AUA Guidelines

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Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART I

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Abbreviations and Acronyms

ADT = Androgen deprivation therapy

CT = Computed tomography

LHRH = Luteinizing hormone-releasing hormone

mHSPC = Metastatic hormone-sensitive prostate cancer

MRI = Magnetic resonance imaging

OS = Overall survival

PET = Positron emission tomography

PSA = Prostate specific antigen

PSADT = Prostate specific antigen doubling time

SOC = Standard of care

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Purpose: The summary presented herein represents Part I of the two-part series dedicated to Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline discussing prognostic and treatment recommendations for patients with biochemical recurrence without metastatic disease after exhaustion of local treatment options as well as those with metastatic hormone-sensitive prostate cancer. Please refer to Part II for discussion of the management of castration-resistant disease.

Materials and Methods: The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. A research librarian conducted searches in Ovid MEDLINE (1998 to January Week 5 2019), Cochrane Central Register of Controlled Trials (through December 2018), and Cochrane Database of Systematic Reviews (2005 through February 6, 2019). An updated search was conducted prior to publication through January 20, 2020. The methodology team supplemented searches of electronic databases with the studies included in the prior AUA review and by reviewing reference lists of relevant articles.

Results: The Advanced Prostate Cancer Panel created evidence- and consensus-based guideline statements to aid clinicians in the management of patients with advanced prostate cancer. Such statements are summarized in figure 1 and detailed herein.

Conclusions: This guideline attempts to improve a clinician's ability to treat patients diagnosed with advanced prostate cancer. Continued research and publication of high-quality evidence from future trials will be essential to improve the level of care for these patients.

Key Words: prostatic neoplasms, androgen antagonists

Prostate cancer is the most commonly diagnosed solid organ malignancy for men in the U.S. and remains the second leading cause of cancer deaths for this population. Approximately 175,000 new diagnoses of prostate cancer and over 31,000 deaths were estimated in the U.S. in 2019.[1] Until recently, androgen deprivation therapy (ADT) was the only therapeutic strategy for men with metastatic disease. However, the field has changed and there are now a multitude of treatments available in combination with ADT to provide overall survival (OS) benefit in both newly diagnosed metastatic and castration-resistant disease states. It is against this backdrop that the Panel provides evidence-based guidance for the treatment of advanced prostate cancer and looks to the future with cautious optimism.

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BIOCHEMICAL RECURRENCE WITHOUT METASTATIC DISEASE

Prognosis	Treatment
Clinicians SHOULD	Clinicians SHOULD
Inform patients regarding the risk of developing metastatic disease and follow patients with serial PSA measurements and clinical evaluation	Offer observation or clinical trial enrollment
Perform periodic staging evaluations consisting of cross sectional imaging (CT,MRI) and technetium bone scan in patients who are at higher risk for development of metastases	Clinicians SHOULD NOT
Clinicians MAY	Routinely initiate ADT
Utilize novel PET-CT scans as an alternative to or in the setting of negative conventional imaging	Clinicians MAY
Consider radiographic assessments based on overall PSA and PSA kinetics	Offer intermittent ADT in lieu of continuous ADT if ADT is initiated in the absence of metastatic disease

METASTATIC HORMONE SENSITIVE PROSTATE CANCER

Prognosis	Treatment
Clinicians SHOULD	Clinicians SHOULD
Assess the extent of metastatic disease (bone, lymph node and visceral metastasis) using conventional imaging	Offer ADT with either LHRH agonists or antagonists or surgical castration
Assess the extent of metastatic disease (high versus low volume)	Offer continued ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel)
Assess if the patient is experiencing symptoms from metastatic disease	Clinicians MAY
Obtain a baseline PSA and serial PSAs at a minimum of three to six month intervals after initiation of ADT and consider periodic conventional imaging	Offer primary radiotherapy to the prostate in combination with ADT in selected patients with low-volume metastatic disease
Offer genetic counseling and germline testing regardless of age and family history	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

Figure 1. Statement Summary

There are several key terms and definitions that should be considered when interpreting this guideline (table 1).

METHODOLOGY

Database searches resulted in 10,517 potentially relevant articles of which 918 were selected for full-text review; 230 publications met inclusion criteria and were included in this review. Forty-six studies were carried over from the prior AUA review.

The AUA categorizes body of evidence strength as Grade A, Grade B, or Grade C.[2] The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (table 2). For a full description of the guideline methodology, refer to the unabridged guideline available at www.auanet.org/guidelines.

