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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Prostate Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Prostate Cancer

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Individuals Who Provided Content Development and/or Authorship Assistance:

The faculty listed below have no relevant financial relationship(s) with ineligible companies to disclose.

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Daniel E. Spratt, MD, Panel Chair, has disclosed receiving consulting fees from Bayer HealthCare; and receiving honoraria from Astellas Pharma US, Inc., AstraZeneca Pharmaceuticals LP, Blue Earth Diagnostics, Janssen Pharmaceutica Products, LP, Novartis Pharmaceuticals Corporation, and Pfizer Inc.

Sandy Srinivas, MD, Panel Vice Chair, has disclosed receiving grant/research support from Novartis Pharmaceuticals Corporation; and serving as a scientific advisor for General Electric Company, Janssen Pharmaceutica Products, LP, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, and Telix Pharmaceuticals Limited.

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Prostate Cancer, Version 5.2026

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Prostate Cancer include recommendations for staging and risk assessment after a prostate cancer diagnosis and for the care of patients with localized, regional, recurrent, and metastatic disease. These NCCN Guidelines Insights summarize the panel's discussions on select 2026 updates to the guidelines regarding nonmetastatic disease: the elimination of the very-low-risk group, updates to the Principles of Active Surveillance, and caution in the use of focal therapy in newly diagnosed patients.

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Overview

Men in the United States currently have a 1 in 8 lifetime risk of developing prostate cancer, making it the most common cancer in this population.¹ An estimated 333,830 new cases of prostate cancer will be diagnosed in the United States in 2026, with an estimated 36,320 deaths.¹ The 5-year relative survival rate for prostate cancer from 2015 to 2021 was >99% for patients diagnosed with localized or regional disease and 38% for those with distant metastases at the time of diagnosis.¹

The management options for patients with localized prostate cancer are determined by the patient's life expectancy and risk stratification to estimate prognosis. The main approaches are observation, active surveillance, radical prostatectomy (RP) with or without adjuvant radiation therapy (RT), and RT with or without androgen deprivation therapy (ADT). Active surveillance is strongly preferred for appropriate patients to avoid overtreatment of indolent disease, as discussed in more detail later. When definitive treatment is warranted as initial therapy, focal/partial gland therapy and whole-gland ablative treatments should be used only within the context of a clinical trial. This topic is also discussed in greater detail later.

Low-Risk Prostate Cancer

Treatment recommendations for individuals with localized prostate cancer are based on prognosis, which is estimated through risk stratification. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer began incorporating risk groups based on clinical and pathologic features, including T stage, prostate-specific antigen (PSA), Gleason score, and the percentage of tumor in the specimen, starting in 2000.² These risk groups have been validated and published widely and are used to provide standardized treatment recommendations.^{3–8} However, it is important to note that there is considerable heterogeneity within each NCCN risk group.

A very-low-risk group was separated from the low-risk group in 2010 based on data showing that certain clinical criteria could predict clinically insignificant cancer.⁹ In the 2025 version of the NCCN Guidelines, active surveillance was the only recommendation for patients with very-low-risk disease and life expectancy ≥ 10 years, with observation recommended for those with shorter life expectancies. For the low-risk group, active surveillance is included as the preferred option for most patients with life expectancy ≥ 10 years, but radical treatment with RT or RP are included as options for select patients.

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Category 1: Based upon high-level evidence (≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus ($\geq 50\%$, but $< 85\%$ support of the Panel) that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

PLEASE NOTE

These NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.

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Preferred: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

At the 2026 panel meeting, the members discussed whether it remained appropriate to maintain the distinction between these 2 risk groups. The rationale for the proposal to remove the very-low-risk group was based on the panel's uniform belief that the vast majority of patients in the low-risk group should be started on active surveillance, and that maintaining the distinction could mislead patients in this group into thinking their risk is higher than it actually is. It might also incorrectly suggest that active surveillance is strongly recommended only for the very-low-risk group. Historically, the panel viewed the very-low-risk group as those for whom active surveillance was most clearly indicated. However, the panel's perspective has evolved over time, and it now considers both groups collectively as strongly appropriate candidates for active surveillance. Panel members noted that they no longer think that a patient with 4 positive cores, for example, is at significantly higher risk for distant metastasis or prostate cancer-specific mortality than a patient with 2 positive cores, and they would strongly recommend active surveillance in both cases. Active surveillance intensity, such as the frequency of prostate biopsies, can be modulated based on a patient's prognostic risk.

