ADVANCED PROSTATE CANCER

AUA/SUO Guideline (Amended 2023)

Purpose

Prostate cancer is the most common solid organ malignancy for men in the United States and remains the second leading cause of cancer deaths for this population. While metastatic prostate cancer remains a lethal disease, improvements in overall survival through combination therapies have resulted in a renaissance in the entire landscape for clinicians caring for men with advanced metastatic prostate cancer. Prostate cancer deaths are typically the result of progression to metastatic castration-resistant prostate cancer. Historically, the median survival for men with metastatic castration-resistant prostate cancer was less than two years, but due to several factors, including the impact of novel therapies, the median survival is now increasing. Furthermore, rapid therapeutic advances in the treatment landscape render treatment decisions and sequencing increasingly complex. Therefore, at present, there is limited data-driven evidence regarding optimal agent combination or sequence. It is against this backdrop that the Panel provides evidence-based guidance for treatment of men with advanced prostate cancer and looks to the future with cautious optimism.

To assist in clinical decision-making, evidence-based guideline statements were developed to provide a rational basis for evidence-based treatment. This guideline covers advanced prostate cancer, including disease stages that range from prostate-specific antigen (PSA) recurrence after exhaustion of local treatment options to widespread metastatic disease. The patient population covered in this guideline is assumed to have already received local or pelvic therapy, including adjuvant and salvage therapy (e.g., exhaustion of local treatment options). Further, neuroendocrine tumors and small cell variants were considered outside the scope of this guideline.

This pocket card was developed as a summary of the full AUA Guideline for this subject. The complete AUA Guideline (available at www.AUAnet.org/Guidelines) should be consulted as the final authority. Please review the online guideline for more information on the appropriate application of the document.

Radiologic Considerations

The prostate cancer community has witnessed considerable developments in the detection of disease with next generation prostate cancer imaging. PET-CT has emerged as a sensitive and specific imaging test to detect prostate cancer metastases, particularly among men with biochemical recurrence after primary therapy. Multiple PET tracers have demonstrated promise in the evaluation of extent of prostate cancer including ^{18}F-fluciclovine, ^{18}F-sodium fluoride, ^{11}C-choline, and various tagged prostate-specific membrane antigen (PSMA) isoforms. While there is an emerging literature detailing the use of next generation imaging to guide management decisions in recurrent prostate cancer, there remains uncertainty about how these image-directed therapies will impact oncologic outcomes. It is important for the practicing clinician to note that the studies underpinning this guideline's recommendations were largely predicated upon the use of conventional imaging including CT, MRI, and bone scan. As the medical evidence evolves to more consistently incorporate next generation imaging, the definition of "non-metastatic" and "metastatic" will evolve owing to the significant differences in sensitivity to detect metastatic disease between conventional and advanced imaging modalities.

Multidisciplinary Nature of Treatment in Today's Advanced Prostate Cancer Care Paradigm

As the therapeutic landscape evolves to include increasingly complex combinations of systemic therapies with or without local therapies, advances in imaging, and germline and somatic genetic testing, treating men with advanced prostate cancer is increasingly one that must embrace multidisciplinary management approaches. Team members should include urologists, medical oncologists, and radiation oncologists at a minimum when supporting treatment decisions for advanced disease. Additional specialists may also include genitourinary pathology, genetic counseling, palliative care, and holistic specialists, as appropriate, in addition to primary care. Best practices must also include clinicians comfortable describing the use of germline and somatic genetic testing, and when advanced imaging techniques could be optimally used or avoided. Radiologists and nuclear medicine specialists are valuable in helping to accurately interpret scans.

Palliative care team members may also play a key role when treating men with symptomatic metastatic disease. Palliative care itself is an interdisciplinary, holistic approach to managing an advanced disease such as prostate cancer with a guarded prognosis. It can include controlling symptoms that are physical, psychological, spiritual, and social. The goal of palliation is to prevent and relieve suffering and to support the best possible quality of life for the patient and family.

Performance Status and Predicted Life Expectancy

Performance status and predicted life expectancy are both critical elements to incorporate into individualized clinical decision-making in men with advanced prostate cancer. Performance status remains a key factor in treatment decision-making, particularly among men with advanced prostate cancer. Performance status generally describes an individual patient's level of functioning and how one's disease impacts a patient's activities of daily living. Thoughtful assessment of performance status and life expectancy are essential components of evaluation and management of men with advanced prostate cancer. Indeed, assessment of performance status and life expectancy are core to establishing goals of care, incorporating individuals' values and preferences to best align available management options with what is most important to patients and their families.

