AUA2018 ANNUAL MEETING HIGHLIGHTS

Advanced and Castration-Resistant Prostate Cancer

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2018 AUA Annual Meeting Highlights: Advanced and Castration-Resistant Prostate Cancer

Method of Participation
To claim CME credit/hours of participation, the learner must read the overview of courses 005IC, 043IC, 058IC, 063IC, 074IC, 078IC, and Urologic Care for the Advanced Practice Provider: 2018 Prostate Cancer Update: Clinical Guidelines & Management, passing with 80% accuracy, and submit the evaluation and credit request form by visiting AUAU.AUAnet.org/18HLPC. Estimated time to complete this activity: 1.25 hours
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Statement of Need
There is a growing need for urologists to be able to effectively manage castration resistant prostate cancer (CRPC). CRPC is defined clinically as a failure of castration or androgen ablation therapy to prevent a worsening of a patient’s prostate cancer and is associated with advanced disease. Approximately 28% of patients with prostate cancer will advance to CRPC. The median age at diagnosis of CRPC is 77 years and, as might be expected, these patients often have comorbidities, the most common of which are hypertension, dyspnea and anemia. More than 84% of patients diagnosed with CRPC have metastatic disease. Of those patients without metastases, 33% can expect to develop them within 2 years. The median survival of patients with CRPC is 9 to 30 months (median 14 months).

Target Audience
Urologists, urologists in training and non-physician providers involved in urology.

Learning Objectives
At the conclusion of this CME activity, participants should be able to:
• Describe the standard of care chemotherapy regimens for genitourinary malignancies
• Recognize newer immunotherapy options in the treatment of genitourinary malignancies
• Identify and manage the toxicities with relation to these agents
• Identify the survivorship issues surrounding patients on systemic treatments for genitourinary malignancies

Learning Objectives
At the conclusion of this CME activity, participants should be able to:
• Diagnose CRPC and have a working knowledge of treatments and the proper order for administration
• Manage CRPC with systemic agents by learning the proper candidates for treatment and be able to counsel patients on the pros and cons of therapy
• Analyze the mechanism of action and risks/benefits of using systemic agents in the treatment of CRPC
• Describe the bone-targeted radiopharmaceutical agent radium-223 and its sequencing
• Review the new generation antian- drogen agent enzalutamide and its sequencing

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Costs
Course 005IC: Chemotherapy and Immunotherapy Options for Genitourinary Malignancies: A Primer for the Advanced Practice Provider

Costs
Course 043IC: Novel Agents and Concepts in the Management of Hormone Naïve and Castration-Resistant Prostate Cancer

Costs
CME Information
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Course 058IC: Management of Common Dilemmas in Prostate Cancer Diagnosis, Staging and Treatment

Learning Objectives
At the conclusion of this CME activity, participants should be able to:
- Use shared decision making to test men with prostate specific antigen (PSA), to decide whom to biopsy and how to biopsy
- Understand the pros and cons of different types of biopsy and how to select men for surveillance, surgery or external beam radiation therapy
- Determine the new therapies for advanced and metastatic cancer with androgen deprivation therapy, chemotherapy and immunotherapies
- Identify the roles of new staging positron emission tomography scans

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AUA NEWS

CME Information

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Course 063IC: Prostate Cancer Update

Learning Objectives

At the conclusion of this CME activity, participants should 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

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Course 074IC: AUA Castration-Resistant Prostate Cancer (CRPC) Guidelines

Learning Objectives

At the conclusion of this CME activity, participants should be able to:
• Identify the active agents and their mechanism of action in the management of metastatic castration resistant prostate cancer (mCRPC)
• Analyze the evidence and outcomes on the treatment of CRPC as outlined in the AUA guidelines and subsequent amendments
• Improve diagnostic and therapeutic decision making processes by illustrating the application of these guidelines in urological practice
• Understand the sequencing and indications for active treatment with approved agents in the management of mCRPC

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Course 078IC: Management of Prostate Cancer: A Case Based Approach with Emphasis on Integrating New Molecular Diagnostics into Clinical Practice

Learning Objectives

At the conclusion of this CME activity, participants should be able to:
• Design appropriate screening strategies based on individual demographics, risk factors and PSA history, and incorporate new biomarkers into routine clinical practice
• Distinguish and understand the use of new molecular and genomic based tests for decisions on initial and re-biopsy, and choosing and following men on surveillance
• Appraise the role of surveillance, focal therapy, surgery, and vari-
ous forms of radiation therapy in patients with low and intermediate risk disease, including adjuvant and salvage radiation

• Review the role of surgery in the multimodality treatment of men presenting with oligometastatic disease
• Describe new therapeutic agents for the management of castrate resistant disease and outline a coherent strategy for their use

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Urologic Care for the Advanced Practice Provider: 2018 Prostate Cancer Update: Clinical Guidelines & Management

Learning Objectives

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

• Review the latest guidelines from the AUA (ASTRO/SUO) for localized prostate cancer
• Identify when to use biomarkers and magnetic resonance imaging
• Describe high intensity focused ultrasound as a primary form of treatment
• Discuss the latest update on clinical trials

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- Limit equipment representatives to providing logistics and operation support only in procedural demonstrations
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Chemotherapy and Immunotherapy Options for Genitoourinary Malignancies: A Primer for the Advanced Practice Provider

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

The paradigm for the treatment of advanced and castration resistant prostate cancer (CRPC) has shifted dramatically in the last 15 years. Historically the urologist had a very small role in treating these patients beyond first line androgen deprivation therapy (ADT), either surgical or medical. Occasionally there could be a brief period of antiandrogen administration and then withdrawal.

However, these manipulations often did nothing but delay an inevitable referral to a medical oncologist for consideration of cytotoxic chemotherapy. In actuality some urologists would stop treating these patients after failure of primary ADT. This scenario left urologists/urologic oncologists feeling helpless, not only because there was nothing more they could offer these patients, but also because they were being forced to abandon a patient whom they had potentially treated through diagnosis, failure of primary therapy(ies) and failure of first line ADT, a relationship that could have spanned many years.

More recently, several agents have become available for advanced and castration resistant disease that not only demonstrate efficacy but can also be safely administered in an office setting, qualities that have attracted urologists to manage prostate cancer beyond primary ADT. In addition, because several of these medications are indicated for patients in whom docetaxel has failed, movement of these patients between the offices of the medical oncologist and the urologic oncologist has become a 2-way street, and the identity of the lead physician, the one who will take charge of these patients, has become less clear.