GUIDELINE STATEMENTS

Early Evaluation and Counseling

1. In patients with suspicion of advanced prostate cancer and no prior histologic confirmation, clinicians should obtain tissue diagnosis from the primary tumor or site of metastases when clinically feasible. (Clinical Principle)
2. Clinicians should discuss treatment options with advanced prostate cancer patients based on life expectancy, comorbidities, preferences, and tumor characteristics. Patient care should incorporate a multidisciplinary approach when available. (Clinical Principle)
3. Clinicians should optimize pain control or other symptom support in advanced prostate cancer patients and encourage engagement with professional or community-based resources, including patient advocacy groups. (Clinical Principle)

Biochemical Recurrence without Metastatic Disease after Exhaustion of Local Treatment Options

After local therapy including surgery or radiation, the first sign of recurrence is typically a rising prostate specific antigen (PSA) in the absence of visible metastases. This is assuming also that all forms of local therapy (eg, salvage radiotherapy after radical prostatectomy, or salvage prostatectomy/salvage local ablative therapy after external beam radiotherapy) have been exhausted. Patients understand that their local treatment has not eradicated the cancer because of continued rises in PSA. Management of this disease state is controversial as evidence for optimal treatment approaches is lacking.

Prognosis. 4. Clinicians should inform patients with PSA recurrence after exhaustion of local therapy regarding the risk of developing metastatic disease and follow such patients with serial PSA measurements and clinical evaluation. Clinicians may consider radiographic assessments based on overall PSA and PSA kinetics. (Clinical Principle)

In the hormone-sensitive setting, PSA recurrence almost always precedes clinical detection of metastases.[3] However, given the indolent nature of some cancers, not all patients with a detectable PSA following primary treatment are destined to experience clinical recurrence or cancer-related death. The incidence of PSA recurrence after primary radical prostatectomy or radiotherapy varies depending on clinical and pathologic risk factors, such as tumor grade, stage, and pre-treatment PSA.[4–7]

5. In patients with PSA recurrence after exhaustion of local therapy who are at higher risk for the development of metastases (eg, PSA doubling

Table 1. *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 0.2 ng/mL and a confirmatory value of 0.2 ng/mL or greater following radical prostatectomy and nadir + 2.0 ng/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 (<50 ng/dL); progression may present as either a continuous rise in serum PSA levels (values identified at a minimum of 1 week intervals with a minimal value of 2.0 ng/mL, with estimations of PSADT with at least 3 values measured ≥4 weeks apart), 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

time [PSADT] <12 months), clinicians should perform periodic staging evaluations consisting of cross-sectional imaging (computed tomography [CT], magnetic resonance imaging [MRI]) and technetium bone scan. (Clinical Principle)

Currently, cross-sectional imaging with CT or MRI along with ^{99m}Tc-methylene diphosphonate bone scintigraphy remain the standard imaging approaches for post-treatment biochemical recurrence, although this is an evolving space. The primary rationale for utilizing these approaches relates to the fact that current standard of care (SOC) systemic treatments in metastatic hormone-sensitive prostate cancer (mHSPC) are based on such conventional imaging approaches rather than advanced/molecular imaging (eg, CHAARTED, STAMPEDE, LATITUDE).[8–10] It should be noted, however, that these modalities infrequently detect metastases in the setting of early PSA recurrence (eg, PSA <5 ng/mL).[11–13]

6. Clinicians may utilize novel positron emission tomography (PET)-CT scans (eg, fluciclovine, choline, PSMA) in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging or in the setting of negative conventional imaging. (Expert Opinion)

Novel PET tracers appear to show greater sensitivity than conventional imaging for the detection of prostate cancer recurrence and metastases at low PSA values (<2.0 ng/mL). While advanced imaging tests may enhance detection of metastatic lesions, the impact on patients and OS has yet to be fully demonstrated. It is still unclear what may be gained by the early detection of recurrent disease. In instances of planned salvage radiation therapy or salvage lymphadenectomy, the treatment templates may be adjusted as a result of novel imaging findings. In addition, oligometastatic disease may be identified, and such patients may be offered management in clinical trials. While such approaches may be intuitively appealing, to date there is only evidence that it may delay initiation of systemic therapy.[14] There is no evidence yet that metastasis directed therapy confers a survival benefit.[15]

Treatment. 7. For patients with a rising PSA after failure of local therapy and no demonstrated metastatic disease by conventional imaging, clinicians should offer observation or clinical trial enrollment. (Clinical Principle)

