THE JOURNAL of UROLOGY®
www.auajournals.org/journal/juro

AUA Guideline Articles

Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, Part I: Introduction, Risk Assessment, Staging, and Risk-Based Management

James A. Eastham,[1]* Gregory B. Auffenberg,[2] Daniel A. Barocas,[3] Roger Chou,[4] Tony Crispino,[5] John W. Davis,[6] Scott Eggener,[7] Eric M. Horwitz,[8] Christopher J. Kane,[9] Erin Kirkby,[10] Daniel W. Lin,[11] Sean M. McBride,[1] Alicia K. Morgans,[12] Phillip M. Pierorazio,[13] George Rodrigues,[14] William W. Wong[15] and Stephen A. Boorjian[16]

[1]*Memorial Sloan Kettering Cancer Center, New York, New York*
[2]*Urology of St. Louis, St. Louis, Missouri*
[3]*Vanderbilt University Medical Center, Nashville, Tennessee*
[4]*Oregon Health & Science University, Portland, Oregon*
[5]*UsTOO, Las Vegas, Nevada*
[6]*MD Anderson Cancer Center, Houston, Texas*
[7]*University of Chicago, Chicago, Illinois*
[8]*Fox Chase Cancer Center, Philadelphia, Pennsylvania*
[9]*UC San Diego Health Physician Group, San Diego, California*
[10]*American Urological Association, Linthicum, Maryland*
[11]*University of Washington Medical Center, Seattle, Washington*
[12]*Dana-Farber Cancer Institute, Boston, Massachusetts*
[13]*Penn Medicine, Philadelphia, Pennsylvania*
[14]*London Health Sciences Centre, London, Ontario, Canada*
[15]*Mayo Clinic, Phoenix, Arizona*
[16]*Mayo Clinic, Rochester, Minnesota*

Abbreviations and Acronyms

ADT = Androgen deprivation therapy
AHRQ = Agency for Healthcare Research & Quality
ASCO = American Society of Clinical Oncology
ASTRO = American Society for Radiation Oncology
AUA = American Urological Association
CT = Computed tomography
DRE = Digital rectal exam
mpMRI = Multi-parametric magnetic resonance imaging
NGI = Next generation imaging
OHSU = Oregon Health & Science University
PDT = Photodynamic therapy
PSA = Prostate-specific antigen
PSMA = Prostate-specific membrane antigen
QOL = Quality of life
SDM = Shared decision-making

Purpose: The summary presented herein represents Part I of the three-part series dedicated to Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, discussing risk assessment, staging, and risk-based management in patients diagnosed with clinically localized prostate cancer. Please refer to Parts II and III for discussion of principles of active surveillance, surgery and follow-up (Part II), and principles of radiation and future directions (Part III).

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, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. 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 Clinically Localized Prostate Cancer Panel created evidence- and consensus-based guideline statements to aid clinicians in the management of patients with clinically localized prostate cancer. Statements regarding risk assessment, staging, and risk-based management are detailed herein.

Conclusions: This guideline aims to inform clinicians treating patients with clinically localized prostate cancer. Continued research and publication of high-quality evidence from future trials will be essential to further improve care for these men.

Accepted for publication April 30, 2022.
The complete unabridged version of the guideline is available at https://www.jurology.com.
This document is being printed as submitted, independent of standard editorial or peer review by the editors of *The Journal of Urology®*.
* Correspondence: Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan Kettering Cancer Center, 353 E. 68th St., New York, New York 10065 (telephone: 646-422-4322; FAX: 212-988-0826; email: easthamj@mskcc.org).

© 2022 by American Urological Association Education and Research, Inc.

RIGHTSLINK nals.org/jurology

Copyright © 2022 American Urological Association Education and Research, Inc. Unauthorized reproduction of this article is prohibited.

Key Words: Prostate cancer, Radical prostatectomy, Radiation therapy for prostate cancer, Active surveillance, Shared decision making

METHODOLOGY

The Localized Prostate Cancer Guideline Panel was created in 2019 by the American Urological Association (AUA). This guideline was developed in collaboration with the American Society for Radiation Oncology (ASTRO).

Primary methodology was provided by the Pacific Northwest Evidence-based Practice Center of Oregon Health & Science University (OHSU).[1] The Panel also utilized the systematic review developed by the Agency for Healthcare Research and Quality (AHRQ) on *Therapies for Clinically Localized Prostate Cancer*.[2] A research librarian conducted searches in Ovid MEDLINE (September 2021), Cochrane Central Register of Controlled Trials (August 2021), and Cochrane Database of Systematic Reviews (September 2021). Searches were supplemented by reviewing reference lists of relevant articles.

