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CLINICALLY LOCALIZED PROSTATE CANCER: AUA/ASTRO GUIDELINE (2022; AMENDED 2026)

Endorsed by SUO

Guideline Panel

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SUMMARY

Purpose

The recommendations discussed herein for the management of clinically localized prostate cancer provide a framework stratified by risk to facilitate care decisions and guide clinicians in the implementation of selected management options.

Methodology

The systematic review that informs this Guideline was based on 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. Criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies and settings (PICOTS) of interest. The target population was patients with clinically localized prostate cancer, defined as up to clinical stage T3 (by digital rectal examination [DRE]) prostate cancer without nodal or distant metastasis (N0M0) on conventional imaging. In 2024, an updated literature search was conducted in OVID covering the period from July 1, 2021 to December 5, 2024, overlapping with the original search from the 2021 systematic review. The search identified 29 studies for full-text review plus an additional 8 studies reviewing artificial intelligence (AI) as it relates to disease management. The subsequent 2026 amendment is based on data released since the initial 2022 publication of this Guideline.

GUIDELINE STATEMENTS

RISK ASSESSMENT

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

STAGING

5. Clinicians may use magnetic resonance imaging (MRI) of the prostate in any risk category to determine extent and location of disease in the prostate, guide surveillance biopsies, or plan treatment. (*Conditional Recommendation; Evidence Level: Grade B*)
6. Clinicians should not routinely perform prostate-specific membrane antigen positron emission tomography (PSMA PET) scan, cross-sectional imaging, or bone scan for nodal or metastatic staging in asymptomatic patients with low- or favorable intermediate-risk prostate cancer. (*Expert Opinion*)
7. Clinicians should stage unfavorable intermediate- and high-risk localized prostate cancer using either PSMA PET scan or a combination of bone scan and cross-sectional imaging. (*Strong Recommendation; Evidence Level: Grade B*)
8. In patients with unfavorable intermediate- and high-risk localized prostate cancer who have negative conventional imaging, clinicians may obtain PSMA PET to evaluate for metastases. (*Expert Opinion*)

RISK-BASED MANAGEMENT

9. Clinicians should inform patients that all prostate cancer treatments carry risk. The risks of treatment 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 (SDM) approach to management. (*Clinical Principle*)
10. Clinicians should provide an individualized risk estimate of post-treatment prostate cancer recurrence to patients with prostate cancer. (*Clinical Principle*)
11. For patients with low-risk prostate cancer, clinicians should recommend active surveillance as the preferred management option. (*Strong Recommendation; Evidence Level: Grade A*)
12. 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*)

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

14. Clinicians should inform patients with low- and intermediate-risk prostate cancer that whole gland or focal ablation remains investigational without high-quality data comparing ablation outcomes to standard of care therapies such as surgery, radiation therapy, and active surveillance. (*Expert Opinion*)

15. 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 androgen deprivation therapy (ADT). (*Strong Recommendation; Evidence Level: Grade A*)

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

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

PRINCIPLES OF MANAGEMENT

Principles of Active Surveillance

18. Patients managed with active surveillance should be monitored with serial PSA values and repeat prostate biopsy. (*Expert Opinion*)

19. In patients selecting active surveillance, clinicians should utilize MRI to augment risk stratification, but this should not replace periodic surveillance biopsy. (*Expert Opinion*)

Principles of Surgery

20. In patients electing radical prostatectomy, nerve-sparing, when oncologically appropriate, should be performed. (*Moderate Recommendation; Evidence Level: Grade B*)

21. Clinicians should inform patients that pelvic lymphadenectomy provides staging information, which may guide future management, but does not have consistently documented improvement in metastasis-free, cancer-specific, or overall survival (OS). (*Moderate Recommendation; Evidence Level: Grade B*)

22. Clinicians should use nomograms to select patients for lymphadenectomy. The potential benefit of identifying lymph node positive disease should be balanced with the risk of complications. (*Clinical Principle*)

23. Clinicians performing pelvic lymphadenectomy should perform an extended dissection, which improves staging accuracy compared to a limited dissection. (*Moderate Recommendation; Evidence Level: Grade: B*)

24. Clinicians should complete a radical prostatectomy if suspicious regional nodes are encountered intraoperatively. (*Moderate Recommendation; Evidence Level: Grade C*)

25. Clinicians should risk stratify patients with positive lymph nodes identified at radical prostatectomy based on pathologic variables and postoperative PSA. (*Expert Opinion*)

26. Clinicians may offer patients with positive lymph nodes identified at radical prostatectomy and an undetectable post-operative PSA adjuvant therapy or observation. (*Conditional Recommendation; Evidence Level: Grade C*)

27. Clinicians should not routinely recommend adjuvant radiation therapy after radical prostatectomy. (*Strong Recommendation; Evidence Level: Grade A*)

Principles of Radiation

28. Clinicians should utilize available target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures to optimize the therapeutic ratio of external beam radiation therapy (EBRT) delivered for prostate cancer. (*Clinical Principle*)
29. Clinicians should utilize dose escalation when EBRT is the primary treatment for patients with prostate cancer. (*Strong Recommendation; Evidence Level: Grade A*)
30. Clinicians may counsel patients with prostate cancer that proton therapy is a treatment option, but it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes. (*Conditional Recommendation; Evidence Level: Grade C*)
31. Clinicians should offer moderate hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT. (*Strong Recommendation; Evidence Level: Grade A*)
32. Clinicians may offer ultra hypofractionated EBRT for patients with low- or intermediate- risk prostate cancer who elect EBRT. (*Conditional Recommendation; Evidence Level: Grade B*)
33. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary high-dose rate (HDR) prostate implant as equivalent forms of treatment. (*Strong Recommendation; Evidence Level: Grade B*)
34. In patients with low- or intermediate-risk prostate cancer electing radiation therapy, clinicians should not electively radiate pelvic lymph nodes. (*Strong Recommendation; Evidence Level: Grade B*)
35. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should not routinely use ADT. (*Moderate Recommendation; Evidence Level: Grade B*)
36. In patients with unfavorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer the addition of short-course (four to six months) ADT with radiation therapy. (*Strong Recommendation; Evidence Level: Grade A*)
37. Clinicians should offer moderate hypofractionated EBRT for patients with high-risk prostate cancer who are candidates for EBRT. (*Moderate Recommendation; Evidence Level: Grade C*)
38. In patients with unfavorable intermediate- or high-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT or combined EBRT + brachytherapy (LDR, HDR) along with a risk-appropriate course of ADT. (*Strong Recommendation; Evidence Level: Grade A/B*)
39. In patients with high-risk prostate cancer electing radiation therapy, clinicians may offer radiation to the pelvic lymph nodes. (*Conditional Recommendation; Evidence Level: Grade B*)
40. When treating the pelvic lymph nodes with radiation, clinicians should utilize intensity-modulated radiation therapy (IMRT) with doses between 45 Gy to 52 Gy. (*Strong Recommendation; Evidence Level: Grade B*)
41. In patients with high-risk prostate cancer electing radiation therapy, clinicians should recommend the addition of long-course (18 to 36 months) ADT with radiation therapy. (*Strong Recommendation; Evidence Level: Grade A*)
42. When combined ADT and radiation are used, ADT may be initiated neoadjuvantly or concurrently. (*Conditional Recommendation; Evidence Level: Grade C*)

43. When combining ADT with radiation therapy, clinicians may use combined androgen suppression (luteinizing hormone-releasing hormone [LHRH] agonist with an antiandrogen), an LHRH agonist alone, or an LHRH antagonist alone. (*Expert Opinion*)

44. When treating a subgroup of high-risk localized patients (≥ 2 of the following: PSA ≥ 40 ng/dL, ≥ Gleason 8, ≥ cT3) or locally advanced prostate cancer (cN1) with radiation therapy, clinicians should combine ADT with abiraterone acetate and prednisone for 24 months. (*Strong Recommendation; Evidence Level: Grade B*)

FOLLOW-UP AFTER TREATMENT

45. Clinicians should monitor patients with prostate cancer post therapy with PSA and symptom assessment. (*Clinical Principle*)

46. Clinicians should support patients with prostate cancer through continued symptom management and encouraging engagement with professional or community-based resources. (*Clinical Principle*)

INTRODUCTION

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) with additional representation from the American Society of Clinical Oncology (ASCO) and Society of Urologic Oncology (SUO). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair and Vice Chair who in turn appointed the additional panel members with specific expertise in this area in conjunction with ASTRO, ASCO, and SUO. Additionally, the Panel included patient representation. Funding of the Panel was provided by AUA and ASTRO; panel members received no remuneration for their work.

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, 3]

The Localized Prostate Cancer Amendment Panel was created in 2024 by the AUA to review new literature and provide updates herein. For this iteration, the systematic review was conducted by an independent methodological consultant, and determination of the guideline scope and review of the final systematic review to inform guideline statements was conducted in conjunction with the Panel.

Data Sources and Searches

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. In 2024, an updated literature search of Ovid MEDLINE identified 29 studies for review that were published between July 2021 and December 5, 2024. Inclusion/exclusion was based on the same PICOTS as the original guideline systematic review. An additional 8 studies were identified reviewing AI as it relates to disease management.

Study Selection

Criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies and settings (PICOTS) of interest. The target population was patients with clinically localized prostate cancer, defined as up to clinical stage T3 (by DRE) prostate cancer without nodal or distant metastasis (N0M0) on conventional imaging. Studies of patients with low-, intermediate-, or high-risk clinically localized prostate cancer were included.

For evaluation of prognostic factors, OHSU included primary studies and systematic reviews that reported risk estimates and controlled for potential confounders, evaluated patients that did not undergo curative treatment or who underwent radical prostatectomy or radiation therapy, and recruited patients in or after 1990. OHSU restricted inclusion to large (n>1,000) studies, unless no such studies were available. Such sample size criterion was only applied to studies of prognosis. For diagnosis, the methodology team included primary studies and systematic reviews that reported diagnostic accuracy or discrimination (e.g., the area under the receiver operating characteristic curve). For evaluation of treatments/management, OHSU focused on randomized trials; if no randomized trials were available, methodologists also included recent, large cohort studies that evaluated comparisons of interest and controlled for confounders. OHSU excluded uncontrolled studies of treatments, case reports, narrative reviews, and non-English language articles. In-vitro and animal studies were also excluded. Articles must have been published in a peer-reviewed journal.

Using the pre-specified criteria, two investigators independently reviewed titles and abstracts of all citations. OHSU used a two-phase method for screening full-text articles identified during review of titles and abstracts. In the first phase, OHSU reviewed full-text articles to identify relevant systematic reviews for inclusion. When there were many primary studies or the primary studies were primarily observational, OHSU utilized systematic reviews that addressed Key Questions, were higher quality, and published within the last five years. The second phase reviewed full-text articles to identify primary studies for key questions not sufficiently answered by previously published systematic reviews, and new studies published after the systematic reviews.

Data Abstraction

For primary studies that met inclusion criteria, a single investigator abstracted information on study design, year, setting, country, sample size, eligibility criteria, dose and duration of the intervention, population characteristics (age, race, tumor stage, tumor grade, PSA level, performance status, prostate cancer risk category), results, and source of funding. For systematic reviews, OHSU abstracted characteristics of the included studies (number, design, and sample sizes of included studies, study settings), population characteristics (inclusion and exclusion criteria), interventions, methods, and ratings for the risk of bias of included studies, synthesis methods, and results. For survival and progression-free survival (PFS), risk estimates were based on the number of deaths or cases of progression, so that estimates <1 indicate improved survival; if necessary, reported risk estimates were converted to this format. Data abstractions were reviewed by a second investigator for accuracy and discrepancies were resolved through discussion and consensus.

