THE JOURNAL of UROLOGY®
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# Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, Part II: Principles of Active Surveillance, Principles of Surgery, and Follow-Up

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

**Materials and Methods:** The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. A research librarian conducted searches in Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. The methodology team supplemented searches of electronic databases with the studies included in the prior AUA review and by reviewing reference lists of relevant articles.

**Results:** The Clinically Localized Prostate Cancer Panel created evidence- and consensus-based guideline statements to aid clinicians in the management of patients with clinically localized prostate cancer. Statements regarding active surveillance, surgical management, and patient follow-up are detailed.

**Conclusion:** This guideline aims to inform clinicians treating patients with clinically localized prostate cancer. Continued research and

**Abbreviations and Acronyms**

ADT = Androgen deprivation therapy
ASTRO = American Society for Radiation Oncology
AUA = American Urological Association
CI = Confidence interval
DRE = Digital rectal exam
HR = Hazard ratio
mpMRI = Multi-parametric magnetic resonance imaging
MRI = Magnetic resonance imaging
PI-RADS = Prostate Imaging-Reporting and Data System
PLND = Pelvic lymph node dissection
PSA = Prostate-specific antigen
QOL = Quality of life
SDM = Shared decision-making

Accepted for publication April 30, 2022.
The complete unabridged version of the guideline is available at https://www.jurooolgy.com.
This document is being printed as submitted, independent of standard editorial or peer review by the editors of *The Journal of Urology®*.
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https://doi.org/10.1097/JU.0000000000002758
Vol. 208, 19-25, July 2022
Printed in U.S.A.

publication of high-quality evidence from future trials will be essential to further improve care for these men.

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

## BACKGROUND

The selection of a management strategy for clinically localized prostate cancer is preference-sensitive and very often based on patients' interpretation of the balance between treatment-specific risks and benefits. The content summarized herein outlines principles of active surveillance and surgery for patients electing these management options as well as appropriate follow-up strategies.

## GUIDELINE STATEMENTS

### Principles of Active Surveillance

**17. Patients managed with active surveillance should be monitored with serial prostate-specific antigen (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,[1,2] 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 digital rectal exam (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.[3] With regard to the use of genomic testing, 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 retesting of PSA as transient PSA elevations are common, and PSA kinetics have variably been associated with pathology among patients on surveillance.[4] Serial PSA increases, new DRE abnormalities, or other concerns for clinical progression should prompt reevaluation with magnetic resonance imaging (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 shared decision-making (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 (QOL) with treatment and disease progression.

**18. In patients selecting active surveillance, clinicians should utilize multiparametric magnetic resonance imaging (mpMRI) 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. mpMRI has been utilized as one such tool for risk assessment in this setting,[5] particularly among patients whose initial prostate biopsy was performed without prior mpMRI 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 mpMRI findings have been found to be more likely to contain clinically significant disease (typically, higher Grade Group).[6]

A role for mpMRI prior to confirmatory biopsy among patients on active surveillance for low-risk prostate cancer was investigated in the prospective,

randomized ASIST trial.[7] 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 mpMRI, a follow-up report from the trial found that patients who underwent mpMRI had fewer active surveillance failures and less grade progression at two years follow-up post biopsy.[8] Thus, the Panel believes that an mpMRI should be obtained if the initial (diagnostic) prostate biopsy was performed without mpMRI guidance. If the mpMRI demonstrates findings suspicious for clinically-significant prostate cancer (Prostate Imaging-Reporting and Data System [PI-RADS] 4 or 5), then timely repeat (confirmatory) targeted biopsy is recommended, with disease risk re-established based on these biopsy results. Conversely, if the mpMRI is assessed as PI-RADS 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.[5,9,10]

Evidence for the utility of serial prostate mpMRI to evaluate for changes in disease risk among patients on surveillance remains mixed; as such, mpMRI cannot be recommended as a stand-alone replacement for periodic repeat biopsy.[11] For example, a recent cohort study demonstrated that a surveillance strategy using mpMRI 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.[12] A subsequent meta-analysis found a pooled sensitivity and specificity for detecting Grade Group of 2 or more of 0.59 (95% Confidence Interval [CI] 0.44 to 0.73) and 0.75 (95% CI 0.66 to 0.84), respectively.[13] It should be noted that interobserver variability in interpreting mpMRI may be a limitation. Therefore, while the Panel recognizes that mpMRI 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

**19. 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.[14,15] The Panel does acknowledge, however, that the systematic review did not identify randomized trials 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.[16] 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.

**20. 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. (Moderate Recommendation; Evidence Level: Grade B)**

**21. 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 (eg, 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 overall survival.[17–19] Two recent prospective trials randomized patients undergoing radical prostatectomy to limited versus extended PLND.[20,21] 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.[20] 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.[22]

Nevertheless, as PLND (specifically, an extended PLND) does facilitate identification of positive nodes,[20,23] 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.[24,25] 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.[26–28] When selecting a model, it is important that clinicians consider the risk profile of the patients included in model development (eg, percentage of high-risk patients) as well as the reference standard (eg, 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.

**22. 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:[17]

- 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.[20,22,23] While a more extensive lymph node dissection increases operative time as well as the risk of lymphocele,[22] the Panel believes that the demonstrated staging benefit supports that extended dissection should be performed for appropriately risk-selected patients undergoing PLND.

**23. 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 androgen deprivation therapy (ADT) alone.[29–31] 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.

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

**25. 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.[32–34] 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.[35]

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).[24] At the median 11.9 year follow-up, immediate ADT was associated with improved progression-free survival (Hazard Ratio [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 overall survival (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. Some found no significant association between treatment with adjuvant ADT and oncologic outcomes including biochemical recurrence-free survival, metastasis-free survival, prostate cancer-specific survival, and overall survival, while others found improvement in various cancer-specific outcomes in certain populations.[36–41]

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.[37,40,42–46] 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.[37,40,43–45] 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.[37] 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 (ie, 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 (eg, number of positive nodes, primary tumor features) as well as the potential toxicities of additional therapies.

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

Three recent 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.[47–49] 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.[50] 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 aforementioned trials with particularly high-risk features (eg, Gleason 8 to 10 disease with extraprostatic extension, positive lymph nodes) and thereby acknowledges a potential role for adjuvant radiation in such select patients.

### Follow-Up after Treatment

**43. 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, in order to monitor the QOL impact from therapy.

**44. 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 (eg, 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/UsTOO − the End of 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.

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