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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.

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The faculty listed below have no relevant financial relationship(s) with ineligible companies to disclose.
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The faculty listed below have the following relevant financial relationship(s) with ineligible companies to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.

Edward M. Schaeffer, MD, PhD, Panel Chair, has disclosed serving as a scientific advisor for Astellas Pharma US, Inc., Lantheus, and Pfizer Inc.
Sandy Srinivas, MD, Panel Vice Chair, has disclosed serving as a scientific advisor for Eli Lilly and Company, Janssen Pharmaceutica Products, LP, and Novartis Pharmaceuticals Corporation; and receiving grant/research support from Novartis Pharmaceuticals Corporation, and Regeneron Pharmaceuticals.
Tanya Dorff, MD, Panel Member, has disclosed serving as a consultant for AbbVie, Inc., AstraZeneca Pharmaceuticals LP, Exelixis Inc., Janssen Pharmaceutica Products, LP, and sanofi-aventis U.S.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

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Prostate Cancer, Version 3.2024

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 for the 2024 update to the guidelines with regard to initial risk stratification, initial management of very-low-risk disease, and the treatment of nonmetastatic recurrence.

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*Provided content development and/or authorship assistance.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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Overview

Prostate cancer is the most common cancer in men in the United States, who currently have a 1 in 8 lifetime risk of developing the disease.[1] An estimated 299,010 new cases of prostate cancer will be diagnosed in the United States in 2024, with an estimated 35,250 deaths.[1] For all stages combined, the 5-year relative survival rate is 97%.[1]

Patients diagnosed with nonmetastatic prostate cancer may have slow-growing, indolent disease that does not require treatment, or they may have more aggressive disease that requires radical therapy. To help determine whether treatment is needed and how intense the treatment should be, the prognosis of individual patients is estimated through risk stratification. This estimation is critical to inform optimal disease management decisions through an assessment of the benefits and harms of a given therapy for a particular patient to prevent overtreatment and undertreatment.

Risk Stratification for Newly Diagnosed Prostate Cancer

Current treatment recommendations for individuals with localized prostate cancer are based on prognosis, which is estimated through risk stratification. This estimation is critical to inform management decisions through an assessment of the benefits and harms of a given therapy for a particular patient, and can be used to estimate the likelihood that (1) an individual's cancer will be confined to the prostate or will spread to the regional lymph nodes, (2) an individual's cancer will progress or metastasize after treatment, and (3) adjuvant or postrecurrence (secondary) radiation will control an individual's cancer after radical prostatectomy.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) have, for many years, used NCCN risk groups as a framework to stratify patients with prostate cancer based on clinical and pathologic features, including T stage, prostate-specific antigen (PSA) levels, Grade Group (see "Very-Low-Risk Prostate Cancer" section). These risk groups have been validated and published widely and are used to provide standardized treatment recommendations.[2–7] However, there is intrinsic heterogeneity in prognosis within each NCCN risk group, and certain other risk classification schemes have been shown to outperform NCCN risk groups.[8,9]

There are also common histopathology variables (eg, cribriform histology, intraductal carcinoma, percent Gleason pattern 4) and clinical variables (eg, PSA density) that are prognostic.[10,11] Imaging (ie, MRI and prostate-specific membrane antigen [PSMA] PET/CT) may also be able to aid in risk stratification.[11,12] However, these factors have rarely been reported in the context of clinical trials.

Certain germline mutations are associated with more aggressive prostate cancer and a poorer prognosis, especially pathogenic germline mutations in *BRCA2* and *BRCA1*.[13–15] Overall, however, the prognostic impact of germline mutations in localized disease has inconsistent results from generally low-quality retrospective studies with moderate-to-high risk of bias. They are therefore not generally considered for risk stratification. However, the presence of germline mutations in patients with prostate cancer should be considered to inform screening recommendations for other cancers, treatment decisions in advanced disease, and cascade germline testing for family members.

Improved prognostication and risk stratification could help identify individual patients with localized prostate cancer who are likely to derive greater or lesser absolute benefit from a given treatment, thus better informing treatment decisions and reducing the likelihood of overtreatment or undertreatment. The panel therefore discussed 2 items regarding risk stratification this year: the utility of the very-low-risk group and advanced risk stratification tools.

Very-Low-Risk Prostate Cancer

In the 1990s, the NCCN Guidelines for Prostate Cancer included only 3 prostate cancer risk groups: low, moderate, and high. These groups were first defined by T stage and the probability of organ-confined disease, and later by Gleason score.[16,17] Beginning in 2000, the guidelines included risk groups based on T stage, PSA, Gleason score, and the percentage of tumor in the specimen.[18] In the 2011 version of the NCCN Guidelines, the very-low-risk group was added based on data showing that certain clinical criteria could predict clinically insignificant cancer: tumor <0.2 cm^3, Grade Group 1, and confined to the prostate.[19] The very-low-risk group criteria added at that time have gone largely unchanged through the present version of the guidelines: cT1c, Grade Group 1, PSA level <10 ng/mL, <3 prostate biopsy fragments/cores positive, $\leq 50\%$ cancer in each fragment/core, and PSA density <0.15 ng/mL/g. In more recent years, the NCCN definition of very-low-risk has included a note that a targeted lesion that is biopsied more than once demonstrating cancer is considered a single positive core regardless of percentage core involvement or number of cores involved.

