhaps with novel radiotracers, the ability to detect earlier lesions with enhanced intraprostatic localization may improve treatment planning and focal therapy options. The concept of combining diagnostic and therapeutic modalities, so-called theranostics, has arrived but is expected to continue refinement. As the field continues to adopt PSMA PET into clinical trials and clinical practice, the hope is for clarity regarding actionable advanced imaging results and harmonization of clinical practice guidelines on appropriate use of these technologies. Although this session in 2023 was labeled a “Crossfire Controversy,” the panel expects that PSMA PET will not only become more standard of care, but also revolutionize the diagnosis, staging, and treatment planning, providing valuable insights into prostate cancer biology and ultimately improving the care for our prostate cancer patients.

The Changing Face of Advanced Prostate Cancer 2023

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Learning Objective

At the conclusion of this activity, participants will be able to discuss how to manage patients with hormone-sensitive M1 prostate cancer and patients with metastatic castrate-resistant prostate cancer according to current AUA Guidelines.

As the course director, I have been fortunate to host a course on advanced prostate cancer at the AUA Annual Meeting since 2012 and the changes over these 11 years have been nothing less than spectacular! Furthermore, the last several years have been interesting, with disruptions due to COVID. It was exciting to see AUA2023 in Chicago feel like it used to feel! Furthermore, Dr Karsh and I welcomed Dr David Morris to the course, and he did a great job facilitating a mock tumor board of illustrative cases. Thanks to advanced technology, Dr Morgans delivered her talk remotely due to an ill child. Fortunately, all was ultimately well, and we look forward to seeing her “live” in 2024.

In the years from 2012-2015, it was all about metastatic (M1) castrate-resistant prostate cancer (mCRPC) with multiple new therapeutic advances starting in 2010 (sipuleucel-T) followed by abiraterone and enzalutamide and a focus on bone-targeted agents. Later, we expanded to cover hormone-sensitive (HS) advanced disease due to the new data on docetaxel and abiraterone extending survival in new M1 patients. In 2017, we added the topic of nonmetastatic (M0) castrate-resistant prostate cancer (CRPC) due to emerging data on use of apalutamide, enzalutamide, and darolutamide in these men. Then in 2019, we doubled down on HS new M1 disease with emerging data that 4 agents (docetaxel, abiraterone, apalutamide, and enzalutamide) all improve survival for men with new metastatic prostate cancer. The hot topic for 2023 was the issue of “doublet” vs “triplet” therapy for HS M1 disease.

Now, from 2020 to today, we have been going boldly into personalized molecular medicine with the addition of both hereditary and somatic testing for cancer-associated gene alterations and several therapeutic agents Food and Drug Administration (FDA)–approved in the past several years to consider based on this molecular testing.

Newly Diagnosed HS M1 Prostate Cancer: Androgen Deprivation Therapy Alone vs Doublet vs Triplet Therapy?

Seven years ago hormone-naïve/HS newly diagnosed metastatic prostate cancer became hot news with the release of the CHAARTED trial data in 2015 and the STAMPEDE trial results in 2016 showing a benefit of up-front docetaxel chemotherapy in new M1 disease.2,3 Primary androgen deprivation therapy (ADT) had been the only treatment for men with new M1 disease for more than three-quarters of a century. In those years CHAARTED and STAMPEDE taught us that adding 6 cycles of docetaxel within 4 months of starting hormone therapy/ADT resulted in a clinically meaningful survival benefit. For high-volume disease (4 or more bone metastases and/ or visceral metastases) the addition of chemotherapy resulted in a 17-month survival advantage compared to ADT alone. However, the initial publication hazard ratio generally supported a benefit of docetaxel for low-volume M1 disease as well. The STAMPEDE trial confirmed the benefit of docetaxel and generally supported the use of chemotherapy for all men with new M1 disease. Median overall survival (OS) was 65 months for men randomized to receive docetaxel vs 43 months for men randomized to standard-of-care ADT alone. In 2018, Kyriakopoulos et al reported longer-term follow-up from CHAARTED confirming the benefit of docetaxel for high-volume disease but not supporting up-front chemotherapy for low-volume disease.4

In 2017 the LATITUDE trial showed that abiraterone added to ADT for men with new M1 disease resulted in a similar survival benefit to docetaxel.5 In 2019, we learned that both apalutamide and enzalutamide also significantly extend survival compared to traditional ADT alone.6,8 The results of TITAN (apalutamide) and ENZAMET and ARCHES (NCT02677896; enzalutamide) were published showing robust benefits. In my mind, this is combined androgen blockade (CAB) or maximal androgen blockade (MAB) finally showing a survival benefit now using second-/third-generation nonsteroidal antiandrogens (AAs).9

In TITAN, 1,052 men were randomized to traditional ADT alone vs ADT plus apalutamide (240 mg orally, daily).6 Ten percent received prior docetaxel, 80% had M1 disease at initial diagnosis, and 63% had high-volume disease. In the final analysis, at a median follow-up of 44 months, 51% remained on apalutamide.10 Apalutamide conferred a 35% reduction in risk of death. This benefit was present regardless of disease volume or receipt of docetaxel. At 4 years, OS was 65% in the apalutamide arm and 51.8% in the ADT plus placebo group.

In a similar fashion, ARCHES and ENZAMET documented a similar benefit to enzalutamide in new M1 HS disease.7,8 ARCHES was the FDA registration trial and enrolled 1,150 new M1 patients receiving testosterone suppression with or without docetaxel,
stratified by high- or low-volume disease men randomized to enzalutamide (N=574) vs placebo (N=576). At ESMO (European Society for Medical Oncology) 2021, Fizazi et al presented the latest trial update. As of the data cutoff of May 28, 2021, 397 (34.5%) patients remained on treatment, with a median follow-up of 44.6 months. The median treatment duration was 40.2 months on enzalutamide+ADT, 13.8 months on placebo+ADT, and 23.9 months for crossover patients. Enzalutamide+ADT extended survival vs placebo+ADT (HR 0.66; 95% CI 0.53 to 0.81; P < .0001).

The above trials represent doublet therapy for M1 HS disease, in other words, adding 1 additional agent (either apalutamide, abiraterone, docetaxel, or enzalutamide) to traditional ADT.

Apalutamide, darolutamide, and enzalutamide are second-generational nonsteroidal oral AAs which are more potent than first-generation agents (flutamide, nilutamide, and bicalutamide). In past times, adding a first-generation AA to ADT was called CAB or MAB. The latest studies of second-generation agents finally prove the concept of CAB/MAB, first proposed by Labrie and others (as reported by Chi et al) in the mid-1980s.

The latest concept is triplet therapy for M1 HS disease. The PEACE-1 trial reported by Fizazi et al at ESMO 2021 studied ADT plus docetaxel plus abiraterone acetate/prednisone (AAP) vs ADT plus docetaxel, finding a survival benefit of the triple therapy. The OS benefit was seen across subgroups, including those with high-volume disease (HR 0.72, 95% CI 0.55-0.95) and low-volume disease (HR 0.83, 95% CI 0.50-1.38; data immature). Adding AAP to ADT plus docetaxel improves both rPFS and OS in men with metastatic castrate-sensitive prostate cancer, even when 84% of mCRPC men from the control arm receive an androgen signaling inhibitor. Toxicity was as expected—no new safety concerns were seen in this new triple combination treatment. From a clinical perspective, the benefit was a median lifetime gain of more than 1.5 years for men with high-volume metastatic castrate-sensitive prostate cancer (5.1 vs 3.5 years). Finally, ARASENS is a phase 3 clinical trial of ADT plus docetaxel plus darolutamide vs ADT plus docetaxel plus placebo that was reported at the American Society of Clinical Oncology Genitourinary Cancers Symposium in February 2022 by Dr Matthew Smith. There was an OS in favor of the triple therapy including darolutamide for both de novo M1 and recurrent M1 disease reported.