Risk of Bias Assessment

Two investigators independently assessed risk of bias using predefined criteria. Disagreements were resolved by consensus. For randomized trials and cohort studies, the methodology team adapted criteria for assessing risk of bias from the U.S. Preventive Services Task Force.[4] Criteria for randomized trials included use of appropriate randomization and allocation concealment methods, baseline comparability of groups, blinding, attrition, and use of intention-to-treat analysis. For cohort studies on prognostic factors, criteria included methods for assembling cohorts, attrition, blinding assessment of outcomes, and adjustment for potential confounding. OHSU assessed systematic reviews using AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) criteria.[5] Criteria included use of pre-specified methods, appropriate search methods, assessment of risk of bias, and appropriate synthesis methods. For diagnostic accuracy studies, OHSU adapted criteria from QUADAS-2 to assess risk of bias related to patient selection, interpretation of the index test, selection and interpretation of the reference standard, and flow and timing (e.g., interval between index test and reference standard, receipt of the reference standard, and exclusion of patients from the analysis).[6] Studies were rated as "low risk of bias," "medium risk of bias," or "high risk of bias" based on the presence and seriousness of methodological shortcomings.

Studies rated "low risk of bias" are generally considered valid. "Low risk of bias" randomized trials include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; blinding of patients, care providers, and outcome assessors; and appropriate analysis of outcomes.

Studies rated "medium risk of bias" are susceptible to some bias, though not necessarily enough to invalidate the results. These studies do not meet all the criteria for a rating of low risk of bias, but no flaw is likely to cause major bias. Studies may be missing information, making it difficult to assess limitations and potential problems. The "medium risk of bias" category is broad, and studies with this rating vary in their strengths and weaknesses. Therefore, the results of some medium risk of bias studies are likely to be valid, while others may be only possibly valid.

Studies rated "high risk of bias" have significant flaws that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of high risk of bias studies could be as likely to reflect flaws in study design and conduct as true difference between compared interventions. OHSU did not exclude studies rated high risk of bias a priori, but high risk of bias studies were considered less reliable than low or medium risk of bias studies.

Data Synthesis and Determination of Evidence Strength

OHSU constructed evidence tables with study characteristics, results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings. OHSU reported pooled estimates and other results from systematic reviews and examined whether the findings of new studies were consistent with the reviews.

The AUA employs a three-tiered strength of evidence system to underpin evidence-based guideline statements. (Table 1) The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable randomized controlled trials [RCTs] or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.[7]

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

AUA Nomenclature: Linking Statement Type to Evidence Strength

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**) Strong Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. Moderate Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. Conditional Recommendations are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm, when benefits and harms are finely balanced, or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and that future research is unlikely to change confidence. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but that better evidence could change confidence. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but that better evidence is likely to change confidence. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is unlikely to change confidence. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence could change confidence. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens; therefore, alternative strategies may be equally reasonable, and better evidence is likely to change confidence.

Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinions with consensus achieved using a modified Delphi technique if differences of opinion emerged.[8] A Clinical Principle is 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 refers to 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.

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and management of Clinically Localized Prostate Cancer. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from ASTRO, ASCO, and SUO as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from December 3-17, 2021, to allow any additional interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation and representation from prostate cancer patient and advocacy organizations to open the document further to the patient perspective. The draft guideline document was distributed to 115 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 78 reviewers provided comments, including 61 external reviewers. At the end of the peer review process, a total of 668 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC, and BOD as well as the governing body of ASTRO for final approval.

For the 2026 Amendment, a call for reviewers was placed on the AUA website from July 30 – August 15, 2025, to allow any additional interested parties to request a copy of the document for review. The draft guideline document was distributed to 126 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 58 reviewers provided comments, including 50 external reviewers. At the end of the peer review process,

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 (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 (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	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		

a total of 364 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the original panel and the AUA PGC, SQC, and BOD as well as the governing body of ASTRO for final approval.

Background

Prostate cancer remains the most common non-cutaneous cancer among US men, with an estimated 333,830 new cases projected and 36,320 expected deaths in 2026.[9] As the vast majority of newly-diagnosed prostate cancer patients have clinically localized disease,[9] providing evidence-based guideline statements to support clinical decision-making represents an important component of facilitating the delivery of standardized, high-quality care. Given the breadth of investigation into various aspects of the evaluation and management of clinically localized disease that has occurred over the past several years, with the resultant emergence of data relevant to patient care delivery, the AUA, in collaboration with ASTRO, undertook to re-evaluate and update the organization's prior prostate cancer guidelines.[10, 11]

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 SDM for treatment recommendations, and facilitates clinical trial enrollment. Recognizing that various risk classifications have been described,[10-14] the Panel elected to maintain a risk group model **(Table 3)**.

TABLE 3: Strength Risk Group Classification for Clinically Localized Prostate Cancer

Risk Group	Description
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.[15] 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 (i.e., 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.[16]

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. In addition to detailing the components of risk stratification, the Guideline is also intended to address indications for staging in the newly diagnosed patient, provide risk-based treatment approaches to be reviewed by the clinician with the patient, and offer recommendations for post-treatment follow-up. Further, information is outlined regarding specifics of care delivery for various therapeutic modalities, such as pelvic lymph node management during radical prostatectomy, radiation dosage, fields, and concurrent ADT usage, as well as principles of conducting active surveillance. Further, the Panel identified several areas of ongoing study that are likely to be of significant relevance in the future for the care of patients with clinically localized disease, including genomic tumor tissue testing and advanced imaging.

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 A*)**

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.[10-14] 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. In total, 30 studies on prognostic factors in localized prostate cancer met inclusion criteria.[12, 17-48] Sample sizes ranged from 1,062 to 19,684 patients.

Nineteen cohort studies evaluated baseline PSA level as a prognostic factor in patients with clinically localized prostate cancer who underwent curative treatment (typically radical prostatectomy or radiation therapy). Higher PSA level was associated with increased risks of biochemical recurrence,[12, 18, 21, 22, 24, 26-30, 32, 35, 37, 40, 44, 45, 47] prostate cancer-specific mortality,[18, 26, 32, 35, 47] and all-cause mortality.[32, 35, 40] Similarly, a separate series evaluated baseline PSA level as a prognostic factor in patients with clinically localized prostate cancer who did not undergo curative treatment and noted an association between higher PSA level and increased risk of prostate cancer mortality.[24] Overall, PSA level was deemed to be an important risk factor that should be assessed, documented, and used to categorize patient risk.

Clinical T-stage is determined by DRE and is defined according to the American Joint Committee on Cancer (AJCC) system.[16, 49] Higher clinical T-stage was found to be associated with increased risk of biochemical recurrence,[18, 21, 23, 33, 36, 38, 41, 46] prostate cancer-specific mortality,[18, 26, 35, 47] and all-cause mortality,[32, 35] including among patients who did not undergo definitive treatment.[17, 24] Thus, clinical T-stage should be ascertained by DRE, documented in the chart, and used to categorize patient risk. Of note, prostate imaging (ultrasound or MRI) is not at this time used to assign clinical T-stage for risk classification. Nevertheless, the Panel acknowledges that imaging (e.g., MRI) findings may provide additional information regarding local tumor extent,[50] and may be utilized in disease prognostication/treatment planning.

Cancer grade on biopsy is assigned using the World Health Organization/ International Society of Urologic Pathologists (WHO/ISUP) Grade Group system or the older Gleason score system. ISUP recommends that Gleason scores 6, 3 + 4 = 7, 4 + 3 = 7, 8 and 9-10, be reported as ISUP grades 1-5, respectively.[51] Fourteen cohort studies evaluated baseline Gleason score as a prognostic factor in patients with clinically localized prostate cancer who underwent curative treatment. Higher Gleason score was associated with increased risks of biochemical recurrence,[21, 23, 33, 35, 37, 38, 41, 46] metastatic disease,[39, 42, 43] prostate cancer-specific mortality,[26, 32, 35, 42, 43, 47] and all-cause mortality.[32, 35, 40] Gleason score was also a strong predictor of prostate cancer mortality in patients who did not undergo curative treatment.[17, 24] As such, Grade Group is included in risk assessment. The Panel acknowledges that certain histologic features, such as intraductal and cribriform patterns, have likewise been associated with worse prognosis.[52-54] Such features, when available, should be considered when counseling an individual patient.

Of note, the Panel did not include PSA density (serum PSA [ng/mL] divided by imaging measured prostate volume [cc]) in the systematic literature review. However, an ad-hoc literature review demonstrated that a PSA density ≥ 0.15 ng/mL/cc has been associated with the risk of upgrading on subsequent biopsy among patients on active surveillance.[55] As such, the Panel believes that PSA density remains an important component of disease risk assessment. Of note, the Panel does recognize the continuous nature of risk associated with the spectrum of PSA density values and cautions against use of threshold values in isolation for management decision-making.

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 (i.e., 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.[19, 20, 56] 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.[57-60] 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.[48]

Thus, based on the level of existing data, the Panel concluded that clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making; however, clinicians may use such tests selectively when added risk stratification may alter SDM. These recommendations are largely consistent with ASCO Guidelines as well.[61] 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 including most men with low-volume (few involved cores) Gleason score 6 cancer and men with favorable intermediate-risk prostate cancer who are interested in treatment.

The Panel recognizes that this is an active area of research. Most notably, prospective validation of the predictive capacity of genomic classifiers (GC) in localized disease will be important to support widespread use for treatment selection. Additional discussion on GCs may be found in Future Directions.

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, HOXB13, MLH1, MSH2, MSH6, NBN, PALB2, PMS2,* and *TP53*. For example, studies have demonstrated that men with prostate cancer harboring BRCA2 genetic aberrations are more likely to have worse disease and a poorer prognosis.[62] Testing is typically performed via a saliva or blood sample. 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 been outlined by a large expert-panel consensus conference.[63] Several 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.

TABLE 4: Indications for Germline Testing in Patients with Localized Prostate Cancer

Indication*	
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.	

STAGING

5. **Clinicians may use MRI of the prostate in any risk category to determine extent and location of disease in the prostate, guide surveillance biopsies, or plan treatment. (*Conditional Recommendation; Evidence Level: Grade B*)**

Although imaging results are not considered in assigning local (T) stage, multi-parametric MRI (mpMRI) of the prostate can provide important information about the extent and location of disease within the prostate, as well as anatomic information, which can influence management decisions.

MRI can localize the index lesion with moderate sensitivity (approximately 0.6) and high specificity (approximately 0.9),[50, 64-74] with a large-scale meta-analysis corroborating these findings, showing a sensitivity of 57-61% and specificity of 88-96% for extraprostatic extension and seminal vesicle involvement.[50] MRI has been compared with DRE for staging in single-institution studies. In one such study including 506 men who underwent clinical staging by DRE alone and then with MRI followed by surgery, MRI had a sensitivity of 51% for ≥ T3a disease as compared with 12% for DRE ($p < 0.01$).[75] However, specificity was somewhat lower for MRI as compared with DRE (82% versus 97%; $p < 0.01$). Nonetheless, while there are several systems for determining the likelihood of extraprostatic extension based on MRI findings, consensus on such a definition is lacking.[76-78] Most systems incorporate tumor-capsule contact length and morphologic features, such as capsular bulge.

Use of higher field strength (i.e., stronger magnet, such as 3T instead of 1.5T) improves sensitivity of MRI, as does the addition of functional sequences, including diffusion-weighted imaging (DWI), dynamic contrast enhanced (DCE) imaging and magnetic resonance spectroscopic imaging (MRSI) to standard T2-weighted imaging. However, biparametric MRI, limited to T2 and diffusion-weighted phases is non-inferior to mpMRI, which adds the dynamic contrast-enhanced phase for detection of grade group 2 or higher prostate cancer. Thus, biparametric MRI is a reasonable substitute for mpMRI.[79]

In men choosing active surveillance, MRI should be used for targeted biopsy if available but should not replace surveillance biopsies. Additionally, MRI and targeted biopsy should be used for patient selection in focal therapy and for follow-up after treatment; however, it should be used as a complementary study and should not replace tissue sampling.

