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LESSON 32

## Localized Prostate Cancer AUA Guideline 2022

**Learning Objective:** At the conclusion of this continuing medical education activity, the participant will be able to risk stratify clinically localized prostate cancer and understand how to incorporate shared decision-making into management decisions; define relevant risk-appropriate management options and associated treatment-related risks; and discuss specific recommendations regarding the details of conducting active surveillance, lymph node dissection during prostatectomy, and radiation therapy for patients with clinically localized prostate cancer across risk strata.

This AUA Update aligns with the American Board of Urology Module on Oncology, Urinary Diversion, and Adrenal. Additional information on this topic can be found in the AUA Core Curriculum section on Oncology-Prostate.



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**KEY WORDS:** prostate cancer, prostatectomy, treatment, guidelines, active surveillance

## INTRODUCTION

Prostate cancer remains one of the most common solid organ malignancies in the United States.<sup>1</sup> Moreover, with widespread PSA testing, most newly diagnosed disease is clinically localized. Continued expansion of diagnostic and therapeutic modalities, together with accumulated data on the outcomes of patients managed with a variety of approaches, has evolved evaluation and treatment options for patients with clinically localized prostate cancer. As such, the AUA, in collaboration with ASTRO (American Society for Radiation Oncology), recently updated the Localized Prostate Cancer Guideline. Of note, the guideline is further endorsed by ASCO (American Society of Clinical Oncology) and the Society of Urologic Oncology.<sup>2-6</sup>

The updated guideline focuses on contemporary prostate cancer risk stratification, including specifically the utilization of disease risk classification as a framework to facilitate shared decision-making (SDM) for treatment options and clinical trial enrollment. The updated guideline also addresses staging for prostate cancer and provides specific recommendations pertaining to active surveillance (AS), radical prostatectomy (RP), and radiation therapy. In this Update, we review the recently published AUA Guideline for Localized Prostate Cancer and highlight the pertinent changes relevant to practicing clinicians managing patients with prostate cancer.

## PROSTATE CANCER RISK STRATIFICATION

The current guideline recommends continued use of prostate risk stratification, though variations exist from the previous

guideline iteration. Specifically, the risk categories of “very low risk” and “low risk” were combined in the updated guideline, given the minimal impact on treatment recommendations that exists between these groups. At present, therefore, patients are classified as “low risk,” “favorable intermediate risk,” “unfavorable intermediate risk,” and “high risk.” Based on a comprehensive review of various prognostic factors, the guideline recommends defining risk categories based on clinical T stage, serum PSA, Grade Group, and tumor volume (Guideline Statement 1). The importance of tumor volume is well addressed in the recent guideline update; for example, patients with Grade Group 1 disease may be categorized as favorable intermediate-risk disease based on tumor volume. Moreover, clarification regarding the multiplicity of targeted cores was provided, with the update recommending considering the multiple cores from the same lesion as a single core. It should be noted that, for the purposes of risk stratification, the guideline recommends T stage be determined by digital rectal examination (DRE), rather than ultrasound or MRI. The risk group classification is summarized in the Table.

Given the emergence of data on genomic biomarkers, the guideline panel did address as well the integration of these biomarkers in patient risk stratification. However, the evidence review demonstrated that, to date, the data supporting many of these genomic tools have been based on results obtained from prostatectomy specimens rather than pretreatment prostate biopsy. Thus, the guideline advises against routine use of the genomic biomarkers for risk stratification. Nevertheless, the guideline panel did offer that genomic biomarkers may be used selectively to aid in SDM (Guideline Statements 2 and 3).

Another important topic the guideline addresses is the role of germline genetic testing among patients with clinically

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

Low-risk	PSA <10 ng/mL AND Grade Group 1 AND clinical stage T1-T2a
Intermediate-risk	PSA 10-<20 ng/mL OR Grade Group 2-3 OR clinical stage T2b-c <ul style="list-style-type: none"><li>• Favorable: Grade Group 1 with PSA 10-&lt;20 ng/mL or clinical stage T2b-c and &lt;50%<sup>a</sup> biopsy cores positive OR Grade Group 2 with PSA &lt;10 ng/mL and clinical stage T1-2a and &lt;50% biopsy cores positive</li><li>• Unfavorable: Grade Group 1 with PSA 10-&lt;20 ng/mL and clinical stage T2b-c OR Grade Group 2 with PSA 10-&lt;20 ng/mL and/or clinical stage T2b-c and/or ≥50%<sup>a</sup> biopsy cores positive OR Grade Group 3 with PSA &lt;20 ng/mL</li></ul>
High-risk	PSA >20 ng/mL OR Grade Group 4-5 OR clinical stage T3