The AUA employs a three-tiered strength of evidence system to underpin evidence-based guideline statements (Table 1). 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).

Background

Prostate cancer remains the most common non-cutaneous cancer among US men, with an estimated 268,490 new cases and 34,500 deaths in 2022.[3] As the vast majority of newly-diagnosed prostate cancer patients have clinically localized disease,[3] providing evidence-based guideline statements to support clinical decision-making represents an important component of facilitating the delivery of standardized, high-quality care.

An important component of the updated guidelines is the continued utilization of a risk stratification classification for patients with newly diagnosed clinically localized disease. The Panel believes that risk stratification facilitates patient counseling, should be used in shared decision-making (SDM) for treatment recommendations, and facilitates clinical trial enrollment. Recognizing that various risk classifications have been described,[4–8] the Panel elected to maintain a risk group model (Table 3). Of note, the Panel did combine the prior risk categories of "very low-risk" and "low-risk" disease together, as the recommended management for these patients is consistent. The Panel understands that risk assessment may be refined as new information becomes available. The intention of the risk groups is to provide a framework to discuss management options. The importance of SDM between patient and clinician is emphasized in the statements and supporting text.

GUIDELINE STATEMENTS

Risk Assessment

1. Clinicians should use clinical T stage, serum PSA, Grade Group (Gleason score), and tumor volume on biopsy to risk stratify patients with newly diagnosed prostate cancer. (Strong Recommendation; Evidence Level: Grade B)

The risk of disease progression and adverse oncologic outcomes of prostate cancer varies widely based on clinicopathologic characteristics. Disease risk stratification is vital at the outset of patient counseling to align the aggressiveness of management to the severity of disease. Several risk stratification systems have been described and have been variously utilized, including risk groups, risk scores, and nomograms.[4–8] The Panel did conduct a systematic review of the literature to verify that the individual features of the risk groups remain associated with likelihood of adverse pathologic findings, biochemical recurrence, metastases, and death, and to evaluate whether mature data exist to support inclusion of additional parameters to enhance risk stratification.

2. Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)

3. Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)

Regarding tissue-based genomic biomarkers, several currently available commercial tests, including Prolaris, Oncotype Dx, and Decipher, variously offer prediction of adverse pathology as well as the risks of biochemical recurrence, metastasis, and prostate cancer death. However, most of the reported studies to date that evaluated the prognostic ability of these genomic tests did not meet inclusion criteria for the systematic review as the studies used surgical (ie, prostatectomy) rather than biopsy specimens. Notably, two studies using biopsy data have shown that a cell cycle progression panel (Prolaris) score was associated with the risks of biochemical recurrence, metastatic disease, and prostate cancer death; however, only one of those studies met inclusion criteria for the systematic review.[9–11] The Oncotype Dx assay has been validated on needle biopsy tissue and found to be associated with adverse pathology, biochemical recurrence, metastasis, and prostate cancer death; again, however, the studies did not meet inclusion criteria for the systematic review.[12–15] Meanwhile, a multi-institutional evaluation of Decipher Biopsy testing found that a high-risk Decipher score was associated with conversion from active surveillance to definitive treatment.[16]

Thus, based on the level of existing data, the Panel concluded that clinicians should not routinely use tissue-based genomic biomarkers for risk stratification

RIGHTSLINK

Copyright © 2022 American Urological Association Education and Research, Inc. Unauthorized reproduction of this article is prohibited.

Table 1. *Strength of Evidence Definitions*

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• Moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

or clinical decision-making; however, clinicians may use such tests selectively when added risk stratification may alter SDM. These recommendations are largely consistent with recent American Society of Clinical Oncology (ASCO) Guidelines as well.[17] Examples of patients for whom tissue-based genomic markers may help clarify risk include patients with high-volume (multiple involved cores) Gleason score 6 cancer as well as select men with favorable intermediate-risk prostate cancer who are interested in active surveillance. Examples of patients for whom tissue-based genomic markers are not recommended include the majority of men with low-volume (few involved cores) Gleason score 6 cancer and men with favorable intermediate-risk prostate cancer who are interested in treatment.