8. ADT should not be routinely initiated in this population (Expert Opinion). However, if ADT is initiated in the absence of metastatic disease, intermittent ADT may be offered in lieu of continuous ADT. (Conditional Recommendation; Evidence Level: Grade B)

There are currently no systemic treatments with proven efficacy in men without metastatic disease who are not candidates for additional local therapy. The overall course of a rising PSA after failure of local therapy is highly variable, with earlier recurrences indicative of more aggressive disease. In one study of men with biochemical recurrence after salvage radiotherapy, over half of the PSA failures occurred within 18 months of radiation, and these men were at a significantly higher risk of distant metastasis and death compared to men with later PSA recurrences.[16]

Any potential benefit of early initiation of systemic therapy must also be weighed against the impact of treatment of adverse events and quality of life. In the TOAD trial, men in the early ADT arm had higher rates of hormone treatment-related symptoms and inferior quality of life related to sexual activity.[17]

While observation or a clinical trial is preferred, it is recognized that ADT is sometimes given to men

Table 2. *AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength*

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence
Moderate Recommendation (Net benefit or harm moderate)	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits=Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits=Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle Expert Opinion	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

with rapid PSA rises in the absence of radiographic metastases. If men start ADT prior to demonstration of metastatic disease, it is often due to the perception of a higher risk of progression to metastatic prostate cancer based on prognostic criteria such as a higher grade or stage, shorter time to biochemical recurrence, and shorter PSADT.[16,18] Although not recommended, if ADT is initiated in the absence of visible metastases for men who have completed maximal local therapy, intermittent ADT may be offered instead of continuous ADT. There is no evidence to determine the best time to start ADT in the absence of radiographic metastases.

Metastatic Hormone-Sensitive Prostate Cancer

mHSPC has been increasingly diagnosed since 2013, likely due to multiple factors, including greater imaging sensitivity and changes to PSA screening guidelines. In addition to being increasingly common, mHSPC and treatment of this disease state has shifted greatly since the first studies testing up-front docetaxel (CHAARTED and STAMPEDE) were reported.[8,9] Metastatic hormone-sensitive disease can occur due to recurrence after initial local therapy for localized prostate cancer or as de novo metastatic disease, a distinction that may be useful when deciding upon systemic therapy. Additionally, the volume and site of metastatic disease are important factors that can affect prognosis and treatment choice.

Prognosis. 9. Clinicians should assess the extent of metastatic disease (bone, lymph node, and visceral metastasis) using conventional imaging in newly diagnosed mHSPC patients. (Clinical Principle)

10. In newly diagnosed mHSPC patients, clinicians should assess the extent of metastatic disease (low- versus high-volume). High-volume is defined as greater than or equal to four bone metastases with at least one metastasis outside of the spine/pelvis and/or the presence of visceral metastases. (Moderate Recommendation: Evidence Level: Grade B)

The presence and extent of metastatic disease plays a central role in determining which and if any therapy is beneficial. Patients without metastatic disease have not been shown to benefit from aggressive systemic therapy. Further, clinicians should categorize patients as de novo metastatic disease or having progression in stage after prior failed treatment. Studies of systemic therapy have demonstrated that extent of metastatic disease influences response. For example, STAMPEDE demonstrated that only the subset of men with low-volume disease showed an improvement in survival with radiotherapy in combination with ADT.[19] As a result, presence of metastatic disease, its burden,

and precise locations should be assessed prior to treatment.

11. Clinicians should assess if a newly diagnosed mHSPC patient is experiencing symptoms from metastatic disease at the time of presentation to guide discussions of prognosis and further disease management. (Moderate Recommendation; Evidence Level: Grade B)

Symptoms in mHSPC have been shown to have prognostic value. In addition, understanding cancer related symptoms is key to optimizing pain and other symptom management in addition to anticancer therapy. In an analysis of patients in the SWOG 8894 trial, presence of bone pain was among the factors associated with poorer 10-year survival.[20]

12. Clinicians should obtain a baseline PSA and serial PSAs at three- to six-month intervals after initiation of ADT in mHSPC patients and consider periodic conventional imaging. (Clinical Principle)

The use of PSA as an instrument of evaluation in metastatic prostate cancers is common practice. In most reported studies, PSA is a measured variable and recorded at several time points at diagnosis and during treatment (baseline, induction [after a defined period of therapy], serial monitoring, and at progression). In many studies, PSA has demonstrated clear prognostic value and is used in many of the risk classification systems. For example, in the SWOG 8894 trial, a comparison of bilateral orchiectomy with or without flutamide for treatment of metastatic prostate cancer, many clinical factors were analyzed in the assessment of risk including the finding that a higher PSA was associated with poorer 10-year survival.[20]