<sup>a</sup>Percent biopsy cores positive is the total number of cores containing cancer divided by total number of cores obtained × 100.<sup>39</sup> This is not the percentage of cancer within a positive core. Regarding assessment of the percent biopsy cores positive for risk stratification, the guideline panel acknowledges that with the increasing use of pre-biopsy MRI and subsequent targeted biopsies, multiple cores may be obtained from a targeted lesion. Multiple cores from the same lesion should be considered as a single core (ie, for the calculation of percentage cores positive in risk assessment). If all cores are negative, that is considered a single negative core. If 1 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.<sup>40</sup> Reprinted with permission from Eastham et al, *J Urol*. 2022;208(1):19-25.<sup>34</sup>

**ABBREVIATIONS:** androgen deprivation therapy (ADT), androgen receptor signaling inhibitor (ARSI), active surveillance (AS), American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), biochemical recurrence (BCR), digital rectal examination (DRE), external beam radiation therapy (EBRT), Food and Drug Administration (FDA), intensity modulated radiation therapy (IMRT), luteinizing hormone-releasing hormone (LHRH), metastases-free survival (MFS), multiparametric (mp), National Comprehensive Cancer Network (NCCN), next-generation imaging (NGI), overall survival (OS), prostate cancer-specific mortality (PCSM), positron emission tomography (PET), pelvic lymph node dissection (PLND), prostate-specific membrane antigen (PSMA), radical prostatectomy (RP), shared decision-making (SDM)

localized disease. 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. Again here, there has been a continued evolution of understanding in the varied potential implications of identifying mutations. As such, the guideline recommends selective testing for germline mutations in high-risk individuals, largely based on the recommendations from the Philadelphia Prostate Cancer Consensus Conferences (Guideline Statement 4).<sup>2</sup>

## STAGING EVALUATION FOR THE NEWLY DIAGNOSED PATIENT WITH CLINICALLY LOCALIZED PROSTATE CANCER

The guideline encourages a risk-based approach to staging. Specifically, for patients with low- or intermediate-risk disease, the panel recommends against routine staging in asymptomatic patients (Guideline Statement 5), given the probability of metastases in these patients is exceedingly low.<sup>3</sup> Of note, the panel did acknowledge that robust evidence to support imaging in unfavorable intermediate-risk disease remains lacking, but offers that staging in these patients may be considered. Meanwhile, for patients with high-risk prostate cancer, the guideline recommends staging with a bone scan and axial imaging, consisting of either computerized tomography or MRI (Guideline Statement 6).

In addition, since the previous iteration of the Localized Prostate Cancer Guideline, there has been a dramatic increase in the role of molecular imaging, also known as next-generation imaging (NGI). Several modalities have in fact recently been approved by the Food and Drug Administration (FDA), including <sup>68</sup>Ga prostate-specific membrane antigen (PSMA)-11 and <sup>18</sup>F-PSMA-DCFPyL positron emission tomography (PET). Randomized and meta-analytical data suggest utility in the initial staging setting and superiority compared to conventional imaging. Nevertheless, the oncologic benefit of treatment based on metastatic disease identified solely on NGI remains uncertain. The new guideline offers that molecular imaging may be obtained in patients with high risk of metastatic disease with negative conventional imaging (Guideline Statement 7). These recommendations are consistent with the recent ASCO guideline.<sup>4</sup>

## RECOMMENDATIONS FOR RISK-BASED MANAGEMENT APPROACH

SDM enables selection of a management strategy that is consistent with a patient's own values and underlying scientific evidence.<sup>5</sup> Randomized data support SDM, demonstrating patients have more realistic expectations, improved participation, and make decisions aligned with their specific preferences.<sup>6</sup> To fulfill an SDM approach, it is recommended that clinicians discuss patient life expectancy and comorbidities, the risk of posttreatment prostate cancer recurrence, and the risks of treatment (Guideline Statements 8 and 9). Integral to the SDM approach, counseling clinicians should elicit patient preferences and concerns regarding outcomes from the various treatment options. For patients with limited life expectancy, the panel recommends discussion of watchful waiting

(Guideline Statement 11), which avoids routine surveillance and intends to provide palliation for symptomatic progression. Data from randomized trials including PIVOT and SPCG-4 demonstrate that, due to competing risks of mortality, a life expectancy of 8–10 years is required to observe a treatment-related reduction in the risk of death.<sup>7,8</sup>