4. Clinicians should perform an assessment of patient and tumor risk factors to guide the decision to offer germline testing that includes mutations known to be associated with aggressive prostate cancer and/or known to have implications for treatment. (Expert Opinion)

Germline testing in patients with clinically localized prostate cancer has several potential goals, including enhanced risk stratification, identification of genes that may guide treatment decisions, and providing information to determine the need for personal and family member cancer screening. Identified prostate cancer associated genes to date include *ATM, BRCA1, BRCA2, CHEK2, HOXB12, MLH1, MSH2, MSH6, NBN, PALB2, PMS2,* and *TP53*. For example, studies have demonstrated that men with prostate cancer harboring BRCA2/BRCA1 genetic aberrations are more likely to have worse disease and a poorer prognosis.[18] Patient education, testing, and referral to a genetic counselor should be considered. Establishing specific indications for genetic testing is beyond the scope of this Guideline; indeed, such recommendations have recently been outlined by a large expert-panel consensus conference.[19] A number of the indications for germline testing are provided in Table 4. Importantly, patient and family history risk factors should be investigated by the clinician through careful history taking, while pathology from biopsy or radical prostatectomy should be reviewed in the consideration of germline testing.

Staging

5. Clinicians should not routinely perform abdomino-pelvic computed tomography (CT) scan or bone scan in asymptomatic patients with low- or intermediate-risk prostate cancer. (Expert Opinion)

Table 2. *AUA Nomenclature*

	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 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 (rarely used to support a Strong Recommendation)
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 (No apparent net benefit or harm)	Benefits=Risks/Burdens Best action depends on individual patient circumstances Future research 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 Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	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		
Expert Opinion	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		

RIGHTSLINK

Copyright © 2022 American Urological Association Education and Research, Inc. Unauthorized reproduction of this article is prohibited.

Table 3. *Risk Group Classification for Clinically Localized Prostate Cancer*

Low-Risk	PSA <10 ng/mL AND Grade Group 1 AND clinical stage T1-T2a
Intermediate-Risk	PSA 10-<20 ng/mL OR Grade Group 2-3 OR clinical stage T2b-c · Favorable: Grade Group 1 with PSA 10-<20 ng/mL or clinical stage T2b-c and <50%* biopsy cores positive OR Grade Group 2 with PSA<10 ng/mL and clinical stage T1-2a and <50% biopsy cores positive · Unfavorable: Grade Group 1 with PSA 10-<20 ng/mL and clinical stage T2b-c OR Grade Group 2 with PSA 10-<20 ng/mL and/or clinical stage T2b-c and/or ≥50%* biopsy cores positive OR Grade Group 3 with PSA <20 ng/mL
High-Risk	PSA ≥20 ng/mL OR Grade Group 4-5 OR clinical stage T3

* Percent biopsy cores positive is the total number of cores containing cancer divided by total number of cores obtained x 100. This is not the percentage of cancer within a positive core. Regarding assessment of the percent biopsy cores positive for risk stratification, the Panel acknowledges that with the increasing use of pre-biopsy magnetic resonance imaging (MRI) and subsequent targeted biopsies, multiple cores may be obtained from a targeted lesion. Multiple cores from the same lesion should be considered as a single core (ie, for the calculation of percentage cores positive in risk assessment). If all cores are negative, that is considered a single negative core. If one or more cores from the same lesion is positive, that is considered a single positive core, with the highest Gleason score used for risk stratification.

6. Clinicians should obtain a bone scan and either pelvic multi-parametric magnetic resonance imaging (mpMRI) or CT scan for patients with high-risk prostate cancer. (Strong Recommendation; Evidence Level: Grade B)

Imaging studies are intended to define the local extent of disease as well as determine the presence of nodal and distant metastases, and thereby inform management. Clinicians should use a risk-based approach to staging patients with newly diagnosed prostate cancer, considering the probability of the patient harboring metastatic disease as well as the sensitivity and specificity of the imaging modality. For asymptomatic patients with low- or intermediate-risk prostate cancer, the probability of nodal or distant metastasis is low.[20,21] Therefore, abdomino-pelvic CT scan and bone scan are unlikely to be helpful and should not be routinely obtained.

For patients with high-risk prostate cancer, CT scan or mpMRI scan should be obtained to evaluate the loco-regional extent of disease and presence of distant metastasis. mpMRI is preferred for local tumor staging, which may thereby inform therapy.[22] For both mpMRI scan and CT scan, the assessment of nodal metastasis is based on size criteria, and these modalities have similar accuracy. To evaluate for the presence of bone metastasis, conventional bone scan should be obtained as the initial staging study. As robust evidence to support an imaging evaluation in unfavorable intermediate-risk disease remains lacking, the Panel offers that clinicians may consider obtaining staging imaging for patients within this risk classification.