The panel discussed several additional benefits of removing the very-low-risk group, including that

(1) it would simplify the guidelines and thus make them easier to implement in clinical practice; (2) it would allow for a stronger focus on optimizing low-risk and favorable intermediate-risk (FIR) active surveillance criteria and improved tailoring of active surveillance intensity; and (3) it would align with other organizations, such as the American Urologic Association (AUA) and the American Society for Radiation Oncology (ASTRO), which removed the very-low-risk category from their risk stratification schema in 2022.¹⁰

Furthermore, the very-low-risk group is not routinely reported or used to define candidacy for active surveillance in clinical studies, and many prognostic features observed in low-risk active surveillance cohorts extend beyond the very-low-risk group criteria. For example, a history of negative biopsies since diagnosis, longer time since diagnosis, slower PSA kinetics, and lower body mass index were all identified as independent

negative predictors of grade reclassification in a large multicenter cohort study.¹¹

The panel consensus was that the very-low-risk group should be removed (see Figure 1).

Active Surveillance in Low-Risk Prostate Cancer

With the removal of the very-low-risk group, the panel wanted to emphasize the heterogeneity of the newly expanded low-risk group as it might relate to the intensity of active surveillance. The panel therefore updated the "Principles of Active Surveillance" to place greater emphasis on factors in the low-risk setting associated with an increased probability of near-term grade reclassification and the subsequent need to transition off active surveillance (see Figure 2). The panel also added a recommendation for the use of a risk calculator for more precise estimates of upgrading probability in this population. However, the panel emphasized that higher-risk features alone do not necessitate immediate treatment; rather, they should inform shared decision-making and help tailor the intensity of active surveillance.

Although the panel strongly recommends active surveillance for most patients with low-risk disease and a life expectancy of ≥ 10 years, a careful discussion should be held with patients who may be less likely to adhere to an active surveillance protocol regarding the potential risks. For some of these patients, upfront treatment with definitive RP or RT may be preferred.

Active Surveillance in FIR Prostate Cancer

Patients with FIR prostate cancer and a life expectancy of > 10 years may also consider active surveillance. However, the panel noted that the criteria used to classify patients in this risk group were not developed for the optimal selection of active surveillance candidates. The panel also highlighted the considerable heterogeneity in this risk group; not all patients with FIR disease are suitable candidates for active surveillance. The panel therefore reinforced its emphasis on prognostic factors and provided examples of patients with FIR disease for whom active surveillance would or would not be preferred (see Figure 3).

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE ⁱ				
Risk Group	Clinical/Pathologic Features (Staging, ST-1)		Additional Evaluation ^{g,1}	Initial Therapy
Very Low	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • <3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g		• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-3
Low ^j	Has all of the following but does not qualify for very-low-risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-3
Intermediate ^j	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▶ cT2b–cT2c ▶ Grade Group 2 or 3 ▶ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores) ^k	PROS-4
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive (eg, ≥6 of 12 cores) ^k	PROS-5
High	Has one or more high-risk features, but does not meet criteria for very high risk: • cT3–cT4 • Grade Group 4 or Grade Group 5 • PSA >20 ng/mL		Bone and soft tissue imaging ^g ▶ If regional metastases are found, see PROS-7 ▶ If distant metastases are found, see PROS-14 for Low-Volume M1 (Metachronous or Synchronous) or Synchronous Oligometastatic CSPEC or PROS-15 for High-Volume M1 CSPEC	PROS-6
Very high	Has at least two of the following: • cT3–cT4 • Grade Group 4 or 5 • PSA >40 ng/mL		Bone and soft tissue imaging ^g ▶ If regional metastases are found, see PROS-7 ▶ If distant metastases are found, see PROS-14 for Low-Volume M1 (Metachronous or Synchronous) or Synchronous Oligometastatic CSPEC or PROS-15 for High-Volume M1 CSPEC	PROS-6

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Footnotes on PROS-2A

PROS-2

Figure 1. PROS-2. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 5.2026.

The panel also added language regarding the need for greater intensity of active surveillance in this population. Furthermore, patients should be counseled that long-term data indicate those with Grade Group 2 disease on active monitoring or watchful waiting may have a higher risk of developing distant metastasis compared with patients receiving immediate radical treatment.¹² Continued refinements in active surveillance protocols and eligibility criteria are expected to enhance the safety of active surveillance for patients with Grade Group 2, FIR disease, and patients should be counseled on the importance of careful longitudinal follow-up.