At the 2024 panel meeting, the panel discussed a recent retrospective analysis of 1,276 individuals diagnosed with prostate cancer from 2000 to 2020 in an institutional active surveillance cohort, which found that the number of patients meeting the NCCN criteria for very-low-risk disease decreased over time.[20] Patients with very-low-risk prostate cancer represented 28.5% of the overall cohort. By year of diagnosis, the rates ranged from approximately 25% to 40% from 2003 through 2014. From 2015 through 2018, a decrease in the rate of very-low-risk prostate

cancer diagnoses was seen, and the group reported that no patients diagnosed in 2019 and 2020 met very-low-risk criteria. The authors noted that the likely reasons for the decrease in very-low-risk disease included the increased use of targeted biopsies, which can increase the number and percentage of positive cores in many individuals. In fact, they reported, the decrease mostly resulted from fewer patients who met the criteria of <3 positive cores.

A panel member noted that the very-low-risk category was recently removed from the risk stratification scheme in the American Urological Association/American Society for Radiation Oncology (AUA/ASTRO) guidelines; it was combined with the low-risk group.[21] Panel members discussed whether they should do the same. The AUA/ASTRO rationale was that their disease management recommendations are identical for low-risk and very-low-risk prostate cancer. In contrast, NCCN Guidelines include different considerations for these 2 risk groups (see "Active Surveillance for Patients With Very-Low-Risk Prostate Cancer" section). Panel members also questioned the generalizability of the single-institution study described earlier.[20] In fact, panel members noted that they continue to see patients who meet the criteria for very-low-risk prostate cancer.

The panel consensus was therefore that the very-low-risk group should remain so that the considerations for the very-low-risk group could be differentiated from those of the low-risk group.

Advanced Risk Stratification Tools

Advanced multivariable models combine clinical and pathologic features with biomarkers such as gene expression assays or artificial intelligence–derived digital histopathology in an attempt to improve risk stratification and help personalize treatment decisions. Several such tools have been developed that have been variably demonstrated to independently improve risk stratification beyond NCCN or Cancer of the Prostate Risk Assessment (CAPRA) risk stratification.

The panel discussed the Principles of Risk Stratification section of the guidelines and decided that, although it provided a lot of information, its utility for clinicians was limited. A robust evidence review was therefore performed, and a level of evidence based on Simon criteria[22] was determined for various risk stratification models (see PROS-H page 2 of 8 in the full version of these guidelines, available at NCCN.org) and advanced risk stratification tools (see Figure 1). Literature published on the 22-gene genomic classifier assay (Decipher),[23–28] the 31 cell cycle progression gene assay (Prolaris),[29–31] the 17-gene assay Genomic Prostate Score assay (GPS),[32] and the multimodal artificial intelligence model (ArteraAI Prostate)[33,34] in both the initial treatment and the post–radical prostatectomy (RP) settings were reviewed.

The potential treatment implications for tools with Simon level of evidence of IB were further described in another set of tables (see Figures 2–4). The results of these

PRINCIPLES OF RISK STRATIFICATION

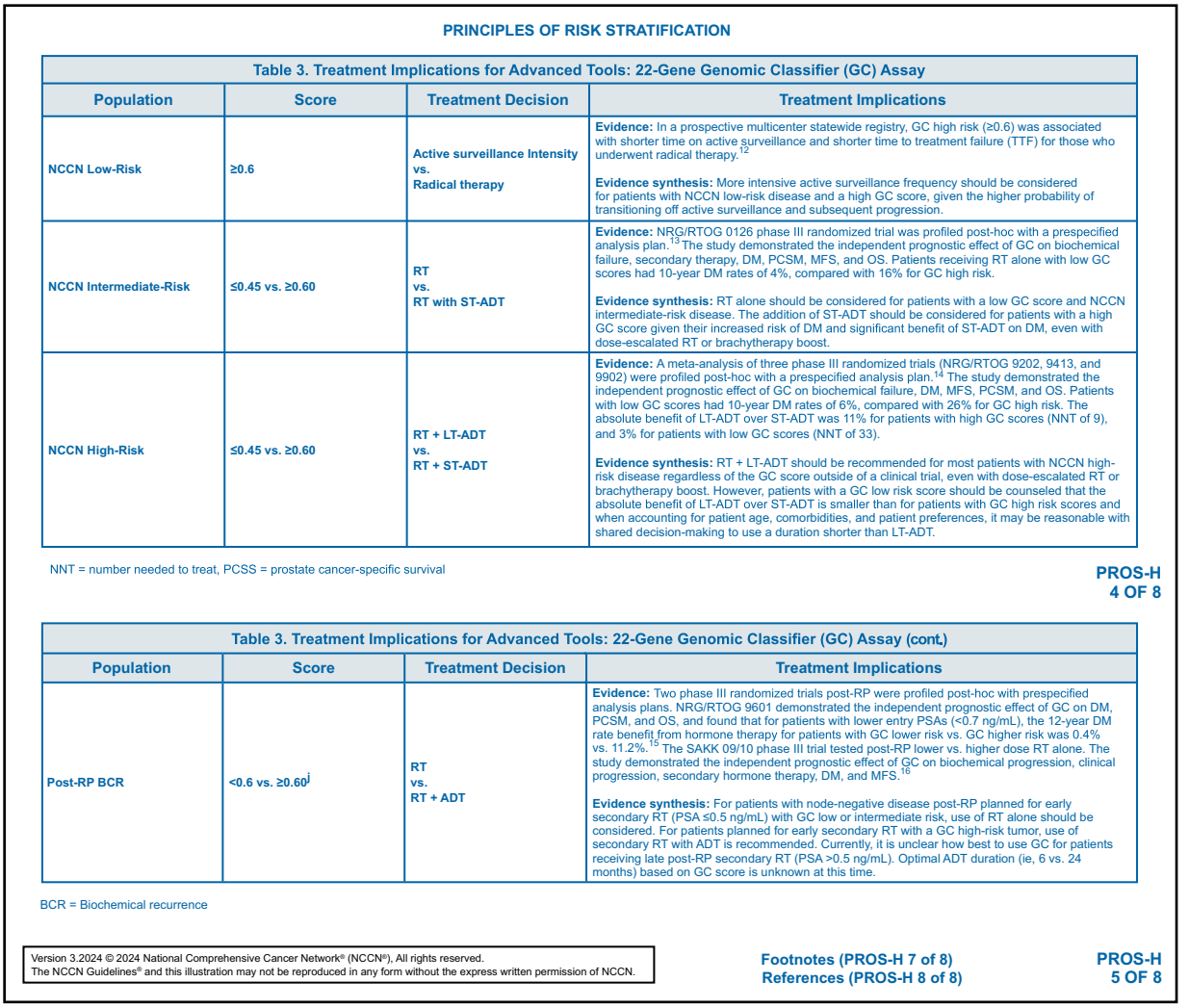
Table 2. Risk Stratification: Selected Advanced Tools for Localized Prostate Cancer