Studies using the SEER registry database have found higher PSA is associated with worse cancer-specific survival (PSA <60 versus ≥ 60: HR $=0.624$; 95% CI 0.535–0.727; $p<0.0001$).[21] Additionally, for studies showing prognostic risk group stratification, PSA or PSA metrics are consistent variables in determination of group assignment.[22–24]

13. In patients with mHSPC, regardless of age and family history, clinicians should offer genetic counseling and germline testing. (Expert Opinion)

In a recent study evaluating 20 DNA-repair genes associated with autosomal dominant cancer-predisposition syndromes in a population of men with metastatic prostate cancer and unselected by family history, the prevalence of inherited (germline) DNA repair mutations was 11.8%.[25] Findings of alterations in homologous recombination DNA repair or tumor mutations resulting in microsatellite instability and deficient mismatch repair may have implications in clinical trial eligibility or therapeutics selection (poly ADP ribose polymerase inhibitors, immunotherapy, or possibly early use of cytotoxic chemotherapy).

Germline testing should include pre-test counselling by someone knowledgeable about the implications of testing. Pre-test counseling needs to include a discussion of possible test results; implications for patients; discussion of the Genetic Information Nondiscrimination Act; possible impact of test results on life, disability, and long-term care insurance; and potential role of cascade testing of family members if a pathogenic or likely pathogenic mutation is identified. Post-test counselling with a genetic counselor is necessary for anyone who is found to have one of these mutations.

Treatment. 14. Clinicians should offer ADT with either luteinizing hormone-releasing hormone (LHRH) agonists or antagonists or surgical castration in patients with mHSPC. (Strong Recommendation; Evidence Level: Grade B)

15. In patients with mHSPC, clinicians should offer continued ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel). (Strong Recommendation; Evidence Level: Grade A)

The use of primary ADT for the management of mHSPC has been the SOC since its discovery by Huggins and colleagues in the 1940's.[26] Castrate levels of testosterone (<50 ng/dL) may be achieved with LHRH analogues, gonadotropin-releasing hormone antagonists or orchiectomy. These treatments are considered equivalent in cancer control, although they have never been compared in large RCTs. Gonadotropin-releasing hormone antagonists and orchiectomy as monotherapy have a rapid onset of action and avoid the 'testosterone flare' seen with LHRH analogues alone making them useful in situations needing rapid hormone ablation such as impending spinal cord compression.

Abiraterone Acetate. In the double-blind, placebo-controlled, phase 3 LATITUDE trial,[10] 1,199 patients were randomly assigned to receive either ADT plus abiraterone acetate plus prednisone or ADT plus placebo. After a median follow-up of 30.4 months, the median OS was significantly longer in the abiraterone acetate group than in the placebo group (not reached versus 34.7 months) (HR $=0.62$; 95% CI 0.51–0.76; $p<0.001$).

In the STAMPEDE trial,[27] 1,917 patients were randomized (1:1) to receive ADT alone or ADT plus abiraterone acetate and prednisolone. The median follow-up was 40 months. There were 184 deaths in the abiraterone acetate group compared with 262 in the ADT group (HR $=0.63$; 95% CI 0.52–0.76; $p<0.001$).

Apalutamide. In the double-blind, phase 3 TITAN study,[28] 525 patients were assigned to receive apalutamide with ADT compared to 527 patients receiving placebo plus ADT. At a median of 22.7 months follow-up, the percentage of patients with radiographic progression-free survival at 24 months was 68.2% in the apalutamide group compared to 47.5% in the placebo group (HR =0.48; 95% CI 0.39−0.60; p <0.001). OS at 24 months was greater with apalutamide compared to placebo (82.4% versus 73.5%; HR=0.67; 95% CI 0.51−0.89; p=0.005).

Enzalutamide. In the open-label, randomized, phase 3 ENZAMET trial,[29] 1,125 men were randomized to receive testosterone suppression plus either open-label enzalutamide or a standard nonsteroidal antiandrogen therapy. With a median follow-up of 34 months, there were 102 deaths in the enzalutamide group compared to 143 deaths in the standard care group (HR=0.67; 95% CI 0.52−0.86; p=0.002). Kaplan-Meier estimates of OS at 3 years were 80% in the enzalutamide group an 72% in the standard care group.