Focal/Partial-Gland Therapy and Whole-Gland Ablative Therapy as Initial Therapy

In addition to the long-established use of RP and RT as definitive treatments for patients with newly diagnosed localized prostate cancer, other therapies have been investigated in this setting. For example, ablative prostate therapies (ie, using a device to destroy tissue in part of or the whole prostate gland) and other partial-gland, hemi-gland, or focal approaches (hereafter referred to collectively as “focal therapies”) have been studied. However, due to the limited prospective data available, whole-gland ablative therapies and focal therapies are not recommended in the NCCN Guidelines for Prostate Cancer as initial treatment of newly diagnosed patients. At present, the only focal therapies included as options in the NCCN Guidelines are cryotherapy, high-intensity focused ultrasound (HIFU), and irreversible electroporation (IRE; category 2B for IRE) in the setting of nonmetastatic RT recurrence,

due to the overall paucity of prospective data across treatment modalities.

In advance of the 2026 meeting, the panel received external requests to add focal therapies to the treatment algorithms for patients with newly diagnosed, localized prostate cancer. For many years, the panel’s stance has been to exclude these treatments from initial therapy because (1) they lack FDA approval for prostate cancer; (2) there is no randomized controlled trial (RCT) evidence with long-term follow-up demonstrating superiority or noninferiority compared with currently recommended management strategies; (3) they have a concerning risk profile; and (4) secondary treatment of recurrences after these treatments can be challenging and variably more toxic. The panel discussed these and additional points and reviewed the available evidence for the use of these modalities in the initial therapy setting at the annual panel meeting. Emphasis was placed on the highest-quality data. Phase I trials and registry data were not discussed; although a high-quality registry can support the conclusions of RCTs, the panel does not generally feel they provide high-level evidence on their own.

Evidence for Whole-Gland Ablative Therapies in the Initial Treatment Setting

Limited data support the use of ablative techniques for delivery to the whole gland, with most studies being retrospective.¹³ One randomized controlled noninferiority trial, published in 2010, compared whole-gland cryoablation versus RT in 244 patients with untreated localized prostate cancer, mostly with intermediate- and

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- The NCCN Prostate Cancer Panel and the NCCN Prostate Cancer Early Detection Panel (NCCN Guidelines for Prostate Cancer Early Detection) remain concerned about overdiagnosis and overtreatment of prostate cancer. The Prostate Cancer Panel recommends that patients and their physicians carefully consider active surveillance based on the patient's prostate cancer risk profile and estimated life expectancy. In settings where the patient's age and comorbidities suggest a shorter life expectancy, observation may be more appropriate. Shared decision-making, after appropriate counseling on the risks and benefits of the various options, is critical.
- Life expectancy is a key determinant for the choice between observation and active surveillance. Multiple tools exist to assist in life expectancy estimation. See Principles of Life Expectancy Estimation (PROS-A).
- There remains no high-level evidence showing clinical benefit of advanced risk stratification tools (eg, gene expression biomarkers, germline or somatic testing, or artificial intelligence (AI)-based digital pathology models), to guide the candidacy for active surveillance.

ACTIVE SURVEILLANCE¹

- Active surveillance involves actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses. It involves PSA monitoring and longitudinal serial pathologic assessments via a prostate biopsy, often guided by MRI.
- There are three phases of active surveillance: 1) candidacy, 2) confirmation of candidacy, and 3) active surveillance.

• Candidacy for Active Surveillance:**▷ NCCN Low-Risk:**

- ◊ Active surveillance is the preferred management approach for patients with low-risk prostate cancer and a life expectancy ≥10 years. Active surveillance is preferred for most patients with low-risk prostate cancer and a life expectancy ≥10 years.
- ◊ The Panel recognizes that there is heterogeneity across this risk group.
 - Some factors may be associated with an increased probability of near-term grade reclassification including:
 - High PSA density (≥0.15)²
 - Increased A-high number of positive cores (eg, ≥3)³
 - Higher body mass index (BMI)³
 - Faster PSA kinetics³
 - High genomic risk (from tissue-based molecular tumor analysis)
 - Conversely a negative biopsy following diagnosis is associated with a decreased probability of grade reclassification.
 - The Canary PASS risk calculator can be used for more precise estimates of upgrading probability on active surveillance (Canary Pass Risk Calculator)
 - Higher risk features alone do not necessitate immediate treatment, but should be used as part of a shared-decision making discussion and in tailoring the intensity of active surveillance.
- ◊ For patients who are at high-risk of suboptimal adherence to an active surveillance protocol, a careful discussion should be had about the potential risks of active surveillance. For some of these patients, upfront treatment with definitive RP or RT may be preferred.