Should all chemotherapy-fit men receive triplet therapy regardless of disease volume (high vs low), or should we reserve this for high-volume patients? Furthermore, the concept of being fit for chemotherapy is not completely standardized. Additionally, in the U.S., systemic chemotherapy can only be administered by medical oncologists, necessitating a multidisciplinary team. Finally, despite the survival benefits proven for doublet and triplet approaches, sadly, up to 30%-40% of U.S. men with M1 HS disease are still just receiving ADT alone.

CRPC

Since 2010, multiple new agents have been approved by the FDA for M1 CRPC, including sipuleucel-T, cabazitaxel, abiraterone acetate, denosumab, enzalutamide, and radium-223. Except for cabazitaxel, all of these agents are commonly available for urologists and oncologists to prescribe. The latest advances are olaparib, rucaparib, and pembrolizumab for patients with somatic or germline mutations in actionable genes implicated in advanced prostate cancer.

Bone Health/Denosumab

Denosumab (Xgeva) is prescribed at a dose of 120 mg subcutaneously monthly to prevent skeletal-related events in men with M1 CRPC with bone metastases. The FDA also approved a 60-mg dose (Prolia) subcutaneously twice a year to prevent bone loss (osteopenia and osteoporosis) in men without bone metastases who are on GnRH (gonadotropin-releasing hormone) analogue therapy for prostate cancer. We continue to remind urologists to be mindful of using supportive agents including vitamin D and calcium supplements, and monitoring for osteopenia and osteoporosis with annual dual-energy x-ray absorptiometry scanning.

Sipuleucel-T

Sipuleucel-T is a novel immunotherapy approved by the FDA in 2010 for asymptomatic or minimally symptomatic M1 CRPC. The ideal patient for sipuleucel-T should have documented clinical metastases and a rising PSA while on continuous hormonal therapy. The patient should not have bone or cancer pain requiring narcotic pain medications. In men with PSA levels in the lowest quartile of the IMPACT trial (PSA less than 22 ng/mL) there was a more robust OS advantage to sipuleucel-T. Specifically, the estimated 3-year survival in this group of treated patients was 62.6% compared to 41.6% for men randomized to the control arm of the study. Data from the PROSEED registry (N=1,902 patients) treated with sipuleucel-T in real-world practice between 2011 and 2014 has also provided confirmatory data. In a respective analysis of 219 African American men disease-matched to a Caucasian cohort, OS was 35.3 months vs 25.8 months. These intriguing data need to be confirmed in prospective fashion. Finally, Hafron and McKay et al published real-world Medicare data on use of sipuleucel-T with or without enzalutamide or abiraterone, finding improved survival in mCRPC patients receiving this immunotherapy vs men who did not. While not a randomized controlled trial, this new information suggests value of this treatment approach despite relatively few men being offered this therapy.

Abiraterone

Abiraterone is a 17-lyase and 17-hydroxysteroid dehydrogenase inhibitor that blocks key pathways in the steroidal synthesis pathways leading to androgen production. Low-dose prednisone (5 to 10 mg daily is a physiological dose) is recommended to be administered with abiraterone to help limit overproduction of aldosterone and limit the side effects of hypertension, hypokalemia, and fluid retention. The FDA-approved indication for abiraterone is before or after docetaxel chemotherapy in men with M1 CRPC based on evidence from the Cougar-AA-301 and 302 clinical trials. The dose for abiraterone is 1,000 mg orally once daily in the fasted state along

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with low-dose steroid (5 mg prednisone orally twice daily). The final analyses of both trials were reviewed, showing clinically meaningful end points of OS and radiographic progression-free survival (Cougar 302) benefits. Abiraterone is also available in a 500-mg oral dose which allows for 2 rather than 4 pills per day, which might help with compliance for some men.

Abiraterone was also FDA approved for use in men with newly diagnosed HS M1 prostate cancer in February 2018. Approval was based on LATITUDE (NCT01715285), a placebo-controlled international clinical trial that randomized 1,199 patients with metastatic high-risk HS disease. Patients received 1,000 mg abiraterone acetate orally once daily with 5 mg prednisone once daily (in 597) or matching placebos orally once daily (in 602). Patients in both arms received a GnRH analogue or underwent bilateral orchiectomy. The major efficacy end point was OS. Median OS was not estimable in the abiraterone acetate arm and 34.7 months in the placebos arm (HR 0.621; 95% CI 0.509, 0.756; \( P < .0001 \)). Median duration of abiraterone use was 24 months. Abiraterone is popular due to its being available as a generic medication over the last few years.

Enzalutamide

Enzalutamide, a second-generation androgen receptor antagonist, was FDA approved in 2012 to treat men with disease that progressed after docetaxel-based chemotherapy based on level 1 evidence from the AFFIRM trial. It received an expanded approval in 2014 for use before chemotherapy in the PREVAIL trial. Enzalutamide is taken orally at a dose of 160 mg daily with or without food, and it does not require prednisone. However, enzalutamide does have an approximate 0.5%-1% risk of seizures associated with its use and crosses the blood-brain barrier, implicating it with some risk of falls and fatigue.

PROSPER is a phase 3, randomized, double-blind, placebo-controlled study of enzalutamide in men with M0 CRPC. It demonstrated an approximate 2-year metastasis-free survival (MFS) benefit over placebo showing that MFS is a meaningful end point. As of July 13, 2018 enzalutamide was the second FDA approved drug for M0 CRPC. Updated data from PROSPER in 2020 confirmed an OS benefit.

In the setting of M1 HS disease, enzalutamide is also FDA approved based on ARCHES and ENZAMET, as noted earlier. Enzalutamide has now been used for over a decade and is widely used in multiple advanced prostate cancer disease states.

Apalutamide

As previously noted, apalutamide, with a mechanism of action similar to enzalutamide, was the first drug for M0 CRPC approved by the FDA, which occurred in February 2018. The data from the SPARTAN trial showed that apalutamide delayed MFS by about 2 years. Overall the drug was very well tolerated. Unique side effects included maculopapular rash in 24% of patients, but only 5%-6% were grade 3-4. The rash usually resolved with topical lotions, drug holiday, and temporary dose reduction. Approximately 4% of patients required systemic corticosteroids. In addition, 8% of patients had decreases in thyroid hormone (considered chemical hypothyroidism), and there were no grade 3-4 adverse events. The FDA did not mandate thyroid testing in the approval label. Seizure was reported in 2 patients (0.2%).

Apalutamide, as noted earlier, was also proven to extend survival in newly diagnosed HS M1 prostate cancer, and final analysis of the TITAN trial showed a robust 35% improvement in OS compared to ADT alone. The TITAN trial is credited with finally proving the OS benefit of CAB, ending a 30+ year quest to prove this concept.

Another topic of interest related to use of abiraterone and enzalutamide/apalutamide is molecular profiling. The discovery of the AR-V7 splice variant of the androgen receptor offers an intriguing glimpse of the future of personalized medicine. Specifically, the response to abiraterone or enzalutamide was less robust in men who harbored this variant in circulating tumor cells. In February 2018 Genomic Health, Inc received FDA approval for the Oncotype DX AR-V7 Nucleus Detect test, a commercially available assay for AR-V7.