Docetaxel. In the phase 3 CHAARTED study,[30] 790 patients with mHSPC were equally randomly assigned to receive either ADT plus docetaxel or ADT alone. At a median follow-up of 53.7 months, the median OS was 57.6 months for the chemohormonal arm versus 47.2 months for ADT alone (HR=0.72; 95% CI 0.59−0.89; p=0.0018).

Similarly, in the STAMPEDE trial,[9] ADT plus docetaxel significantly improved median OS compared with ADT alone. The study randomly assigned 2,962 men 2:1:1:1 to receive SOC defined as hormone therapy for at least 2 years, SOC plus zoledronic acid, SOC plus docetaxel, or SOC with zoledronic acid and docetaxel. Docetaxel was given for six 3-week cycles with prednisolone daily. At a median follow-up of 43 months, median OS was 71 months for SOC compared to 81 months for SOC plus docetaxel (HR=0.78; 95% CI 0.66−0.93; p=0.006).

16. In selected mHSPC patients with low-volume metastatic disease, clinicians may offer primary radiotherapy to the prostate in combination with ADT. (Conditional Recommendation; Evidence Level: Grade C)

Two recent Phase 3 randomized trials examining ADT and prostate radiotherapy versus ADT alone in men with metastatic prostate cancer demonstrated no difference in OS. However, the subgroup analysis for the low-volume group in STAMPEDE Arm H revealed a survival benefit in patients with low-volume metastatic cancer.[19] Given that this was a secondary analysis and few of the patients had received optimized systemic therapy, the Panel provides a conditional recommendation for ADT plus radiation as an option for patients with minimal metastatic disease willing to undergo the risks associated with local therapy.

Physicians have suggested these results point to the benefits of local therapy raising the question whether radical prostatectomy might have the same results. These trials are ongoing, and at present the use of surgery should be considered investigational and only conducted within the context of a trial. In the STAMPEDE trial,[19] no patients had concurrent abiraterone acetate and only 18% had early docetaxel, so no clear recommendation can be made about other drug combinations combined with prostate radiation in the metastatic setting.

17. Clinicians should not offer first generation antiandrogens (bicalutamide, flutamide, nilutamide) in combination with LHRH agonists in patients with mHSPC, except to block testosterone flare. (Strong Recommendation; Evidence Level: Grade A)
18. Clinicians should not offer oral androgen pathway directed therapy (eg, abiraterone acetate plus prednisone, apalutamide, bicalutamide, darolutomide, enzalutamide, flutamide, nilutamide) without ADT for patients with mHSPC. (Expert Opinion)

With compelling level A evidence supporting the use of docetaxel, abiraterone acetate plus prednisone, apalutamide, or enzalutamide in combination with ADT in men with newly diagnosed mHSPC, the Panel believes that long-term use of first generation antiandrogens bicalutamide, flutamide, nilutamide in lieu of the above noted agents cannot be supported.

Further, non-steroidal antiandrogen therapy without ADT in advanced prostate cancer is not recommended. Evidence based on 11 studies encompassing 3,060 patients suggests that use of non-steroidal antiandrogens without ADT compared with medical or surgical castration monotherapy for advanced prostate cancer is less effective in terms of OS, clinical progression, treatment failure, and treatment discontinuation due to adverse events.[31]

FUTURE DIRECTIONS

Several key areas of future research need emphasis to improve clinical care and provide a path to better outcomes for patients with advanced prostate cancer. It is now more clear than ever that multimodality approaches and integration of care are critical to improving the care for men with prostate cancer. Multidisciplinary clinics and the resulting multimodality treatment approaches can optimize treatment selection, maximize results, and minimize overtreatment and side effects.[32] Many clinical

trials are evaluating the concepts of integrating systemic therapy with radiation and/or surgery, such as optimizing treatment of men with locally advanced primary tumors, assessing the benefit of local therapy in men with metastatic disease, or determine the impact of metastasis-directed therapy in the oligometastatic setting. The results of these studies are likely to substantially impact the standard approaches to newly diagnosed patients with advanced disease.

Disclaimer: This document was written by the Advanced Prostate Cancer Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2018. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology, oncology, and radiation oncology with specific expertise on this disease space. The mission of the panel was to develop recommendations that are analysis based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the treatment of advanced prostate cancer. Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA, and the Panel Chair, with the support of AUA Guidelines staff and the PGC, reviews all disclosures and addresses any potential conflicts per AUA's Principles, Policies and Procedures for Managing Conflicts of Interest. While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases. Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances. Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

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