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Figure 2. PROS-F 1 of 5. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 5.2026.

high-risk disease.^{14,15} Fewer positive biopsies were seen after cryoablation than after external-beam RT (EBRT), but greater declines in sexual function were observed in the cryoablation group. Disease progression was very low across all participants during the 36-month follow-up; therefore, inferiority could not be ruled out. In another randomized study published in 2012 involving 62 patients with previously untreated cT2c–cT3b prostate cancer, whole-gland cryoablation with ADT was associated with a worse 8-year biochemical disease-free survival rate compared with EBRT plus ADT (17.4% vs 59.1%; $P = .01$).¹⁶

More recently, whole-gland transurethral ultrasound ablation (TULSA) was studied in a single-arm, phase II trial involving 115 patients with untreated low- to intermediate-risk prostate cancer, with 12 months of follow-up.¹⁷ A total of 37% of the participants had Grade Group 1 disease. Among the 68 individuals with Grade Group 2 cancer, 21% had Grade Group 2 disease on biopsy at 12 months; 35% of the total population who had biopsy data available showed evidence of cancer. Grade 3 events occurred in 8% of the participants. Grade 2 or 3 urinary retention occurred in 9% of the study population. Grade 1 or 2 erectile dysfunction occurred in 43% of participants and was ongoing at 12 months in 35%. The rate of grade 1 and 2 urinary incontinence at 12 months was 11%, with 3% of individuals requiring pad use.

One large, multicenter, nonrandomized prospective trial conducted in France compared RP with whole-gland or partial-gland HIFU for initial treatment.¹⁸ Most of the 3,328 participants had intermediate-risk disease (61% in the HIFU group; 64% in the RP group). A total of 80% of participants received whole-gland treatment, and the remaining 20% received partial-gland

treatment that was delivered to at least 70% of the gland. The primary endpoint of secondary therapy-free survival was noninferior at 30 months. Rates of grade >IIIa complications were similar between the 2 groups, whereas urinary incontinence and erectile dysfunction appeared to be more frequent in the RP group. The panel noted that the study's lack of randomization and the age difference between groups (median ages of 75 and 65 years in the HIFU and RP groups, respectively) represent limitations.

Evidence for Focal Ablative Therapies in the Initial Treatment Setting

There is less evidence supporting the use of ablative therapies for newly diagnosed prostate cancer when delivered as focal therapy compared with whole-gland therapy. The highest-quality data available come from single-arm phase I and II trials, many of which are funded by industry. Randomized evidence demonstrating the effectiveness of these techniques for long-term cancer control and/or improving quality of life when delivered as focal therapy, compared with RT or RP, is lacking. One RCT has been reported; however, the study compared photodynamic therapy (PDT) with active surveillance in 413 patients with low-risk prostate cancer—a population that should not generally receive treatment.¹⁹ Furthermore, the panel expressed concerns about the high rate of disease progression in the control arm (58% at 2 years). Grade 3–4 adverse events that were significantly more frequent in the PDT arm than in the active surveillance group included prostatitis (2%) and acute urinary retention (2%).

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

• **Candidacy for Active Surveillance (continued):**▶ **NCCN Favorable Intermediate-Risk (FIR)**

- ◊ Patients with FIR prostate cancer and a life expectancy of >10 years may also consider active surveillance. **Particular consideration may be appropriate for those patients with a low percentage of Gleason pattern 4, low tumor volume, low PSA density, or low genomic risk (from tissue-based molecular tumor analysis).**
- ◊ The FIR group was not created for optimal selection of active surveillance candidacy, and there is considerable heterogeneity in this risk group. Not all patients with FIR disease are suitable candidates for active surveillance. For example:
 - A patient with Grade Group 1 in a single biopsy core, cT1c, PSA of 12 ng/mL, and PSA density of 0.15 ng/mL/g has FIR disease and a favorable prognostic outcome. Therefore, active surveillance is preferred.
 - A patient with GG2 in 5 of 12 cores, cribriform architecture, cT1c, PSA of 8 ng/mL, and PSA density 0.30 ng/mL/g has FIR disease, but active surveillance would not be the preferred strategy.
- ◊ In addition to prognostic factors listed for Low Risk, additional prognostic factors relevant for FIR include:
 - Increased percentage pattern 4.
 - Presence of unfavorable histology such as expansile/large cribriform histology and/or intraductal carcinoma.
- ◊ Active surveillance is not recommended for patients with FIR and unfavorable histology (eg, expansile/large cribriform histology, intraductal carcinoma). See Discussion.
- ◊ Intensity of active surveillance should generally be greater for patients with FIR disease.
- ◊ Patients should be counseled that long-term data show that patients with GG2 disease managed with active monitoring or watchful waiting had an increase in the development of distant metastasis as compared to those receiving immediate radical treatment.⁴ Continued refinements in active surveillance protocols and active surveillance candidacy are expected to improve the safety of active surveillance for GG2 FIR disease, and patients should be counseled on the importance of longitudinal follow-up.