Clinical Trial Enrollment

Clinicians should inform patients about suitable clinical trials and encourage patients to consider participation in such trials based on eligibility and access. Treatment options can be characterized as standard and as investigational (clinical trial). In general, standard therapies have proven efficacy and risks determined by prospective trials.

In appropriate patients, clinical trial options should be considered, and trial options should be discussed with patients as part of the shared decision-making process. Clinical trials are listed by diagnosis and stage on the Clinicaltrials.gov website.

Early Evaluation

Clinicians SHOULD

- Obtain tissue diagnosis from primary tumor or site of metastases when clinically feasible in patients without prior histologic confirmation
- Discuss treatment options based on patient life expectancy, comorbidities, preferences, and tumor characteristics
- Treat patients incorporating a multidisciplinary approach
- Optimize pain control or other symptom support and encourage engagement with professional or community-based resources, including patient advocacy groups

Bone Health

Clinicians SHOULD

- Discuss the risk of osteoporosis associated with ADT and assess the risk of fragility fracture
- Recommend preventative treatment for fractures and skeletal-related events, including supplemental calcium, vitamin D, smoking cessation, and weight-bearing exercise, to patients on ADT
- Recommend preventative treatments with bisphosphonates or denosumab to patients at high fracture risk due to bone loss and recommend referral to physicians who have familiarity with the management of osteoporosis
- Prescribe a bone-protective agent (denosumab or zoledronic acid) for mCRPC patients with bony metastases to prevent skeletal-related events

BIOCHEMICAL RECURRENCE WITHOUT METASTATIC DISEASE

Prognosis

Clinicians SHOULD

- Inform patients regarding the risk of developing metastatic disease and follow patients with serial PSA measurements and clinical evaluation
- Perform periodic staging evaluations consisting of cross-sectional imaging (CT,MRI) and technetium bone scan, and/or preferably PSMA PET imaging in patients who are at higher risk for development of metastases
- Utilize PSMA PET imaging preferentially, where available, as an alternative to conventional imaging due to its greater sensitivity or in the setting of negative conventional imaging

Clinicians MAY

- Consider radiographic assessments based on overall PSA and PSA kinetics

Treatment

Clinicians SHOULD

- Offer observation or clinical trial enrollment

Clinicians SHOULD NOT

- Routinely initiate ADT

Clinicians MAY

- Offer intermittent ADT in lieu of continuous ADT if ADT is initiated in the absence of metastatic disease

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- *Pfizer, Inc.*

Consistent with the AUA strict conflict of interest policy, these companies had no access to the AUA guidelines panels and played no part in the research or development of AUA guidelines. The support offered by these companies, and gratefully accepted by the AUA, sincerely was in the best interest of the educational mission of the guideline, to help you and your practice.

METASTATIC HORMONE-SENSITIVE PROSTATE CANCER (mHSPC)

Prognosis

Clinicians SHOULD

- Assess the extent of metastatic disease (lymph node, bone, and visceral metastases)
- Assess the extent of metastatic disease (high- versus low-volume)
- Assess if the patient is experiencing symptoms from metastatic disease
- Obtain a baseline PSA and serial PSAs at three- to six-month intervals after initiation of ADT and consider periodic conventional imaging
- Offer germline testing, and consider somatic testing and genetic counseling

Treatment

Clinicians SHOULD

- Offer ADT with either LHRH agonists or antagonists or surgical castration
- Offer ADT in combination with either androgen pathway directed therapy or chemotherapy (docetaxel)
- Offer ADT in combination with docetaxel and either abiraterone acetate plus prednisone or darolutamide in selected patients with de novo mHSPC

Clinicians MAY

- Offer primary radiotherapy to the prostate in combination with ADT in selected patients with low-volume metastatic disease

Clinicians SHOULD NOT

- Offer first generation antiandrogens in combination with LHRH agonists, except to block testosterone flare
- Offer oral androgen pathway directed therapy without ADT

NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (nmCRPC)

Prognosis

Clinicians SHOULD

- Obtain serial PSA measurements at three to six month intervals and calculate PSA doubling time starting at time of development of castration-resistance
- Assess for development of metastatic disease using conventional imaging or PSMA PET imaging at intervals of 6 to 12 months