Radium-223

Radium-223 is a parenteral radiopharmaceutical that can be ordered by urologists. It is usually given in a nuclear medicine or radiation oncology department setting, but many large group practices have incorporated it into their centers. It is an α-emitting liquid radiopharmaceutical product that received FDA approval in May 2013 based on results from the ALSYMPCA trial. Radium-223 is indicated for the treatment of patients with symptomatic M1 CRPC with bone metastases and no known visceral metastatic disease. The dose regimen is 50 kBq (1.35 μCi) per kilogram body weight, given at 4-week intervals in 6 injections.

Urologists may be familiar with earlier generation β radiopharmaceuticals such as samarium and strontium. However, radium-223 is different. It is a large molecule α particle and does not penetrate the bone marrow to the degree of older agents. In other words, radium-223 is much less likely to cause serious bone marrow toxicity. In addition, the use of radium-223 was associated with an OS benefit whereas the older β-emitting radiopharmaceuticals were never proven to extend survival. For radium-223 to be associated with improved survival, at least 4 monthly cycles must be administered.

Radium-223 should not be used in patients currently being treated with AAP. The phase 3 ERA223 trial compared AAP plus radium-223 vs AAP plus placebo in patients with asymptomatic or mildly symptomatic chemotherapy-naïve mCRPC. The study was unblinded in late 2017. Bayer, the manufacturer of radium-223, reported that the unblinding followed the recommendation of an independent data-monitoring committee that observed an imbalance with more fractures and deaths in patients receiving radium-223 and AAP vs abiraterone alone. Radium-223 had a resurgence in use in 2022-2023 due to drug shortage of the new agent, Pluvicto (lutetium-177).

Darolutamide

In mid-2019, darolutamide was FDA approved for M0 CRPC based on the
ARAMIS trial, making this the third agent approved (apalutamide, enzalutamide, and darolutamide) in this disease state. This third-generation non-steroidal oral antiandrogen prolonged MFS also by approximately 2 years compared to placebo in M0 CRPC and more recently showed an OS advantage compared to placebo in M0 CRPC.

The hot topic in 2023 is whether PARP inhibition is beneficial in men who do not have the above-mentioned detectable mutations.

**Lutetium-177**

Sartor et al conducted an international, open-label, phase 3 trial evaluating 177Lu-PSMA-617 in patients who had mCRPC previously treated with at least 1 androgen receptor pathway inhibitor and 1 or 2 taxane regimens, and who had PSMA-positive gallium-68 (68Ga)–labeled PSMA-11 positron emission tomographic-CT scans. From June 2018 to mid-October 2019, a total of 831 patients underwent randomization. The baseline characteristics of the patients were balanced between the groups and the median follow-up was 20.9 months. 177Lu-PSMA-617 plus standard care significantly prolonged, as compared with standard care, both imaging-based progression-free survival (median, 8.7 vs 3.4 months; hazard ratio for progression or death, 0.40; 99.2% CI, 0.29 to 0.57; P < .001) and OS (median, 15.3 vs 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; P < .001). All the key secondary end points significantly favored 177Lu-PSMA-617. The incidence of adverse events of grade 3 or above was higher with 177Lu-PSMA-617 than without (52.7% vs 38.0%), but quality of life was not adversely affected. This agent is administered in nuclear medicine or radiation oncology, depending on local customs.

**Summary**

The management of advanced prostate cancer continues to evolve in exciting and sometimes unexpected ways, and 2023 has brought further options to our patients, including abiraterone, enzalutamide, and apalutamide in newly diagnosed, HS M1 prostate cancer as well as apalutamide, enzalutamide, and darolutamide for M0 CRPC. The personalized medicine era is upon us also with approval of 3 agents for patients with actionable germline or somatic mutations. Interested readers should review the latest AUA Guidelines on this topic. 

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Genetic Testing in Prostate Cancer: Understanding Clinical Implications for Early Detection and Management of Localized and Advanced Disease

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Learning Objective

At the conclusion of this activity, participants will be able to counsel men with BRCA1/2 mutations, Lynch syndrome, and other key inherited syndromes regarding their prostate cancer risk and appropriate strategies for cancer screening, and utilize the results of genetic testing to improve outcomes among patients with metastatic prostate cancer, including recommendations regarding PARP-inhibition, chemotherapy, and immunotherapy.

Introduction

Our understanding of germline mutations as an important cause of aggressive prostate cancer has dramatically increased in recent years. Urologists treating men with prostate cancer need to incorporate germline genetics into routine prostate cancer care, from early detection to management of men with localized or metastatic prostate cancer. Multiple organizations now provide guidance to aid in the appropriate use of genetic testing, but significant work is still needed to bring appropriate genetic testing into clinical practice.

Hereditary and Familial Prostate Cancer

Family history is a critical consideration for prostate cancer risk. Men with a family history of prostate cancer have a higher incidence of prostate cancer and higher prostate cancer–specific mortality compared to men without a family history of prostate cancer. In addition, men with a family history of breast, ovarian, or pancreatic cancer have a significantly higher risk of developing prostate cancer than men without a family history of these cancers. Interestingly, family history is an independent risk factor for developing prostate cancer, even when accounting for known genetic changes. This is in part related to social and environmental factors, but also likely related to currently unknown genetic factors. Thus, familial prostate cancer is a broad term that encompasses 13%-20% of cases and can include those...
Germline Alterations

A number of rare pathogenic mutations have been implicated in heritable prostate cancer, most of which have important roles in the DNA damage repair machinery. These include \textit{BRCA1}, \textit{BRCA2}, \textit{CHEK2}, \textit{ATM}, and \textit{PALB2}, along with mismatch repair (MMR) mutations responsible for Lynch syndrome (\textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2}). \textit{BRCA1} and \textit{BRCA2} are critical proteins in the process of homologous recombination repair, and pathogenic mutations in these genes have long been known to increase the risk of breast and ovarian cancers in women. Germline \textit{BRCA1} and \textit{BRCA2} mutations in men are associated with a significant increase in the risk of prostate cancer, and men with pathogenic \textit{BRCA2} mutations are typically diagnosed at a younger age, have higher Gleason Grade Group tumors, and have a shorter median survival time than men with sporadic prostate cancers. \(^3\)

Several options for germline genetic testing are now available for those men with prostate cancer who meet clinical guidelines (eg, National Comprehensive Cancer Network) for germline testing. While single-gene testing, such as for \textit{BRCA1} or \textit{BRCA2}, can be performed, multigene panel testing is now standard in the absence of a known familial mutation. These tests include a panel of genes associated with the disease of interest. For prostate cancer, these panels typically include \textit{BRCA1}, \textit{BRCA2}, \textit{ATM}, \textit{CHEK2}, \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}, \textit{EPCAM}, and \textit{TP53} among others specific to the individual platform. Importantly, while many of the genes included in these panels have a clear association with prostate cancer risk, others carry a still unknown clinical significance with poorly defined cancer risk. Particular caution should be taken before performing a test that includes >20-30 genes, as these often include genes without confirmed relevance to prostate cancer risk.

Before performing testing, patients should understand the possible testing results and the potential impact on themselves and family members. For example, many variants identified on multigene panel testing may not be clinically relevant. Some are known to be nonpathogenic, while others are indeterminate and classified as variants of uncertain significance. This occurs when a genetic change is present that differs from a normal control but there is insufficient information to classify it as deleterious or benign with respect to cancer risk. The possibility of a variant of uncertain significance, or “gray area,” result should be discussed up front before any testing is performed. Thus germline testing is different from many routine laboratory tests ordered by urologists, as it is critical to perform pre-test counseling and obtain verbal or written consent outlining the benefits and risks of testing prior to ordering the test. Patients may also view high-quality educational videos or meet with a genetic counselor prior to testing.