Category	Tool	Predictive	Prognostic	Prognostic Endpoint Trained For[f]	Simon Level of Evidence[1,d]	Treatment Implications
Gene Expression						
	22-gene genomic classifier (GC) (Decipher)	No	Yes	Metastasis	IB	See Table 3
	31-gene cell cycle progression (CCP) assay (Prolaris)	No	Yes	See footnote[g]	IIIC[i]	
	17-gene Genomic Prostate Score (GPS) assay	No	Yes	Adverse pathology	IIIC	
AI Pathology						
	Multimodal artificial intelligence (ArteraAI Prostate)	Yes	Yes	BCR, DM, PCSM[h]	IB Predictive IB Prognostic	See Table 3
Germline						
	HRD	No	Unclear	—	VD	
Risk Stratification: Selected Advanced Tools Post-RP						
Gene Expression						
	22-gene GC	No	Yes	Metastasis	IB	See Table 3
	31-gene CCP assay	No	Yes	See footnote[g]	IVD	
	17-gene GPS assay	No	Yes	Adverse pathology	IVD	

HRD = Homologous recombination deficiency, DM= distant metastases, PCSM = Prostate cancer-specific mortality

Footnotes (PROS-H 7 of 8)
References (PROS-H 8 of 8)
PROS-H 3 OF 8

Figure 1. Principles of risk stratification: Table 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 3.2024 [PROS-H 3 of 8].



PRINCIPLES OF RISK STRATIFICATION

Table 3. Treatment Implications for Advanced Tools: 22-Gene Genomic Classifier (GC) Assay

Population	Score	Treatment Decision	Treatment Implications
NCCN Low-Risk	≥0.6	Active surveillance Intensity vs. Radical therapy	**Evidence:** In a prospective multicenter statewide registry, GC high risk (≥0.6) was associated with shorter time on active surveillance and shorter time to treatment failure (TTF) for those who underwent radical therapy.[12] **Evidence synthesis:** More intensive active surveillance frequency should be considered for patients with NCCN low-risk disease and a high GC score, given the higher probability of transitioning off active surveillance and subsequent progression.
NCCN Intermediate-Risk	≤0.45 vs. ≥0.60	RT vs. RT with ST-ADT	**Evidence:** NRG/RTOG 0126 phase III randomized trial was profiled post-hoc with a prespecified analysis plan.[13] The study demonstrated the independent prognostic effect of GC on biochemical failure, secondary therapy, DM, PCSM, MFS, and OS. Patients receiving RT alone with low GC scores had 10-year DM rates of 4%, compared with 16% for GC high risk. **Evidence synthesis:** RT alone should be considered for patients with a low GC score and NCCN intermediate-risk disease. The addition of ST-ADT should be considered for patients with a high GC score given their increased risk of DM and significant benefit of ST-ADT on DM, even with dose-escalated RT or brachytherapy boost.
NCCN High-Risk	≤0.45 vs. ≥0.60	RT + LT-ADT vs. RT + ST-ADT	**Evidence:** A meta-analysis of three phase III randomized trials (NRG/RTOG 9202, 9413, and 9902) were profiled post-hoc with a prespecified analysis plan.[14] The study demonstrated the independent prognostic effect of GC on biochemical failure, DM, MFS, PCSM, and OS. Patients with low GC scores had 10-year DM rates of 6%, compared with 26% for GC high risk. The absolute benefit of LT-ADT over ST-ADT was 11% for patients with high GC scores (NNT of 9), and 3% for patients with low GC scores (NNT of 33). **Evidence synthesis:** RT + LT-ADT should be recommended for most patients with NCCN high-risk disease regardless of the GC score outside of a clinical trial, even with dose-escalated RT or brachytherapy boost. However, patients with a GC low risk score should be counseled that the absolute benefit of LT-ADT over ST-ADT is smaller than for patients with GC high risk scores and when accounting for patient age, comorbidities, and patient preferences, it may be reasonable with shared decision-making to use a duration shorter than LT-ADT.

NNT = number needed to treat, PCSS = prostate cancer-specific survival

PROS-H 4 OF 8

Table 3. Treatment Implications for Advanced Tools: 22-Gene Genomic Classifier (GC) Assay (cont.)