In radiotherapy, the FLAME trial demonstrated improved 5-year biochemical disease-free survival in intermediate- and high-risk patients who received a radiation 'boost' to MRI-visible targets in addition to whole-gland radiation compared to whole-gland treatment alone (92% versus 85%; HR: 0.45; $p < 0.01$).[80, 81] Follow-up showed a lower probability of local failure (HR: 0.33; 95% CI: 0.14 to 0.78) and regional or distant recurrence (HR: 0.58; 95% CI: 0.35 to 0.93) in the group that received the boost.[82] There was no difference between groups in toxicity. Observational studies have found comparable results.[83]

Regarding patients undergoing surgery, despite the accuracy with which MRI can detect index lesions, extraprostatic extension, and seminal vesicle involvement in addition to the frequency with which treatment plan is altered by MRI findings, the evidence regarding whether preoperative MRI lowers positive surgical margin rates or subsequent biochemical recurrence is mixed.[84-87] A 2019 meta-analysis of 6 studies that directly compared preoperative MRI to no preoperative MRI, including 1 RCT, showed an absolute risk reduction of 5.2% in the likelihood of positive margins at final pathology in patients who had undergone preoperative MRI compared to those who had not (OR: 0.74; 95% CI: 0.63 to 0.87; $p < 0.001$).[85] Additionally, these studies have consistently shown increased use of nerve-sparing among patients who underwent preoperative MRI, suggesting that there may also be benefits in terms of functional outcomes.

In reviewing these studies, the Panel concluded that clinicians may use MRI for local staging in any risk category, not only to refine patient selection for active surveillance and to direct focal therapy, but also to guide treatment in ways that may improve oncologic and functional outcomes. It must be acknowledged, however, that access to MRI may be limited in some settings, and MRI scanner quality and radiologist expertise may influence the utility of MRI and the rate of false-positives and false-negatives.

6. **Clinicians should not routinely perform PSMA PET scan, cross-sectional imaging, or bone scan for nodal or metastatic staging in asymptomatic patients with low- or favorable intermediate-risk prostate cancer. (*Expert Opinion*)**

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 favorable intermediate-risk prostate cancer, the probability of nodal or distant metastasis is low.[88-90] Therefore, molecular imaging (i.e., PSMA PET-CT scan), bone scan, or cross-sectional imaging (contrast-enhanced abdomino-pelvic computed tomography [CT] scan or MRI) for nodal and metastatic staging are unlikely to be helpful and should not be routinely obtained. However, even in the low- and favorable intermediate-risk patients, there may be instances in which symptoms, laboratory abnormalities, or disease characteristics warrant further investigation with imaging.

7. **Clinicians should stage unfavorable intermediate- and high-risk localized prostate cancer using either PSMA PET scan or a combination of bone scan and cross-sectional imaging. (*Strong Recommendation; Evidence Level: Grade B*)**

8. **In patients with unfavorable intermediate- and high-risk localized prostate cancer who have negative conventional imaging, clinicians may obtain PSMA PET scan to evaluate for metastases. (*Expert Opinion*)**

Historically, prostate cancer has been staged with conventional imaging (bone scan plus either CT or MRI). Since many of the studies supporting therapeutic interventions for prostate cancer are predicated on the results of conventional imaging (bone scan plus either CT or MRI), there remains some uncertainty regarding the potential for improved outcomes based on PSMA PET imaging modalities. Nonetheless, there is ample evidence of the greater sensitivity of PSMA PET as compared with conventional imaging for identification of nodal and distant disease, and evidence that findings of PSMA PET imaging can substantially alter the treatment plan and expectations regarding outcomes of treatment (e.g., finding small volume metastatic disease on PSMA PET in a patient otherwise thought to have localized disease by conventional imaging).[91]

PET imaging using F-18 piflufolastat or Gallium-68 PSMA-11 has been approved by the FDA for staging prostate cancer, and additional agents are approved for detection of recurrence and metastatic disease. PSMA PET imaging with these tracers is performed in conjunction with CT or MRI for localization. PSMA PET imaging is standard of care for staging in the setting of recurrence after primary treatment as well as in certain scenarios of advanced disease.[92]

In localized disease, the data regarding sensitivity of PSMA PET for nodal staging vary widely depending on the study. For example, a single-arm study of 764 men with unfavorable intermediate- and high-risk disease using gallium-68 PSMA-11 PET CT showed a relatively low sensitivity for lymph node involvement (40%) with a specificity of 95%.[93] Meanwhile, the proPSMA trial, which enrolled 302 men with similar disease characteristics, showed far higher sensitivity for lymph node involvement using gallium-68 PSMA-11 PET CT (91%).[91] By contrast, in detection of nodal metastasis, MRI has been found to be associated with a low to moderate sensitivity (range 0.09 to 0.44) and high specificity (range 0.88 to 1.0).[65, 69, 70, 94, 95] Therefore, most studies in which PSMA PET has been compared with conventional imaging for nodal staging have shown greater sensitivity and overall accuracy for PSMA PET. In the proPSMA trial, sensitivity for pelvic lymph nodes was 59% for conventional imaging, a 32% absolute difference compared to 91% for gallium-68 PSMA-11 PET CT; PSMA PET also had an advantage in sensitivity for detection of metastatic disease (74% versus 95%).[93] A meta-analysis including 31 studies (2,431 patients) of patients with intermediate- and high-risk disease, showed PSMA PET to be more sensitive and specific than mpMRI (73.7% versus 38.9% and 97.5% versus 82.6%) and CT (73.2% versus 38.5% and 97.8% versus 83.6%) for detection of nodal involvement.[96] Additionally, PSMA PET was more sensitive and specific than bone scan for skeletal metastases (98.0% versus 73.0% and 96.2% versus 79.1%, respectively). Because of the incremental predictive value of PSMA PET, it has been incorporated into nomograms designed to predict lymph node metastases.[97] Importantly, however, the studies showing low sensitivity of PSMA PET imaging for nodal metastases (e.g., the Hope study, which showed only 40% sensitivity) indicate that a negative PSMA PET scan does not rule out nodal involvement.[93]

Taken together, the Panel recommends staging imaging for patients with unfavorable intermediate- and high-risk prostate cancer. PSMA PET imaging, where available, provides improved sensitivity for identification of lymph node involvement and metastatic disease and, therefore, may be preferred. However, many of the treatment paradigms are predicated on conventional imaging, and the association between staging with PSMA PET imaging and downstream oncologic outcomes has not been established. While some studies of PSMA PET for initial staging have included all intermediate-risk patients,[98] the evidence is strongest for the high-risk and unfavorable intermediate-risk patients. Therefore, the Panel determined that the data were insufficient to warrant recommending routine use of staging imaging in favorable intermediate-risk patients.

RISK-BASED MANAGEMENT

9. **Clinicians should inform patients that all prostate cancer treatments carry risk. The risks of treatment 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 SDM approach to management. (*Clinical Principle*)**

The selection of a management strategy for clinically localized prostate cancer is preference-sensitive and very often based on patient 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 and seek their engagement in the decision-making process. The clinician then helps the patient arrive at a decision and then evaluate that decision. 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.[99-102] 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.[101, 103] The National Academy 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.[104, 105] Key components of SDM are illustrated by the Agency for Healthcare Research and Quality SHARE approach in Table 5.

Table 5: AHRQ SHARE Approach to Shared Decision-Making[106]

Seek your patient's participation
Help your patient explore and compare treatment options
Assess your patient's values and preferences
Reach a decision with your patient
Evaluate your patient's decision

In addition to assessing the patient's preferences and facilitating the communication, key roles of the clinician include informing patients about the risks and benefits of each management option. Because prostate cancer is so variable in aggressiveness, 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.

The expected harms of treatment include immediate risks (e.g., perioperative risks associated with surgery), short-term side effects, and long-term (typically quality of life [QOL]) implications. Local treatments are associated with differing profiles of urinary, sexual, and bowel side effects (variously termed 'functional outcomes'), which may evolve or resolve over time.[107] Meanwhile, hormonal therapy, which is sometimes used in conjunction with radiation therapy, is associated with systemic side effects, some of which are symptomatic (e.g., hot flashes, fatigue, cognitive changes, sexual dysfunction) and some of which remain asymptomatic (e.g., changes in metabolic syndrome parameters). The patient must be informed about the expected risks and side effects of each management option in order to compare the options and to facilitate clear expectations. Specifying the likelihood of various outcome scenarios with each treatment can facilitate SDM, and there are tools available to estimate the likelihood of functional outcomes with each treatment.[108]

Since baseline function is one of the strongest predictors of functional outcomes,[107] the clinician should ascertain the patient's pre-treatment urinary, bowel, and sexual function (and hormone therapy-related domains if concurrent hormone therapy and radiation is being considered). These functional domains are best assessed using standardized instruments to minimize clinician bias and to facilitate longitudinal comparisons. The Expanded Prostate Cancer Index Composite (EPIC)-26 is one such validated instrument, and it has been selected by the International Consortium on Health Outcomes Measurement (ICHOM) as part of the 'standard set' of data that should be collected on each patient with clinically localized prostate cancer. A shorter instrument tailored to clinical care is the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP).[109, 110] The 5-item Sexual Health Inventory for Men (SHIM)[111] is an instrument designed to assess erectile function as is the longer 15-item International Index of Erectile Function (IIEF).[112] Alternative questionnaires for assessment of urinary continence include the International Continence Society Male Short-Form (ICSmaleSF)[113] and International Consultation on Incontinence Questionnaires (ICIQ).[114] The EORTC has developed and validated QOL instruments pertinent to a general oncology population (QLQ-C30) and has refined sets for specific cancers, including prostate cancer. The EORTC-QLQ-PR25 assesses urinary function, sexual function, bowel function, and hormone therapy symptoms.[115] Similarly, the Functional Assessment of Cancer Therapy (FACT) measurement system has developed a 12-item prostate cancer subscale (PCS), appended to the 35-item FACT-G for the general oncology population.[116] The

Patient-Reported Outcomes Measurement Information System (PROMIS), initiated by the National Institutes of Health, curates a wide variety of QOL measures, and some have been used to assess symptoms after prostate cancer treatment.[117]

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

Post-treatment cancer recurrence risk is dependent on a number of clinicopathologic factors, including most notably tumor grade and stage, as well as pretreatment PSA and, for patients undergoing radical prostatectomy, surgical margin status.[118] Multiple predictive models and nomograms have been developed to estimate the risks of biochemical recurrence, metastases, and death from prostate cancer.[12, 13, 119-121] 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.

11. 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' 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,[122] 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.[18] 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. These results from ProtecT reinforced numerous cohort studies that have documented the outcomes of patients managed with active surveillance for low-risk prostate cancer and consistently demonstrated low rates of metastases (<1.5%) and prostate cancer related death (<1%) within 10 years after diagnosis.[123-129]

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.[130-132] 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 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 (e.g., high-volume cancer, higher PSA density) or other risk factors for harboring higher-risk disease (e.g., family history of lethal prostate cancer, germline mutation associated with adverse pathology).[133]

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.

12. 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 ≤5 years do not benefit from prostate cancer screening, diagnosis, or treatment[134] as prostate cancer treatment does not improve survival within five years of follow-up.[135] 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.[136, 137]

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 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.

The Panel acknowledges that life expectancy is difficult to predict and notes the existence of several predictive tools to help with this assessment, such as the Kent model.[138]

13. **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.[122] 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,[125, 139] as well as the relatively limited data on very long-term follow-up of such patients and thereby emphasizes the importance of informed SDM. Again, patients electing active surveillance should be informed of the importance of regular cancer surveillance to avoid missing the window of curability. Further, for favorable intermediate-risk patients electing treatment with radiation, at this time, ADT should not be used. The Panel recognizes the ongoing accumulation of evidence on this topic (e.g., NRG RTOG 08-15 trial, the results of which have been presented but not yet published to date). Thus, it remains unclear at this time what the benefit for these patients will be in adding ADT to their radiation treatment. Evolving evidence will inform future practice for these patients.

14. **Clinicians should inform patients with low- and intermediate-risk prostate cancer that whole gland or focal ablation remains investigational without high-quality data comparing ablation outcomes to standard of care therapies such as surgery, radiation therapy, and active surveillance. (*Expert Opinion*)**

Current ablative modalities include high-intensity focused ultrasound (HIFU), cryoablation, focal laser, irreversible electroporation (IRE), and photodynamic therapy (PDT) which are FDA- approved for the treatment of prostate tissue only.[140] Patient selection criteria in reported studies have varied widely as has treatment planning approach (e.g., lesion-based focal therapy, hemi-ablation, whole-gland). An early randomized trial demonstrated that focal PDT lowered the likelihood of cancer progression and rates of surgery compared to active surveillance.[141] However, active surveillance remains the preferred approach for patients with low-risk prostate cancer.