Guideline Statements on Testing and Early Detection

In recognizing the importance of germline mutations, National Comprehensive Cancer Network guidelines distinguish indications according to tumor characteristics vs family/ancestry indications. Tumor-specific indications include metastatic prostate cancer or high-/very-high-risk prostate cancer. Family history characteristics include 1 or more close blood relatives with breast cancer diagnosed at ≤50 years of age; ovarian cancer; pancreatic cancer; or metastatic, intraductal/crribriform, or high-/very-high-risk prostate cancer. Additional indications include 2 or more relatives with breast or prostate cancer (any grade), or individuals with Ashkenazi Jewish ancestry.

In terms of early detection for men without a diagnosis of prostate cancer, current guidelines suggest that men with germline mutations that increase the risk of prostate cancer undergo prostate cancer screening starting at age 40 after a risk and benefit discussion. These guidelines recommend biopsy for PSA >3 ng/mL or for suspicious exam in these high-risk men. Furthermore, the guidelines suggest follow-up based upon initial PSA level for those whose initial screening does not trigger a biopsy. However, there is a need to better define the early detection approach for these high-risk men.

The role for dedicated and early screening in men with known or potential germline mutations predisposing to prostate cancer is being evaluated in a number of settings, including the IMPACT and PROFILE trials in the UK. \(^4,5\) At the University of Michigan Prostate Cancer Risk Clinic, men who are known carriers of germline pathogenic mutations related to prostate cancer (eg, \textit{BRCA1/2}) are offered PSA screening and digital rectal exam starting at age 35, with a low PSA threshold for biopsy. PSA thresholds are set at 2 ng/mL for men under 50 years old and 2.5 ng/mL for men 50 years and over. \(^6\) This is combined with additional urine biomarker testing (SelectMDx) with the objective of better defining the role for intensified risk-based prostate cancer screening in the United States. Another open study out of the National Cancer Institute (NCT03805919) utilizes a similar algorithm but also adds multiparametric MRI.

Treatment Implications

Men with \textit{BRCA2} mutations are clearly at risk for more aggressive prostate cancer, with decreased survival rates compared to patients with sporadic prostate cancer. Key questions regarding eligibility of active surveillance in low-risk disease or treatment intensification in men with high-risk localized
disease remain to be answered. In the metastatic setting, there is strong evidence of the efficacy of poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors and platinum-based chemotherapy in patients with germline and/or somatic biallelic defects in BRCA1 or BRCA2. In the TOPARP-A trial, which led to Food and Drug Administration (FDA) breakthrough designation for olaparib in metastatic castration-resistant prostate cancer (mCRPC), having a DNA damage repair alteration appeared to predict response to olaparib. This is particularly relevant in the context of the work by Pritchard and colleagues, finding germline DNA damage repair mutations in 11.8% of men with metastatic prostate cancer. Further evidence for the phase 3 PROFOUND trial demonstrated the efficacy of olaparib in mCRPC patients with a mutation in BRCA1 or BRCA2, or ATM, leading to FDA approval in this setting. Additionally, in the single-arm TRITON2 trial, the large proportion of men with germline or somatic alterations in BRCA1 or BRCA2 who responded to rucaparib led to its approval in BRCA1- and BRCA2-mutated mCRPC as well. More recently, the PROPEL trial resulted in approval of olaparib plus abiraterone for BRCA-mutated mCRPC, and TALAPRO-2 led to approval of talazoparib plus enzalutamide in homologous recombination repair–mutated mCRPC.

There is also evidence of increased sensitivity to platinum-based chemotherapy in metastatic prostate cancer patients with germline DNA repair mutations, likely related to the mechanism of action through DNA damage. Due to the treatment implications and potential relevance for family members along with inconsistent insurance coverage and access to services, studies are ongoing to explore novel methods of delivering cancer genetic testing and counseling to men with metastatic prostate cancer. One of these is the University of Washington/Fred Hutch Cancer Center web-based GENTleMEN study (www.clinicaltrials.gov, NCT03503097). There are also a number of ongoing therapeutic trials in this space (see Table).

Finally, there is also evidence across multiple different cancers that patients with increased tumor mutational burden, such as those with DNA MMR-deficient tumors, are particularly sensitive to immune checkpoint inhibition. This is most commonly seen in colorectal cancer, which is the most common malignancy associated with Lynch syndrome. However, as mentioned above, mutations in MMR genes are also associated with prostate cancer and are likely present in approximately 5% of advanced prostate cancers. The emerging data regarding MMR deficiency and checkpoint inhibition sensitivity have led to an FDA approval for pembrolizumab, a PD-1 inhibitor, in solid tumors with MMR deficiency such as in Lynch syndrome. While there are still only limited data surrounding PD-1 sensitivity in MMR-deficient prostate cancer, there are reports of extreme responses to pembrolizumab in this setting.

**Conclusion**

Germline mutations predisposing to prostate cancer have an increasing impact on the clinical management of prostate cancer—from pre-diagnosis genetic counseling, to screening and early detection, to newly diagnosed localized prostate cancer, and to metastatic disease. Utilizing platinum-based therapies, immunotherapy, or PARP inhibitors in men with metastatic prostate cancer who have known germline mutations may lead to improved long-term outcomes, though additional research in these areas is needed. Given emerging evidence and guidelines, clinical pathways are now needed to facilitate germline testing in appropriately selected patients in order to inform treatment plans. Further work to improve access to genetic counseling, cancer screening, and treatment options for men with relevant germline mutations is likely to yield significant long-term benefits for these patients.

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**Table. Select Ongoing Trials With Relevance to DNA Damage Repair Deficiency**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Agent</th>
<th>Short name</th>
<th>Clinicaltrials.gov</th>
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<tbody>
<tr>
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<td>Rucaparib (mCRPC)</td>
<td>TRITON3</td>
<td>NCT02975934</td>
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<tr>
<td>III</td>
<td>Niraparib+Abi+Pred vs Abi+Pred (mCSPC)</td>
<td>AMPLITUDE</td>
<td>NCT04497844</td>
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<tr>
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<td>PLATIPARP</td>
<td>NCT03442556</td>
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<td>II</td>
<td>Neoadjuvant niraparib</td>
<td>NCT04030559</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Talazoparib+Enza or talazoparib+placebo (mCSPC)</td>
<td>TALAPRO-3</td>
<td>NCT04821622</td>
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<tr>
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<tr>
<td>II</td>
<td>Olaparib (BCR)</td>
<td>BRCAway</td>
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</tr>
</tbody>
</table>

**Abbreviations:** Abi, abiraterone; BCR, biochemical recurrence; Enza, enzalutamide; MCRPC, metastatic castration-resistant prostate cancer; MCSPC, metastatic castration-sensitive prostate cancer; Pred, prednisone.

AUA2023 ANNUAL MEETING HIGHLIGHTS IN PROSTATE CANCER

AUA2023 COURSE

AUA Guidelines on Advanced Prostate Cancer

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Learning Objective

At the conclusion of this activity, participants will be able to describe the various disease states comprising advanced prostate cancer and advancements in management.