Population	Score	Treatment Decision	Treatment Implications
Post-RP BCR	<0.6 vs. ≥0.60[j]	RT vs. RT + ADT	**Evidence:** Two phase III randomized trials post-RP were profiled post-hoc with prespecified analysis plans. NRG/RTOG 9601 demonstrated the independent prognostic effect of GC on DM, PCSM, and OS, and found that for patients with lower entry PSAs (<0.7 ng/mL), the 12-year DM rate benefit from hormone therapy for patients with GC lower risk vs. GC higher risk was 0.4% vs. 11.2%.[15] The SAKK 09/10 phase III trial tested post-RP lower vs. higher dose RT alone. The study demonstrated the independent prognostic effect of GC on biochemical progression, clinical progression, secondary hormone therapy, DM, and MFS.[16] **Evidence synthesis:** For patients with node-negative disease post-RP planned for early secondary RT (PSA ≤0.5 ng/mL) with GC low or intermediate risk, use of RT alone should be considered. For patients planned for early secondary RT with a GC high-risk tumor, use of secondary RT with ADT is recommended. Currently, it is unclear how best to use GC for patients receiving late post-RP secondary RT (PSA >0.5 ng/mL). Optimal ADT duration (ie, 6 vs. 24 months) based on GC score is unknown at this time.

BCR = Biochemical recurrence

Footnotes (PROS-H 7 of 8)
References (PROS-H 8 of 8)

PROS-H 5 OF 8

Figure 2. Principles of risk stratification: Table 3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 3.2024 [PROS-H 4 and 5 of 8].

models may play a role in initial treatment decisions for patients with localized prostate cancer (eg, use and/or intensity of active surveillance vs radical therapy; radiation therapy [RT] alone vs RT with short-term androgen deprivation therapy [ADT]; RT with short-term ADT vs RT with long-term ADT). In the setting of biochemically recurrent prostate cancer after RP, these tests may play a role in treatment decisions, including the use of secondary RT versus secondary RT with ADT.

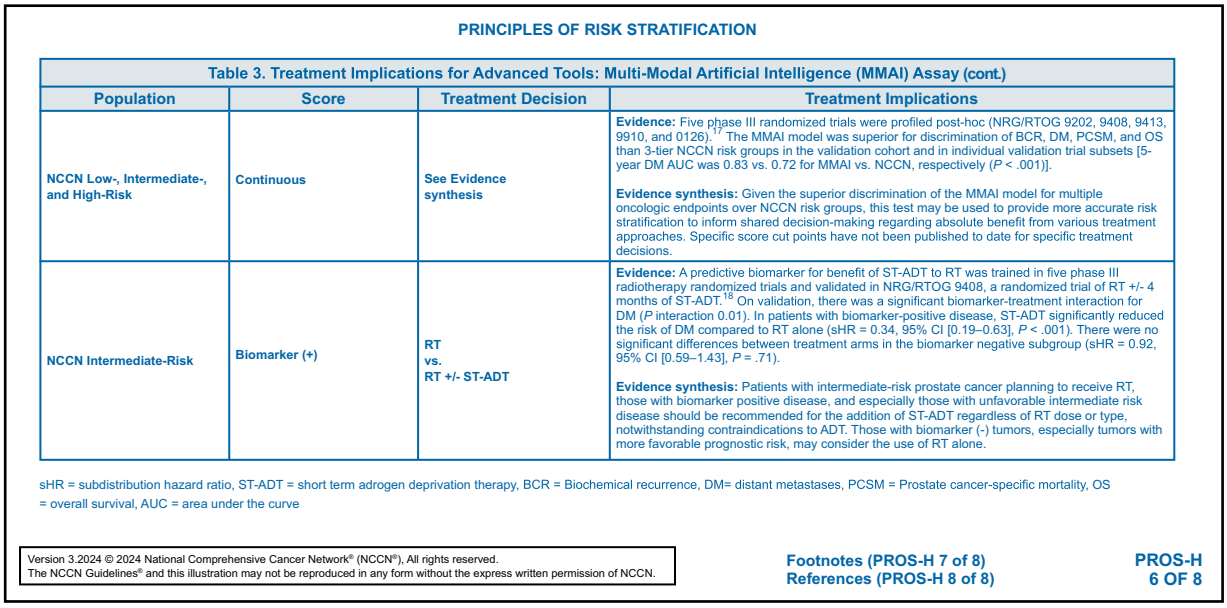
The panel consensus was that these tables will be useful to help clinicians judge the potential utility of these tools for individual patients and to help them use the results in shared decision-making with patients. Panel members continued to emphasize that use of these risk stratification tools is only recommended when they have the possibility to influence disease management; they should not be ordered reflexively. Furthermore, the panel notes that the ability of these tools to inform treatment recommendations is limited because they have not been routinely used in clinical trials.

Management of Nonmetastatic Prostate Cancer

The panel discussed many topics related to the management of nonmetastatic prostate cancer. Details of 2 topics are explained in this section: the use of active surveillance for very-low-risk prostate cancer and the various disease management options for patients with recurrent disease that remains nonmetastatic after maximal therapy directed to the pelvis.

Active Surveillance for Patients With Very-Low-Risk Prostate Cancer

Widespread use of PSA testing for early detection of prostate cancer has led to an increase in the diagnosis



PRINCIPLES OF RISK STRATIFICATION

Table 3. Treatment Implications for Advanced Tools: Multi-Modal Artificial Intelligence (MMAI) Assay (cont.)