7. In patients with prostate cancer at high risk for metastatic disease with negative conventional imaging, clinicians may obtain molecular imaging to evaluate for metastases. (Expert Opinion)

The role of molecular imaging, also referred to as next generation imaging (NGI), continues to evolve as new and more sensitive radiotracers become available. Recently, both the Gallium 68 prostate-specific membrane antigen (PSMA)-11 (Ga 68 PSMA-11) and piflufolastat F-18 PSMA (18F-DCFPyL) PET scanning have been FDA approved for initial staging for patients at high risk of metastasis (as well as for evaluation of biochemical relapse after treatment).[23,24] In a multicenter randomized trial, Ga-68 PSMA PET scan was compared with conventional imaging using CT scan and bone scan in patients with high-risk prostate cancer before definitive therapy. Ga-68 PSMA PET scan was found to have a 27% greater accuracy than conventional imaging, with better sensitivity and specificity, in the detection of nodal or distant metastasis.[25] While data to date supporting a clinical benefit to novel imaging modalities for patients with negative conventional imaging remain quite limited, the Panel did conclude that clinicians may offer molecular imaging in patients at high risk for metastatic disease based on the demonstrated enhanced staging accuracy. This recommendation is consistent with recent ASCO Guidelines as well.[26] The Panel recognizes that the identification of disease with molecular imaging may influence treatment (eg, the addition of systemic therapy or metastases-directed therapy) and underscores the current uncertainty regarding an incremental

Table 4. *Indications for Germline Testing in Patients with Clinically Localized Prostate Cancer**

Strong family history of prostate cancer	Examples: first-degree relative or multiple second-degree relatives diagnosed with Grade Group 2 or higher prostate cancer, particularly at early age (<60 years), particularly if metastatic or lethal
Strong personal or family history of related cancers	Examples: breast, colorectal, ovarian, pancreatic, upper tract urothelial carcinoma
Known family history of familial cancer risk mutation	Examples: *BRCA1, BRCA2, ATM*, Lynch-syndrome associated genes
Ashkenazi Jewish ancestry	Particularly in patients with Grade Group 2 or higher disease
Adverse tumor characteristics	Examples: High-risk disease; intermediate-risk disease with intraductal or cribriform morphology

* The Panel recognizes that this list is not exhaustive.

RIGHTSLINK

Copyright © 2022 American Urological Association Education and Research, Inc. Unauthorized reproduction of this article is prohibited.

oncologic benefit of altering treatment based on the identification of metastases with molecular imaging among patients with negative conventional imaging.

Risk-Based Management

8. Clinicians should inform patients that all prostate cancer treatments carry risk. The risks of treatment, in particular to patients' urinary, sexual, and bowel function, must be incorporated with the risk posed by the cancer, patient life expectancy, comorbidities, pre-existing medical conditions, and patient preferences to facilitate a shared decision-making approach to management. (Clinical Principle)

9. Clinicians should provide an individualized risk estimate of post-treatment prostate cancer recurrence to patients with prostate cancer. (Clinical Principle)

The selection of a management strategy for clinically localized prostate cancer is preference-sensitive and very often based on patients' interpretation of the balance between treatment-specific risks and benefits. With that in mind, clinicians must inform patients thoroughly regarding the risks and benefits of the various management options. Clinicians also must elicit from patients their values, preferences, and concerns about outcomes of treatment. This collaborative SDM process is designed to yield a well-informed, high-quality decision that is consistent with patients' preferences and values.

SDM aims to improve the quality of medical decisions by helping patients choose options consistent with their own values and in accordance with the best available scientific evidence.[27,28] RCTs of SDM versus routine care have demonstrated that patients engaged in SDM are more knowledgeable, have more realistic expectations, participate more actively in the care process, and more frequently arrive at decisions aligned with their personal preferences.[27] The Institute of Medicine and the AUA have both articulated strong support for the use of SDM for complex decisions such as treatment for localized prostate cancer.[29,30] Key components of SDM in selecting a management option for localized prostate cancer are provided in Table 5.

Clinicians should counsel patients regarding the severity of disease and documented natural history to provide perspective regarding the tradeoff between treatment-related side effects and the likelihood of disease progression. Furthermore, risk level dictates the intensity of the staging evaluation and the intensity of treatment, so a discussion of risk level sets the foundation for patient understanding of these decisions. Similarly, as the intensity of treatment is also tied to the patient's life expectancy, an estimate of life expectancy should factor into the SDM discussion.

Post-treatment cancer recurrence risk is dependent on a number of clinicopathologic factors, including most notably tumor grade and stage, as well as pre-treatment PSA and, for patients undergoing radical prostatectomy, surgical margin status. Multiple predictive models and nomograms have been developed to estimate the risks of biochemical recurrence, metastases, and death from prostate cancer.[6,7,31–33] These tools may be used to support discussions with patients regarding their personalized risk. In addition, competing risks of mortality from patient age and comorbidity status should be considered. Discussion of risk is a particularly important aspect of patient counseling and SDM.