However, instead of creating controversy this situation underscores the importance of multidisciplinary care of genitourinary malignancies and open communication among all clinicians. A team approach allows for the development of an initial patient specific treatment strategy and an understanding of which specialist would be most appropriate to provide a given treatment within that strategy. The team approach would also further allow for revisiting the strategy at appropriate intervals, at which point a decision would be made about the need to continue or revise the strategy. Accordingly, as the patient disease state evolves, so might the clinician who dictates care.

Treatment of patients with advanced prostate cancer has provided a unique opportunity for the advanced practice provider (APP), who often interacts with these patients and serves as the first line clinician for discussions on survivorship related issues. This role requires an intimate knowledge of these newer agents, including their relative efficacies and unique side effect profiles. In fact, at a well organized institution with APPs (nurse practitioner or physician assistant) who have focused training in urologic oncology, significant input regarding patient care would fall on that clinician, who would be serving as an extender for a urologic oncologist. Accordingly, our course at AUA2018 focused on advanced prostate cancer and CRPC and the knowledge that we considered important for the APP.

Some of the newer agents currently available for the treatment of advanced CRPC include sipuleucel-T, abiraterone, enzalutamide, apalutamide, cabazitaxel and radium-223. Certainly the androgen receptor (AR) targeted therapies are popular among practicing urologists, in part because abiraterone and enzalutamide are regularly prescribed by urologists. Since we last wrote this review 1 year ago apalutamide, a new kid on the block, has arrived with potential in an earlier space of CRPC, and it may also readily be prescribed by urologic oncologists. For urologists to prescribe these medications for advanced prostate cancer, basic knowledge of their mechanisms, indications and potential side effects is paramount. Additionally, because many of these patients are on a continuous and repeating cycle of 3 to 6-month office visits for prostate specific antigen (PSA) and wellness checks, this responsibility often falls on the APP.

Abiraterone acetate is an inhibitor of CYP17A1 and targets 17-hydroxylase and 17-20-lyase activities, thereby inhibiting residual androgen biosynthesis. Concurrent administration of low dose prednisone (5 mg twice daily) is required to prevent hypokalemia, hypertension and fluid retention due to adrenocorticotropic generated mineralocorticoid excess.

Abiraterone was first approved for progressive CRPC in patients with prior docetaxel therapy in a phase III placebo controlled trial after an interim analysis demonstrated better than expected results, and this was later expanded into the chemotherapy naïve setting. However, it is the results of the LATITUDE and STAMPEDE trials that have thrust this medication further into the realm of urologists.

Both trials demonstrated increased overall survival in men with locally advanced or hormone sensitive metastatic prostate cancer when adding abiraterone to standard of care ADT. Abiraterone can have multiple drug interactions and requires dose reduction or possible discontinuation in patients with liver dysfunction. As a result, in addition to PSA checks these patients...
require monthly physical examinations focusing on fluid retention, as well as electrolyte monitoring and liver function tests. Although intensive, this routine can easily be performed by the APP.

Enzalutamide is a second-generation, nonsteroidal AR inhibitor that affects the AR pathway in multiple, synergistic pathways. It is also approved for the post-chemotherapy CRPC space and shows activity in the pre-chemotherapy space. Enzalutamide can have significant drug-drug interactions, and is contraindicated in patients with severe hepatic dysfunction and/or seizure disorder, a history of closed head injury or stroke. Like other antiandrogens it is orally administered on a daily basis. Because urologists have significant experience prescribing the older generation antiandrogens, they (and their physician extenders) are likely to prescribe enzalutamide.

Apalutamide binds the AR with five-fold greater affinity than bicalutamide. It has a lower central nervous system penetration with reduced effect on \( \gamma \)-aminobutyric acid inhibition, the mechanism believed to increase the risk of seizure during enzalutamide therapy. The positive results of the SPARTAN trial in patients with nonmetastatic CRPC were released in April 2018, demonstrating a significant difference in metastasis-free survival when apalutamide was added to ADT in this disease setting. Additionally, apalutamide is well tolerated and, thus, can be easily administered in a urology office. The only idiosyncratic side effect is hypothyroidism, for which regular thyroid stimulating hormone monitoring is recommended, with variations managed with increases in or initiation of thyroid replacement therapy. These responsibilities will likely fall on an APP well trained in urologic oncology.

Along with understanding the hormone dependency of prostate cancer, a clinician who treats advanced prostate cancer must grasp the clinical implications of a prolonged state of castration. Beyond this, interventions that mitigate these potentially severe side effects from years of androgen deprivation should consistently be explained to the patients. Again, because many of these patients are on a repeating 3-month cycle of PSA checks and injection of a gonadotropin-releasing hormone agonist, these appointments are often quickly transitioned to the APP. This extender should be prepared to counsel the patient regarding behavioral, dietary and pharmacological interventions to counteract the metabolic, musculoskeletal, cardiovascular, cognitive and psychosocial side effects of these therapies. Additionally, when appropriate, the APP in urologic oncology should know when to order and how to interpret a dual-energy x-ray absorptiometry scan to screen for osteoporotic changes with ADT. Resultant administration of antiresorptive agents such as denosumab and zoledronic acid should also be among their responsibilities.

Finally, interpreting PSA and testosterone level for a patient receiving ADT, calculating a PSA doubling time and its application to a clinical situation, and determining when to order imaging are important skills for these clinicians. They are often the first of the oncology team to detect failure of a therapy and, thus, know when it should be switched for an alternative. Also, as a front line clinician the extender can be a lookout for patients who qualify for enrollment onto a clinical trial.

In conclusion, the migration of the treatment of advanced and metastatic prostate cancer into a multidisciplinary domain, the availability of newer agents that are more user-friendly with regard to administration and followup, and the universal practice pattern for surveillance of these patients carve out a clear role for the APP trained in urologic oncology.

Novel Agents and Concepts in the Management of Hormone Naïve and Castration-Resistant Prostate Cancer

Judd W. Moul, MD, FACS, Course Director; Lawrence I. Karsh, MD, FACS and Christopher Sweeney, MBBS, Faculty

The management of advanced prostate cancer continues to evolve and the AUA2018 version of our course showcased important new work from the last year. Using a case based format and relying on the audience response system to poll our attendees, we had an intense 2-hour session. Probably the biggest news covered was the FDA (Food and Drug Administration) approval of apalutamide on Valentine’s Day 2018, making it the first therapeutic agent approved for nonmetastatic castration resistant prostate cancer (M0 CRPC). Furthermore, this agent was also the first to receive FDA approval on the end point of metastasis-free survival (MFS). Also, updated data from the CHAARTED trial confirmed the benefit of up-front docetaxel for high volume, newly diagnosed M1 prostate cancer but did not confirm this benefit for low volume M1 disease.