Population	Score	Treatment Decision	Treatment Implications
NCCN Low-, Intermediate-, and High-Risk	Continuous	See Evidence synthesis	**Evidence:** Five phase III randomized trials were profiled post-hoc (NRG/RTOG 9202, 9408, 9413, 9910, and 0126).[17] The MMAI model was superior for discrimination of BCR, DM, PCSM, and OS than 3-tier NCCN risk groups in the validation cohort and in individual validation trial subsets [5-year DM AUC was 0.83 vs. 0.72 for MMAI vs. NCCN, respectively ($P < .001$)]. **Evidence synthesis:** Given the superior discrimination of the MMAI model for multiple oncologic endpoints over NCCN risk groups, this test may be used to provide more accurate risk stratification to inform shared decision-making regarding absolute benefit from various treatment approaches. Specific score cut points have not been published to date for specific treatment decisions.
NCCN Intermediate-Risk	Biomarker (+)	RT vs. RT +/- ST-ADT	**Evidence:** A predictive biomarker for benefit of ST-ADT to RT was trained in five phase III radiotherapy randomized trials and validated in NRG/RTOG 9408, a randomized trial of RT +/- 4 months of ST-ADT.[18] On validation, there was a significant biomarker-treatment interaction for DM (P interaction 0.01). In patients with biomarker-positive disease, ST-ADT significantly reduced the risk of DM compared to RT alone (sHR = 0.34, 95% CI [0.19–0.63], $P < .001$). There were no significant differences between treatment arms in the biomarker negative subgroup (sHR = 0.92, 95% CI [0.59–1.43], $P = .71$). **Evidence synthesis:** Patients with intermediate-risk prostate cancer planning to receive RT, those with biomarker positive disease, and especially those with unfavorable intermediate risk disease should be recommended for the addition of ST-ADT regardless of RT dose or type, notwithstanding contraindications to ADT. Those with biomarker (-) tumors, especially tumors with more favorable prognostic risk, may consider the use of RT alone.

sHR = subdistribution hazard ratio, ST-ADT = short term adrogen deprivation therapy, BCR = Biochemical recurrence, DM= distant metastases, PCSM = Prostate cancer-specific mortality, OS = overall survival, AUC = area under the curve

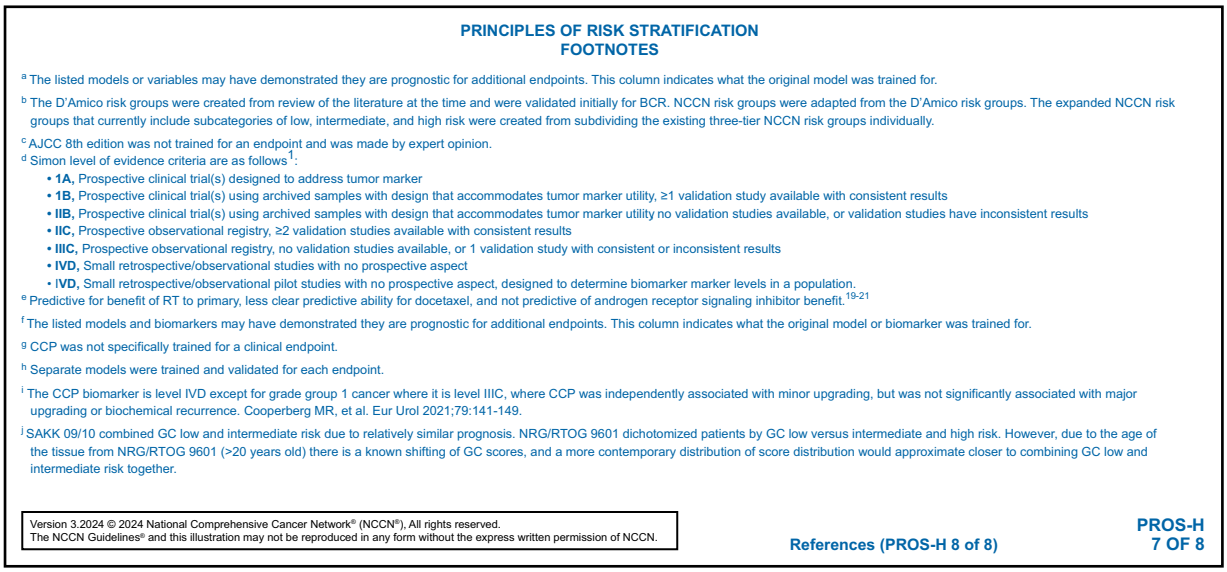
Footnotes (PROS-H 7 of 8)
References (PROS-H 8 of 8)
PROS-H 6 OF 8

Figure 3. Principles of risk stratification: Table 3 (cont.). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 3.2024 [PROS-H 6 of 8].

of indolent disease. The NCCN Guidelines for Prostate Cancer Early Detection (available at NCCN.org) provide strategies to mitigate this overdetection, but recommendations in the NCCN Guidelines for Prostate Cancer to prevent overtreatment are still essential. Many patients with prostate cancer can safely undergo a careful active surveillance program and avoid the morbidities associated with prostate cancer treatment. Selecting the correct patients for this approach, however, is critical to prevent undertreatment.

Although active surveillance has been the preferred option for patients with very-low-risk prostate cancer who have a life expectancy >20 years, radical therapy with RP or RT have still been options for these patients.

Several panel members noted that evidence does not support radical therapy in patients with very-low-risk prostate cancer, citing the recent 15-year follow-up publication from the ProtecT trial.[35] ProtecT randomized 1,643 patients with localized prostate cancer to active surveillance, RP, or RT and found no significant difference in



PRINCIPLES OF RISK STRATIFICATION
FOOTNOTES

[a] The listed models or variables may have demonstrated they are prognostic for additional endpoints. This column indicates what the original model was trained for.