10. For patients with low-risk prostate cancer, clinicians should recommend active surveillance as the preferred management option. (Strong Recommendation; Evidence Level: Grade A)

The intent of active surveillance is to maintain patients' quality of life (QOL) by deferring or delaying definitive treatment when prostate cancer is unlikely to cause mortality or significant morbidity, while simultaneously maintaining the potential to implement definitive treatment with curative intent should this become necessary. Relevant data to inform management for patients with low-risk prostate cancer may be found in the ProtecT trial,[34] which randomized 1,643 patients with clinically localized prostate cancer to surgery, radiation therapy, or active surveillance (referred to as active monitoring in the trial). In total, 77% of patients in the trial had a Gleason score of 6, 76% had clinical stage T1c (non-palpable) disease, and approximately two-thirds of patients had low-risk prostate cancer. The incidence of all-cause mortality for radical prostatectomy, radiation therapy, and active monitoring was 10.1, 10.3, and 10.9 per 1,000 person-years, respectively ($p=0.87$). Moreover, no significant differences were identified in prostate cancer-specific mortality. As such, the trial provides high-level evidence supporting the concept that selected patients with prostate cancer can delay or altogether avoid treatment.

Given the demonstrated relative safety of active surveillance, the Panel believes that the benefits of aggressive treatment do not outweigh the risk of treatment-related harms for most patients with low-risk disease. Indeed, the potential adverse events associated with prostate cancer treatment, predominantly urinary morbidity, bowel complications, and sexual dysfunction, have been well documented.[35] The Panel nevertheless acknowledges that select patients with low-risk disease may elect definitive local therapy after an informed discussion between clinician and patient. In particular, clinicians may

RIGHTSLINK

Copyright © 2022 American Urological Association Education and Research, Inc. Unauthorized reproduction of this article is prohibited.

Table 5. *Components of Shared Decision-Making for Clinically Localized Prostate Cancer Treatment Selection*

Informing patients about the severity of their cancer (risk level)*
Assessing patients' relevant comorbidities and life expectancy**
Informing patients about the likelihood of cure, recurrence, and other oncologic endpoints of each management strategy/treatment option (ideally using a risk calculator or nomogram)
Assessing patients' baseline disease-specific function (e.g., urinary, sexual, and bowel function) and the value or utility they place on each (ideally using standardized instruments, with or without decision aids)
Informing patients about their likelihood of specific short- and long-term side effects of each management strategy/treatment option

* See Table 3 and associated text.
** An accurate determination of a man's life expectancy based on age and comorbidities is difficult. Methods available to determine life expectancy include clinician prediction, model prediction, and publicly available calculators (eg, https://www.ssa.gov/OACT/population/longevity.html). Life expectancy may be assessed in conjunction with a patient's primary care physician.

offer immediate treatment to select patients who are fully informed as to all options and risks with low-risk prostate cancer such as those who have a high probability of disease risk reclassification on active surveillance (eg, high-volume cancer, higher PSA density) or other risk factors for harboring higher-risk disease (eg, family history of lethal prostate cancer, germline mutation associated with adverse pathology).[36]

Patients electing to proceed with active surveillance should be informed of the importance of regular cancer surveillance to avoid missing the window of curability. Strategies for monitoring disease in patients electing active surveillance are detailed further in Principles of Active Surveillance available in Part II of this series.

11. In asymptomatic patients with prostate cancer and limited life expectancy (determined on a patient-specific basis), clinicians should recommend watchful waiting. (Strong Recommendation; Evidence Level: Grade A)

Patients with a life expectancy of $\leq$5 years do not benefit from prostate cancer screening, diagnosis, or treatment[37] as prostate cancer treatment does not improve survival within five years of follow-up.[38] The PIVOT and SPCG-4 randomized trials of radical prostatectomy versus observation/watchful waiting collectively demonstrate the relative importance of competing risks of mortality and of patient longevity (minimum estimated life expectancy of 8-10 years) in order for treatment to result in a reduction in the risk of death.[39,40]

Watchful waiting does not involve routine cancer surveillance, but rather aims to deliver palliative therapy for relief of symptoms should they develop. The critical goal of watchful waiting is to maintain the patient's QOL by avoiding treatment when prostate cancer is unlikely to cause mortality or significant morbidity. One of the principal aims of watchful waiting is avoidance of side effects from local treatment or androgen deprivation therapy (ADT). Watchful waiting is appropriate for elderly patients or patients with significant comorbidities in whom competing risks of mortality are considerably greater than the risk of death from prostate cancer.