Several institutional, multi-site, and population-based studies have reported outcomes of various ablative therapies for intermediate-risk disease; however, in the 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.[142] Several studies report in-field recurrence rates of 10-40% for any disease, and generally <20% for residual pattern 4 across treatment modalities. However, no trials have compared ablative approaches to each other and detailed outcomes including frequency of salvage radical treatment, and long-term oncologic outcomes are lacking.

Prospective trials publishing early results in focal therapy for prostate cancer demonstrate feasibility and safety. The HIFI study was a nonrandomized prospective study of over 3,300 patients with predominantly intermediate-risk prostate cancer comparing radical prostatectomy to HIFU. The study demonstrated that 30-month salvage treatment-free survival with whole gland or subtotal HIFU was noninferior to that of radical prostatectomy with fewer urinary and sexual side effects. Evidence remains very limited by 2-3 years of follow up, lack of randomization, and large age difference (median 74.7 versus 65.1 years in HIFU versus radical prostatectomy groups, respectively).[143] In another single-arm phase 2b multicenter study, MRI-guided focused ultrasound focal therapy for intermediate-risk prostate cancer achieved a 24-month in-field disease-free rate of ~88% (defined as Grade Group ≥2 cancer in the treated area) with potential to safely delay or eliminate the need for radical whole-gland treatment in the long term. There are no RCTs comparing HIFU to standard of care treatment modalities including radical prostatectomy, radiation, or active surveillance. While HIFU may have benefit in select patients, its long-term efficacy relative to standard treatments remains unproven, and the appropriate patient population remains undefined. The panel cautions against wide implementation of HIFU in the absence of high-level evidence.

Retrospective Surveillance, Epidemiology, and End Results (SEER) studies have examined population-based outcomes from cryoablation compared to radiation in low- and intermediate-risk patients, and differences in patient selection temper any conclusions.[144, 145] There are no rigorous, contemporary trials comparing cryoablation to surgery or radiation therapy. The Panel considers cryotherapy to be a non-standard option for intermediate-risk patients.

Similarly, published data on focal laser ablation is limited to single center retrospective series comparing selected patients to younger and healthier patients undergoing prostatectomy or radiation therapy. No clear difference in cancer-specific survival is demonstrated. Other modalities including IRE and PDT are being tested in intermediate-risk prostate cancer. Early functional outcomes show minimal urinary and sexual side effects, but oncologic outcomes comparing their use to standard of care are not proven.

Currently, the Panel believes that broader use of ablative techniques should be limited to clinical trial enrollment. They can be used in appropriately informed patients with intermediate-risk prostate cancer declining standard therapies, and ideally in a prospective study.[146] Patients with low-risk cancers should still be offered active surveillance. Patients considering ablation should be counseled regarding side effects and recurrence risk and should be followed post-ablation with routine PSA, MRI, and biopsy tailored to their specific health and cancer characteristics to detect disease, persistence, or recurrence.

15. **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.[148-151] 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.[152, 153] 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). 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 ³ 40 ng/mL, or ³ Gleason 8), treatment with radiation and ADT can include two years of concurrent abiraterone acetate plus prednisone as well.[154]

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

Currently, patients being considered for ablation should have intermediate-risk prostate cancer.[146] Patients with high-risk disease should not be recommended ablative techniques due to lack of evidence and risk of missing or delaying definitive approaches with proven benefit.

17. **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. Indeed, among eight cohort studies evaluating survival outcomes between primary ADT and observation in prostate cancer populations of various risk categories - all of which were rated as having a moderate risk of bias - none demonstrated improvements in all-cause or prostate cancer-specific survival.[39, 155-161] Moreover, in a cohort study of patients with unfavorable intermediate- or high-risk clinically localized prostate cancer, no significant differences were identified between immediate treatment with primary ADT versus observation with regard to all-cause (adjusted HR: 0.69; 95% CI: 0.45 to 1.07) or prostate cancer-specific mortality (adjusted HR: 2.69; 95% CI: 0.77 to 9.32).[155] Likewise, in a population-based analysis of patients with poorly differentiated tumors using SEER Medicare data, no significant differences were noted between immediate treatment with primary ADT versus observation with regard to overall mortality (adjusted HR: 1.04; 95% CI 0.97 to 1.13) or prostate cancer-specific mortality (adjusted HR: 1.12; 95% CI: 0.96 to 1.29).[157] Of note, in one trial, patients with clinically localized prostate cancer who were unfit for (or declined) local treatment were randomized to immediate versus delayed (at the time of symptomatic progression or metastatic disease) ADT.[162] Although the trial did not report outcomes specifically for patients with high-risk prostate cancer, immediate treatment with ADT was associated with a decrease in overall mortality (HR: 0.80; 95% CI: 0.68 to 0.95), but not prostate cancer-specific mortality (10-year incidence 24.8% versus 26.0%, p=0.44) or disease progression. Further, the study was rated as having moderate risk of bias due to open-label design and unclear blinding of outcomes.

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.

PRINCIPLES OF MANAGEMENT

Principles of Active Surveillance

18. **Patients managed with active surveillance should be monitored with serial PSA values and repeat prostate biopsy. (*Expert Opinion*)**

Patients managed with active surveillance need to be counseled regarding the importance of continued follow-up as part of this management strategy. Indeed, active surveillance is distinct as a management strategy from watchful waiting, or passive surveillance, by the incorporation of follow-up cancer testing, including prostate biopsy. While the intensity of monitoring has varied among the various reported large active surveillance cohorts to date, [125, 126, 129, 163, 164] critical components include following PSA values, which the Panel advises be in general obtained no more frequently than every six months and updating a symptom assessment and physical examination with DRE every one to two years.

Notably, the monitoring regimen for patients managed with active surveillance may be individualized. For example, among patients at low risk of progression or with a more limited life expectancy, a less intense follow-up schedule may be implemented.[165] With regard to the use of genomic testing, as previously noted, while biopsy-based genomic testing may impact the decision of surveillance versus treatment, robust data are currently lacking for meaningful long-term outcomes among contemporary patients managed with active surveillance. In addition, serial genomic testing among patients on active surveillance should be discouraged.

An increase in PSA in a patient being managed with active surveillance should initially prompt re-testing of PSA as transient PSA elevations are common and PSA kinetics have variably been associated with pathology among patients on surveillance.[166, 167] Serial PSA increases, new DRE abnormalities, or other concerns for clinical progression should prompt re-evaluation with MRI and possible prostate biopsy; less frequently, direct conversion to treatment may be considered. Detection of significantly higher-volume or higher-grade disease on surveillance biopsy should then prompt discussion of definitive therapy. The decision to continue surveillance versus proceed with treatment should incorporate the principles of SDM and include the factors of age, comorbidity status, estimated life expectancy, cancer characteristics, and patient preference, balancing the relative risks of impacting quality-of-life with treatment and disease progression.

19. In patients selecting active surveillance, clinicians should utilize MRI to augment risk stratification, but this should not replace periodic surveillance biopsy. (*Expert Opinion*)

The purpose of active surveillance for suitable patients is to maintain patients' QOL by deferring or delaying definitive treatment when prostate cancer is unlikely to cause mortality or significant morbidity, while simultaneously ensuring the appropriate potential to implement definitive treatment with curative intent should this become necessary. As such, a critical component of management with active surveillance for patients with newly diagnosed prostate cancer is an assessment of the patient's risk for harboring more aggressive disease in the prostate than was detected on biopsy, which would thereby render the patient at increased risk for experiencing subsequent disease progression. MRI has been utilized as one such tool for risk assessment in this setting,[168, 169] particularly among patients whose initial prostate biopsy was performed without prior MRI guidance. The purported rationale here has been to obtain complete gland imaging, potentially allowing detection of more aggressive disease in the prostate in regions not sampled on the patient's diagnostic biopsy. Patients with positive MRI findings have been found to be more likely to contain clinically significant disease (typically, higher Grade Group).[170]

A role for MRI prior to confirmatory biopsy among patients on active surveillance for low-risk prostate cancer was investigated in the prospective, randomized ASIST trial.[171] Although the initial report of the trial did not find a statistically significant difference in the rate of biopsy upgrading among patients with versus without a pre-confirmatory biopsy MRI, a follow-up report from the trial found that patients who underwent MRI had fewer active surveillance failures and less grade progression at two years follow-up post biopsy.[172] Thus, the Panel believes that an MRI should be obtained if the initial (diagnostic) prostate biopsy was performed without MRI guidance. If the MRI demonstrates findings suspicious for clinically significant prostate cancer (PIRADS 4 or 5), then timely repeat (confirmatory) targeted biopsy is recommended, with disease risk re-established based on these biopsy results. Conversely, if the MRI is assessed as PIRADS 1, 2, or 3, then repeat biopsy may be performed within approximately 12 months after diagnosis. Thereafter, serial surveillance biopsies are recommended every one to four years depending on patient age, health, risk of progression, and preference.[168, 173, 174]

Evidence for the utility of serial prostate MRI to evaluate for changes in disease risk among patients on surveillance remains mixed; as such, MRI cannot be recommended as a stand-alone replacement for periodic repeat biopsy.[175] For example, a cohort study demonstrated that a surveillance strategy using MRI or clinical changes as the sole indicator for repeat biopsy would have missed upgrading to Grade Group 2 or higher in 169 of every 1,000 patients on surveillance, leading to the conclusion by the authors that periodic biopsy should remain a component of the management of patients on surveillance.[176] A subsequent meta-analysis found a pooled sensitivity and specificity for detecting Grade Group of 2 or more of 0.59 (95% CI: 0.44 to 0.73) and 0.75 (95% CI: 0.66 to 0.84), respectively.[177] It should be noted that interobserver variability in interpreting MRI may be a limitation. Therefore, while the Panel recognizes that MRI may be utilized in patients electing active surveillance, further study is warranted to determine the optimal timing and incorporation of continued imaging for patient management.

Principles of Surgery

20. In patients electing radical prostatectomy, nerve-sparing, when oncologically appropriate, should be performed. (*Moderate Recommendation; Evidence Level: Grade B*)

Preservation of the neurovascular bundles during radical prostatectomy has consistently been associated with a lower likelihood of postoperative erectile dysfunction, has variously but favorably been associated with improved urinary continence after surgery, and has not been found to significantly compromise the rates of positive surgical margins or biochemical recurrence.[178-181] The Panel does acknowledge, however, that the systematic review did not identify RCTs of nerve-sparing versus non-nerve sparing radical prostatectomy. The Panel also recognizes the balance between nerve preservation and optimizing cancer control. Indeed, the decision to perform nerve-sparing is frequently multifactorial, and may include PSA, DRE, biopsy findings (grade, tumor volume, and location), MRI findings, as well as the patient's baseline erectile function and stated prioritization of sexual function. The

Panel further asserts that MRI should not be used in isolation to determine nerve-sparing, as the ability of MRI to predict extracapsular extension, particularly when microscopic, is suboptimal.[182] Importantly, the Panel notes that nerve-sparing does not necessarily entail an "all or none" decision, and both partial nerve preservation and unilateral nerve-sparing may be utilized.