Advanced prostate cancer (APC) is a term attributed to a diverse disease state encompassing biochemical recurrence, metastatic hormone-sensitive (mHSPC), nonmetastatic castration-resistant, and metastatic castration-resistant prostate cancer (mCRPC). Over the past several decades many advances have yielded improvements in patient quality of life and survival, but prostate cancer still accounts for 29% of new cancer cases and 11% of cancer-related deaths in men in the United States.1 Perhaps most concerning is the fact that since 2014, the rate of newly detected disease has increased by 3% per year overall and by about 5% per year for advanced-stage diagnoses. Despite improvements in cancer detection, APC is increasing, and urologists will need to continue to remain up to date in the management of these men. This AUA2023 course highlighted the current and rapidly evolving diagnostic and treatment landscape for men with APC.

With respect to imaging, the updated Guidelines state clinicians should utilize prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging preferentially, where available, in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging due to its greater sensitivity or in the setting of negative conventional imaging. It is well established that prostate cancer is an androgen-driven disease, and in patients with APC, androgen deprivation therapy (ADT) remains the mainstay of treatment. However, the course reviewed updated 2023 Guidelines which note that men with biochemical recurrence alone should not routinely initiate ADT. When considering factors such as total PSA, PSA doubling time, and patient comfort, ADT may be initiated in select, truly high-risk patients. In the absence of metastatic disease, intermittent ADT may be considered, given noninferior overall survival (OS) and improved patient quality of life, and in fact, this is the one place the Guidelines consider intermittent ADT.2

The course reviewed exciting and rapidly advancing management options for patients with mHSPC. Discussion centered on important treatment-related considerations like baseline presentation (de novo vs progression) and volume of disease. In accordance with the Guidelines, clinicians should discuss treatment options with these patients based on life expectancy, comorbidities, preferences, and tumor characteristics. Patient care should incorporate a multidisciplinary approach when available. Regarding disease extent, the CHAARTED definitions of high-volume (visceral metastasis and/or 4+ bone metastases with at least 1 beyond the pelvis and vertebral column) and low-volume disease were reviewed, noting the impact of disease burden on response to therapy.3 Additionally, for mHSPC and throughout the continuum of APC, the course discussed the recommendation for germline testing and genetic counseling. This is particularly important given that newly diagnosed metastatic patients have~12% chance of harboring an inherited DNA repair gene mutation—a scenario where genetic counseling may be beneficial not only for the patient, but also where the implications of cascade testing are reviewed.4

The course stressed that, while androgen deprivation with medical or surgical castration is essential, no longer is ADT alone the standard of care (SOC) in men with mHSPC. The course reviewed robust, high-level evidence demonstrating that either docetaxel chemotheraphy or an androgen pathway-directed

Continued on page 13
therapy with either abiraterone, apalutamide, or enzalutamide in combination with ADT improves survival. CHAARTED stratified men according to several factors including extent of metastatic disease and performance status prior to randomization. Results indicated improved OS with the addition of docetaxel and a more robust advantage in high-volume patients. Similarly, in STAMPEDE, patients who received docetaxel with ADT experienced a highly significant OS benefit although there was no survival difference by volume status, likely reflecting differences in the study populations. Abiraterone, a potent androgen synthesis inhibitor, is also approved for treatment of mHSPC based on LATITUDE, which demonstrated OS and progression-free survival (PFS) benefits, and STAMPEDE, with an OS benefit favoring combination therapy over ADT alone. The course also reviewed that mode of therapy in this setting remains investigational. The course also reviewed that androgen receptor–targeted treatments have established superiority over ADT alone with apalutamide in the TITAN trial and enzalutamide in ARCHES and ENZAMET. We discussed the role for local radiation treatment to the primary tumor in select patients with low-volume mHSPC based upon STAMPEDE, but additional data are needed prior to offering surgery to men with metastatic disease, and at present that mode of therapy in this setting remains investigational.

The course highlights included the updated Guidelines regarding early treatment intensification with triple therapy in men with mHSPC based on the results of 2 recent studies. The PEACE-1 trial, a multicentered phase 3 trial, demonstrated benefit of adding abiraterone to ADT and docetaxel, with or without radiation. Results were highly significant with improvements in radiographic PFS and OS. Subgroup analysis showed a benefit in both high- and low-volume patients, although intensification yielded more adverse events including hypertension and liver toxicity. The second recent study, ARASENS, also demonstrated significant improvement in mHSPC with the addition of darolutamide to ADT and docetaxel. This international, randomized, double-blind, placebo-controlled trial demonstrated a highly significant survival benefit without any increase in adverse events. The benefit of treatment intensification for mHSPC is intriguing, but there remain unanswered questions regarding the potential for overtreatment and increased side effects. Currently, the Guidelines recommend in selected patients with de novo mHSPC, clinicians should offer ADT in combination with docetaxel and either abiraterone acetate plus prednisone or darolutamide. This is based on the fact that the majority of patients treated in both PEACE-1 and ARASENS had de novo metastatic disease. Ultimately, an adaptive treatment approach may be required with consideration of fitness for chemotherapy, symptom burden, cost, patient preference, disease volume, and histological or molecular features.

We then reviewed management of patients with nonmetastatic castration-resistant prostate cancer, focusing on 3 trials evaluating androgen-targeted therapies in men with a rapid PSA doubling time (≤10 months) at high risk for metastasis. In SPARTAN, apalutamide was compared to placebo, and initial publication demonstrated a significant delay in metastasis-free survival (MFS) while mature data indicated a survival benefit. With a similar trial design and outcome, PROSPER results showed improved MFS with enzalutamide and ultimately a risk of death 27% lower than placebo. Darolutamide with ADT was compared to placebo for M0 castration-resistant prostate patients in ARAMIS, again yielding impressive MFS and OS benefits.

Over the past several years, numerous therapies have emerged offering a survival benefit for men with mCRPC, a disease generally associated with poor outcomes. Many of these agents were first approved in this advanced state and have since been successfully trialed earlier in the disease continuum as discussed above, including docetaxel, abiraterone, and enzalutamide. We reviewed the mechanism of action and data in support of the novel immunotherapeutic sipuleucel-T and the radiopharmaceutical radium-223, both which have demonstrated an OS advantage for specific mCRPC patient subsets.

One of the most exciting recent advances in mCRPC highlighted at this year’s course was the approval of poly (ADP-ribose) polymerase inhibitors. These novel drugs target defects in DNA repair genes in mCRPC patients resulting in antitumor activity and more favorable outcomes. In the phase 3 PROfound trial, patients with prespecified gene alterations experienced improved clinical outcomes (radiographic PFS, OS) with olaparib following progression through at least 1 novel androgen-directed therapy. The TRITON2 study, rucaparib benefited patients with germline or somatic BRCA1/2 alterations who had progressed through both a second-generation antiandrogen and taxane-based chemotherapy. Here again, we reviewed the importance of somatic and genetic testing in conjunction with genetic counseling, and in this setting there was an emphasis on precision-based medicine.