• **Confirmation of Candidacy:**

- ▶ Goals of confirmation testing are to help facilitate early identification of patients who may be at a higher risk of grade reclassification or cancer progression.
- ▶ An initial prostate biopsy may underestimate tumor grade or volume, thus confirmatory testing is strongly recommended **within the first 6- to 12 months of diagnosis** for patients who are considering active surveillance.
- ▶ A repeat biopsy is a routine component of confirmatory testing.
 - ◊ The timing of repeat biopsy can be based on the patient's risk of progression. Patients with a higher risk should have a repeat biopsy earlier than those with a lower risk.
 - ◊ If the initial prostate biopsy was performed without mpMRI guidance, then the Panel recommends an earlier repeat biopsy (eg, within the first 6–12 months) and recommends mpMRI prior to the biopsy. A systematic biopsy should be included. **Early confirmatory testing may not be necessary in patients who have had an mpMRI prior to diagnostic biopsy.**
 - ◊ For most patients, the timing is generally within 6 to 24 months of diagnostic biopsy, but all patients on active surveillance should undergo a confirmatory prostate biopsy within 3- to 4 years of their diagnostic biopsy, **irrespective of prior mpMRI findings.**
- ▶ Confirmatory testing should also include mpMRI with calculation of PSA density.
- ▶ Advanced risk stratification tools lack high level evidence to obviate other testing at this time.
- ▶ Other forms of imaging are discouraged.

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Figure 3. PROS-F 2 of 5. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 5.2026.

HIFU has been assessed in several phase II studies. The largest study was a phase IIb trial assessing MRI-guided HIFU for the initial treatment of 101 patients with intermediate-risk prostate cancer.²⁰ After 24 months, there was evidence of any cancer and Grade Group ≥ 2 cancer in the HIFU-targeted area in 20% and 12% of patients, respectively. The corresponding rates in the whole prostate were 60% and 40%. Of the evaluable 98 patients, 15 had Grade Group ≥ 3 disease at 2 years (15.3%). The most common grade 1 or 2 adverse events included hematuria (24%), erectile dysfunction (20%), urinary incontinence (18%), and urinary retention (15%). Three additional, smaller phase II studies evaluating HIFU for initial treatment have been published, all demonstrating similar results.^{21–23}

Focal laser ablation (FLA) was studied in a small, single-arm phase II study with 12 months of follow-up.²⁴ Of the 27 participants, 85% had Grade Group 1 cancer at diagnosis, and the median PSA level was 4.4 ng/mL. After the 12 months of follow-up, 11% had cancer in the treatment field and 37% had cancer evident in the whole gland. Common adverse effects included erectile dysfunction (19%), hematuria (15%), and acute urinary retention (8%).

Results from a phase III RCT were presented at the 2025 AUA meeting.²⁵ The single-center study from Oslo University Hospital is a noninferiority trial comparing RP with focal ablation using HIFU or TULSA in 213 patients with localized prostate cancer (Grade Group 1 that is >5 mm or any Grade Group 2). Although 106 participants were randomized to the RP group, 25% refused RP and were included in the focal ablation group.

Individuals in the focal ablation arm underwent MRI and systematic biopsies at 1 and 3 years. At 3 years, 6.5% of participants in the focal ablation group required secondary RP or RT for high-risk disease that was deemed ineligible for repeat focal ablation. In the RP group, 8.5% of participants experienced a posttreatment PSA >0.2 ng/mL. Based on these results, the authors concluded that ablation was noninferior to RP with regards to its primary objective of treatment failure at 3 years, with the noninferiority margin set at 15%. The panel noted that it is not clear how many patients in the focal ablation group were deemed eligible for repeat ablation.

A recent systematic review and meta-analysis identified 49 unique cohorts of patients who received focal therapy for prostate cancer between 2008 and 2024 (21 cryotherapy, 20 HIFU, and 8 IRE).²⁶ Most of the studies were retrospective analyses. Pooled overall survival (98.0%), cancer-specific survival (99.3%), and metastasis-free survival (98.5%) were favorable, but follow-up times were short (median, 27.8 months; range, 6–63 months) and many of the cohorts comprised a significant proportion of patients with NCCN low-risk or Grade Group 1 disease. The pooled rate of biochemical progression was 9.4% per year, and the pooled rate of cancer detected on post-focal therapy biopsy within 24 months was 44.6% overall, including 21.4% occurring within the ablation field. Additional treatment was administered to 15.5% of patients. Among studies reporting on sexual function, 54.3% observed a moderate to severe impact from focal treatment. Another systematic review encompassed retrospective studies as well as phase I and II trials, identifying only a

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General

- Ablative therapy refers to the use of a device to destroy tissue that can be directed at part of the prostate gland (termed partial gland, hemi-gland, or focal therapy [FT]) or the whole prostate gland.
- FT includes ablative therapies and non-ablative therapies, such as partial prostatectomy and focal radiation therapy.^a
- Presently, FT is an experimental and emerging technology for the initial treatment of localized prostate cancer that lacks randomized controlled trial evidence with long-term follow-up showing its superiority or noninferiority to current recommended management strategies. As such, FT meets the criteria as an alternative therapy, or a non-standard treatment.