Newly Diagnosed Hormone Sensitive M1 Prostate Cancer

Several years ago hormone naïve/hormone sensitive newly diagnosed metastatic (M1) 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 for new M1 disease. 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 the last few years CHAARTED and STAMPEDE taught us that adding 6 cycles of docetaxel within 4 months of starting hormone therapy/ADT resulted in a major 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 Kyriakopoulou et al reported longer term followup from CHAARTED confirming the benefit of docetaxel for high volume disease but not supporting up-front chemotherapy for low volume disease.

In 2017 the LATITUDE trial showed that abiraterone added to ADT for men with new M1 disease resulted in a similar survival benefit as docetaxel. We have now had a year to absorb and ponder these data, yet we do not have any level I head-to-head comparison between docetaxel and abiraterone or data to suggest that patients receive both agents. However, with less support for the use of docetaxel for low volume M1 disease, will urologists treating men with low volume M1 disease now forgo referral to medical oncology in favor of giving abiraterone? Will urologists lobby to have their new patients with high volume M1 disease receive docetaxel and abiraterone even though this combo is yet to be supported by phase III data? Are 6 cycles of docetaxel easier on patients than longer term use of oral abiraterone or vice versa? In any case, we debated the pros and cons of both drugs in the setting of new M1 prostate cancer and presented case scenarios for both.

Hormone Sensitive Biochemically Recurrent M0 Prostate Cancer

In the area of hormone naïve advanced prostate cancer, we also briefly covered the use of ADT for biochemically recurrent/prostate specific antigen (PSA) recurrent prostate cancer. While the timing (early vs later), method (intermittent vs continuous) and agent (luteinizing hormone-releasing hormone [LHRH] agonist, antagonist etc) remain debated, we also addressed a number of interesting ongoing clinical trials that may shed some light. In particular, the EMBARK trial is now closed to enrollment for patients with high risk PSA recurrent disease. These men were randomized to LHRH alone, enzalutamide alone or LHRH plus enzalutamide. We anticipate that the eventual results will help put to rest some of the controversies. In particular, is there a role for enzalutamide alone in earlier advanced prostate cancer and is this “modern era combined androgen blockade” (ie enzalutamide or apalutamide plus LHRH) more effective than monotherapy?

Oligometastatic Prostate Cancer

An emerging concept in advanced prostate cancer is the idea of offering definitive local therapy, such as radical prostatectomy, to men who have limited metastatic disease. While this would almost seem heretical to classically trained urological oncologists, this idea of taking an aggressive treatment stance for men who have oligometastatic disease is developing, particularly in the era of presumed better imaging for early

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metastases. We discussed a number of ongoing clinical trials addressing local therapy in the setting of oligometastatic disease (see Appendix).

The HORRAD trial, one of the key trials, was also presented at AUA2018 (PD10 Prostate Cancer: Advanced Podium, Friday, May 18, 2018). It was a multicenter, randomized controlled trial of men with bone metastatic M1 prostate cancer comparing ADT alone (in 226) to ADT + radiation therapy (RT) (70 Gy) (in 216). Men with a PSA less than 20 ng/ml or men more than 80 years old were excluded from study. The primary end point was overall survival. At a median follow-up of 47 months there was no significant difference (45 months for ADT + external beam RT and 43 months for ADT alone). However, this study was not mainly in patients with oligometastatic disease and, in fact, the concept of oligometastatic disease was not even on the radar when the trial started in 2004. In an exploratory nonplanned subgroup analysis of 74 men with fewer than 5 osseous metastases, there was a survival benefit of local radiotherapy to the prostate in the face of bony M1 disease.

Castration Resistant Prostate Cancer

Since 2010, 6 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. Some of the new concepts related to the agents that urologists may use for CRPC are discussed.

Denosumab

Denosumab is prescribed at a dose of 120 mg (trade name XGEVA) subcutaneously monthly to prevent skeletal related events in men with M1 CRPC with bone metastases. The FDA also approved a 60 mg dose (trade name Prolia) subcutaneously twice a year to prevent bone loss (osteopenia and osteoporosis) in men without bone metastases who are on gonadotropin-releasing hormone (GnRH) analogue therapy for prostate cancer. We reminded 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 overall survival 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. Sartor et al presented intriguing data at AUA2017 to suggest that this agent may be more effective in African American men. At the course in 2018 we reminded attendees that this agent should be used early in the course of M1 CRPC.

Abiraterone

Abiraterone is a 17-lyase and 17-hydroxylase 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 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 (Cougars 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 FDA approved for use in men with newly diagnosed hormone sensitive M1 prostate cancer on February 7, 2018. Approval was based on LATITUDE (NCT01715285), a placebo controlled international clinical trial that randomized 1,199 patients with metastatic high risk 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 overall survival. Median OS was not estimable and 34.7 months in the abiraterone acetate and placebo arms, respectively (HR 0.621; 95% CI 0.509, 0.756; p <0.0001). Median duration of abiraterone use was 24 months.

Enzalutamide

Enzalutamide, a next 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 unlike abiraterone, it does not require prednisone. However, enzalutamide does have an approximate 1% risk of seizures associated with its use and crosses the blood-brain barrier, implicating it with some risk of falls and fatigue.

Presented at ASCO GU on February
that apalutamide and enzalutamide are FDA approved for M0 CRPC, how will urologists decide between them? Finally, while delaying metastases and the transition from M0 to M1 CRPC for an average of 2 years with apalutamide or enzalutamide is important for patients, is the use before documented metastases truly helping our patients to live longer and better? Both PROSPER (enzalutamide) and SPARTAN (apalutamide) showed trends toward an overall survival benefit when used for M0 CRPC. However, the OS data are not yet mature or proven for either drug. Some clinicians may still choose to hold novel therapy until M1 disease develops or use abiraterone (as it is or soon will be generic and possibly less expensive), despite the fact that it is not FDA approved for M0 CRPC.

Another topic of interest related to the 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. On February 26, 2018 Genomic Health, Inc. (Redwood City, California) received FDA approval for Oncotype DX® AR-V7 Nucleus Detect™ test, a commercially available assay for AR-V7. It carries a relatively high price tag and is not yet covered by most payers.

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 alpha-emitting liquid radiation 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 microcurie) per kg body weight, given at 4-week intervals in 6 injections.

Urologists may be familiar with earlier generation beta radiopharmaceuticals such as samarium and strontium. However, radium-223 is different. It is a large molecule alpha 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 overall survival benefit whereas the older beta-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.