Throughout the course, faculty discussed the indications and appropriate use of PSMA PET imaging in APC based on the updated Guidelines. Specifically, PSMA PET was noted to be the preferred imaging over conventional imaging when available. In December 2020, the FDA (Food and Drug Administration) approved the first PSMA-targeted PET imaging drug (Ga68 PSMA-11) for men with prostate cancer and a rising PSA after failed local therapy. This approval was based on data indicating that PSMA PET offers a high positive predictive value and provides important information that impacts therapeutic approach, even at very low PSA values. In May 2021, the FDA approved a second PSMA-targeted PET imaging for men with prostate cancer (piflufolastat F18) based on 2 studies.
In the CONDOR study, men with a rising PSA after failed local therapy underwent 18F-DCFPyL-PET which resulted in a change in management. In OSPREY, 2 populations were examined—those with high-risk prostate cancer undergoing prostatectomy with lymphadenectomy and those with rising PSA after prior local therapy. Again, results indicated with PSMA PET indicated a high positive predictive value for the discovery of metastatic deposits. As mentioned earlier, PSMA PET imaging is the preferred imaging for men with PSA recurrence after failed local therapy, but also to assess patients at high risk for metastatic disease, and among men with mCRPC with disease progression having previously received docetaxel and androgen pathway inhibitors, who are considering 177Lu-PSMA-617. The phase 3 VISION study enrolled 831 men with mCRPC previously treated with at least 1 anrogen pathway inhibitor and 1 or 2 prior taxane regimens who had PSMA-positive 68Ga-PSMA-11 PET/CTs. Patients were randomized 2:1 to receive either 177Lu-PSMA-617 every 6 weeks for 4-6 cycles plus protocol-permitted SOC vs SOC alone. At a median follow-up of approximately 21 months, 177Lu-PSMA-617 plus SOC improved both PFS and OS compared to SOC alone. The incidence of grade 3 or higher adverse events was 52.7% vs 38% for 177Lu-PSMA-617 vs SOC; however, quality of life was no different between the treatment arms. The landscape for men with APC continues to evolve. Key themes that will be further explored as we go forward include moving effective agents up earlier in the disease state, treatment intensification, combinations that have different mechanisms of action, and a greater role for precision medicine. We are also beginning to get a much clearer picture on treatment sequencing. We look forward to continuing to present these updates and new trial information as it becomes available, so stay tuned.

Prostate Cancer Diagnostics: Biomarkers, Biopsy Techniques, and MRI

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Faculty

Sigrid Carlsson, MD, PhD
Faculty

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Author, Faculty

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Learning Objective
At the conclusion of this activity, participants will be able to apply evidence-based prostate cancer screening practices that maximize detection of high-grade disease while minimizing risks of overdetection and overtreatment, and discuss available biomarkers, describe how and when to use MRI for prostate cancer detection, and use best prostate biopsy practices while minimizing risks, including infections.

Prostate cancer (PCa) detection is a rapidly evolving and controversial field. This course presents the topic in context of the 2023 AUA/Society of Urologic Oncology (SUO) Guidelines for early PCa detection.

I. Screening Recommendations

Dr Eggener presented data on PCa screening and its optimization to minimize mortality and avoid overdetection of indolent PCa:

• Stop screening old or sick men: Avoid screening men with a life expectancy <10 years because they have higher risk of competing mortality.

• Be fair when explaining the risks/benefits of screening: Shared decision-making is the cornerstone for PCa screening. Recent data demonstrated that the numbers needed to invite and diagnose for PSA testing to save a life are 221 and 9, respectively.1

• Always repeat a newly elevated PSA: PSA levels tend to vary, where 40%-55% of men with abnormal PSA findings will have a normal finding on follow-up.2

• Don’t give empiric antibiotics for elevated PSA: Randomized data show no benefit of antibiotics for asymptomatic men with an elevated PSA.3

• Don’t biopsy based on PSA velocity alone: PSA velocity does not add value to other important clinical variables, including PSA and rectal exam, and therefore is not an indication for biopsy in men who otherwise do not meet criteria for biopsy.4,5

• % Free PSA: % Free PSA is valuable in predicting clinically significant cancer (≥ grade group [GG] 2) when PSA is 2.5-10 ng/mL.6,7

• PSA density: PSA density is independently associated with clinically significant PCa. In one study, PSA density cutoffs of 0.10 ng/mL2 and 0.15 ng/mL2 resulted in the detection of 77% and 49% tumors ≥GG2, respectively.8

• Know when to stop screening: Consider stopping/relaxing screening when life expectancy is <10-15 years or PSA <1 ng/mL at age ≥60.

II. Use of PSA, PSA Isoforms, and Risk Calculators

Dr Carlson discussed the use of risk calculators and MRI in PCa screening. She emphasized the importance of selecting a risk calculator calibrated to the target population. Furthermore, she highlighted the trial by Hugosson et al, which invited men between 50-60 years to regular PSA screening followed by an MRI if PSA ≥3 ng/mL.9 The authors found that omitting systematic biopsy and only utilizing target biopsies (lesions PI-RADS [Prostate Imaging Reporting & Data System] ≥3) halved the rate of detecting GG1 cancer while maintaining a similar GG ≥2 detection rate.
Dr Carlsson elaborated on ongoing screening trials that integrate MRI and biomarkers into the diagnostic pathway, aimed at maintaining the benefits of screening while minimizing harms of overdetection and overtreatment. While not yet part of the AUA/SUO Guidelines, these strategies have the potential to improve the risk/benefit ratio of PCA detection substantially.

III. Molecular Testing for PCA Diagnosis

Dr Salami discussed blood-, urine-, and tissue-based biomarkers designed to improve the specificity of PCA detection by avoiding unnecessary biopsies in men at low risk for high-grade disease. Each provides an estimated likelihood of identifying PCa and/or clinically significant PCa, which can be used to decide whether to biopsy. The AUA/SUO Guideline recommends that such biomarkers be used only if further risk stratification will alter management. Reflex testing is not recommended.

The Prostate Health Index is an FDA (Food and Drug Administration)-approved blood test for PCA diagnosis in men with PSA levels 4-10 ng/mL. The Prostate Health Index combines total PSA, % free PSA, and [2]proPSA.² The 4Kscore, which is also FDA approved, includes total PSA, % free PSA, intact PSA, and human kallikrein 2. A large prospective multi-institutional trial found that 43% of biopsies could be avoided at the expense of only missing 2.4% of high-grade cancers at a 4Kscore cutoff ≥9.³⁹

Next, he discussed urine biomarkers, including PCA3, which is FDA approved for use after a prior negative biopsy, where the negative predictive value (NPV) is 88% for PCA3 score <20.³⁰ MyProstateScore combines urinary PCA3 and T2:ERG with serum PSA to predict the risk of clinically significant PCa, with a very high NPV.³¹ ExoDx detects SPDEF, ERG, and PCA3 RNA in urine exosomes (small fragments of cells), and unlike the previous 2 tests, ExoDx does not require a digital rectal exam. One study found that using ExoDx avoids 20% of negative biopsies and only misses 2% of GG2 tumors and no GG3 cancers.²¹ Select-

MDx detects DLX1 and HOXC6, providing a binary result that, combined with clinical risk factors, improves the detection of clinically significant PCAs.²²

The only tissue-based biomarker is ConfirmMDx, used on prior negative biopsies to assess the epigenetic field effect. The NPV is 90%, decreasing the repeat biopsy rate by 64%.²³

Dr Salami also discussed indications for germline testing in men with localized PCa, where up to 17% may have a germline variant,²⁴ including DNA damage response genes (eg BRCA2), which are associated with more aggressive PCa. Dr Salami highlighted the importance of developing a streamlined approach to germline testing, including obtaining detailed family history beyond PCa, using effective communication strategies to counsel patients, and understanding insurance coverage vs fixed out-of-pocket costs.²⁵

IV. MRI for PCA Diagnosis

Dr Barocas discussed the role of MRI in several aspects of PCa diagnosis. First, in the initial biopsy setting, where obtaining an MRI is optional, if a lesion is detected (PI-RADS ≥3), clinicians should perform a targeted biopsy because evidence from randomized trials suggests that a targeted biopsy will increase the detection of GG ≥2 PCAs.²⁶ He also explained that clinicians may add a systematic template biopsy in the presence of MRI targets because approximately 10%-15% of GG ≥2 PCas in combined biopsies are found on the systematic cores. Moreover, in the initial biopsy setting, systematic biopsy should be performed when the MRI is negative because the NPV of MRI is only 91%.