Treatment

Clinicians SHOULD

- Offer apalutamide, darolutamide, or enzalutamide with continued ADT to patients at high risk for developing metastatic disease

Clinicians MAY

- Recommend observation with continued ADT, particularly for those at lower risk for developing metastatic disease

Clinicians SHOULD NOT

- Offer systemic chemotherapy or immunotherapy outside the context of a clinical trial

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Prognosis

Clinicians SHOULD

- Obtain baseline labs and review location of metastatic disease, disease-related symptoms, and performance status
- Perform imaging at least annually in mCRPC patients without PSA progression or new symptoms
- Order PSMA PET imaging in mCRPC patients, who are considering ^{177}Lu-PSMA-617, with disease progression having previously received docetaxel and androgen pathway inhibitor
- Offer germline (if not already performed) and somatic genetic testing

Treatment

Clinicians SHOULD

- Offer continued ADT with abiraterone acetate plus prednisone, docetaxel, or enzalutamide in mCRPC patients who have not received prior androgen receptor pathway inhibitors
- Offer radium-223 to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm
- Offer ^{177}Lu-PSMA-617 to patients with progressive mCRPC having previously received docetaxel and androgen pathway inhibitor with a positive PSMA PET imaging study
- Recommend cabazitaxel rather than an alternative androgen pathway directed therapy in patients who received prior docetaxel and abiraterone acetate plus prednisone or enzalutamide
- Offer a PARP inhibitor to patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC following prior treatment with enzalutamide or abiraterone, and/or a taxane-based chemotherapy; platinum-based chemotherapy may be offered for patients who cannot use or obtain a PARP inhibitor
- Offer pembrolizumab to patients with mismatch repair deficient or microsatellite instability high mCRPC

Clinicians MAY

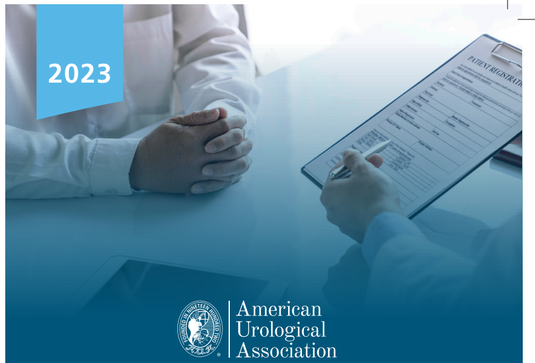
- Offer sipuleucel-T to asymptomatic/minimally symptomatic patients
- Offer cabazitaxel to patients who received prior docetaxel with or without prior abiraterone acetate plus prednisone or enzalutamide

The complete Advanced Prostate Cancer Guideline is available at **www.AUAnet.org/Guidelines**.

KEY TERMINOLOGY

Term	Definition
DISEASE STATES	
Biochemical recurrence without metastatic disease	a rise in PSA in prostate cancer patients after treatment with surgery or radiation (PSA of 0.2ng/mL and a confirmatory value of 0.2ng/mL or greater following radical prostatectomy and nadir + 2.0ng/mL following radiation); this may occur in patients who do not have symptoms
Hormone-sensitive prostate cancer	prostate cancer that has either not yet been treated with ADT or is still responsive to ADT
Castration-resistant prostate cancer	disease progression despite ADT and a castrate level of testosterone (<50ng/dL); progression may present as either a continuous rise in serum PSA levels, the progression of pre-existing or new radiographic disease, and/or clinical progression with symptoms
High-volume metastatic disease	presence of visceral metastases and/or greater than or equal to four bone metastases with at least one outside of the vertebral column and pelvis
High-risk metastatic disease	disease that has a poorer prognosis in the presence of two of the three following high-risk features: Gleason ≥8, ≥3 bone lesions, or measurable visceral metastases
De novo metastatic disease	metastatic disease that is present at the time of initial prostate cancer diagnosis rather than recurring after previous treatment of localized cancer
DISEASE MANAGEMENT	
PSA doubling time	the number of months required for the PSA value to increase two-fold
Conventional imaging	CT, MRI, and ^{99m}Tc-methylene diphosphonate bone scan

ADT: androgen deprivation therapy; CT: computed tomography; HRR: homologous recombination repair; LHRH: luteinizing hormone-releasing hormone; mCRPC: metastatic castration-resistant prostate cancer; MRI: magnetic resonance imaging; PET: positron emission tomography; PSA: prostate-specific antigen



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FOR UROLOGISTS