12. For patients with favorable intermediate-risk prostate cancer, clinicians should discuss active surveillance, radiation therapy, and radical prostatectomy. (Strong Recommendation; Evidence Level: Grade A)

The management of patients with intermediate-risk disease may likewise be informed in part by the ProtecT trial, as approximately one third of patients therein had intermediate- or high-risk disease.[34] Of note, in the trial, active monitoring was found to be associated with an increased risk of clinical progression compared to radical prostatectomy or radiotherapy (22.9 per 1,000 person-years versus 8.9 per 1,000 person-years for radical prostatectomy and 9.0 per 1,000 person-years for radiation therapy, $p<0.001$). Similarly, an increased risk of metastatic disease was seen for patients managed with active monitoring (6.3 per 1,000 person-years versus 2.4 per 1,000 person-years for radical prostatectomy and 3.0 per 1,000 person-years for radiation therapy, $p=0.004$). Nevertheless, all-cause mortality was low in each treatment arm, and no difference was noted in prostate cancer deaths. As such, the Panel believes that, with appropriate counseling, favorable intermediate-risk patients should be offered active surveillance, radical prostatectomy, and radiation therapy. Patients with favorable intermediate-risk disease who may be considered for active surveillance include those with a low PSA density, low tumor volume, as well as a low percentage of Gleason pattern 4 disease on biopsy. The Panel does recognize the noted increased risk of disease progression with active surveillance among intermediate-risk (versus low-risk) patients, particularly those with Grade Group 2 disease,[41] as well as the relatively limited data on very long-term follow-up of such patients, and thereby emphasizes the importance of informed SDM.

13. Clinicians should inform patients with intermediate-risk prostate cancer considering whole gland or focal ablation that there are a lack of high-quality data comparing ablation outcomes to radiation therapy, surgery, and active surveillance. (Expert Opinion)

Numerous ablative modalities, relying on differing energy sources/differing mechanisms of action, are

RIGHTSLINK

Copyright © 2022 American Urological Association Education and Research, Inc. Unauthorized reproduction of this article is prohibited.

currently available to patients with clinically localized prostate cancer.[42] Patient selection criteria in reported studies have varied widely as has treatment planning approach (eg, lesion-based focal therapy, hemi-ablation, whole-gland). The only properly powered randomized trial reported to date on prostate ablation was restricted to patients with low-risk prostate cancer and demonstrated that focal photodynamic therapy (PDT) lowered the likelihood of cancer progression and rates of surgery/radiation compared to active surveillance, at an expense of an increased likelihood of mild urinary or erectile dysfunction.[43] However, PDT is not approved in the United States. Further, active surveillance is the preferred approach for patients with low-risk prostate cancer.

Institutional, multi-site, and population-based studies have reported outcomes of various ablative therapies; however, with absence of randomization, non-standardized protocols, and insufficient follow-up, the role of ablative therapy in the management of clinically localized prostate cancer remains to be defined. Fortunately, randomized trials are ongoing and more are anticipated.

Currently, the Panel believes that ablation may be considered in select, appropriately informed patients (with clinical trial enrollment prioritized). Patients being considered for ablation should have intermediate-risk prostate cancer,[44] as data supporting treatment of high-risk disease with ablation are lacking, while patients with low-risk cancers should be preferentially managed with active surveillance. Patients considering ablation should be counseled regarding side effects and recurrence risk and should be followed post-ablation with PSA, digital rectal exam (DRE), MRI, and biopsy tailored to their specific health and cancer characteristics.[45]

14. For patients with unfavorable intermediate- or high-risk prostate cancer and estimated life expectancy greater than 10 years, clinicians should offer a choice between radical prostatectomy or radiation therapy plus ADT. (Strong Recommendation; Evidence Level: Grade A)

For patients with unfavorable intermediate- or high-risk clinically localized prostate cancer, definitive local therapy is advised.[46,47] The optimal treatment for these patients remains a topic of active study, and prior published meta-analyses have reported relatively disparate findings as to comparative survival following each of these treatment approaches.[48,49] The Panel supports offering patients with unfavorable intermediate- and high-risk disease either radical prostatectomy or radiation with ADT (see Principles of Surgery and Principles of Radiation in Parts II and II, respectively, of this series). For patients with sufficiently high-risk disease (clinically node positive, or with 2 of 3 of the following criteria: clinical stage T3 or T4, PSA $\geq$40 ng/mL, or $\geq$Gleason 8), treatment with radiation and ADT can include two years of concurrent abiraterone acetate plus prednisone as well.[50]

15. Clinicians should not recommend whole gland or focal ablation for patients with high-risk prostate cancer outside of a clinical trial. (Expert Opinion)

As previously discussed, the only properly powered randomized trial reported to date on prostate ablation included only patients with low-risk prostate cancer. Currently, patients being considered for ablation should have intermediate-risk prostate cancer,[44] as there is a lack of data supporting treatment of high-risk disease with ablation, while again, patients with low-risk cancers should be managed with surveillance.