Regarding risk-based management recommendations, the guideline states that, for patients with low-risk prostate cancer, the preferred management option is AS (Guideline Statement 10). The intention of AS is to defer treatment and treatment-associated morbidity without oncologic compromise. Indeed, patients with low-risk prostate cancer have been demonstrated to have a low rate of metastatic progression and prostate cancer-specific mortality (PCSM) based on AS series and data from the ProtecT trial.<sup>9,10</sup> At the same time, the guideline does acknowledge that, for select patients with low-risk disease, immediate treatment may be considered based on SDM.<sup>11</sup>

For patients with favorable intermediate-risk prostate cancer, the guideline offers that management options to be discussed include AS, radiation therapy, and RP (Guideline Statement 12). Data supporting this recommendation come from the ProtecT trial.<sup>9</sup> It should be noted that AS (denoted as “active monitoring” in the trial nomenclature) was associated in that trial with an increased risk of clinical progression and metastases compared to patients undergoing RP or radiotherapy. Despite these associations, all-cause mortality and PCSM were low and comparable across groups.

Patients with unfavorable intermediate- and high-risk disease should be offered RP or radiation therapy plus androgen deprivation therapy (ADT) if their estimated life expectancy is greater than 10 years (Guideline Statement 14). The guideline acknowledges that the optimal treatment approach for this cohort remains an area of active discussion and investigation, with comparable oncologic outcomes based on meta-analyses.<sup>12</sup> In patients with high-risk disease and a short life expectancy, ADT alone may be considered in symptomatic patients in whom definitive therapy is not advised or is refused (Guideline Statement 16).

## PRINCIPLES OF AS

Counseling of patients considering AS should include the importance of compliance with the surveillance strategy. Specifically, the guideline outlines that patients on AS should be monitored with serial PSA values and repeat prostate biopsies (Guideline Statement 17). The guideline recommends PSA values no more frequently than every 6 months, and assessment of symptoms and DRE at least every 2 years. Evaluation with either a multiparametric (mp) MRI or repeat biopsy should be considered in patients on AS with an increasing PSA level or new DRE abnormality. In the absence of radiographic, clinical, or biochemical change, the guideline recommends surveillance biopsy every 1 to 4 years. Of note, the guideline does provide flexibility to enable clinicians to provide an individualized AS protocol based on age, health, and risk of progression.<sup>13</sup>

mpMRI has been shown to improve risk stratification.<sup>14</sup> In a patient who received diagnostic biopsy without an mpMRI, mpMRI enables complete gland imaging and may enable the identification of more aggressive disease and guide confirmatory biopsy. Data from the ASIST trial reported that mpMRI

prior to confirmatory biopsy was associated with fewer AS failures and less grade progression.<sup>15</sup> However, data assessing serial MRI during AS to evaluate for progression are conflicting, and as such, mpMRI should not replace prostate biopsy.<sup>16</sup> For example, one series reported that use of mpMRI as a sole trigger for repeat biopsy would have missed upgrading to Grade Group 2 or higher in 160 out of 1,000 patients with Grade Group 1 disease on AS.<sup>17</sup> The guideline therefore concluded that mpMRI may be considered in patients on AS to augment risk stratification but should not replace serial prostate biopsy (Guideline Statement 18).

## PRINCIPLES OF FOCAL ABLATION

The guideline states that patients with intermediate-risk prostate cancer considering focal ablation should be informed that there is a lack of high-quality data comparing focal ablation outcomes with AS, prostatectomy, or radiotherapy (Guideline Statement 13). Indeed, previously published series comparing focal ablation with other standard treatment options are limited by the lack of randomization, heterogeneous protocols, insufficient follow-up, and nonstandardized outcomes. Moreover, it is a point of emphasis in the guideline that patients with low-risk disease should be preferentially managed with AS. Nevertheless, the guideline offers that focal ablation therapy may be considered in select, appropriately informed patients with intermediate-risk disease. In addition, the guideline advises that patients treated with focal ablation should be followed with an individualized surveillance protocol consisting of postablation PSA, DRE, mpMRI, and repeat biopsy. Further, for patients with high-risk disease, focal therapy was not recommended by the guideline outside of a clinical trial (Guideline Statement 15).

## PRINCIPLES OF SURGERY

The guideline acknowledges that preservation of the neurovascular bundles during RP 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 (BCR). The guideline recommends that when oncologically appropriate, nerve-sparing should be performed.