The big news in 2018 and discussed at the course was that radium-223 should not be used in patients currently being treated with abiraterone/prednisone. The phase III ERA223 trial compared abiraterone/prednisone plus radium-223 vs abiraterone/prednisone plus placebo in patients with asymptomatic or mildly symptomatic chemotherapy naïve metastatic castration resistant prostate cancer. 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 abiraterone/prednisone vs abiraterone alone. The big question is what about prior treatment with abiraterone and subsequent use of radium-223? Opinions vary among experts in the field and this was a hot topic of conversation at this year’s course.

Summary

The management of advanced prostate cancer continues to evolve in exciting and sometimes unexpected ways, and 2018 has brought further options to our patients, including abiraterone in newly diagnosed, hormone sensitive M1 prostate cancer, and apalutamide and enzalutamide for M0 CRPC. Furthermore, the AR-V7 molecular assay
Management of Common Dilemmas in Prostate Cancer Diagnosis, Staging and Treatment

Gerald L. Andriole, Jr., MD, Course Director; Anthony D’Amico, MD, PhD, Adam Kibel, MD and Oliver Sartor, MD, Faculty; Eric H. Kim, MD, Highlight Coauthor

During the last decade the management of advanced and metastatic prostate cancer (PCa) has dramatically evolved due to advances in imaging, the development of new therapeutics and the publication of a number of landmark trials demonstrating survival benefit with new treatment paradigms. We will focus on imaging and the newest evidence in the treatment of advanced and castration resistant prostate cancer (CRPC) with an emphasis on clinical management. The evidence supporting local therapy (eg surgery or radiation) for metastatic PCa also continues to develop, particularly oligometastatic PCa, but is beyond the scope of this summary.

Imaging

Recent technological improvements in multiparametric magnetic resonance imaging (mpMRI) and positron emission tomography/computed tomography (PET/CT) have led to drastic increases in their use in patients with PCa. Undoubtedly, mpMRI has changed the diagnostic model for PCa while PET/CT imaging appears to be gaining an ever expanding role in the evaluation of high risk patients at presentation or with biochemical recurrence (BCR) after local therapy. Although the value of mpMRI is not debatable in the initial diagnosis of PCa, pre-biopsy risk discrimination as well as biopsy targeting, the value of mpMRI in advanced PCa is limited. The pretreatment identification of enlarged pelvic lymph nodes or extra-prostatic extension on mpMRI may be beneficial for patient counseling. However, these findings on mpMRI alone are unlikely to change clinical decision making before local therapy.1 Similarly, mpMRI findings in the setting of BCR must be confirmed with histopathology.

and coupled with imaging of distant sites before consideration of salvage local treatment.

Bone imaging is indicated in the initial staging of unfavorable intermediate, high and very high risk PCa. The National Comprehensive Cancer Network guideline recommends initial conventional 99mtechnetium MDP bone scan, with 18F-sodium fluoride (NaF) PET/CT imaging used for further evaluation of equivocal findings. Although more expensive, the improved test performance of NaF PET/CT over conventional bone scan for the evaluation of PCa bone metastases is unquestionable, with sensitivity and specificity of 100% and 100% with NaF PET/CT vs 92% and 82% for conventional bone scan, respectively.

11C-choline and 18F-fluciclovine (FACBC) PET/CT have been approved by the FDA (Food and Drug Administration) for localization of disease recurrence or metastases in the evaluation of BCR. For both modalities the test performance depends heavily on pretest probability, which is based on conventional clinical parameters such as prostate specific antigen (PSA), PSA velocity and Gleason score. For instance, in the case of 11C-choline, the detection rate increases from 19% to 46% to 82% for PSA thresholds of 0.2 to 1 ng/ml, 1 to 3 ng/ml and greater than 3 ng/ml. For this reason 11C-choline is not recommended if PSA is less than 2 ng/ml. In the case of FACBC, the detection rate increases from 59% to 75% to 85% for PSA thresholds of 0.8 to 2 ng/ml, 2 to 6 ng/ml and greater than 6 ng/ml. Although positive predictive values for local, lymph node and bone recurrence are high for both modalities, FACBC seems to be outperforming 11C-choline with 100%, 91%, 100% vs 91%, 82%, 83%, respectively. Importantly, pathological confirmation of disease recurrence should be performed if feasible, given the not insignificant rate of false-positive results.

Prostate specific membrane antigen (PSMA) targeted agents, including 18F-DCFPyL and 68Ga-PSMA, seem to further improve detection rates over FACBC PET/CT. However, definitive comparative studies are not available. These small molecule ligands target the extracellular domain of PSMA, which is highly expressed in PCa cells, particularly when tumors become castration resistant. As a result, early studies demonstrate higher sensitivity with PSMA targeted agents, even at PSA values as low as 0.2 ng/ml. Based on this early evidence PSMA will likely become the preferred imaging modality for BCR and may prove to be clinically useful for initial staging of newly diagnosed PCa.

Castration Resistant Prostate Cancer

The efficacy of next generation androgen deprivation therapy (ADT), abiraterone and enzalutamide, and the subsequent FDA approval of their use in the post-chemotherapy and pre-chemotherapy settings, have drastically changed the management of metastatic CRPC. To date no study has prospectively compared the sequencing of abiraterone and enzalutamide, but retrospective studies suggest that even though cross-resistance between agents is high, outcomes favor abiraterone followed by enzalutamide.

Technological advances in molecular diagnostics have allowed for the identification of gene variants in the DNA from circulating tumor cells. One potentially impactful variant in the case of metastatic CRPC is the androgen receptor splice variant AR-V7, which has been shown to predict resistance to abiraterone and enzalutamide as well as improve survival with up-front chemotherapy. However, at this time some patients harboring the AR-V7 mutation have still demonstrated responses to next generation ADT and, so, treatment decisions cannot be based solely on the presence of this variant.

Finally, the role of therapy in the nonmetastatic CRPC setting is also continuing to change, as apalutamide has demonstrated improved metastasis-free survival compared to placebo, and enzalutamide has demonstrated improved progression-free survival compared to bicalutamide. Importantly, future studies are needed to inform clinicians if initiation of these therapies for nonmetastatic CRPC improves overall survival in addition to prolonging the time to metastases.