16. Clinicians may recommend palliative ADT alone for patients with high-risk prostate cancer, local symptoms, and limited life expectancy. (Expert Opinion).

Due to the lack of evidence indicating a significant oncologic benefit to treatment with primary ADT for clinically localized prostate cancer, the Panel concluded primary ADT should only be recommended for palliation of local disease-related symptoms in select patients with a limited life expectancy for whom definitive local therapy is not advised.

For such patients, the primary goals of care include symptom control/palliation and maintenance of QOL. As such, ADT may be used to manage urinary tract sequelae of local tumor growth through (albeit transient) cytoreduction.

REFERENCES

1. Chou R, Griffin J, Cheney T et al: Management of clinically localized prostate cancer: a systematic evidence review. Portland, OR: Pacific Northwest Evidence-based Practice Center 2022.
2. Wilt TJ, Ullman KE, Linskens EJ et al: Therapies for clinically localized prostate cancer: a comparative effectiveness review. J Urol 2021; **205:** 967.
3. Siegel RL, Miller KD, Fuchs HE et al: Cancer statistics. Ca Cancer J Clin 2022; **72:** 7.
4. Sanda MG, Cadeddu JA, Kirkby E et al: Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. J Urol 2018; **199:** 683.
5. Sanda MG, Cadeddu JA, Kirkby E et al: Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part II: recommended approaches and details of specific care options. J Urol 2018; **199:** 990.
6. Cooperberg MR, Pasta DJ, Elkin EP et al: The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 2005; **173:** 1938.

RIGHTSLINK

Copyright © 2022 American Urological Association Education and Research, Inc. Unauthorized reproduction of this article is prohibited.