The guideline provided several statements on the issue of pelvic lymph node dissection (PLND) at the time of prostatectomy in patients electing surgery. Specifically, the guideline recommends that clinicians counsel patients regarding the benefit of PLND for providing staging information, but in addition that the absence of a consistently documented improvement in metastases-free survival (MFS), PCSM, or overall survival (OS) with PLND should also be recognized (Guideline Statement 20).<sup>18</sup> The guideline states that patients should be selected for PLND based on nomograms which assess the likelihood of identifying a positive lymph node at the time of PLND. The decision to perform PLND should then be informed from the nomogram prediction of node-positive disease, balanced with the risk of complications from performing PLND, such as adjacent organ injury or lymphocele (Guideline Statement 21). Further, the guideline

advises that, when the decision has been made for PLND, an extended dissection should be performed, which includes the obturator, external iliac, and internal iliac nodes (Guideline Statement 22). The rationale for this recommendation is based on primarily improved staging accuracy by virtue of increased lymph node counts and a greater positive lymph node yield.<sup>19</sup> The review underpinning the guideline development did, however, also recognize 2 recent randomized controlled trials comparing limited to extended PLND which did not demonstrate an improved BCR-free survival.<sup>19,20</sup>

The updated guideline also provided statements regarding the postoperative management of patients found to have positive lymph nodes at the time of surgery. Recognizing that up to 30% of patients with positive lymph nodes may remain disease-free at long-term follow-up without further therapy,<sup>21</sup> the guideline offers that patients with positive lymph nodes should be risk stratified based on pathologic variables and postoperative PSA (Guideline Statement 24). Consideration of such variables may enable the judicious use of adjuvant therapies and minimize overtreatment. For patients with lymph node-positive disease and an undetectable PSA post-prostatectomy, the guideline states that both adjuvant therapy and observation may be offered (Guideline Statement 25).<sup>18</sup> Meanwhile, the role of adjuvant radiation in this setting is ill defined, with an absence of prospective data, though retrospective data suggest superior MFS compared to patients who received no treatment or salvage radiation.<sup>18</sup>

A final topic in the domain of surgery that was addressed by the guideline update was the role of postoperative radiotherapy after prostatectomy. In fact, the role of adjuvant radiation therapy vs a management strategy of PSA surveillance with early salvage radiation therapy for patients who experience BCR has been addressed in 3 recent randomized trials (GETUG-AFU 17, RAVES, and RADICALS) and a resulting meta-analysis. The outcomes of these trials were congruent and demonstrated no difference in oncologic outcomes. Moreover, the systematic review of these trials corroborated these findings, with a pooled event-free survival of HR 0.95 (95% CI 0.75-1.21)<sup>22</sup> with early salvage radiation therapy. Additionally, in the early salvage cohort, roughly one-third to one-half of the patients were spared radiotherapy. Based on these data, the guideline recommends against routine adjuvant radiation therapy after RP (Guideline Statement 26).

## PRINCIPLES OF RADIOTHERAPY

The guideline notes that treatment with radiotherapy should abide by the overarching theme of balancing therapeutic benefit while minimizing toxicity. This may be achieved by utilizing target localization technologies, avoidance of normal tissue, simulation, treatment planning, and image guidance to optimize the delivery of external beam radiation therapy (EBRT; Guideline Statement 27).

The Guideline recognizes that 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. Clinicians should utilize dose escalation when EBRT is the primary treatment for patients with prostate cancer. The current standard technique of EBRT is intensity modulated radiation therapy (IMRT;

Guideline Statement 28). The guideline also acknowledges that proton beam radiation therapy is supported by limited prospective comparative data assessing oncologic outcomes and toxicity profiles. Accordingly, the guideline states that clinicians should counsel patients that proton therapy is an option, though it has not been shown to be superior in terms of toxicity and/or cancer outcomes (Guideline Statement 29).