Hormone Naive Metastatic Prostate Cancer

The combination of up-front docetaxel and conventional ADT for hormone naïve metastatic PCa has demonstrated a significant survival benefit over conventional ADT alone in 2 landmark trials. In both studies the median overall survival improved from approximately 45 months in the control arm to 60 months in the study arm. Subsequent analysis of the CHARTED trial found that the survival benefit in the study appears to be confined to those patients with high volume disease, defined as visceral metastases or 4+ bone metastases with at least 1 outside of the axial skeleton. More recently, 2 studies have demonstrated a significant survival benefit with the addition of abiraterone to conventional ADT in patients with newly diagnosed hormone naïve metastatic PCa. The improvements are substantial with the median overall survival not reached by the abiraterone arm in either study. The design of the STAMPEDE trial allows for direct comparison of the abiraterone + ADT and the docetaxel + ADT arms, which showed no difference in survival. The results from the final arm of the STAMPEDE trial, which includes treatment with abiraterone + enzalutamide + conventional ADT, will provide further clarity in our approach to hormone naïve metastatic PCa.

As our diagnostic technologies improve, new therapeutics become approved for use and the evidence of ongoing trials becomes available, our management of advanced and CRPC will continue to evolve. There are sev-
AUA NEWS

COURSE #058IC

Prostate Cancer Update

William J. Catalona, MD, Course Director; Douglas M. Dahl, MD, FACS, Stanley L. Liauw, MD, Stacy Loeb, MD, MSc, Robert B. Nadler, MD and Russell Szumulewitz, MD, Faculty

This course highlights the important findings on prostate cancer (PCa) published during the last year.

Statistics and Epidemiology

During the prostate specific antigen (PSA) screening era there has been an 80% decrease in the proportion of patients with PCa with metastases at diagnosis and a greater than 53% decrease in PCa specific mortality. Five-year survival is approximately 99% for patients presenting with local or regional disease and 29% for those with distant metastases.1,2

The incidence of PCa plummeted after the USPSTF (U.S. Preventive Services Task Force) issued a grade D recommendation against screening in 2012, and the rate of positive nodes and PCa mortality began to rise.3 In 2018 the USPSTF upgraded their recommendation to grade C for shared decision making for men 55 to 69 years old, but not in men older than 70 or for other high risk men4 for whom stronger recommendations should be considered.5

Modeling reanalysis of the PLCO (Prostate, Lung, Colorectal, and Ovarian) cancer screening trial revealed a PCa mortality reduction comparable to that of the ERSPC trial.6 The Göteborg trial reported a 35% decrease in PCa mortality, and men age 55 to 59 had a 53% decrease in mortality.7 The CAPS trial, testing 1-time PSA screening, reported

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no mortality reduction but has substantial methodological limitations.8

Genetic testing for DNA repair gene mutations (BRCA1/2, ATM, Lynch syndrome) and for HOXB13 is encouraged for patients with a positive family history and for those with metastases.9

Epidemiological studies suggest that vasectomy is associated with a small risk of low grade PCa that should not change practice.10 Statin11 and aspirin12 use are associated with reduced PCa mortality but have not been tested in randomized trials.

Biopsy

Magnetic resonance imaging (MRI) targeted biopsies diagnose more high grade tumors and transrectal ultrasound guided biopsies diagnose more low grade tumors. Significant cancer is missed with MRI targeted biopsy alone and, thus, routine 12-core biopsy is also warranted.13

MRI should be considered for patients with a prior negative biopsy.14 MRI has a low sensitivity in patients on active surveillance (AS).15 A 1.5 T MRI machine is safe for patients with implanted devices containing metal.16 PSA based tests such as PSA density and the Prostate Health Index improve the negative predictive value of MRI.17

Recent antibiotic treatment, foreign travel and being a health care worker are risk factors for post-biopsy infections. Targeted prophylaxis based on rectal swab cultures, the local antibiotic or use of transperineal biopsy are options to reduce post-biopsy infections.18 Disinfecting biopsy needles with formalin or alcohol slightly decreases the risk of infection.19

The extent of biopsy core involvement is not highly predictive of prostatectomy pathology.20 The cribriform pattern of Gleason 4 cancer is less frequently detected on MRI.21

Predictive Markers, Staging and Imaging

The PCa intermediate risk group is heterogeneous, with cribriform and intraductal being the most aggressive patterns. Genetic tests may help in distinguishing aggressiveness.22 The new American Joint Committee on Cancer clinical staging system now incorporates Gleason and PSA.23 New imaging tracers for staging include Na18F positron emission tomography (PET)/computed tomography, fluciclovine 18F/PET, PSMA 68Ga/PET and 18F-PSMA/PET.24,25

Active Surveillance

AS is gaining increasing acceptance, especially in the Veterans Affairs (VA) system.26 Compliance with AS biopsies is low and biennial biopsies may be sufficient.27 Any Gleason pattern 4 on biopsy is associated with more adverse pathology and biochemical failure.28,29

Focal Therapy

Focal therapy has a high failure rate and should be considered investigational.30 Most positive posttreatment biopsies occur in treated regions and MRI detects only a minority of these persistent cancers. Complications of partial gland ablation include incontinence and erectile dysfunction, and are more frequent in radiation failures, especially fistulas.31,32 Electroporation has a high positive repeat biopsy rate, especially with higher grade tumors.33 Photodynamic therapy decreases PSA but posttreatment positive biopsies are not uncommon.34

Prostatectomy

Retrospective studies report a higher risk of death with radiotherapy than with radical prostatectomy but are confounded by biases.35 The PIVOT compared surgery with observation in a largely VA population and concluded that the results were equivalent between surgery and observation.36 However, all outcomes favored surgery and intermediate risk patients had a significant benefit from surgery. There is no difference in recurrence-free survival with standard vs extended node dissection, as metastases may occur in regions where nodes are not dissected and where radiation is not delivered.37 Treatment for oligometastatic disease reduces local recurrences and improves time to androgen deprivation therapy (ADT) but does not increase survival.38 Testosterone (T) replacement is safe except in physiologically hypogonadal men.39 Orgasmic dysfunction is common after radical prostatectomy.40

Radiotherapy

Dose escalated radiotherapy improves PSA control but has not yet been shown to improve survival (followup is short and event rate is low).41 For intermediate risk disease dose escalation reduces PSA recurrence and metastases with minimally increased toxicity.42 In very high risk disease external beam radiotherapy with a brachytherapy boost yielded better local control than conventional radiotherapy.43 External beam radiotherapy with a brachytherapy boost is beneficial mainly to men with multiple risk factors but has more toxicity.44

Hypofractionated radiotherapy (4 to 5 weeks vs 8 to 9-week course) yields equivalent results for disease control or late toxicity with only a slight increase in acute gastrointestinal (GI) toxicity.45 Stereotactic body radiation is extreme hypofractionation (less than 5 days).46