7. D'Amico AV, Whittington R, Malkowicz SB et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998; **280:** 969.
8. National Comprehensive Cancer Network: Prostate Cancer Version 2.2022. 2021
9. Canter DJ, Freedland S, Rajamani S et al: Analysis of the prognostic utility of the cell cycle progression (CCP) score generated from needle biopsy in men treated with definitive therapy. Prostate Cancer Prostatic Dis 2020; **23:** 102.
10. Canter DJ, Reid J, Latsis M et al: Comparison of the prognostic utility of the cell cycle progression score for predicting clinical outcomes in African American and non-African American men with localized prostate cancer. Eur Urol 2019; **75:** 515.
11. Bishoff JT, Freedland SJ, Gerber L et al: Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol 2014; **192:** 409.
12. Knezevic D, Goddard AD, Natraj N et al: Analytical validation of the Oncotype DX prostate cancer assay - a clinical RT-PCR assay optimized for prostate needle biopsies. BMC Genomics 2013; **14:** 690.
13. Eggener S, Karsh LI, Richardson T et al: A 17-gene panel for prediction of adverse prostate cancer pathologic features: prospective clinical validation and utility. Urology 2019; **126:** 76.
14. Klein EA, Cooperberg MR, Magi-Galluzzi C et al: A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol 2014; **66:** 550.
15. Van Den Eeden SK, Lu R, Zhang N et al: A biopsy-based 17-gene genomic prostate score as a predictor of metastases and prostate cancer death in surgically treated men with clinically localized disease. Eur Urol 2018; **73:** 129.
16. Vince RA Jr, Jiang R, Qi J et al: Impact of Decipher Biopsy testing on clinical outcomes in localized prostate cancer in a prospective statewide collaborative. Prostate Cancer Prostatic Dis 2021; **20:** 20.
17. Eggener SE, Rumble RB, Armstrong AJ et al: Molecular biomarkers in localized prostate cancer: ASCO guideline. J Clin Oncol 2020; **38:** 1474.
18. McNevin CS, Cadoo K, Baird AM et al: Pathogenic BRCA variants as biomarkers for risk in prostate cancer. Cancers (Basel) 2021; **13:** 5697.
19. Giri VN, Knudsen KE, Kelly WK et al: Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 2020; **38:** 2798.
20. Merdan S, Womble PR, Miller DC et al: Toward better use of bone scans among men with early-stage prostate cancer. Urology 2014; **84:** 793.
21. Risko R, Merdan S, Womble PR et al: Clinical predictors and recommendations for staging computed tomography scan among men with prostate cancer. Urology 2014; **84:** 1329.
22. Abrams-Pompe RS, Fanti S, Schoots IG et al: The role of magnetic resonance imaging and positron emission tomography/computed tomography in the primary staging of newly diagnosed prostate cancer: a systematic review of the literature. Eur Urol Oncol 2021; **4:** 370.
23. US Food & Drug Administration: FDA approves second PSMA-targeted PET imaging drug for men with prostate cancer. 2021.
24. US Food & Drug Administration: FDA approves first PSMA-targeted PET imaging drug for men with prostate cancer. 2020.
25. Hofman MS, Lawrentschuk N, Francis RJ et al: Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020; **395:** 1208.
26. Trabulsi EJ, Rumble RB, Jadvar H et al: Optimum imaging strategies for advanced prostate cancer: ASCO guideline. J Clin Oncol 2020; **38:** 1963.
27. Stacey D, Légaré F, Col NF et al: Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2014; **1:** CD001431.
28. Légaré F, Stacey D, Turcotte S et al: Interventions for improving the adoption of shared decision making by healthcare professionals. Cochrane Database Syst Rev 2014; **9:** CD006732.
29. Institute of Medicine: Crossing the quality chasm: a new health system for the 21st century. Washington, DC: The National Academies Press 2001.
30. Makarov DV, Chrouser K, Gore JL et al: AUA white paper on implementation of shared decision making into urological practice. Urol Pract 2016; **3:** 355.
31. Cooperberg MR, Hilton JF and Carroll PR: The CAPRA-S score: a straightforward tool for improved prediction of outcomes after radical prostatectomy. Cancer 2011; **117:** 5039.
32. Stephenson AJ, Scardino PT, Eastham JA et al: Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 2006; **98:** 715.
33. Zelefsky MJ, Kattan MW, Fearn P et al: Pretreatment nomogram predicting ten-year biochemical outcome of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for prostate cancer. Urology 2007; **70:** 283.
34. Hamdy FC, Donovan JL, Lane JA et al: 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016; **375:** 1415.
35. Chen RC, Basak R, Meyer AM et al: Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. JAMA 2017; **317:** 1141.
36. Carter HB, Helfand B, Mamawala M et al: Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. Eur Urol 2019; **75:** 743.
37. Schroder FH, Hugosson J, Roobol MJ et al: Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012; **366:** 981.
38. Wilt TJ, Brawer MK and Jones KM: Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012; **367:** 203.
39. Wilt T, Jones KM, Barry MJ et al: Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 2017; **377:** 132.
40. Bill-Axelson A, Holmberg L, Garmo H et al: Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014; **370:** 932.
41. Musunuru HB, Yamamoto T, Klotz L et al: Active surveillance for intermediate risk prostate cancer: survival outcomes in the Sunnybrook experience. J Urol 2016; **196:** 1651.
42. Hopstaken JS, Bomers JGR, Sedelaar MJ et al: An updated systematic review on focal therapy in localized prostate cancer: what has changed over the past 5 years? Eur Urol 2022; **81:** 5.
43. Gill IS, Azzouzi AR, Emberton M et al: Randomized trial of partial gland ablation with vascular targeted phototherapy versus active surveillance for low risk prostate cancer: extended followup and analyses of effectiveness. J Urol 2018; **200:** 786.
44. Weinstock C, Suzman D, Kluetz P et al: Development of treatments for localized prostate cancer in patients eligible for active surveillance: U.S. Food and Drug Administration Oncology Center of Excellence Public Workshop. J Urol 2020; **203:** 115.
45. Lebastchi AH, George AK, Polascik TJ et al: Standardized nomenclature and surveillance methodologies after focal therapy and partial gland ablation for localized prostate cancer: an international multidisciplinary consensus. Eur Urol 2020; **78:** 371.

RIGHTSLINK

Copyright © 2022 American Urological Association Education and Research, Inc. Unauthorized reproduction of this article is prohibited.

46. Abdollah F, Sun M, Thuret R et al: A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. Eur Urol 2011; **59:** 88.

47. Widmark A, Klepp O, Solberg A et al: Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 2009; **373:** 301.

48. Wallis CJD, Saskin R, Choo R et al: Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis. Eur Urol 2016; **70:** 21.

49. Guy DE, Chen H, Boldt RG et al: Characterizing surgical and radiotherapy outcomes in non-metastatic high-risk prostate cancer: a systematic review and meta-analysis. Cureus 2021; **13:** e17400.

50. Attard G, Murphy L, Clarke NW et al: Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet 2022; **399:** 447.

RIGHTSLINK

Copyright © 2022 American Urological Association Education and Research, Inc. Unauthorized reproduction of this article is prohibited.