Newly Diagnosed or Previously Untreated Prostate Cancer

- Pathologic confirmation of prostate cancer and risk stratification is required prior to consideration of ablative or FT.
- Active surveillance is the preferred treatment for low-risk prostate cancer, and ablative and focal therapies are discouraged in this population.
- The Panel also believes that ablative FT should be discouraged in patients with high- or very-high-risk, regional, or metastatic prostate cancer outside of a clinical trial.
- There is currently insufficient comparative effectiveness evidence for FT to be recommended for patients with intermediate-risk prostate cancer, and the Panel believes there is uncertainty about the long-term efficacy and toxicity of these treatments. Therefore, ablative and focal therapies in this population should be utilized only in the context of a clinical trial.
- The following device categories are currently FDA approved or cleared for the initial treatment of prostate cancer, but randomized evidence to the superiority in long-term cancer control and/or quality of life are lacking when delivered as focal rather than whole gland therapy. These treatments may be considered as FT for patients with previously untreated, localized prostate cancer only in the context of a clinical trial:
 - ▶ External beam radiotherapy^a
 - ▶ Brachytherapy
 - ▶ Cryotherapy ablation
- The following device categories are currently not FDA approved or cleared for the treatment of prostate cancer as focal or whole gland therapy, and should only be used for patients with previously untreated, localized prostate cancer in the context of a clinical trial:
 - ▶ High-intensity focused ultrasound (HIFU)
 - ▶ Transurethral ultrasound ablation (TULSA)
 - ▶ Focal laser ablation (FLA)
 - ▶ Radiofrequency ablation (RFA)
 - ▶ Irreversible electroporation (IRE)
 - ▶ Photodynamic therapy (PDT)
 - ▶ Histotripsy
 - ▶ Partial prostatectomy

^a Although ultra-hypofractionated EBRT, also known as stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), is considered by some as an ablative technology, it does not fall within the general class of ablative therapies. EBRT is recommended in multiple contexts for the treatment of prostate cancer, and when delivered to the prostate it is recommended to be delivered to the whole prostate gland (discussed within Principles of Radiation Therapy (PROS-J)). However, when delivered as FT it should be viewed within the context of other ablative therapies at this time given similar quality of evidence and risks of residual cancer and retreatment.

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Figure 4. PROS-I 1 of 3. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 5.2026.

single randomized trial.²⁷ The authors concluded that the current evidence is insufficient to support focal therapy as a standard treatment.

Overall, the data indicate high rates of residual or recurrent cancer and clinically meaningful toxicity (ie, incontinence, obstruction, and erectile dysfunction) following focal ablation techniques.

Regulatory Approvals of Ablative Therapies

The panel then discussed the regulatory history of ablative devices for prostate cancer. EBRT, brachytherapy, and whole-gland cryoablation are currently the only devices FDA-approved or -cleared for the initial treatment of prostate cancer. Other devices—such as HIFU, TULSA, FLA, radiofrequency ablation, IRE, PDT, histotripsy—are FDA-approved or -cleared for the ablation of *tissue*. These approvals occurred following denial of some devices for the ablation of prostate cancer due to a lack of evidence of efficacy. In fact, the labels for some of these devices specifically note that the effectiveness of the device “in treating any specific prostate disease has not been established.”

Current Use of Focal Therapies

The panel discussed a National Cancer Database (NCDB) analysis that assessed the use of cryoablation, laser ablation, or “other method of local tumor destruction,” including HIFU, for the treatment of newly diagnosed, localized prostate cancer across the United States from 2010 to 2017.²⁸ Only 1.3% of patients were treated with these techniques. Approximately 78.8% of these

individuals were treated with cryoablation, 15.6% with laser ablation, and 5.7% with HIFU or another method. Furthermore, 40% of the patients treated with ablative therapies had low-risk disease, for which active surveillance is strongly preferred. Predictors of ablative therapies use included low income, Medicare or Medicaid insurance, older age, presence of comorbidities, and Black race. A separate, similar NCDB analysis was presented at the 2025 AUA meeting.²⁹ The study included patients diagnosed with localized prostate cancer between 2004 and 2021, and identified initial treatment with focal therapy, RP, RT, or observation. In this study, 6.9% of the population received focal therapy in 2021, compared with 2.3% in 2004. Factors associated with the use of focal therapy included several previously identified factors—comorbidities, low income, Medicaid or lack of insurance—as well as Grade Group 1, cT1 stage, and treatment at a community center. Thus, in both studies, patients who were eligible for active surveillance received these treatments. Furthermore, there appear to be inequities in the use of focal therapies related to social determinants of health. The panel further noted that patients who pay out of pocket for these treatments might not be included in the study populations; thus, the true use of these techniques is likely to be higher than reported. Furthermore, the panel noted that patients paying out of pocket may experience financial toxicity.