Proton beam radiotherapy theoretically provides better dosimetry with less genitourinary toxicity but more GI toxicity, and a marginal overall benefit at double the cost.47 Toxicity is comparable for stereotactic body radiation but the cost is less. Proton beam or brachytherapy are not preferred for salvage treatment. Hydrogel spacers provide only a small benefit in GI toxicity.47

After prostatectomy, prospective trial results are pending comparing adjuvant radiotherapy vs early salvage therapy.48,49 Hypofractionation is also effective in the postoperative setting.50 ADT improves the results of salvage radiotherapy for patients with a high risk of metastases.51 There are no definitive

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Metastasis-free duration is a strong surrogate for survival in drug studies.58 Testing for the abnormal androgen receptor, AR-V7, is now available to predict response to ADT.59 ADT + abiraterone + prednisone is the standard of care for advanced castrate sensitive PCa.60 Abiraterone costs $10,000 to $12,000 per month but the response is the same with half the dose if taken with a low fat breakfast.61 Abiraterone failures have a brief response to enzalutamide.62 Docetaxel improves survival but ADT/Abi/prednisone may be better (more expensive with high co-pay insurance).63 Apalutamide (an androgen receptor antagonist) was recently FDA approved for nonmetastatic castration resistant prostate cancer with rapid PSA doubling times, and greatly improves metastasis-free survival.64 The 177Lu-PSMA-617 conjugated antibody targets prostate specific membrane antigen on PCa cells (phase 2 study of its efficacy ongoing) and the PSA response rate was 60%.65

Conclusions

Advances have been made in PCa care. Hopefully, new guidelines incorporating shared decision making about PSA screening will enhance benefits and decrease harms going forward. New biomarkers and imaging techniques offer promise for new and better treatment selection.

The complete list of references for this summary can be obtained by contacting wcatalona@nm.org.
Enzalutamide before chemotherapy in men with asymptomatic or mildly symptomatic mCRPC was discussed in the context of the PREVAIL trial, a randomized trial of enzalutamide compared to placebo in men with mCRPC before docetaxel therapy. The study demonstrated significant improvement in the 2 co-primary end points of overall survival (HR 0.706, 95% CI 0.60-0.84, p <0.001) and radiographic progression-free survival (HR 0.186, 95% CI 0.15-0.23) in patients treated with enzalutamide vs placebo. Previously, abiraterone plus prednisone (HR 0.186, 95% CI 0.15-0.23) in patients treated with enzalutamide vs placebo. These 2 studies are considered practice changing in that for the first time we now have 2 agents proven to delay the development of metastases in men with a rapidly rising PSA in the setting of normal conventional imaging (M0 CRPC). It is also the first time that an agent has been approved for men with CRPC based on this new primary end point. What is not known is the impact of these treatments on ultimate survival at this juncture in the disease spectrum, and this issue will require additional long-term followup.

Enzalutamide, prednisone, and prior docetaxel. Clinicians should offer abiraterone + prednisone or enzalutamide + prednisone to select patients with metastases with use of enzalutamide vs placebo. These approvals and others anticipated in the not too distant future highlight the need for continuous periodic updating of the guidelines to inform clinicians regarding the rapidly evolving management of this disease.

The CRPC guidelines were developed using 6 index cases intended to represent the most common scenarios encountered in clinical practice. Accordingly, cases with CRPC were categorized based on the presence or absence of metastases, degree and severity of symptoms, overall performance status and prior treatment with docetaxel chemotherapy. Guideline statements for each of the index cases were rated as a standard, a recommendation, an option or an expert opinion based on the grading of the strength and quality of the evidence, as well as panel assessment of the benefits and harms of treatment. The statements were also formatted into an algorithm. A summary of the revised CRPC guideline statements for each index case along with clinical case scenarios were presented for illustration.

Index patient 1 is asymptomatic with an increasing prostate specific antigen and no radiographic evidence of metastases. Currently abiraterone is FDA approved for patients with M0 CRPC based on data from the SPARTAN trial. However, based on previously presented data from the PROSPER trial it is highly anticipated that enzalutamide will soon be approved for these patients. Accordingly, the panel thought that clinicians should offer abiraterone or enzalutamide with continued ADT to patients with nonmetastatic CRPC at high risk for metastasis.

Clinicians may also recommend observation with continued ADT to patients with nonmetastatic CRPC at high risk for metastasis who do not want or cannot have one of the standard therapies. Clinicians may offer treatment with a second-generation androgen synthesis inhibitor (ie abiraterone + prednisone) to select patients with M0 CRPC at high risk for metastasis who do not want or cannot have one of the standard therapies and are unwilling to accept observation. Currently chemotherapy or immunotherapy should not be offered to patients with nonmetastatic CRPC outside of a clinical trial.

Clinicians should offer abiraterone + prednisone, enzalutamide, docetaxel or sipuleucel-T to index 3 patients. Index patient 3 is symptomatic, has metastases and a poor performance status, and has not previously received docetaxel. Clinicians should offer abiraterone + prednisone, enzalutamide or docetaxel chemotherapy in this setting. Clinicians may offer radium-223. Clinicians should not offer estramustine or sipuleucel-T to index 3 patients.

Index patient 4 is symptomatic with metastases, a poor performance status and no prior docetaxel treatment. Clinicians may offer treatment with abiraterone + prednisone or enzalutamide to these patients and ketoconazole + steroid or radionuclide therapy to those who are unable or unwilling to receive abiraterone + prednisone or enzalutamide. When performance status is directly related to the cancer, clinicians may offer docetaxel or mitoxantrone chemotherapy. Radium-223 may be offered to select patients with symptomatic bone metastases and without known visceral disease, specifically when performance status is directly related to symptoms of bone metastases.

Index patient 5 is symptomatic with metastases, a good performance status and a history of docetaxel use. Clinicians should offer treatment with abiraterone + prednisone, cabazitaxel or abiraterone + prednisone or enzalutamide before docetaxel chemotherapy, he should be offered cabazitaxel. Keto-
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conzalone + steroid may be offered if abiraterone + prednisone, cabazitaxel or enzalutamide is unavailable. Re-treatment with docetaxel may be suggested for patients who were benefitting at the time of docetaxel discontinuation (due to reversible side effects). Patients with symptomatic bone metastases and no visceral metastases should be offered radium-223.

Index patient 6 is symptomatic, with metastases, a poor performance status and prior docetaxel treatment. The goal of palliation is to prevent and relieve suffering, and to support the best possible quality of life for the patient and family. Palliative radiotherapy can be an option to control bone pain in some patients and should be offered. Alternatively, in select cases clinicians may offer treatment with abiraterone + prednisone, enzalutamide, ketoconazole + steroid or radionuclide therapy. Clinicians should not offer systemic chemotherapy or immunotherapy to these patients.