21. Clinicians should inform patients that pelvic lymphadenectomy provides staging information, which may guide future management, but does not have consistently documented improvement in metastasis-free, cancer-specific, or OS. (*Moderate Recommendation; Evidence Level: Grade B*)

22. Clinicians should use nomograms to select patients for lymphadenectomy. The potential benefit of identifying lymph node positive disease should be balanced with the risk of complications. (*Clinical Principle*)

The systematic review supporting this guideline identified 44 studies (N=244,889 patients) detailing the outcomes of patients who variously did or did not undergo pelvic lymph node dissection (PLND) at the time of radical prostatectomy for clinically localized prostate cancer. Of note, the absence of robust prospective clinical trials comparing the results of patients undergoing PLND versus not, as well as significant methodological issues (e.g., heterogeneity in risk of harboring lymph node positive disease among the populations studied, lack of standardized dissection templates) and bias limit the level of evidence from the reported outcome data. That said, from the existing literature, no consistent benefit to PLND can be derived with regard to oncologic outcomes such as biochemical recurrence, metastasis-free, cancer-specific, and OS.[183-188] Two prospective trials randomized patients undergoing radical prostatectomy to limited versus extended PLND.[189, 190] In both trials, no statistically significant difference in subsequent biochemical recurrence-free survival was identified between the treatment arms, although one of the trials did note improved biochemical recurrence-free survival with extended lymph node dissection in an exploratory subgroup analysis of patients with Grade Group 3 to 5 tumors.[189] At the same time, the systematic review did demonstrate a higher risk of adverse perioperative outcomes in patients undergoing PLND (operating time, blood loss, length of stay) and post-operative complications – most notably lymphocele.[191]

Nevertheless, as PLND (specifically, an extended PLND) does facilitate identification of positive nodes,[189, 192] the Panel concluded that patients should be counseled regarding the staging benefit of PLND. Identifying positive nodes not only contributes to refined risk stratification/patient counseling, but may further be used to guide the selective application of secondary therapies.[193, 194] Given the uncertain oncologic benefit and noted – albeit small – increased risk of complications with PLND, the Panel believes that PLND should be advised according to a risk stratified approach, using nomograms for risk assessment. Several nomograms exist to facilitate selection of patients for PLND.[195-197] When selecting a model, it is important that clinicians consider the risk profile of the patients included in model development (e.g., percentage of high-risk patients) as well as the reference standard (e.g., extended versus limited PLND) utilized to establish the model's predictive capacity. Existing national and organizational guidelines have proposed various thresholds of nomogram-predicted probability of lymph node positive disease for clinicians to perform a PLND at the time of radical prostatectomy. Recognizing varying individual risk tolerance, the Panel believes that the patient's calculated risk of harboring positive nodes should be discussed along with the utility of establishing the presence of positive nodes to inform future management and the risks associated with PLND and to facilitate the SDM approach to performing lymph node dissection.

23. Clinicians performing pelvic lymphadenectomy should perform an extended dissection, which improves staging accuracy compared to a limited dissection. (*Moderate Recommendation; Evidence Level: Grade: B*)

Using anatomic landmarks, PLND templates may be considered as follows:[187]

- Limited = obturator fossa
- Standard = limited plus external iliac lymph nodes
- Extended = Standard plus internal iliac lymph nodes
- Super-extended = Extended plus common iliac, presacral and/or other nodes

Extended PLND results in higher lymph node counts as well as a greater positive lymph node yield.[189, 191, 192, 198] While a more extensive lymph node dissection increases operative time as well as the risk of lymphocele,[191] the Panel believes that the demonstrated staging benefit supports that extended dissection should be performed for appropriately risk-selected patients undergoing PLND.

24. Clinicians should complete a radical prostatectomy if suspicious regional nodes are encountered intraoperatively. (*Moderate Recommendation; Evidence Level: Grade C*)

The Panel acknowledges the absence of prospective trial testing in this setting. Numerous retrospective series – largely in historic cohorts of patients from an era during which frozen section analysis of pelvic lymph nodes at the time of prostatectomy was routine – have reported a benefit to completion of radical prostatectomy among patients found to have positive nodes versus patients whose surgery was aborted and who were then treated with ADT alone.[199-202] Recognizing the design/methodologic limitations of these studies, the Panel believes that completion of surgery remains warranted among patients for whom lymph nodes suspicious for harboring malignancy are encountered during surgery, particularly given the overall demonstrated safety of radical prostatectomy in contemporary series.[203]

25. Clinicians should risk stratify patients with positive lymph nodes identified at radical prostatectomy based on pathologic variables and postoperative PSA. (*Expert Opinion*)

26. Clinicians may offer patients with positive lymph nodes identified at radical prostatectomy and an undetectable post-operative PSA adjuvant therapy or observation. (*Conditional Recommendation; Evidence Level: Grade C*)

Importantly, the documented postoperative natural history of patients with lymph node positive disease at radical prostatectomy is relatively heterogeneous. In fact, up to 30% of patients with positive lymph nodes may remain free of disease long-term following surgery without further therapy.[204-206] As such, assessment of the risk for subsequent disease progression among patients with positive lymph nodes is warranted to guide the judicious use of secondary therapy. Various clinicopathologic features have been associated with oncologic outcomes in this setting, particularly the number of positive nodes identified.[207]

Further, while salvage therapy would be appropriate for such patients with a persistently detectable PSA after radical prostatectomy, the Panel believes that patients with an undetectable PSA may be offered adjuvant treatment versus continued PSA surveillance. Of note, a randomized trial in 98 patients assessed the use of immediate, indefinite ADT after radical prostatectomy for patients with lymph node positive disease versus delayed treatment with ADT (largely at the time of systemic progression).[193] At the median 11.9 year follow-up, immediate ADT was associated with improved PFS (HR: 3.42; 95% CI: 1.96 to 5.98), prostate cancer-specific survival (HR: 4.09; 95% CI: 1.76 to 9.49), and OS (HR: 1.84; 95% CI: 1.01 to 3.35). However, relevant to contemporary management, the trial did not assess the comparative outcomes of adjuvant ADT versus ADT initiated at the time of biochemical recurrence, thus the optimal timing to initiate postoperative ADT for patients with lymph node positive disease remains to be determined. Interestingly, six cohort studies investigating this topic have reported mixed findings.[208-213] Three studies found no significant association between treatment with adjuvant ADT[208, 210, 213] and oncologic outcomes including biochemical recurrence-free survival, metastasis-free survival, prostate cancer-specific survival, and OS, while three studies found improvement in various cancer-specific outcomes in certain populations.[209, 211, 212]

The role of postoperative radiation for patients with lymph node positive disease has not to date been addressed in the prospective clinical trial setting. Rather, a number of cohort studies have reviewed the outcomes of patients with lymph node positive disease treated with adjuvant ADT with or without adjuvant radiation as well.[210-212, 214-218] Five of those studies demonstrated improvements in a variety of oncologic outcomes, including overall and cause-specific survival when adjuvant radiation therapy was added to ADT.[210, 211, 214, 217, 218] In addition, a retrospective analysis noted superior metastases-free survival among patients with lymph node positive disease treated with adjuvant radiation versus a cohort who received no treatment/salvage radiation.[210] Nevertheless, the absence of prospective data preclude definitive recommendations regarding the optimal timing of radiation in patients with lymph node involvement at surgery.

Therefore, the Panel believes that both adjuvant therapies (e.g., ADT, radiation) as well as surveillance with the option for early salvage therapy should the patient experience PSA relapse may be utilized for patients with positive lymph nodes at radical prostatectomy and an undetectable postoperative PSA. The approach taken should be based on SDM, including an assessment of disease risk stratification (e.g., number of positive nodes, primary tumor features) as well as the potential toxicities of additional therapies.

27. Clinicians should not routinely recommend adjuvant radiation therapy after radical prostatectomy. (*Strong Recommendation; Evidence Level: Grade A*)

Three randomized trials (GETUG-AFU 17, RAVES, RADICALS) evaluated adjuvant radiation therapy versus surveillance with early salvage radiation therapy for PSA increase in patients with high-risk localized prostate cancer following radical prostatectomy.[219-221] The criteria for early salvage therapy was a PSA >0.1 ng/mL or >0.2 ng/mL depending on the trial; the proportion of patients in the early salvage therapy groups that received radiation therapy ranged from one third to one half. All three trials demonstrated no significant difference in oncological outcomes between patients who received adjuvant radiation therapy versus patients managed with surveillance and early salvage therapy. Moreover, a prospectively planned systematic review of these trials found no evidence of improvement in event-free survival (pooled HR: 0.95; 95% CI: 0.75 to 1.21) with receipt of adjuvant therapy and noted that adjuvant radiation was associated with increased risk of genitourinary toxicity.[222] Given these findings, together with the observation that between one third and one half of the patients in the surveillance arm of the trials did not require salvage therapy, the Panel concluded adjuvant radiation therapy should not be routinely recommended, and patients should be initially managed with PSA surveillance after radical prostatectomy. The Panel does recognize the relatively limited number of patients included in the trials with particularly high-risk features (e.g., Gleason 8 to 10 disease with extraprostatic extension, positive lymph nodes) and thereby acknowledges a potential role for adjuvant radiation in such select patients.[223]

Principles of Radiation

28. Clinicians should utilize available target localization, normal tissue avoidance, simulation, advanced treatment planning/delivery, and image-guidance procedures to optimize the therapeutic ratio of EBRT delivered for prostate cancer. (*Clinical Principle*)

As is common with other tumor systems in which radiation therapy is delivered for therapeutic benefit, an overarching paradigm in prostate cancer radiation therapy is the application of appropriate evidence-based dosages to the cancer target while simultaneously avoiding sensitive adjacent normal tissues. In this way, the therapeutic ratio between tumor control and normal tissue injury is established to maximize therapeutic benefit while minimizing toxicity, morbidity, and potentially treatment-related mortality. Over the past few decades, the specialty of radiation oncology has leveraged various technologies to achieve this goal of improved cancer outcomes with equal or improved toxicity profiles.

A variety of approaches exist to optimize the therapeutic ratio in radiation oncology. A non-exhaustive list of these approaches includes the following:

- Simulation procedures: Bladder/rectum filling instructions, patient immobilization, placement of fiducial markers, and use of rectal spacers
- Imaging procedures: CT simulations, integrations of fusion imaging (e.g., MRI prostate), image-guided radiation therapy (IGRT) approaches (e.g., cone-beam CT)
- Planning procedures: Use of highly conformal radiation therapy such as IMRT, volumetric modulated arc therapy (VMAT), and stereotactic body radiation therapy (SBRT), combined with published target and normal tissue dose objectives to optimize planning

Most of these approaches have not been subject to prospective randomized phase III trial testing. One exception is the use of rectal spacers, which was evaluated in a trial that randomized 222 patients 2:1 to either a rectal spacer or control group prior to 79.2 Gy in 1.8 Gy fractions to the prostate ± seminal vesicles.[224, 225] With a median follow-up of three years, improvements in low-grade (one and two) rectal toxicity, no difference in urinary toxicity, and improvements in bowel health-related QOL were identified.[225] Device-related toxicity events were not detected in this trial.[224] Of note, the utility of this technology in conjunction with hypofractionated or ultra hypofractionated radiation therapy has not been reported in prospective randomized clinical trials to date.

29. Clinicians should utilize dose escalation when EBRT is the primary treatment for patients with prostate cancer. (*Strong Recommendation; Evidence Level: Grade A*)

With the introduction of modern treatment planning software and CT scans in the late 1980s and early 1990s, radiation oncology techniques evolved from basic conventional techniques using simple 2-dimensional planning. Prior to the implementation of sophisticated treatment planning software and CT scans, radiation doses used in the treatment of prostate cancer were limited to between 65-70 Gy.

Advances in radiation treatment planning software and imaging technology have allowed delivery of higher doses to the prostate while limiting doses to the surrounding normal tissues such as rectum and bladder, thus improving the therapeutic ratio.[226, 227] The current standard technique of EBRT is IMRT, which allows dose escalation to greater than 80 Gy safely.