[b] The D'Amico risk groups were created from review of the literature at the time and were validated initially for BCR. NCCN risk groups were adapted from the D'Amico risk groups. The expanded NCCN risk groups that currently include subcategories of low, intermediate, and high risk were created from subdividing the existing three-tier NCCN risk groups individually.

[c] AJCC 8th edition was not trained for an endpoint and was made by expert opinion.

[d] Simon level of evidence criteria are as follows[1]:
- **1A,** Prospective clinical trial(s) designed to address tumor marker
- **1B,** Prospective clinical trial(s) using archived samples with design that accommodates tumor marker utility, ≥1 validation study available with consistent results
- **IIB,** Prospective clinical trial(s) using archived samples with design that accommodates tumor marker utility no validation studies available, or validation studies have inconsistent results
- **IIC,** Prospective observational registry, ≥2 validation studies available with consistent results
- **IIIC,** Prospective observational registry, no validation studies available, or 1 validation study with consistent or inconsistent results
- **IVD,** Small retrospective/observational studies with no prospective aspect
- **IVD,** Small retrospective/observational pilot studies with no prospective aspect, designed to determine biomarker marker levels in a population.

[e] Predictive for benefit of RT to primary, less clear predictive ability for docetaxel, and not predictive of androgen receptor signaling inhibitor benefit.[19-21]

[f] The listed models and biomarkers may have demonstrated they are prognostic for additional endpoints. This column indicates what the original model or biomarker was trained for.

[g] CCP was not specifically trained for a clinical endpoint.

[h] Separate models were trained and validated for each endpoint.

[i] The CCP biomarker is level IVD except for grade group 1 cancer where it is level IIIC, where CCP was independently associated with minor upgrading, but was not significantly associated with major upgrading or biochemical recurrence. Cooperberg MR, et al. Eur Urol 2021;79:141-149.

[j] SAKK 09/10 combined GC low and intermediate risk due to relatively similar prognosis. NRG/RTOG 9601 dichotomized patients by GC low versus intermediate and high risk. However, due to the age of the tissue from NRG/RTOG 9601 (>20 years old) there is a known shifting of GC scores, and a more contemporary distribution of score distribution would approximate closer to combining GC low and intermediate risk together.

References (PROS-H 8 of 8)
PROS-H 7 OF 8

Figure 4. Principles of risk stratification: footnotes. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 3.2024 [PROS-H 7 of 8].

the primary outcome of prostate cancer mortality at a median of 10 years follow-up.[36] Of 17 prostate cancer deaths (1% of study participants), 8 were in the active surveillance group, 5 were in the surgery group, and 4 were in the radiation group (P=.48 for the overall comparison). Approximately 23% of participants had Gleason scores of 7 through 10, and 5 of 8 deaths in the active surveillance group were in this subset.

In the recent publication, the median follow-up was 15 years for 1,610 (98%) patients.[35] Death from prostate cancer occurred 17 (3.1%) patients from the active surveillance group, 12 (2.2%) from the RP group, and 16 (2.9%) in the RT group (P=.53 for the overall comparison). Death from any cause also did not differ between the groups (124, 117, and 115 participants, respectively). Development of distant or regional node metastases was more common in the active surveillance group (n=51; 9.4%) compared with the RP group (n=26; 4.7%) and RT group (n=27; 5.0%). In addition, initiation of long-term ADT was higher in the active surveillance group (12.7% vs 7.2% and 7.7%, respectively). By D'Amico criteria, 66% of the participants in ProtecT had low-risk prostate cancer, 24% had intermediate-risk, and 10% had high-risk. There is also evidence from the patients in the study who underwent RP that high-risk features were missed in some patients, suggesting that the proportion of the study population that truly had low-risk disease was lower than 66%. Even with the substantial portion of participants with intermediate- and high-risk prostate cancer, these higher rates of metastases did not lead to higher rates of death from prostate cancer or death from any cause.

Patient-reported outcomes were compared among the 3 groups.[37,38] The RP group experienced the greatest negative effect on sexual function and urinary continence, whereas bowel function was worst in the RT group.

Overall, panel members agreed that results of ProtecT demonstrate that radical treatment reduces the incidence of metastases, local progression, and use of long-term ADT, but these reductions do not result in a mortality difference. Importantly, radical treatment is associated with significant adverse effects.

Therefore, the panel's strong consensus was to remove radical treatment options for patients with very-low-risk prostate cancer. Thus, the only options for this population provided in the 2024 version of the guidelines are active surveillance or observation, depending on life expectancy (see Figure 5). Panel members emphasized the importance of confirmatory testing to verify accurate risk stratification before initiating an active surveillance program for patients with prostate cancer. The panel also noted that the surveillance intensity can be individualized based on patient life expectancy and the