For patients with low- or favorable intermediate-risk disease who elect to proceed with radiation therapy, the guideline advises that clinicians should offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate implant, or temporary high-dose rate prostate implant as equivalent forms of treatment (Guideline Statement 32). Further, for patients with low- or intermediate-risk disease electing EBRT, the guideline states that clinicians should offer moderate hypofractionated EBRT (Guideline Statement 30) or may offer ultrahypofractionated EBRT (Guideline Statement 31). The use of hypofractionated radiation is more convenient and provides comparable outcomes compared to conventional fractionation. A recent systematic review reported comparable BCR-free survival (HR 1.14, 95% CI 0.88-1.47), PCSM (HR 1.00, 95% CI 0.72-1.39), and OS (HR 1.06, 95% CI 0.93-1.20) and reported similar genitourinary and gastrointestinal toxicity.<sup>23</sup> Similar findings have been observed in ultrahypofractionation.<sup>24</sup> In addition, it was recommended that lymph node radiation (Guideline Statement 33) and ADT (Guideline Statement 34) not be used routinely for patients with low- or favorable intermediate-risk disease undergoing radiation therapy. These recommendations are based on prospective trials that have not demonstrated progression-free survival benefit to whole pelvis radiation<sup>25</sup> or OS benefit with ADT<sup>26</sup> in this setting.

The updated guideline provides several recommendations regarding the use of radiation therapy for unfavorable intermediate- and high-risk disease. Specifically, for patients with unfavorable intermediate- and high-risk disease who elect to proceed with EBRT, clinicians should offer dose-escalated hypofractionated EBRT with or without brachytherapy (low dose rate or high dose rate; Guideline Statement 37). In addition, for patients with unfavorable intermediate-risk disease who elect treatment with radiation, the guideline advises 4-6 months of ADT (Guideline Statement 35), while for high-risk patients being treated with radiation, 18-36 months of ADT is advised (Guideline Statement 40). In this context, ADT may be initiated neoadjuvantly, concurrently, or adjuvantly (Guideline Statement 41). To date, the optimal timing of providing ADT has not been clearly identified. The guideline also offers that clinicians may use ADT with radiation therapy with combined androgen suppression (luteinizing hormone-releasing hormone [LHRH] agonist with an antiandrogen), an LHRH agonist alone, or an LHRH antagonist alone (Guideline Statement 42).

Regarding management of the pelvic lymph nodes in patients with high-risk disease who elect treatment with radiation, the guideline notes that radiation to the pelvic lymph nodes may be offered (Guideline Statement 38), using IMRT with doses between 45 and 52 Gy (Guideline Statement 39). Supporting evidence for pelvic lymph node radiation may be derived from the POP-RT trial, which compared IMRT to the whole pelvis vs the prostate only<sup>27</sup> and reported that whole

pelvis radiation was associated with improved 5-year BCR-free survival (HR 0.23, 95% CI 0.10-0.52), MFS (HR 0.35, 95% CI 0.15-0.82), and disease-free survival (HR 0.40, 95% CI 0.22-0.73).

## FOLLOW-UP AFTER TREATMENT

Monitoring after treatment of clinically localized prostate cancer with serial PSA measurements and symptom assessments is necessary to identify recurrence as well as complications from treatment facilitating 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 3 to 6 months for the first 2 years after treatment. Subsequent monitoring between years 2 and 5 should occur every 6 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 quality of life impact from therapy.

## FUTURE DIRECTIONS

The guideline highlights several areas of future study, including the ongoing investigations using prostate biopsy specimens to better define the role of genomic classifiers as well as prospective trials which are currently underway utilizing genomic classifiers to alter treatment protocols (NRG Oncology protocols GU009 and GU010).

Likewise, the panel acknowledged the increased interest in PSMA-based PET imaging given the recent FDA approval of 2 PSMA-based tracers, <sup>68</sup>Ga PSMA-11 and <sup>18</sup>F-DCFPyL. PSMA PET imaging has in fact demonstrated superiority in detection of distant disease compared to conventional imaging.<sup>28,29</sup> However, it should be noted that current data used to make treatment recommendations are based on conventional imaging. Further prospective studies incorporating NGI as staging are therefore needed to provide data on how to optimally incorporate these modalities into clinical decision-making.

The guideline as well recognizes the recent data supporting intensification of hormonal deprivation with androgen receptor signaling inhibitors (ARSI) in high-risk localized and node-positive patients undergoing definitive local therapy with radiation. Specifically, results from the STAMPEDE trial noted that, compared with standard of care, ARSI was associated with an improved MFS (HR 0.53, 95% CI 0.44-0.64), although in this analysis no difference was observed in OS, PCSM, BCR-free survival, and progression-free survival.<sup>30</sup> Further trials assessing the addition of ARSI to conventional ADT are underway, including ENZARAD and PROTEUS.<sup>31,32</sup>

## DIFFERENCES WITH THE NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINE

Overall, the recommendations outlined in the guideline are largely congruent with those provided by the 2022 National

Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology: Prostate Cancer.<sup>33</sup> In terms of notable differences between the guidelines, regarding risk stratification, the NCCN guideline does include the categories of very-low and very-high risk, while as noted above, the current guideline classification is restricted to low, intermediate (favorable/unfavorable), and high risk. Further, the NCCN guideline, acknowledging the increased sensitivity and specificity of PSMA PET tracers compared to conventional imaging, does not specify a requirement of conventional imaging being negative prior to obtaining a PSMA PET scan, while the Clinically Localized Prostate Cancer Guideline only recommends such NGI in high-risk patients who have negative conventional imaging. In addition, regarding the use of PLND at the time of prostatectomy for patients who elect surgery, the NCCN guideline recommends performing PLND if the predicted probability of lymph node metastases is  $\geq 2\%$ , whereas the Localized Prostate Cancer AUA Guideline 2022 recommends utilizing a nomogram to select patients for lymphadenectomy but does not prescribe a specific threshold to conduct PLND, but rather advises that the decision be based on a balanced discussion with the patient regarding the relative risks and benefits of PLND.

## SUMMARY OF CHANGES

The recently published Clinically Localized Prostate Cancer: AUA/ASTRO Guideline<sup>34-36</sup> updates an iteration published in 2017.<sup>37,38</sup> Several notable changes have been made. Risk stratification categories have been amended, specifically with the elimination of substratification of low-risk disease as management did not differ substantially between the groups. Further, with the introduction of NGI, the updated guideline provides recommendation that such imaging modalities may be considered in patients who are suitable for staging and have had negative conventional imaging.

The updated guideline suggests focal ablation may be a suitable approach in selected well-informed patients with intermediate-risk disease, though the limited existing

comparative data should be disclosed. Regarding RP, the current guideline diverges from the initial iteration, which recommended PLND in patients with unfavorable intermediate- or high-risk disease. Instead, the use of published nomograms is recommended, with a resulting balanced discussion involving the potential staging benefits of PLND with the risk of morbidity. For the postprostatectomy setting, the updated guideline provides recommendations on the management of patients with N1 disease. Further, a recommendation away from routine adjuvant radiation therapy was made, in favor of an early salvage approach. The new guideline also provides a detailed discussion of radiation therapy, including the role of/timing of ADT and the selection of patients for nodal radiation. Finally, the guideline encourages practitioners and patients to take advantage of numerous educational resources including patient support and advocacy groups.

## DID YOU KNOW?

- The latest AUA Localized Prostate Cancer Guideline provides an updated framework for prostate cancer risk stratification including low-risk, favorable intermediate-risk, unfavorable intermediate-risk, and high-risk prostate cancer.
- Using an SDM approach, risk-appropriate treatment options should be considered in the context of patient comorbidities, life expectancy, and patient expectations
- The AUA localized prostate cancer update provides recommendations for each management option for localized prostate cancer, including AS, RP, and radiotherapy.
- Subtle but pertinent differences exist in the recommendations between the AUA Localized Prostate Cancer Guideline and the guideline published by the NCCN.

## REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72(1):7-33.
2. Giri VN, Knudsen KE, Kelly WK, Cheng HH, Cooney KA, Cookson MS. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. *J Clin Oncol.* 2020;38(24):2798-2811.
3. Risko R, Merdan S, Womble PR, Barnett C, Ye Z, Linsell SM. Clinical predictors and recommendations for staging computed tomography scan among men with prostate cancer. *Urology.* 2014;84(6):1329-1334.
4. Trabulsi EJ, Rumble RB, Jadvar H, Hope T, Pomper M, Turkbey B. Optimum imaging strategies for advanced prostate cancer: ASCO guideline. *J Clin Oncol.* 2020;38(17):1963-1996.
5. Légaré F, Ratté S, Stacey D, Kryworuchko J, Gravel K, Graham ID. Interventions for improving the adoption of shared decision making by healthcare professionals. *Cochrane Database Syst Rev.* 2010;(5):CD006732.
6. O'Connor AM, Llewellyn-Thomas HA, Flood AB. Modifying unwarranted variations in health care: shared decision making using patient decision aids. *Health Aff (Millwood).* 2004;(Suppl Variation):Var63-72.
7. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med.* 2014;370(10):932-942.
8. Wilt TJ, Jones KM, Barry MJ, Andriole GL, Culkin D, Wheeler T. Follow-up of prostatectomy versus observation for early prostate cancer. *N Engl J Med.* 2017;377(2):132-142.
9. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med.* 2016;375(15):1415-1424.
10. Welty CJ, Cowan JE, Nguyen H, Shinohara K, Perez N, Greene KL. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. *J Urol.* 2015;193(3):807-811.