In men with suspicion of PCa after an initial negative biopsy, MRI should be performed if it was not done previously. MRI will show a suspicious target in 36%-90% in this setting. Unlike the initial biopsy setting, if the MRI is negative, a systematic biopsy is optional, but one must keep in mind that an MRI can miss 10%-15% of GG2 ≥2 PCa, and clinicians should base whether to biopsy on other factors (eg, PSA density >0.15 ng/mL). Lastly, explained that clinicians may use either cognitive fusion or computer fusion, if available, because they have similar detection rates.²⁷

V. Prostate Biopsy Techniques

Dr Wei emphasized the importance of counseling patients prebiopsy on the possibility of diagnosing low-risk disease that can be safely monitored with active surveillance. He also mentioned that clinicians should inform patients of the risk of complications, including hematuria (days), rectal bleeding [days], hematospermia [months], infections, and lower urinary tract symptoms.

He then provided tips on how to minimize infections when performing transrectal biopsies, such as using local antibiotic resistance data, use of an augmented approach by adding parenteral gentamicin, performing a prebiopsy rectal swab to look for quinolone resistance, formalin dipping after each biopsy core, or using a transperineal approach instead.

He then discussed some differences between transrectal and transperineal biopsies, such as the limited sampling ability of the anterior and apical prostate in the former. The transperineal approach is associated with more discomfort but fewer sepsis episodes, whereas transrectal biopsy is associated with more rectal bleeding and fever. However, both approaches have equivalent cancer detection rates.²⁸ Furthermore, he discussed the role of local anesthesia in limiting patient pain and discomfort in both approaches allowing for adequate sampling.

Lastly, Dr Wei highlighted some pathology findings, such as high-grade prostatic intraepithelial neoplasia. Focal high-grade prostatic intraepithelial neoplasia should not trigger additional evaluation beyond regular screening, whereas multifocal (≥2 sites) is associated with an 8% GG ≥2 PCa risk, and clinicians may perform further testing. Additionally, atypical small acinar proliferation and atypia are associated with a 10% risk of GG ≥2 PCa, and further evaluation with repeat biopsy and/or biomarkers is warranted.

In summary, this course summarized the current approach for PCA detection in the context of the 2023 AUA/SUO Guidelines and provided an overview
of ongoing studies and possible future paradigms.


screened starting at age 40 and annually thereafter.

If any patient has an elevated PSA, biomarkers tests are available to individualize risk assessment for prostate cancer. These biomarkers by and large perform similarly with the goal of avoiding 20%-40% of benign biopsies at a cost of missing a small proportion (usually less than 5%) of clinically significant cancers. The urine tests are PCA3, ExoDx, and SelectMDx. Each requires collection of first-catch urine. In all cases, an elevated value is associated with increased risk. The utility of the test is primarily to avoid biopsy in men with a low value since they are less likely to have significant disease. Similarly, serum-based tests such as Prostate Health Index and 4KScore may be used to guide biopsy. Their utility is particularly useful in conjunction with multiparametric (mp) MRI.

Comparison among the available biomarkers is difficult as head-to-head studies are not presently available. For now, practitioners should individually evaluate the properties of the available reflex biomarkers and choose the one that works best in their practice.

Image-guided biopsy using MRI is preferred by many organizational guidelines. Compared to systematic biopsy, mpMRI-targeted biopsy identifies more clinically significant cancer and fewer insignificant cancers. However, combined targeted and systematic cores are recommended, since mpMRI may miss up to 20% of significant cancers. A randomized trial compared systematic 12-core transrectal ultrasound (TRUS) needle-guided biopsy of the prostate to detect prostate cancer to biopsies directed at the mpMRI defined lesion(s) or both. The radical prostatectomy (RP) specimen was used as the gold standard for the final Gleason score. The authors found that higher-grade cancer was missed in 30.2% of men based on the 12-core systematic biopsy, compared to only 6.7% for those who had both systematic TRUS- and targeted mpMRI-guided biopsies. Performing only mpMRI-guided biopsies missed higher-grade disease in 18.3% of patients.

There is increasing recognition that conventional TRUS-guided transrectal biopsy may cause infections, which has spurred development of novel biopsy approaches. Transperineal biopsy is resurgent and can be performed under local anesthesia, while “saturation” grid-guided biopsies usually require sedation. Transperineal biopsy eliminates infectious complications, has a high detection rate as it assesses all parts of the prostate, and, in comparison to conventional biopsy, has a higher detection of significant cancer on initial and follow-up biopsy (if on active surveillance).

Image-guided biopsy may also be performed using micro ultrasound, a 29-megahertz probe with resolution of 70 microns. It enables real-time targeting of suspicious regions of the prostate without the costs of mpMRI and image fusion. Micro ultrasound images of the prostate are categorized using the PRI-MUS (Prostate Risk Identification using Micro-ultrasound) System, which is analogous to the PI-RADS (Prostate Imaging Reporting & Data System) mpMRI classification. The learning curve for micro ultrasound ranges between 15 and 40 cases. Micro ultrasound biopsies may be performed transrectally or transperineally and can also include targeted mpMRI-fusion biopsies if desired. Micro ultrasound yields similar sensitivity and negative predictive value to mpMRI in several single-institution and 1 multi-institutional study. A randomized trial comparing micro ultrasound and mpMRI is underway.

Contemporary data on the management of localized prostate cancer are available. The 15-year results of the PROTECT (Prostate Testing for Cancer Treatment) trial were recently published. Patients were randomly assigned to active monitoring with serum PSA, open RP, or 3D conformal external beam radiation (RT) and short-course testosterone-lowering therapy or hormonal therapy. Prostate cancer-specific mortality was the primary end point, and metastasis a secondary end point. Prostate cancer-specific mortality was numerically higher in the active monitoring arm (3.1%) as compared with the RP (2.2%) and RT/hormonal therapy (2.9%) arms but not significantly different; however, given the event rate the study was underpowered to assess this end point at this time. The metastasis rate in the active monitoring was significantly higher compared to the radical treatment arms (9.4% vs 4.7% to 5.0%). MRI is being explored to assess risk of recurrence following treatment. PI-RADS recurrence reporting (PI-RR) uses a 5-point scale to classify risk of recurrence after RT or RP. PI-RR relies heavily on diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging. Here the highest score on DWI or DCE determines overall score, except when a PI-RR 4 is scored on both DCE and DWI and they match locations; then the lesion is upgraded to PI-RR 5. The reproducibility and performance PI-RR has been good. A study by Pecoraro et al showed a positive predictive value of a PI-RR score of 3 or greater showed 77%-88% accuracy for RT and 75%-85% accuracy for RP; this study was performed with experienced mpMRI readers.

Management of biochemical recurrence following surgery is also evolving. In RADICALS RT patients were randomized to adjuvant RT or early salvage RT at a PSA of 0.1 ng/mL and could not establish superiority for the use of adjuvant RT as compared to early salvage RT. However, there are some caveats. There were very few patients with 2 high-risk factors (prostatectomy Gleason score 8, 9, or 10 and prostatectomy T3 or T4). There are other data that suggest in men with 2 high-risk factors, adjuvant RT should be delivered prior to the PSA reaching 0.10 ng/mL to avoid an increased all-cause mortality risk.