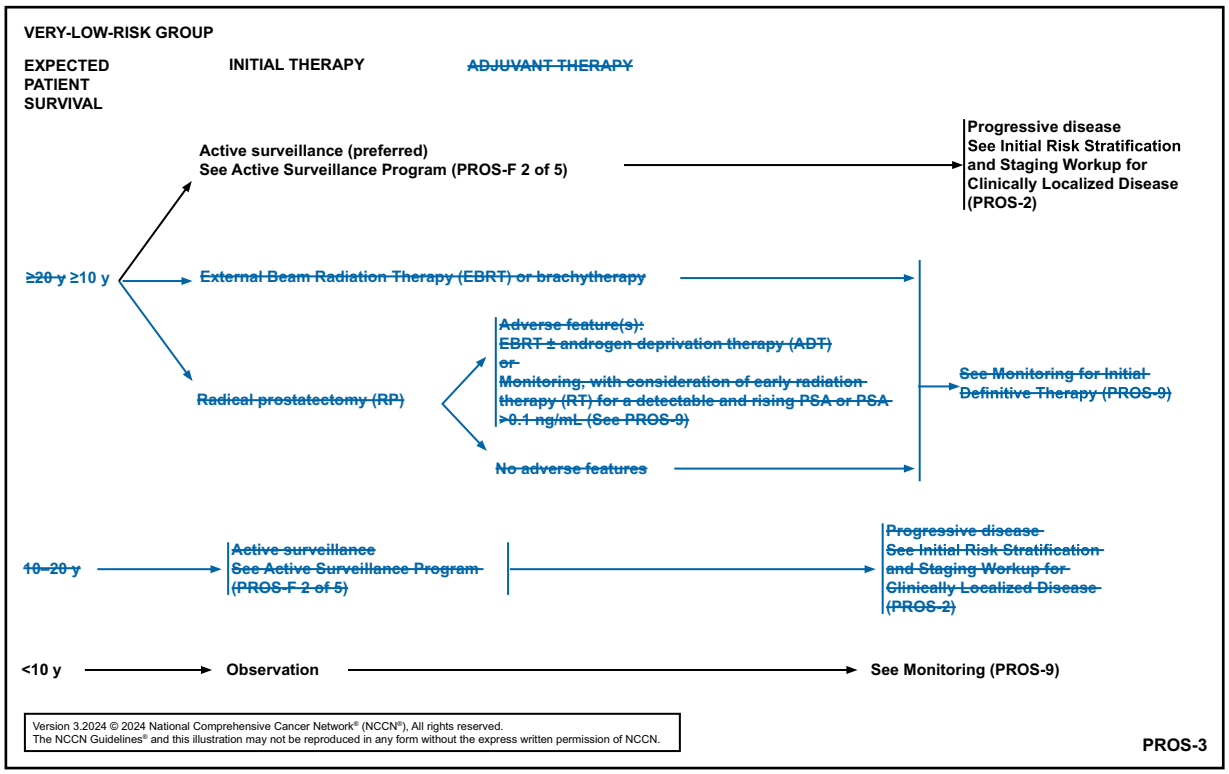


Figure 5. Treatment options for very-low-risk prostate cancer based on life expectancy. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 3.2024 [PROS-3].

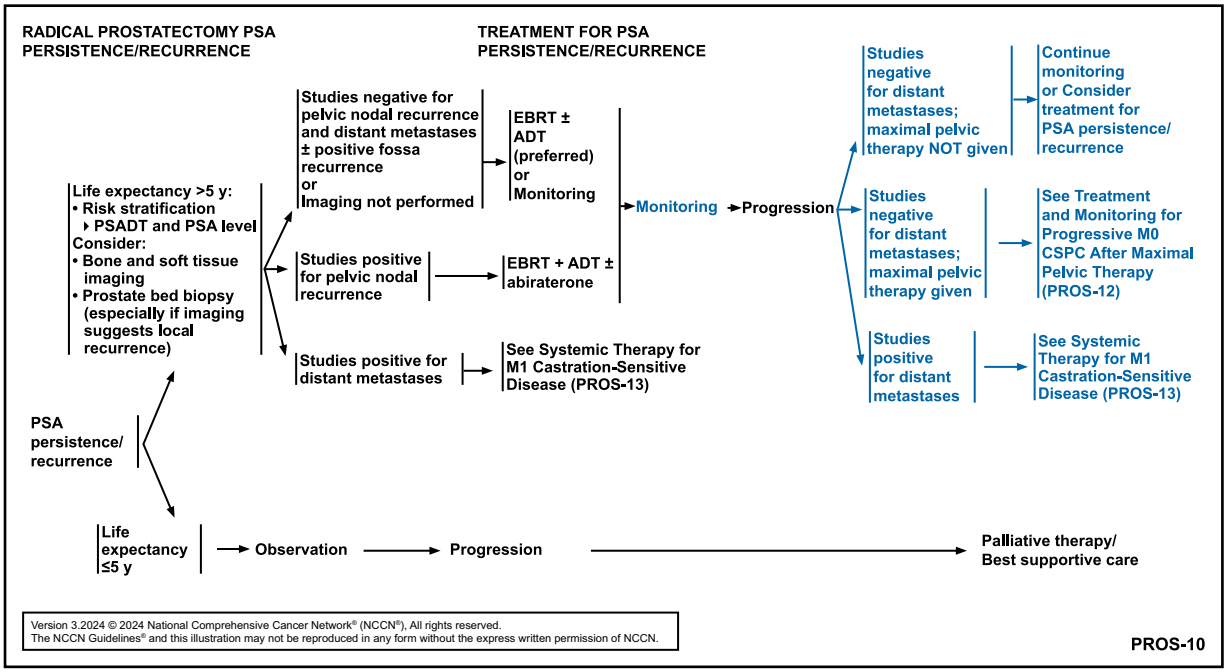


Figure 6. PSA persistence/recurrence after radical prostatectomy. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 3.2024 [PROS-10].

risk of disease reclassification. In general, patients with very-low-risk prostate cancer can receive lower-intensity surveillance.