Since the 1990s, multiple phase III randomized prospective studies have compared dose-escalated EBRT (DE-EBRT) using both 3-D conformal radiation therapy (3DCRT) and IMRT with standard dose EBRT and have consistently demonstrated improved biochemical PFS with dose escalation. Multiple randomized trials (sample sizes 126 to 1,499) compared escalated versus conventional dose radiation therapy in patients with localized prostate cancer.[228-242] The trials enrolled a mix of low-, intermediate-, and high-risk patients. Escalated doses ranged from 74 to 79.2 Gy, while conventional doses ranged from 64 to 70.2 Gy. The trials consistently demonstrated that escalated dose radiation therapy was associated with decreased rates of biochemical failure or recurrence. Of note, the Panel acknowledges that estimates from these trials for the endpoints of metastatic-disease free survival, prostate cancer-specific survival, and OS were imprecise and did not indicate a benefit to dose escalation, with the exception of one trial[236, 238, 240] that did report reduced risks of distant metastatic failure (HR: 0.33; 95% CI: 0.13 to 0.82) and prostate cancer mortality (HR: 0.52; 95% CI: 0.27 to 0.98). The largest of the trials was NRG-RTOG 0126 (n=1,499) which looked at standard versus dose-escalated radiation therapy in patients with intermediate-risk prostate cancer.[237] This trial demonstrated improvements in biochemical failure and distant metastases; however, the dose-escalated radiation therapy arm was not associated with improvements in OS. Furthermore, higher radiation doses were also associated with lower rates of post-radiation salvage at the expense of higher rates of late toxicity. Importantly, this trial has provided clinicians valuable information about radiation dose constraints for the safe planning of dose-escalated radiation therapy for intermediate-risk prostate cancer.[243]

30. Clinicians may counsel patients with prostate cancer that proton therapy is a treatment option, but it has not been shown to be superior to other radiation modalities in terms of toxicity profile and cancer outcomes. (*Conditional Recommendation; Evidence Level: Grade C*)

To date, no prospective study has demonstrated improved disease control or side effects with proton beam radiation therapy (PBRT) compared to intensity-modulated radiotherapy (IMRT). Proponents of PBRT have offered that it has dosimetric advantages compared to IMRT. That is, while the target volume for both techniques includes the prostate and a margin of normal tissue (bladder and rectum) that is irradiated to the prescribed dose, proton beam delivers lower integral doses and mean doses to normal tissues compared to IMRT.[244] However, this dosimetric difference has not been shown to result in fewer side effects or better patient reported QOL. Indeed, the existing peer-reviewed literature suggests that clinical outcomes (e.g., complications, patient-reported QOL) are similar.[245]

Comparative effectiveness studies have been published to evaluate relative toxicity and oncologic outcomes between proton and photon therapies. Three studies comparing patients treated with proton therapy or photon therapy reported similar toxicity rates and patient reported outcomes. A prospective comparison of patients treated with IMRT (n=204) and patients treated with proton therapy (n=1,234) with regard to patient-reported outcomes measured using the EPIC instrument concluded that "no differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts" after up to 2 years of follow-up.[246] Meanwhile, a retrospective analysis of Medicare data from 421 patients treated with proton therapy and a matched cohort of 842 patients treated with IMRT showed less genitourinary toxicity at 6 months with proton therapy, although the difference disappeared after 1 year.[247] No other significant differences were seen between the groups. A more recent large observational study of 772 low- or intermediate-risk group prostate cancer patients treated with either PBT or IMRT compared patient-reported gastrointestinal and genitourinary toxicities.[248] Authors found no significant difference in late gastrointestinal or genitourinary toxicities between the two treatment modalities at 12 and 24 months. After adjusting for factors such as age and risk group, both PBT and IMRT demonstrated low rates of toxicity.

A report compared PBRT to IMRT using a case-matched approach.[249] This observational study of 177 patients found that oncological outcomes (long-term biochemical failure-free survival, prostate cancer-specific survival, and OS) were similar between PBT and IMRT (all p>0.05).

Randomized trials are ongoing comparing IMRT and PBRT using long-term side effects and QOL as the primary endpoints. The PARTIQoL trial, which has a primary endpoint of bowel function at 24 months, has three preliminary reports including a description of baseline characteristics of the study participants.[250-252]

31. **Clinicians should offer moderate hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT. (*Strong Recommendation; Evidence Level: Grade A*)**

32. **Clinicians may offer ultra hypofractionated EBRT for patients with low- or intermediate-risk prostate cancer who elect EBRT. (*Conditional Recommendation; Evidence Level: Grade B*)**

Using fewer (but larger dose) radiation treatments (i.e., hypofractionation) may be more convenient for patients with prostate cancer electing radiation therapy.[253] Nevertheless, demonstrating equivalent cancer control and toxicity profiles with such an approach is paramount.

A systematic review compared hypofractionated (>2 Gy per fraction, range 2.35 to 3.4 Gy) versus conventionally fractionated (1.8 to 2 Gy) EBRT in patients with localized prostate cancer.[253] This review included 10 randomized trials (N=8,278); seven trials used highly conformal radiation therapy, six used IGRT, and two trials reported some form of motion management. In pooled analyses, no differences were noted between hypofractionation versus conventional fractionation with regard to biochemical recurrence-free survival (HR: 0.88; 95% CI: 0.68 to 1.13, 5 trials), metastasis-free survival (MFS) (HR: 1.07; 95% CI: 0.65 to 1.76, 5 trials), prostate cancer-specific survival (HR: 1.00; 95% CI: 0.72 to 1.39, 8 trials), or OS (HR: 0.94; 95% CI: 0.83 to 1.07, 10 trials). There were also no differences identified regarding acute genitourinary radiation therapy toxicity (Relative Risk [RR]: 1.03; 95% CI: 0.95 to 1.11, 4 trials), late genitourinary radiation therapy toxicity (RR: 1.05; 95% CI: 0.93 to 1.18), or late gastrointestinal radiation therapy toxicity (RR: 1.10; 95% CI: 0.68 to 1.78). Findings were consistent in stratified analyses based on radiation therapy dose (≥74 Gy or <74 Gy), difference in radiation therapy doses between hypofractionation and conventional fractionation, radiation therapy technique (highly conformal versus 3DCRT), and use of ADT (≤50% of >50%). Moreover, three trials (n=92, 139, and 303) published subsequent to the systematic review likewise found no clear differences between moderate hypofractionation (fraction size 2.25 to 2.7 Gy, total 70 to 72 Gy) versus conventional fractionation (fraction size 2.0 Gy, total 74 to 80 Gy) in oncological outcomes, QOL, or adverse events, though some estimates were imprecise.[254-257]

One randomized trial (HYPO-RT, n=1,200) compared ultra hypofractionation (42.7 Gy in 7 fractions, fraction size 6.1 Gy) versus conventional fractionation (78.0 Gy in 39 fractions, fraction size 2 Gy) in patients undergoing radiation therapy with image-guided 3DCRT, IMRT, or VMAT for intermediate- or high-risk localized prostate cancer.[258, 259] Ultra fractionation was found to be non-inferior to conventional fractionation with regard to failure-free survival (HR: 1.00; 95% CI: 0.76 to 1.32), prostate cancer mortality (incidence at 5 years 2% versus 1%, p=0.46), and OS (HR: 1.11; 95% CI: 0.73 to 1.69). In addition, although ultra hypofractionation was associated with increased incidence of acute urinary and bowel symptoms, no differences were found in late symptoms or QOL.

Currently, data on long-term control with ultra hypofractionated compared to moderate hypofractionation is less well documented; however, data to date support the use of hypofractionated EBRT. Of note, the recommendations herein are consistent with existing guidance provided by ASTRO/ASCO/AUA.[260]

33. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary high-dose rate (HDR) prostate implant as equivalent forms of treatment. (*Strong Recommendation; Evidence Level: Grade B*)

Trial data support the use of dose-escalated hypofractionated EBRT or brachytherapy including temporary high-dose rate (HDR) or permanent low-dose rate (LDR) prostate implants as appropriate treatment options for patients with low- or favorable intermediate-risk prostate cancer.[261]

Importantly, the systematic review undertaken for guideline development identified no randomized trials comparing EBRT to brachytherapy. Of note, a retrospective analysis among patients with intermediate-risk prostate cancer (n=684) found no difference between EBRT (75.3 Gy) versus brachytherapy (radioactive iodine seeds at minimum peripheral dose of 145 Gy), with or without neoadjuvant ADT, in propensity score adjusted 10-year MFS (91% versus 94%), prostate cancer-specific survival (96% versus 95%), or OS (76% versus 78%).[262] EBRT was associated with decreased likelihood of freedom from biochemical failure (57% versus 80%).

To note as well, in a Phase II trial of 170 patients randomized to receive HDR as either a single (19 Gy) fraction or as two fractions (13.5 Gy), the 5-year biochemical disease-free survival and cumulative incidence of local failure was 73.5% and 29% in the single fraction arm and 95% ($p = 0.001$) and 3% ($p < 0.001$) in the 2-fraction arm, respectively.[263] Toxicity results from this study were reported separately; in the single fraction arm, the 5-year cumulative incidence of Grade 2 or higher genitourinary and gastrointestinal toxicity was 62% and 12%, and was 47% and 9% in the two-fraction arm. Grade 3 genitourinary toxicity was only seen in the single fraction arm. No significant differences in mean urinary health related QOL were seen compared to baseline in the two-fraction arm, in contrast to the single-fraction arm, wherein a decline in urinary health-related QOL was seen at 4 and 5 years. The authors ultimately concluded that both single fraction and 2-fraction HDR monotherapy were well tolerated.[264]

34. In patients with low- or intermediate-risk prostate cancer electing radiation therapy, clinicians should not electively radiate pelvic lymph nodes. (*Strong Recommendation; Evidence Level: Grade B*)

A prior trial (n=446) that compared whole pelvis (46 Gy with cone-down to prostate) to prostate-only (66 to 70 Gy) radiation therapy among low-, intermediate-, and high-risk patients with clinical stage T1b-T3 localized prostate cancer found no difference in PFS (adjusted HR: 0.96; 95% CI: 0.64 to 1.43) or OS between the treatment arms.[265, 266] Similarly, the RTOG 9413 trial, which contained intermediate-risk patients and utilized a 2 x 2 factorial design, demonstrated no significant difference in biochemical failure when comparing whole pelvic radiation therapy to prostate-only radiation.[267-269] As these are the only prospective trials with sub-groups of intermediate-risk patients, and no benefit was found with nodal radiation, the Panel recommends against the routine use of elective pelvic nodal irradiation for low- and intermediate-risk patients electing radiation therapy.

35. In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should not routinely use ADT. (*Moderate Recommendation; Evidence Level: Grade B*)

ADT is associated with well-recognized side effects and may significantly impact patients' health-related QOL.[270, 271] These side effects commonly include (but are not limited to) decreased libido, erectile dysfunction, hot flashes, depression and other mood disturbances, fatigue, and weight gain. In addition, treatment with ADT may result in significant changes in metabolic function, including reduction in bone mineral density, increased insulin resistance, and changes in blood lipid profiles.[272]

Given the potential deleterious short- and long-term effects of ADT, its application in the treatment of localized prostate cancer must be based on an individualized risk-benefit balance. While a number of randomized trials have investigated the use of ADT in combination with radiation therapy versus radiation therapy alone,[273-286] most of these studies have investigated intermediate- and high-risk cancer populations. However, in a large trial (n=2,028) that included patients in all risk strata, the use of ADT was not associated with improved OS outcome for low-risk patients (HR: 0.93; 95% CI: 0.72 to 1.20).[281] Moreover, although trials have demonstrated a benefit to ADT with radiation for intermediate-risk patients, these trials have not consistently sub-stratified intermediate-risk patients into favorable and unfavorable risk for separate outcome reporting. In line with recommendations of other organizations,[14] the Panel believes that routine use of ADT in favorable intermediate-risk patients is not recommended given the observed positive cancer outcomes of radiotherapeutic monotherapy for this patient population (acknowledging the exception of unique circumstances such as planned prostate gland volume reduction prior to definitive radiation therapy, in which ADT may be useful). At the same time, the Panel recognizes that the utility of ADT for favorable intermediate-risk localized prostate cancer is currently under investigation (e.g., NRG Oncology/RTOG 0815).

36. In patients with unfavorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer the addition of short-course (four to six months) ADT with radiation therapy. (*Strong Recommendation; Evidence Level: Grade A*)

Given the higher risk of local and distant relapse with unfavorable intermediate-risk disease, the use of ADT is recommended for this patient population. Eight randomized trials have evaluated the role of ADT with radiation therapy versus radiation therapy alone.[273-286] All eight trials included intermediate-risk patients, with one trial including patients from all risk strata[281] and one trial exclusive to intermediate-risk patients only.[286] These trials were heterogeneous in terms of radiation therapy dosage (ranging from 65 to 78 Gy) and technique (3DCRT and IMRT), as well as ADT duration (three to six months in all trials except one trial, which treated for three years), ADT timing (neoadjuvant in five trials, concurrent in two trials, and unknown in one trial), and ADT type (LHRH agonist plus antiandrogen in six trials, LHRH agonist alone in one trial, and antiandrogen in one trial). Regardless, these studies collectively demonstrated a consistent benefit regarding oncologic outcomes among the patients who received ADT with radiation. In an analysis stratified by prostate cancer risk category from one of these trials (n= 2,028), radiation therapy plus short-term ADT was associated with improved OS among patients with intermediate-risk disease (HR: 0.81; 95% CI: 0.67 to 0.98).[281] The benefit of hormonal therapy was also demonstrated in the published MARCAP meta-analysis, which demonstrated that the addition of ADT to radiotherapy significantly improved MFS (HR: 0.83; 95% CI: 0.77 to 0.89; p<0·0001).[287]

Toxicity was assessed in seven of the trials indicated above.[273-278, 280-286] The use of ADT was associated with expected toxicities during ADT administration. These effects generally diminished or resolved after discontinuation of ADT treatment.[286] Notably, late gastrointestinal and genitourinary effects were not impacted using ADT with radiation therapy.[275, 282, 286]

With regard to the duration of ADT with radiation in unfavorable intermediate-risk disease, six clinical trials assessed very short course ADT (eight weeks to three months) versus standard short course ADT (six months) in intermediate-risk disease, five of which demonstrated that the six-month approach had superior cancer outcomes, including all-cause mortality and/or prostate cancer-specific mortality.[276, 279, 288-297] Nevertheless, the Panel acknowledges that a four-month course of ADT is also commonly given to patients with radiation therapy for intermediate-risk disease in an effort to mitigate the deleterious effects of ADT while maintaining the benefit of combination therapy for cancer control.