In the setting of oligometastatic disease (defined as no more than 3 sites of metastatic bone and/or lymph node disease found on conventional imaging and no visceral metastasis), radiation therapy to the primary tumor has been shown to delay time to progression and possibly prolong overall survival. How this number translates in the era of prostate-specific membrane antigen (PSMA) PET imaging remains to be determined.

PSMA is a type 2 transmembrane glycoprotein used in PET imaging and is especially valuable for small-volume lymph node and bone metastatic disease. There are many PSMA ligands. F-18 DCFPyl (Plarify) has less renal excretion limits radiotracer accumulation in the bladder, which may obscure

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A particularly exciting area in the management of advanced prostate cancer disease has been the utilization of molecularly targeted radiation such as lutetium-177 PSMA-617. A recent FDA approval has been granted for patients with metastatic castrate-resistant prostate cancer previously treated with novel hormones and a taxane and lutetium-177 PSMA-617 has now been shown to prolong survival in that difficult-to-treat setting.22

One novel area getting additional investigation is the area of artificial intelligence. By combining traditional prognostic factors such as age, PSA, and Gleason score and then utilizing machine learning to examine digitized pathological specimens, algorithms have been created to separate those men who benefit from androgen deprivation therapy and those men who do not.23 Clearly there is much more to explore as we go forward in the broad realm of artificial intelligence.

In conclusion, management of prostate cancer is undergoing rapid evolution. Updates on diagnosis, imaging, and therapies allow state-of-the-art management of our prostate cancer patients.3

Managing Toxicities of Checkpoint Inhibitors: A Urologist’s Guide

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Learning Objective

At the conclusion of this activity, participants will be able to identify organizational and clinical factors to safely manage toxicities from checkpoint inhibitors.

The impact of checkpoint inhibitors (CPIs) in oncology over the past decade cannot be overstated. In 2011, ipilimumab, the first antibody blocking an immune checkpoint, was approved. This was subsequently followed by the development of monoclonal antibodies targeting programmed death-1 receptor (pembrolizumab and nivolumab) and its ligand (atezolizumab and durvalumab). Since that time, there has been a surge of CPI approvals in virtually every type of advanced solid organ malignancy. These treatments have demonstrated dramatic benefits on cancer recurrence, progression, and survival even in patients with heavily pretreated and late-stage disease. Equally importantly, these therapies are demonstrating excellent tolerability and preserving quality of life in many patients in whom competing treatments may cause severe morbidity.

Urologic oncology has been especially fortunate in this era, with several recent Food and Drug Administration approvals along with an explosion of clinical trial activity that has greatly expanded the options for patients with cancers of the urinary tract. The last 3 years have seen the emergence of “urological” indications for nonmetastatic disease with CPIs now moving earlier in urologic disease states. There is quite a bit of interest within the urological community in becoming more active participants in urological cancer care. Recent survey data from independent group urology meetings have suggested 20% of large community-based urology groups are currently administering CPI therapies in their practice today and up to 50% are interested in doing this in the near future.

The most common barrier to starting a program is concern about CPI immune-related adverse event (irAE) management. Studies of CPI use in nonmetastatic urological cancer patients demonstrate up to 30% of patients will have high-grade toxicity and 11%-18% of patients will discontinue treatment due to side effects. In the authors’ experience the evaluation and management of these irAEs can be protocolled and centralized to promote safety and success. The AUA2023 Course “Managing Toxicities of Checkpoint Inhibitors: A Urologist’s Guide” aimed to provide urologists and urological cancer providers a practical approach at understanding and managing adverse events from these therapies.

The course was case based and divided into 3 main sections: pathophysiology of irAEs, strategies for treatment, and strategies for prevention. Dr Brian Rini covered pathophysiology and identification of irAEs. This portion provided a broad overview of the incidence and nature of irAEs. Several points were notable, including: (1) irAEs (all grades) are very common after administration of checkpoint inhibitors. (2) The common theme of these toxicities is inflammation, with any organ system in the body potentially being affected. (3) There are common irAEs (endocrine, pulmonary, gastrointestinal, dermatological) as well as relatively uncommon irAEs (ocular, neurological, cardiac) that have different time courses, presentations, and natural histories. irAEs and antitumor activity are thought to be the result of the same common mechanism—stimulation of the host immune system which leads to an enhanced antibody and cytokine response. Dr Rini continued his section by emphasizing that timing and severity of toxicities can be variable; however, certain trends have been noted. While adverse events can occur at any time, the majority occur within the first 3 months of therapy initiation. Fatal toxicity is extremely rare, carrying an incidence of less than 1%. Furthermore, certain toxicities such as myocarditis and myositis are more frequently associated with death. The majority of irAEs the urologists will encounter will be low grade in nature, and conservative measures and/or a corticosteroid taper will be indicated.

The second portion of the course dealt with strategies for treatment for irAEs. Dr Gautam Jayram highlighted the importance of understanding the

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3 major categories of toxicity: mild, moderate, and severe. Almost all patients on CPI therapy will experience mild toxicity, and these usually can be managed conservatively with symptomatic supportive treatments or drug holds. Moderate side effects are those that usually affect patient quality of life or activities of daily living, and are managed most often by corticosteroid taper. More severe side effects are rare, but typically are managed with high-dose steroids and consideration of in-patient treatment depending on patient morbidity. A central point during the course was that of close monitoring, especially after an irAE has been diagnosed. The clinical team prescribing steroids needs to keep in close touch with patients in an ambulatory setting as 10%-20% of irAEs are refractory to this approach and may progress. In this situation multidisciplinary and/or medical oncology assistance is required as more complex immunosuppressive agents (infliximab, mycophenolate mofetil, etc) may be required. The cases presented broadly covered common and uncommon irAEs—colitis, rash, nephritis, and neuropathy were all discussed, with common management strategies to all. A special note was made for immune-mediated endocrinopathy as this is the only class of irAEs where treatment is solely in the form of hormonal replacement therapy; CPIs rarely need to be stopped and steroids usually are not necessary. The concept of rechallenge was also examined during this section. When symptoms and/or laboratory values revert to baseline, rechallenging with CPI may be offered; however, in certain patients (early onset, frail, recurrent high grade or debilitating toxicity), permanent discontinuation is warranted, except for endocrinopathies that have been controlled by hormone replacement.

The final portion of the course took a deep dive into adverse event prevention, which focused on the infrastructure and process required to manage a CPI program safely and efficiently. Dr Michael Johnson asserted the most important factor was the assembly and development of a multidisciplinary care team featuring, but not limited to, a champion physician, infusion nurse, and oncology-focused advanced practice provider (APP). Training must be provided to triage staff in order to adequately approach patient concerns and symptoms while on immunotherapy. The course reviewed existing available resources (National Comprehensive Cancer Network Guidelines, American Society of Clinical Oncology Clinical Practice Guidelines, etc) which can be utilized by practices to assist in this training.8-10 The authors have found that APP support in the form of nurse practitioners and physician assistants is instrumental in providing timely and quality care. While a busy urologist often is in operating rooms or procedures, an APP can quickly evaluate an infusion patient in clinic who may be developing an emerging immunotoxicity and provide prompt treatment.

“While a busy urologist often is in operating rooms or procedures, an APP can quickly evaluate an infusion patient in clinic who may be developing an emerging immunotoxicity and provide prompt treatment.”

Conclusions

In summary, CPIs have emerged as exciting and transformative therapeutic options in multiple urological cancers. Adverse event management of these therapies is a new concept for many urological cancer providers but proving to be critical as these treatments become more mainstream. An understanding of the mechanism of action, treatment options, and development of a centralized, team-based approach is the key to safely monitor and manage irAEs.

References

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