Panel Discussion Regarding Focal Therapies

Overall, the panel consensus was that these technologies currently lack sufficient evidence to demonstrate clinical benefit to patients. Current studies are mainly small, phase II trials with

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- Patients should be counseled prior to receiving FT or whole gland ablative therapy as follows:
 - ▶ HIFU, TULSA, FLA, RFA, IRE, PDT, and histotripsy are not FDA approved or cleared for the treatment of prostate cancer.
 - ▶ Currently, no treatment delivered as FT, including radiotherapy or partial prostatectomy, have demonstrated superiority or non-inferiority to guideline-recommended therapies in randomized trials with long-term follow-up. The importance of long-term follow-up is of increased importance in this setting given the high rates of secondary therapy after FTs and potential for increased toxicity.
 - ▶ For patients with low- and intermediate-risk disease¹⁻⁷:
 - ◊ Biopsy-detected (any) cancer after FT is common within 2 years post-treatment (20%–70%).
 - ◊ Erectile dysfunction (10%–40%) and urinary incontinence (0%–20%) have been reported to occur of variable severity within 2 years post-treatment.
 - ▶ FT or whole gland ablative therapy may impact the safety and/or efficacy of subsequent local therapy.
 - ▶ Moderate toxicity (grade 2) is common, and severe toxicity (grade 3 or higher) is possible with reported rates in trials from approximately 1%–14% in the first 2 years post-FT.¹⁻⁷
 - ▶ Currently, there is no evidence-based, universally agreed upon follow-up protocol after FT. Patients often undergo serial imaging and prostate biopsies.

¹ Ehdiaie B, Tempany CM, Holland F, et al. MRI-guided focused ultrasound focal therapy for patients with intermediate-risk prostate cancer: a phase 2b, multicentre study. *Lancet Oncol* 2022;23:910-918.

² Duwe G, Boehm K, Haack M, et al. Single-center, prospective phase 2 trial of high-intensity focused ultrasound (HIFU) in patients with unilateral localized prostate cancer: good functional results but ontologically not as safe as expected. *World J Urol* 2023;41:1293-1299.

³ Ganzer R, Hadaschik B, Pahernik S, et al. Prospective multicenter phase II study on focal therapy (hemiblation) of the prostate with high intensity focused ultrasound. *J Urol* 2018;199:983-989.

⁴ Ghai S, Finelli A, Corr K, et al. MRI-guided focused ultrasound focal therapy for intermediate-risk prostate cancer: final results from a 2-year phase II clinical trial. *Radiol* 2024;310:e231473.

⁵ Klotz L, Pavlovich CP, Chin J, et al. Magnetic resonance imaging-guided transurethral ultrasound ablation of prostate cancer. *J Urol* 2021;205:769-779.

⁶ Mehraviand S, George AK, Hoang AN, et al. MRI-guided focal laser ablation of prostate cancer: a prospective single-arm, single-center trial with 3 years follow-up. *Diagn Interv Radiol* 2021;27:394-400.

⁷ Eggener SE, Yousuf A, Watson S, et al. Phase II evaluation of magnetic resonance imaging guided focal laser ablation of prostate cancer. *J Urol* 2016;196:1670-1675.

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Figure 5. PROS-I 2 of 3. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 5.2026.

short follow-up. Outcomes reported in these trials show variable success at ablating tissue, with up to 35% of patients experiencing in-field recurrences within 2 years. Furthermore, with focal treatment, rates of recurrent or residual cancer in the whole gland can be much higher, with some reports reaching up to 70%. Toxicities are also significant. Focal therapy should thus be viewed as experimental and emerging technology for the initial treatment of localized prostate cancer, as evidence from RCTs with long-term follow-up demonstrating its superiority or non-inferiority to current recommended management strategies is lacking.

The panel also discussed the uncertainty around the reliability of grading recurrent cancer in the ablation zone, the accuracy of MRI in this setting, and the safety and efficacy of secondary treatment following ablation. Anecdotally, panel members noted that they often treat patients with recurrent disease following ablation and see significant rates of grade 3 toxicities upon secondary treatment. Panel members also noted that surgery following ablation can be technically challenging.