37. Clinicians should offer moderate hypofractionated EBRT for patients with high-risk prostate cancer who are candidates for EBRT. (*Moderate Recommendation; Evidence Level: Grade C*)

As noted previously, moderate hypofractionation holds important advantages in terms of patient convenience and resource utilization. Moreover, multiple large-scale randomized prospective clinical trials have been completed comparing moderately hypofractionated and conventionally fractionated EBRT.[231, 256, 298, 299] These studies have demonstrated that moderate hypofractionation confers similar prostate-cancer-control outcomes and similar rates of late toxicity compared to conventional fractionation. In one study, men with intermediate- to high-risk prostate adenocarcinoma were randomized to receive C-IMRT (76 Gy in 38 fractions; n=152) or H-IMRT (70.2 Gy in 26 fractions; n=151).[256] High-risk patients were prescribed 24 months of ADT.

Intermediate-risk patients were prescribed 4 months of ADT at the discretion of the treating physician. The primary end point was the cumulative incidence of biochemical and/or clinical disease failure. Median follow up was 130 months (range 7 to 181 months). Ten-year biochemical disease-free survival was similar in both arms (25.9% in the C-IMRT arm and 30.6% in the H-IMRT arm; HR: 1.31; 95% CI: 0.82 to 2.11). The two treatment groups also had similar rates of 10-year freedom from metastatic disease, prostate cancer-specific, and OS. The authors concluded that H-IMRT demonstrated no difference in disease outcomes when compared to C-IMRT at 10 years.[256]

Of note, ultra hypofractionation in high-risk patients receiving EBRT with elective nodal coverage is not currently recommended outside a clinical trial or multi-institutional registry due to insufficient comparative evidence.[260]

38. In patients with unfavorable intermediate- or high-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT or combined EBRT + brachytherapy (LDR, HDR) along with a risk-appropriate course of ADT. (*Strong Recommendation; Evidence Level: Grade A/B*)

Trials have demonstrated a benefit in clinical control for unfavorable intermediate- or high-risk prostate cancer patients who receive either dose-escalated moderately hypofractionated IMRT or EBRT plus a brachytherapy boost (HDR temporary prostate implant or LDR permanent prostate implant).[300-305] Combining EBRT and brachytherapy has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials.[300-302, 305]

Interestingly, the phase III randomized ASCENDE-RT trial compared two methods of dose escalation in 398 patients with intermediate- or high-risk prostate cancer: DE-EBRT boost to 78 Gy or LDR brachytherapy boost.[302-304] All patients were initially treated with 12 months of ADT and pelvic EBRT to 46 Gy. The primary endpoint of control (biochemical, no evidence of disease) was 89% versus 84% at 5 years; 86% versus 75% at 7 years; and 83% versus 62% at 9 years for the LDR versus EBRT boost arms (log-rank P < .001). However, toxicity was higher in the brachytherapy arm, with a cumulative incidence of grade 3 genitourinary events at 5 years of 18.4% for brachytherapy boost and 5.2% for EBRT boost (P < .001). In addition, increased gastrointestinal toxicity among patients treated with a brachytherapy boost was also seen (cumulative incidence of grade 3 events at 5 years, 8.1% versus 3.2%; P = .12).

39. In patients with high-risk prostate cancer electing radiation therapy, clinicians may offer radiation to the pelvic lymph nodes. (*Conditional Recommendation; Evidence Level: Grade B*)

The published POP-RT trial randomized patients (n=214) with NCCN high- (~50%) and very high-risk (~50%) prostate cancer[306] to IMRT to the whole pelvis (68 Gy in 25 fractions to prostate with 50 Gy to pelvic lymph nodes) versus prostate-only (68 Gy). This currently represents the only trial of elective pelvic nodal irradiation that delivered both modern standard-of-care radiotherapy doses and ADT duration while looking exclusively at high-risk patients.

All patients received ADT (surgical or medical) starting eight weeks prior to radiation therapy; medical ADT was via an LHRH agonist and was administered for two years. The trial demonstrated improved 5-year biochemical failure-free survival (HR: 0.23; 95% CI: 0.10 to 0.52; trial's primary endpoint), distant MFS (HR: 0.35; 95% CI: 0.15 to 0.82), and disease-free survival (HR: 0.40; 95% CI: 0.22 to 0.73) with whole pelvis IMRT, although no difference was detected in OS (HR: 0.92; 95% CI: 0.41 to 2.05).

Despite not showing an OS benefit, the Panel notes that elective nodal irradiation for high-risk patients may be offered given the reasonable morbidity (higher late grade II genitourinary toxicity with whole pelvis radiation but no difference in late gastrointestinal toxicity and no difference in grade III/IV genitourinary or gastrointestinal toxicity noted) as well as the reductions in biochemical failure and distant metastases. The Panel recognizes that neither the previous GETUG-01[266] nor RTOG 9413[269] trials demonstrated a benefit to elective nodal irradiation, but submits that those studies included variably-defined high-risk sub-groups (and lower risk than the POP-RT trial), used simpler radiation technologies with more limited pelvic fields, included a shorter duration of ADT, and delivered lower doses of radiation to the prostate; collectively, these differences may have blunted the impact of elective regional irradiation; as such, may be less relevant to inform contemporary practice.

40. When treating the pelvic lymph nodes with radiation, clinicians should utilize IMRT with doses between 45 Gy to 52 Gy. (*Strong Recommendation; Evidence Level: Grade B*)

As the POP-RT trial[306] outlined above utilized IMRT for the treatment of the pelvic lymph nodes, the Panel concludes that clinicians should utilize IMRT when treating the nodes electively in high-risk patients. Meanwhile, various reported trials that included pelvic nodal irradiation treated the nodes with doses from 45 Gy to 52 Gy (50 Gy in POP-RT);[306] as such, the Panel supports this range when nodal radiation is utilized.

41. In patients with high-risk prostate cancer electing radiation therapy, clinicians should recommend the addition of long-course (18 to 36 months) ADT with radiation therapy. (*Strong Recommendation; Evidence Level: Grade A*)

Multiple prospective RCTs have informed the management of high-risk localized prostate cancer to include ADT with radiation based on improved cancer outcomes.[273-286] In particular, the primary evidence for the use of ADT with radiation in high-risk disease comes from EORTC 22863, a trial that randomized 415 patients with locally advanced prostate cancer to 3 years of ADT plus 70 Gy of prostate radiation therapy versus radiation therapy alone.[273-276] Benefits were noted in the combination treatment arm with regard to both prostate cancer-specific survival (HR: 0.38; 95% CI: 0.24 to 0.60) and OS (HR: 0.60; 95% CI: 0.45 to 0.80). From this study, three years of ADT was established as a reference standard ADT treatment for the duration of combined ADT with radiation therapy in the treatment of patients with high-risk prostate cancer. A subsequent RCT among high-risk patients tested 18 versus 36 months of ADT.[294] This trial did not demonstrate differences in disease-free survival (HR 0.84, 95% CI 0.68 to 1.02), disease-specific survival (HR: 0.95; 95% CI: 0.58 to 1.55), or OS (HR: 1.02; 95% CI: 0.81 to 1.29) between the treatment durations, and has thereby introduced a minimum threshold duration of ADT when combined with radiation therapy for the management of high-risk disease. The published MARCAP meta-analysis further demonstrates the benefit of ADT in patients treated with radiation therapy.[287]

42. When combined ADT and radiation are used, ADT may be initiated neoadjuvantly or concurrently. (*Conditional Recommendation; Evidence Level: Grade C*)

The optimal sequencing of ADT and radiation has not been clearly defined, but RCT data, meta-analyses, and a systematic review have been published to provide some information on this topic.

In the randomized Ottawa 0101 study, neoadjuvant and concurrent ADT for 6 months was compared with concurrent and adjuvant ADT for 6 months.[307] No differences were detected in biochemical relapse-free survival or OS. Meanwhile, in NRG/RTOG 9413, a 2 x 2 factorial design was used whereby patients with prostate cancer were randomized to 4 months of neoadjuvant and concurrent ADT (starting 2 months before radiation) versus 4 months of adjuvant ADT, with a second randomization to prostate-only versus whole pelvis irradiation.[269, 308] Interestingly, among patients who underwent prostate-only radiation, adjuvant ADT was associated with improved PFS compared to neoadjuvant ADT. However, among patients who received whole pelvis radiation, adjuvant ADT was associated with worse PFS compared to neoadjuvant ADT.

In a 2021 meta-analysis by Spratt et al. (including data from Ottawa 0101 and NRG/RTOG 9413), patients receiving neoadjuvant and concurrent ADT and prostate-only radiation were combined into the neoadjuvant group, and patients receiving concurrent and adjuvant ADT were combined into the adjuvant group.[309] After a median follow-up of 14.9 years, the adjuvant group had significantly better biochemical control, PFS, and MFS compared to the neoadjuvant group. Of note, patients receiving whole pelvic nodal radiation in NRG/RTOG 9413 were not included in the analysis. There were also systematic differences between the two trials (e.g., duration of ADT, inclusion of more aggressive disease in the NRG/RTOG 9413). As a result, the authors acknowledged that their ability to soundly perform comparative subset analyses was hindered.

A 2023 systematic review assessed the question of optimal timing to start ADT in localized prostate cancer.[310] A total of 24 studies were included, with 5 studies specifically assessing ADT sequencing with radiotherapy in either the neoadjuvant, concurrent, or adjuvant setting. Included studies were made up of two RCTs, two retrospective studies and one individual patient data meta-analysis. Studies were qualitatively synthesized, and the review found conflicting results. One included study found no difference in any oncological outcomes between adjuvant and neoadjuvant ADT and radiotherapy, while others found that neoadjuvant ADT improved OS, PFS, and biochemical failure. Two included studies, however, found that a concurrent adjuvant sequence of ADT improved biochemical relapse free survival, PFS, biochemical failure, and distant metastasis.[310]

The authors acknowledged several methodological issues with this systematic review including a limited number of trials comparing neoadjuvant versus concurrent ADT, lack of trials assessing ADT timing in high-risk prostate cancer patients treated with pelvic radiotherapy and ADT, as well as significant heterogeneity of trials in terms of inclusion criteria, risk stratification, and radiation protocols. Despite these methodological shortcomings, the authors supported the use of concurrent ADT for intermediate-risk patients (with neoadjuvant ADT initiation as an acceptable option particularly for patients that may benefit from pre-radiotherapy prostate volume reduction). Short-term neoadjuvant ADT followed by concurrent and long-term adjuvant ADT is recommended (versus concurrent initiation) for high-risk prostate cancer patients. Due to the evolving data in this space, the initiation of adjuvant ADT is no longer recommended.

43. When combining ADT with radiation therapy, clinicians may use combined androgen suppression (LHRH agonist with an antiandrogen), an LHRH agonist alone, or an LHRH antagonist alone. (*Expert Opinion*)

Various compositions of ADT have been used in combination with radiation in randomized trials to date. For example, a number of studies used combined androgen suppression for the entire course of treatment,[275, 276, 278, 292, 295] while other series used an LHRH agonist for the duration of treatment with an initial a short course of antiandrogen at the early phase of treatment,[294, 296] and some trials used LHRH agonists alone.[286, 289] The Panel believes that clinicians may use any one of these options in combination with radiation.