The guidelines also address bone health and indicate that all patients with CRPC should be offered preventative treatment (eg supplemental calcium, vitamin D) to reduce the risk of fractures and skeletal related events. Denosumab or zoledronic acid may be selected as preventive treatment for skeletal related events in patients with mCRPC and bony metastases. The treatment of CRPC is undergoing an evolution with multiple new agents on the horizon, from immune modulators to vaccines to novel antiandrogens. In addition, use of approved agents is being clinically trialed in earlier disease stages of the disease state. The potential benefits beyond delaying the development of metastases in the M0 CRPC disease state, as well as the impact on subsequent therapies and quality of life, are just a few of the anticipated questions to be answered. In addition, the use of genetic testing appears to be gaining attention in men with CRPC, particularly in areas where there is an actionable therapeutic associated with the mutation. It is anticipated that the AUA CRPC guidelines will be modified again in the near future, coinciding with the completion of ongoing trials. The goal remains to keep clinicians abreast of this rapidly changing CRPC landscape.


COURSE #078IC
Management of Prostate Cancer: A Case Based Approach with Emphasis on Integrating New Molecular Diagnostics into Clinical Practice

Eric A. Klein, MD, Course Director; Andrew J. Stephenson, MD, Faculty

Precision medicine is a concept defined by the idea that medical decision making, be it a decision to treat or not to treat, or choosing a specific drug or therapy, is based on the molecular characteristics of the disease or tumor. The theme of our postgraduate course this year was that the era of precision medicine in prostate cancer has continued to mature. The ability to characterize an individual’s risk of prostate cancer based on germline genetics (future risk of disease), the likelihood that he has an aggressive prostate cancer at the moment of consultation (current risk of disease, how aggressive the known cancer is, whether the cancer has progressed biologically while on active surveillance, the likely benefit of adjuvant radiotherapy for those with adverse pathology on radical prostatectomy, and the specific choice of therapy for those with castrate resistant disease) can now be informed by new biomarkers and commercially available genomic and gene expression based tests. These efforts at better biological characterization of disease risk and aggressiveness promise to improve clinical decision making, so that the right decision can be made at the right time.

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time for every patient along the entire disease spectrum.

The USPSTF (U.S. Preventive Services Task Force) recently upgraded its recommendation for prostate specific antigen (PSA) screening from “D” to “C” for men 55 to 69 years old, recognizing the long-term result of the ERSPC (European Randomized Study of Screening for Prostate Cancer) and the widespread adoption of active surveillance, the latter of which has reduced the harms of over diagnosis and overtreatment. There are several next generation biomarkers on the market that have better diagnostic accuracy than PSA and can further reduce unnecessary biopsies by about 30% to 35% (fig. 1). We reviewed data on a new assay called IsoPSA™ that measures multiple cancer specific isoforms of PSA in the serum based on structure rather than concentration. A validation study confirmed the high sensitivity and specificity of the assay demonstrated in the initial study, and if widely adopted could reduce unneeded biopsy by almost 50% (fig. 2).1

As the power of DNA sequencing advances, the ability to identify genes in germline DNA (ie DNA that an individual is born with) has expanded. While not all men with prostate cancer should undergo germline DNA testing, the consensus is that men with known syndromes should be tested, including those with familial breast cancer/ovarian cancer syndrome (BRCA families), Lynch syndrome and known mutations in the HOXB13 gene. There are several commercially available gene panels for testing but it is important that the results be interpreted and put into context with the help of a certified genetic counselor. Emerging discussion centers around whether patients with many first-degree relatives and those who present with high grade (Gleason 8 or greater) or metastatic disease also be tested. Data on this issue are maturing. Increasing data demonstrate that prostate cancers in men who have germline BRCA mutations behave more aggressively, respond less well to androgen deprivation and androgen receptor blockade, but may be more sensitive to inhibition by a class of drugs known as PARP (poly[ADP-ribose] polymerase) inhibitors. Studies of the 3ßHSD gene have demonstrated an inherited mutation that prevents its degradation, allowing dihydrotestosterone to accumulate in the prostate at higher levels than in wild-type men.2 Several studies have shown that men who inherit this mutation respond less well to androgen deprivation and are likely best treated with combined blockade including a luteniz ing hormone-releasing hormone agonist/antagonist plus an androgen receptor blocker.

The use of active surveillance continues to grow nationally, aided in part by the demonstrated utility of magnetic resonance imaging (MRI) to reduce under sampling and genomic tests to help assign biological risk. These technologies provide complementary information about the suitability for active surveillance (see Appendix). Accumulated experience and data demonstrate that MRI improves the likelihood of finding Gleason 7 or higher cancer, although it is limited by the fact that MRI does not identify smaller tumors even if they are high grade, and generally requires a second biopsy to confirm clinical suspicion of high grade disease. MRI

Appendix.
is further limited by its operator dependence. Genomics has the advantage of providing a direct estimate of biological potential but is limited by tumor heterogeneity. When used wisely these technologies can help correctly identify or exclude men using hard biological criteria.

All of this work demonstrates that recent advances in genomic and biomarker science (including IsoPSA and MRI) can be usefully applied to the treatment of men at risk for and diagnosed with prostate cancer.


PRESENTATION

Urologic Care for the Advanced Practice Provider: 2018 Prostate Cancer Update: Clinical Guidelines & Management

Heather Schultz, RN, MSN, NP-C and Kenneth Mitchell, MPAS, PA-C, Course Co-Directors, and Daniel Park, PA, MHA, Faculty

With major advancements in primary treatment options, screening guidelines, biomarkers to aid in prognostication and treatment planning and multiparametric (mp) magnetic resonance imaging (MRI), our approach to caring for patients with prostate cancer (PCa) continues to evolve. PCa screening and the latest USPSTF (U.S. Preventive Services Task Force) recommendations are topics about which practitioners need to be continuously updated as many patients receive questionable counseling regarding prostate specific antigen (PSA) depending on who they have spoken with or what news article they have read. It is up to us, active members of the AUA, to provide clear, concise, data driven recommendations to help patients sort through the noise.

The presentation opened with a brief overview of prostate cancer statistics in the United States and then moved to the latest guidelines for localized prostate cancer based on current AUA guidelines. Also mentioned was the expanding use of biomarkers currently available along with the clinical use of mpMRI. In addition, focal therapy, in the form of cryotherapy and high intensity focused ultrasound (HIFU), was reviewed as a primary method of prostate cancer treatment. Lastly, a few ongoing clinical trials were discussed in addition to some of the latest hot topics in the foreseeable future of prostate cancer treatment.