Panel members noted that companies and institutions may make non-evidenced-based claims about the evidence, efficacy, and safety of focal therapy. Thus, patients may believe that these techniques are safer than standard treatments, even if data do not support such assertions. The inequities associated with focal ablation use (see “Current Use of Focal Therapies”), especially in patients who are candidates for active surveillance, suggest that vulnerable populations may be specifically targeted with this marketing.

The panel discussed their thoughts on the use of ablative treatments for 3 groups of newly diagnosed patients:

- Low-risk disease: These patients are candidates for active surveillance and should be discouraged from any treatment, including whole-gland ablative or focal therapies.
- High-risk, very-high-risk, regional, or metastatic disease: These patients can consider initial treatment with focal therapies only on a clinical trial, but the panel cautions that outcomes are likely to be worse than after current standard treatments. Patients in this population are more likely to harbor cancer outside of the ablation zone and are thus particularly poor candidates for focal treatment.
- Intermediate-risk disease: These patients may consider focal therapy within the context of a clinical trial, ideally one that compares focal treatment with a current standard treatment option.

One panel member also noted having observed patients without a pathologic diagnosis of prostate cancer undergoing focal ablation at the time of biopsy. This practice is strongly discouraged.

Following the data review and panel discussion, a proposal was made to include a new Principles section in the NCCN Guidelines that would explain the current state of data on these techniques and outline counseling points for patients considering these modalities for initial treatment. The panel supported this proposal and created the section, as shown in Figures 4–6.

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Management of Recurrence After Focal Ablative or Whole Gland Ablative Therapy

- Presently, the optimal management of residual or recurrent disease after receipt of these treatments is unknown and limited evidence exists. A multi-disciplinary discussion with experienced prostate cancer specialists is recommended.
- If there is suspicion of residual or recurrent prostate cancer, a biopsy should be performed to confirm the presence of residual or recurrent prostate cancer.
 - ▶ Histologic grading of the cancer is recommended if located in previously untreated areas of the prostate. Reliability of grading within a previously treated area of the prostate is unknown at this time, and patients should be informed of this uncertainty.
- Staging imaging should be performed based on the patient's NCCN risk group at time of recurrence (see PROS-2). However, PSA groupings as used for newly diagnosed prostate cancer may underestimate the burden of disease after prior FT or ablative therapy.
 - ▶ Interpretation of imaging (ie, assessment of cT3 disease by MRI near ablation zone) after FT or whole gland ablative therapy may be less reliable.⁸
 - ▶ Advanced risk stratification tools (eg, gene expression or digital pathology-based biomarkers) have not been adequately studied for use in the context of focal or whole gland ablative therapy and are not recommended to guide treatment decisions in this setting.
- Patients with a clinically significant recurrence after initial focal therapy should be offered radical prostatectomy or prostate RT if appropriate based on life expectancy.
- Patients should be counseled as follows:
 - ▶ There is limited evidence on how to optimally manage a FT or whole gland ablative therapy recurrence.
 - ▶ Patients are at an increased risk of toxicity from subsequent local therapy compared to the primary treatment setting.
 - ▶ It is not known if radical therapy has equivalent long-term success after FT or whole gland ablative therapy given lack of trials with long-term follow-up in this setting.
 - ▶ Secondary treatment should be reserved for patients with appropriate life expectancy and Grade Group 2 and higher recurrences detected on biopsy.

Local Recurrence After Radiation Therapy

- Patients with biopsy-proven recurrence in the prostate after prior RT and without distant metastatic disease can be considered for local secondary therapy.
- However, clinicians and patients should be aware that no local therapy currently has level 1 evidence for the management of a local recurrence after definitive RT.
- Treatments with higher quality of evidence are recommended. These are discussed in the Principles of Local Secondary Therapy Post-Radiation (PROS-L) and include select forms of FT or whole gland ablative therapy.

⁸ Lai AL, Velaga J, Tay KJ, et al. Multiparametric MRI before and after focal therapy for prostate cancer: pearls and pitfalls for the reporting radiologist. *Radiol*;7:e240269.

Figure 6. PROS-I 3 of 3. NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 5.2026.

Conclusions

Active surveillance is strongly recommended for newly diagnosed patients with low-risk prostate cancer, and can be considered for appropriate candidates with FIR cancer. The intensity of active surveillance should be individualized so that patients with risk factors for grade reclassification can be transitioned to a definitive treatment approach in a timely manner.

High-level data supporting the safety and efficacy of focal therapies for the initial treatment of localized prostate cancer are

lacking. Patients with FIR or higher-risk prostate cancer can consider focal therapy within a clinical trial—not simply a registry—preferably one comparing focal therapy with current standard options.



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