11. Carter HB, Helfand B, Mamawala M, Wu Y, Landis P, Yu H. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. *Eur Urol*. 2019;75(5):743-749.
12. Wallis CJ, Saskin R, Choo R, Herschorn S, Kodama RT, Satkunasivam R. Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis. *Eur Urol*. 2016;70(1):21-30.
13. Cooperberg MR, Zheng Y, Faino AV, Newcomb LF, Zhu K, Cowan JE. Tailoring intensity of active surveillance for low-risk prostate cancer based on individualized prediction of risk stability. *JAMA Oncol*. 2020;6(10):e203187.
14. Tran GN, Leapman MS, Nguyen HG, Cowan JE, Shinohara K, Westphalen AC. Magnetic resonance imaging-ultrasound fusion biopsy during prostate cancer active surveillance. *Eur Urol*. 2017;72(2):275-281.
15. Klotz L, Pond G, Loblaw A, Sugar L, Moussa M, Berman D. Randomized study of systematic biopsy versus magnetic resonance imaging and targeted and systematic biopsy in men on active surveillance (ASIST): 2-year postbiopsy follow-up. *Eur Urol*. 2020;77(3):311-317.
16. Chu CE, Lonergan PE, Washington SL, Cowan JE, Shinohara K, Westphalen AC. Multiparametric magnetic resonance imaging alone is insufficient to detect grade reclassification in active surveillance for prostate cancer. *Eur Urol*. 2020;78(4):515-517.
17. Chesnut GT, Vertosick EA, Benfante N, Sjoberg DD, Fainberg J, Lee T. Role of changes in magnetic resonance imaging or clinical stage in evaluation of disease progression for men with prostate cancer on active surveillance. *Eur Urol*. 2020;77(4):501-507.
18. Tilki D, Preisser F, Tennstedt P, Tober P, Mandel P, Schlomm T. Adjuvant radiation therapy is associated with better oncological outcome compared with salvage radiation therapy in patients with pN1 prostate cancer treated with radical prostatectomy. *BJU Int*. 2017;119(5):717-723.
19. Lestini JF, Guglielmetti GB, Trinh Q-D, Coelho RF, Pontes J, Bastos DA. Extended versus limited pelvic lymph node dissection during radical prostatectomy for intermediate- and high-risk prostate cancer: early oncological outcomes from a randomized phase 3 trial. *Eur Urol*. 2021;79(5):595-604.
20. Touijer KA, Sjoberg DD, Benfante N, Laudone VP, Ehdaie B, Eastham JA. Limited versus extended pelvic lymph node dissection for prostate cancer: a randomized clinical trial. *Eur Urol Oncol*. 2021;4(4):532-539.
21. Touijer KA, Mazzola CR, Sjoberg DD, Scardino PT, Eastham JA. Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. *Eur Urol*. 2014;65(1):20-25.
22. Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet*. 2020;396(10260):1422-1431.
23. Hickey BE, James ML, Daly T, Soh FY, Jeffery M. Hypofractionation for clinically localized prostate cancer. *Cochrane Database Syst Rev*. 2019;9:CD011462.
24. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet*. 2019;394(10196):385-395.
25. Pommier P, Chabaud S, Lagrange J-L, Richaud P, Le Prise E, Wagner J-P. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Update of the long-term survival results of the GETUG-01 randomized study. *Int J Radiat Oncol Biol Phys*. 2016;96(4):759-769.
26. Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med*. 2011;365(2):107-118.
27. Murthy V, Maitre P, Kannan S, Panigrahi G, Krishnatre R, Bakshi G. Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): outcomes from phase III randomized controlled trial. *J Clin Oncol*. 2021;39(11):1234-1242.
28. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet*. 2020;395(10231):1208-1216.
29. Perera M, Papa N, Roberts M, Williams M, Udovicich C, Vela I. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer-updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. *Eur Urol*. 2020;77(4):403-417.
30. Attard G, Murphy L, Clarke NW, Cross W, Jones RJ, Parker CC. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet*. 2022;399(10323):447-460.
31. Williams S, Davis ID, Sweeney C, Stockler MR, Martin AJ, Hague W. Randomised phase 3 trial of enzalutamide in androgen deprivation therapy (ADT) with radiation therapy for high risk, clinically localized prostate cancer: ENZARAD (ANZUP 1303). *J Clin Oncol*. 2018;36(6\_suppl):TPS156-TPS156.
32. Taplin M-E, Gleave M, Evans CP, Efstathiou E, Kantoff PW, Ross A. PROTEUS: a randomized, double-blind, placebo (PBO)-controlled, phase 3 trial of apalutamide (APA) plus androgen deprivation therapy (ADT) versus PBO plus ADT prior to radical prostatectomy (RP) in patients with localized high-risk or locally advanced prostate cancer (PC). *J Clin Oncol*. 2019;37(15\_suppl):TPS5100-TPS5100.
33. Schaefer E, Srinivas S, An Y, et al. *NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Version 4.2022*. [https://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf) 2022
34. Eastham JA, Auffenberg GB, Barocas DA, Chou R, Crispino T, Davis JW. Clinically localized prostate cancer: AUA/ASTRO guideline, part I: introduction, risk assessment, staging and risk-based management. *J Urol*. 2022;208(1):10-18.
35. Eastham JA, Auffenberg GB, Barocas DA, Chou R, Crispino T, Davis JW. Clinically localized prostate cancer: AUA/ASTRO guideline, part II: principles of active surveillance, principles of surgery, and follow-up. *J Urol*. 2022;208(1):19-25.
36. Eastham JA, Auffenberg GB, Barocas DA, Chou R, Crispino T, Davis JW. Clinically localized prostate cancer: AUA/ASTRO guideline. Part III: principles of radiation and future directions. *J Urol*. 2022;208(1):26-33.
37. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. *J Urol*. 2018;199(3):683-690.

38. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part II: recommended approaches and details of specific care options. *J Urol.* 2018;199(4):990-997.
39. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Fondurola J, Chen M-H. Clinical utility of the percentage of positive prostate biopsies in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer. *J Clin Oncol.* 2000;18(6):1164-1172.
40. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK. The eighth edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin.* 2017;67(2):93-99.

## Study Questions Volume 42 Lesson 32

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1. Each of the following variables is included in the risk stratification for clinically localized prostate cancer except
  - a. PSA
  - b. PSA density
  - c. Clinical T stage
  - d. Gleason Grade
2. Based on the Clinically Localized Prostate Cancer Guideline 2022 update, an asymptomatic patient with clinical stage T2a, PSA 9.2 ng/mL, and Grade Group 2 prostate cancer should receive
  - a. No imaging
  - b. Computerized tomography and bone scan
  - c. Multiparametric (mp) MRI and bone scan
  - d. Prostate-specific membrane antigen positron emission tomography
3. The Clinically Localized Prostate Cancer Guideline 2022 update recommends that patients considering active surveillance (AS) should be advised that
  - a. Focal ablation represents a recommended treatment alternative to AS in low-risk disease
  - b. Follow-up for AS includes PSA check at 3-month intervals, digital rectal exam at 6-month intervals, and prostate MRI every 18-24 months
  - c. mpMRI should be obtained prior to confirmatory biopsy particularly in patients whose initial prostate biopsy was performed without MRI guidance
  - d. Serial mpMRI may be used to replace serial biopsy
4. Which of the following treatments fall within the Clinically Localized Prostate Cancer Guideline 2022?
  - a. AS for a healthy 60-year-old patient with Gleason  $4 + 3 = 7$  disease, PSA = 11.2, cT2a
  - b. Radical prostatectomy + no pelvic lymph node dissection for a patient with Gleason  $4 + 3 = 7$ , PSA 5.5, cT1c
  - c. Focal ablation for a patient with Gleason  $4 + 4 = 8$  disease, PSA 9.2, cT2c
  - d. External beam radiation therapy + androgen deprivation therapy (12 months) for a patient with Gleason  $4 + 5 = 9$  disease, PSA 10.8, cT3
5. Regarding germline testing in prostate cancer in the Clinically Localized Prostate Cancer Guideline 2022 update, which of the following is correct?
  - a. Widespread availability and cost-effectiveness have enabled routine testing of any confirmed diagnosis of prostate cancer
  - b. Germline testing should only be performed in the setting of metastatic prostate cancer
  - c. Potential benefits of germline testing include enhanced risk stratification and identification of genes that may guide treatment decisions
  - d. Current guidelines are based loosely on the recommendations of the National Comprehensive Cancer Network Guideline for Prostate Cancer