PCa continues to be the most common, noncutaneous malignancy in American men, representing an astounding 30% of all new cancer diagnoses. PCa is responsible for approximately 9% of all cancer related deaths and the lifetime risk of the disease is currently 1 in 7. Fortunately only 1 in 39 actually die of the disease. Interestingly, since the 2012 USPSTF recommendations were released, advising against screening, there has been a significant drop in the incidence of PCa. In 2013 there were approximately 238,000 new cases of PCa. The latest 2018 projections from the American Cancer Society note that the number of new cases this year is estimated to be 165,000, which represents a 30% decrease in diagnosis since the 2012 PCa screening era. The question remains, are there truly fewer cases of PCa or are we just catching the disease later?

Studies have indicated that there has been an estimated near tripling of biochemical recurrence and a quadrupling of nodal metastatic disease. Yes, there has been an overall drop in the number of new Gleason 6 (Grade Group 1) disease but, conversely, there has been a significant rise in the diagnosis of high grade PCa and biochemical recurrence rates. The importance of risk stratification was discussed, and the agreement of the USPSTF and the AUA on screening for men between 55 and 69 years old was solidified as this age group showed the greatest benefit from screening. What remains critical is asking ourselves who should be screened and then, perhaps more importantly, who should be treated?

Therefore, we turn to the myriad of biomarkers currently available to clinicians today. We are fortunate to have such incredible genomic tools at our disposal but there are certainly limitations to these tests such as clinical utility. We must ask ourselves, “Does ordering this test truly effect clinical decision making processes and benefit the patient in the long term? Is it cost-effective? Do the results only validate that which we already assumed or do they make an impact on our treatment recommendations?” If the answer is the latter, then these tests can become a good resource and help us reassure a subset of patients in our joint decision making regarding treatment. Since a biomarker is defined as “a biological feature that can be used to measure the presence or progress of disease or the effects of treatment,” then mpMRI can also be considered a biomarker. In fact, we use biomarkers daily in our practice, with PSA, vital signs,
body mass index all biomarkers. But what makes MRI particularly impactful? It can change the way we practice.

MRI is a game changer in the field of prostate cancer. mpMRI can help avoid the detection of clinically unimportant, indolent cancer that would likely never cause harm or impact a patient’s overall survival. Likewise, it can help detect clinically significant cancers that have been missed with traditional sextant biopsies, such as lesions in the anterior region. MRI can also help better classify disease with targeted, 3-dimensional fusion biopsies that can better assess the volume of disease rather than rely on a random sampling of the gland.

In a recent study published in *The New England Journal of Medicine*, mpMRI helped detect 50% more clinically significant cancer versus standard biopsies. Perhaps the time is coming when MRI can be used as a screening tool for PCa. However, multiple factors would certainly need to be considered such as cost of the machine, radiologist expertise and insurance coverage. Nevertheless, MRI will likely have a greater role as other potential features are added, including magnetic resonance spectroscopy, MRI parameters in active surveillance, visual cues with focal therapy treatment planning and preoperative risk assessment.

The rationales associated with focal vs radical therapy were also presented. Research going back more than 2 decades indicates that the index lesion drives tumor biology in the prostate. That is, the majority of the tumor bulk is in direct correlation with the index lesion. Prostate cancer is typically multifocal and bilateral, but the clinical characteristics of the disease are invariably defined by the index lesion. We have learned from years of radical treatments for other soft tissue cancers, including cancers of the breast and kidney, that radical surgery may not be required for select patients. Enter the era of focal therapy, namely cryotherapy and HIFU. Both modalities were explained, including ideal patient selection for each, in addition to other focal therapy options on the horizon, i.e focal electroporation and vascular targeted photodynamic therapy.

Many patients with PCa are Internet savvy and have done their due diligence with online research. On occasion, clinicians might have a newly diagnosed patient with PCa entering the office asking for HIFU treatment by name. Although approved by the U.S. Food and Drug Administration for prostate ablation, and not explicitly for PCa treatment, HIFU is an option clinicians should be aware of with the growing demand and market drivers evident from a simple Google search.

The latest 2017 AUA guidelines state that there is a lack of robust evidence of the efficacy of HIFU and that it may not be curative, potentially warranting further treatment. However, if one has a patient in clinic who is risk averse and adamantly refuses surgery or radiation, HIFU is an option that should be discussed. There remain strict inclusion and exclusion criteria for potential HIFU cases, including gland size volumetrics, clusters of intraprostatic calculi larger than 1 cm and other measures that need to be considered before determining if a patient is a HIFU candidate. Case studies were discussed, including the use of contrast enhanced ultrasound indicating perfusion immediately before and after HIFU ablation, and the correlation with posttreatment re-staging histology. Pros and cons of focal therapies were addressed and the need for re-staging biopsies was emphasized.

Finally, clinical trials were presented, including the first study of focal chemotherapy targeting the prostate gland directly. The study involved the use of paclitaxel placed in nanoparticles and injected precisely into 1 lobe of the prostate gland 1 month before prostatectomy. Predclinical studies have demonstrated tumor regression in mice, and the potential for PCa treatment via injection can be groundbreaking pending final study results. There was also a brief discussion on photodynamic therapy, whereby a bacterium on the ocean floor, when exposed to a certain spectrum of light, can produce enough energy to destroy tissue without thermal insult. We are certainly living in exciting times for innovative PCa treatment.

What about patients with biochemical recurrent PCa who have had negative traditional imaging evaluation, including computerized tomography and bone scan? We are entering the new age of positron emission tomography (PET) imaging in prostate cancer. There are multiple types of PET scans available today including PET-Axumin®, prostate specific membrane antigen PET and 11C-acetate PET. These special scans can yield metabolic uptake and help aid targeted therapies for a select group of patients. We may ask how this affects long-term overall survival but it is still too early to determine. Nevertheless, PET scanning can open doors to potential further treatment for men unwilling to remain on androgen deprivation therapy.

Lastly, we discussed the University of Southern California’s PA Fellowship in Clinical Urology. As our nation faces a dramatic rise in our baby boomer population and a shortage of urologists to meet that demand, advanced practice providers (nurse practitioners, physician assistants) will be called upon to help assist the needs of this patient demographic. Developing a formal program with standardized postgraduate training specifically designed for the vast array of urological diseases, including procedural training and robotic first assisting, can have a major impact on the quality and timing of urological care rendered. Doing so may provide our urologist colleagues more time to spend with complex cases, as well as with their families.
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