44. When treating a subgroup of high-risk localized patients (≥ 2 of the following: PSA ≥ 40 ng/dL, ≥ Gleason 8, ≥ cT3) or locally advanced prostate cancer (cN1) with radiation therapy, clinicians should combine ADT with abiraterone acetate and prednisone for 24 months. (*Strong Recommendation; Evidence Level: Grade B*)

A meta-analysis of phase 3 STAMPEDE trials included patients with high-risk prostate cancer (having ≥ 2 of the following: PSA ≥ 40 ng/dL, ≥ Gleason 8, ≥ cT3) or clinical evidence of pelvic lymph node involvement. In this investigation, patients treated with ADT plus abiraterone acetate 1000 mg PO daily with prednisolone 5 mg PO daily for 24 months in combination with definitive radiation treatment had improved MFS and OS when compared with patients receiving ADT for 24 months with definitive radiation alone.[154]

FOLLOW-UP AFTER TREATMENT

45. Clinicians should monitor patients with prostate cancer post therapy with PSA and symptom assessment. (*Clinical Principle*)

Monitoring after treatment for clinically localized disease with serial PSA measurements and symptom assessments is necessary to identify recurrence as well as complications from treatment and thereby facilitate early intervention as appropriate. The specific intervals for PSA follow-up may be tailored to disease risk based on clinicopathologic features. Initial monitoring should in general be performed more frequently and is recommended every three to six months for the first two years after treatment. Subsequent monitoring between years two and five should occur every six months, with monitoring annually thereafter. The duration and interval of follow-up beyond 10 years for patients with an undetectable PSA at that time should be a shared decision based on patient disease risk, age, comorbidity status, and preference. Urinary, bowel, and sexual function should likewise be routinely queried, with the use of standardized/validated instruments recommended, to monitor the QOL impact from therapy.

46. Clinicians should support patients with prostate cancer through continued symptom management and encouraging engagement with professional or community-based resources. (*Clinical Principle*)

Multiple resources for support exist for patients with prostate cancer and their loved ones. These resources may be engaged at any time in the patient's clinical course, including at the time of diagnosis (pre-treatment) as well as following definitive local therapy. Important psychosocial support can be provided through social work services and local virtual and in-person prostate cancer support groups, as well as through national patient advocacy organizations (e.g., Active Surveillance Patients International [aspatients.org], AnCan Foundation [ancan.org], Prostate Cancer Foundation [pcf.org], Prostate Cancer Research Institute [PCRI.org], Prostate Cancer Supportive Care Program [pcscprogram.ca], the Prostate Health Education Network [prostatehealthed.org], the Urology Care Foundation [urologyhealth.org], ZERO Prostate Cancer [zerocancer.org]). Additional physical and lifestyle survivorship support may be provided through referrals to dietary and nutrition services, physical therapists, pelvic floor rehabilitation specialists, and psychosexual therapists. The array of survivorship needs for an individual patient and caregiver may be broad and should be explored by the clinician and team to ensure that appropriate support, especially peer support, is offered.

FUTURE DIRECTIONS

Clinically localized prostate cancer remains one of the most active areas of investigation in urology. A few topics of practice-changing study are highlighted here:

TREATMENT INTENSIFICATION FOR HIGH-RISK DISEASE

Multiple trials evaluating next generation androgen signaling inhibitors in high-risk clinically localized disease have accrued and are awaiting results. In the Apa-RP trial, adjuvant apalutamide for high-risk prostatectomy patients has demonstrated excellent biochemical control.[311] This phase 2 trial showed a 100% biochemical recurrence-free survival at 24 months among 108 high-risk prostate cancer patients who received 12 months of apalutamide combined with ADT following radical prostatectomy. PROTEUS, a randomized, double-blind, placebo-controlled, phase 3 trial of apalutamide plus ADT versus placebo plus ADT prior to radical prostatectomy in patients with localized high-risk or locally advanced prostate cancer has also completed enrollment. PROTEUS aims to improve pathologic complete response rates and MFS. Final outcomes should be available in late 2028. Further, DASL-HiCaP randomized in a 1:1 fashion 1100 patients with planned radiation therapy with very high-risk localized prostate cancer on conventional imaging or very high-risk features with PSA persistence or rise within 12 months of radical prostatectomy. Patients were randomized to receive darolutamide or placebo twice daily for 96 weeks in combination with 96 weeks of ADT plus radiation therapy starting 8-24 weeks from randomization. The primary endpoint is MFS.

SURGICAL INNOVATION

Intraoperative imaging for robotic surgery has the potential to improve functional outcomes, margin status, and node dissection. PSMA targeting fluorophores and radioguided surgery enable real-time tumor visualization. Early studies show safety and feasibility. Fluorescence–guided prostatectomy (first-in-human) for margin status and nerve preservation demonstrate early improvements in surgical technique particularly in reoperative or node-positive settings.[312, 313] Focal therapy in prostate cancer including all modalities such as HIFU, IRE, PDT, and cryoablation are undergoing extensive evaluation in prospective studies. Future practice must balance long-term oncologic outcomes with preserving urinary and sexual function.

BIOMARKERS

The ability for commercially available GCs to improve the outcomes of patients with clinically localized prostate cancer has not been validated in prospective clinical trials to date. Thus, routine use is not recommended at this time. A specific important limitation of the existing data supporting the prognostic capacity of GCs is that studies have been primarily based on tissue analysis of radical prostatectomy specimens. As such, the impact of tissue heterogeneity and under-sampling on the prognostic ability of GCs for assessing the risks of recurrence, metastasis, and death from prostate cancer biopsies remains uncertain. Of note, accumulating evidence has indicated that GC scores, specifically Decipher, derived from biopsy specimens do correlate with cancer outcomes. For example, Nguyen et al. reported on 235 radical prostatectomy/radiation therapy patients for whom Decipher was run on biopsy specimens and found that, on multivariable analysis, Decipher score was associated with both the risks of metastasis and prostate cancer-specific mortality.[314] In addition, the prognostic capacity of biopsy-based Decipher was validated using prospectively collected, banked specimens from RTOG 9202, 9413, and 9902. After adjusting for age, PSA, Gleason score, cT-stage, trial and randomized treatment arm, Decipher score was associated with distant metastases, prostate cancer-specific mortality, and OS.[315]

Prospective validation of the predictive capacity of GCs in localized disease will be important to support widespread use for treatment selection. Several ongoing clinical trials (e.g. NRG GU009 and GU 010) are indeed evaluating treatment intensification and de-intensification based on GC (Decipher) results in both intermediate- and high-risk patient populations.

AI for interpretation of hematoxylin and eosin slides will also be practice-changing. Artera AI's multimodal AI biomarker test applies a deep learning algorithm to digitized biopsy slides developed and validated in large cooperative group trials such as NRG/RTOG 9202, 9408, 9413, 9910, and 0126.[316] Artera AI not only stratifies risk, but also predicts which patients benefit from adding ADT to radiation, enabling more precise personalization of therapy while reducing overtreatment and toxicity.

IMAGING

The PRIME study demonstrated that a two-sequence (bi-parametric) MRI was non-inferior to standard contrast-enhanced mpMRI for detecting clinically significant prostate cancer, which may reduce cost, improve access, and increase screening efficiency. Utilization of bi-parametric MRI is likely to increase diagnosis, and improve monitoring during active surveillance and treatment planning.[79]

High-resolution micro-ultrasonography (microUS) is an alternative to mpMRI for detecting clinically significant prostate cancer.[317] While MRI is still standard, microUS can be considered when MRI is inconclusive, if the patient is claustrophobic, or the patient has metal implants.

As noted in the updated guideline statements, PSMA PET has greater sensitivity than conventional imaging for identification of nodal and distant disease, and evidence that PSMA PET imaging can substantially alter the treatment plan and expectations regarding outcomes of treatment [91] (e.g., finding small volume metastatic disease on PSMA PET in a patient otherwise thought to have localized disease by conventional imaging). PSMA PET is a first-line option for staging in patients with unfavorable intermediate-risk or high-risk prostate cancer.

Several imaging radiotracers utilizing PET-based technology have been demonstrated to improve detection of disease over conventional imaging. Broadly, these imaging modalities have been referred to as next-generation imaging (NGI); among these, PSMA-based PET scanning has received the most attention. This interest has been bolstered by FDA approval of two PSMA-based tracers: Gallium 68 PSMA-11 (Ga 68 PSMA-11) and piflufolastat F-18 (18F-DCFPyL).[318, 319] Moreover, continued evaluation of novel PSMA PET agents remains ongoing.[320] As such, PSMA PET is an accepted standard in the staging evaluation of patients with localized high-risk prostate cancer. Nevertheless, future studies are needed to determine how the information from NGI should be incorporated into clinical decision-making due to both the limitations of these advanced imaging techniques and the fact that the data to date on outcomes following treatment upon which management recommendations are based on patients evaluated with conventional imaging. For example, in the OSPREY trial in which patients underwent F-18 DCFPyl-PET/CT followed by radical prostatectomy and extended PLND, the sensitivity of the scan for detection of pelvic lymph node disease was only 40.3%, suggesting this study alone could not be used to triage patients as to whether or not to undergo lymph node dissection at the time of surgery.[321] At the same time, in 12.3% of high-risk patients, F-18 DCFPyl identified extra-pelvic disease, indicating patients for whom additional therapy would be indicated.[321] Prospective studies incorporating NGI as staging will be required to determine clinical utility. Until such data are available, clinicians should exercise caution when using PSMA PET results to justify substantial alterations in standard-of-care treatments the utility of which has been established among patients who were staged with conventional imaging.

ABBREVIATIONS

3DCRT	3-D conformal radiation therapy
ADT	Androgen deprivation therapy
AHRQ	Agency for Healthcare Research & Quality
AI	Artificial intelligence
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
BOD	Board of Directors
CI	Confidence interval
CT	Computed tomography
DE-EBRT	Dose-escalated external beam radiation therapy
DRE	Digital rectal exam
EBRT	External beam radiation therapy
EPIC	Expanded Prostate Cancer Index Composite
EPIC-CP	Expanded Prostate Cancer Index Composite for Clinical Practice
FACT	Functional Assessment of Cancer Therapy
GC	Genomic classifier
HDR	High-dose rate
HR	Hazard ratio
ICHOM	International Consortium on Health Outcomes Measurement
ICIQ	International Consultation on Incontinence Questionnaires
ICSmaleSF	International Continence Society Male Short-Form
IGRT	Image-guided radiation therapy
IIEF	International Index of Erectile Function
IMRT	Intensity-modulated radiation therapy
ISUP	International Society of Urologic Pathologists
LDR	Low-dose rate
LHRH	Luteinizing hormone-releasing hormone
MFS	Metastasis-free survival
mpMRI	Multi-parametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NGI	Next-generation imaging
OHSU	Oregon Health & Science University
OS	Overall survival
PBRT	Proton beam radiation therapy
PCS	Prostate cancer subscale
PDT	Photodynamic therapy
PET	Positron emission tomography
PFS	Progression-free survival
PGC	Practice Guidelines Committee
PICOTS	Populations, interventions, comparators, outcomes, timing, types of studies and settings
PLND	Pelvic lymph node dissection
PROMIS	Patient-Reported Outcomes Measurement Information System
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relative Risk
SBRT	Stereotactic body radiation therapy
SDM	Shared decision-making
SEER	Surveillance, Epidemiology, and End Results
SHIM	Sexual Health Inventory for Men
SQC	Science & Quality Council
SUO	Society of Urologic Oncology
VMAT	Volumetric modulated arc therapy
WHO	World Health Organization

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DISCLAIMER

This document was written by the Clinically Localized Prostate Cancer Panel of the American Urological Association Education and Research, Inc., which was created in 2019 and updated in 2026. The PGC of the AUA selected the Panel Chair. Panel members were selected by the Panel and PGC Chair.

Membership of the Panel included specialists in urology, oncology, and radiation oncology with specific expertise on this disorder. 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 evaluation and treatment of clinically localized 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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