Although the panel recommends active surveillance for most patients with low-risk disease, panel consensus was that shared decision-making is warranted in this

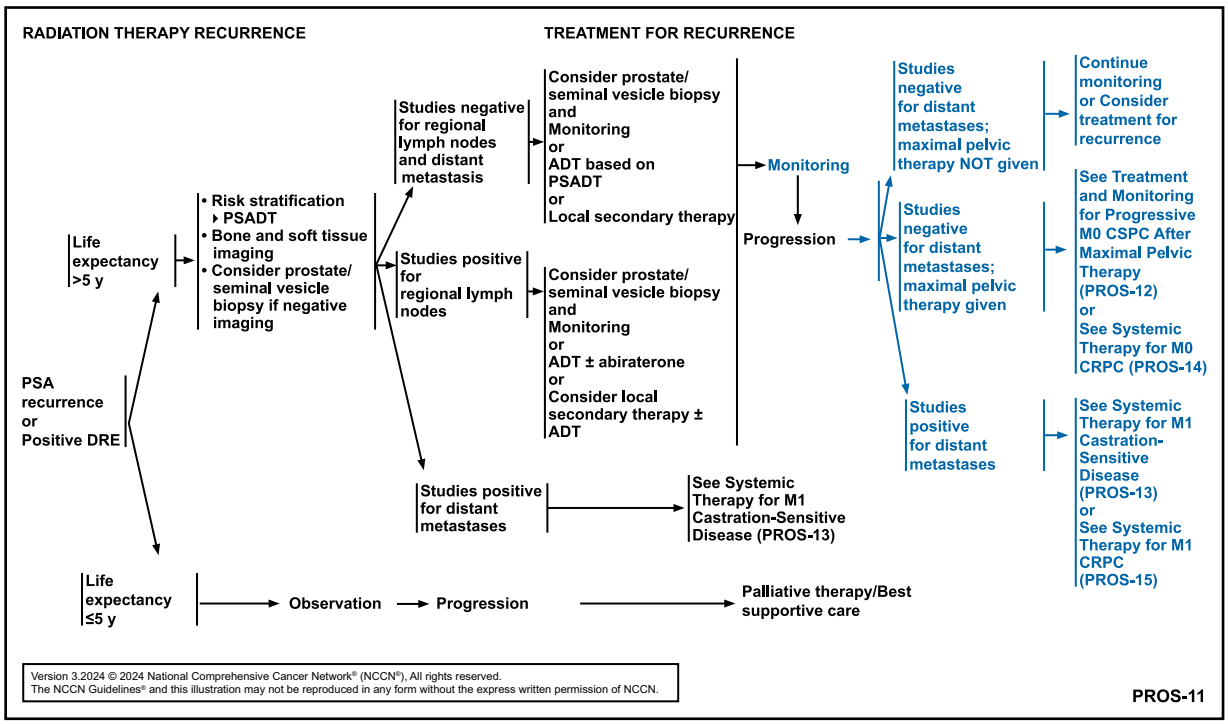


Figure 7. Recurrence after radiation therapy. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 3.2024 [PROS-11].

setting. The panel recognized that there is heterogeneity across the low-risk group, and that some factors may be associated with an increased probability of near-term grade reclassification, including high PSA density, a high number of positive cores (eg, ≥3), high genomic risk (from tissue-based molecular tumor analysis), and/or a known *BRCA2* germline mutation. In some of these cases, up-front treatment with RP or RT may be preferred in the low-risk group setting based on shared decision-making with the patient.

Nonmetastatic Disease After Maximal Pelvic Therapy

EMBARK was a double-blind, randomized, controlled phase III trial that included 1,068 participants with biochemically recurrent prostate cancer without evidence of distant metastases by conventional imaging.[39] Patients were deemed to be at high-risk for the development of metastatic disease, with a PSA doubling time (PSADT) of ≤9 months and a PSA level ≥2 ng/mL above nadir after RT or ≥1 ng/mL after RP with or without postoperative RT. Patients were excluded if they were considered as candidates for pelvic-directed therapy. Participants were randomly assigned 1:1:1 to receive enzalutamide + leuprolide, placebo + leuprolide, or enzalutamide monotherapy. At 5 years, metastasis-free survival was 87.3% (95% CI, 83.0–90.6) in the enzalutamide/leuprolide group, 71.4% (95% CI, 65.7–76.3) in the placebo/leuprolide group, and 80.0% (95% CI, 75.0–84.1) in the enzalutamide monotherapy group. The combination of enzalutamide + leuprolide was superior to leuprolide alone (hazard ratio [HR] for metastasis or death, 0.42; 95% CI, 0.30–0.61; $P<.001$), as was enzalutamide monotherapy (HR for metastasis or death, 0.63; 95% CI, 0.46–0.87; $P=.005$). Overall survival data were immature at the time of analysis. The most common adverse effects associated with combination therapy and enzalutamide monotherapy were hot flashes and fatigue. Enzalutamide monotherapy was also significantly associated with gynecomastia (45% vs 8%–9% in the combination and leuprolide alone groups), nipple pain (15% vs 1%–3%), and breast tenderness (14% vs 1%). Cognitive dysfunction was about twice as common in the arms that contained enzalutamide.

Treatment was suspended at week 37 if PSA was undetectable. Panel members expressed concerns that the numbers of patients who were able to suspend treatment significantly differed between the groups (91%, 86%, and 68% in the enzalutamide/leuprolide, enzalutamide monotherapy, and placebo/leuprolide groups, respectively). In addition, the median duration of treatment suspension was shorter in the enzalutamide monotherapy group than

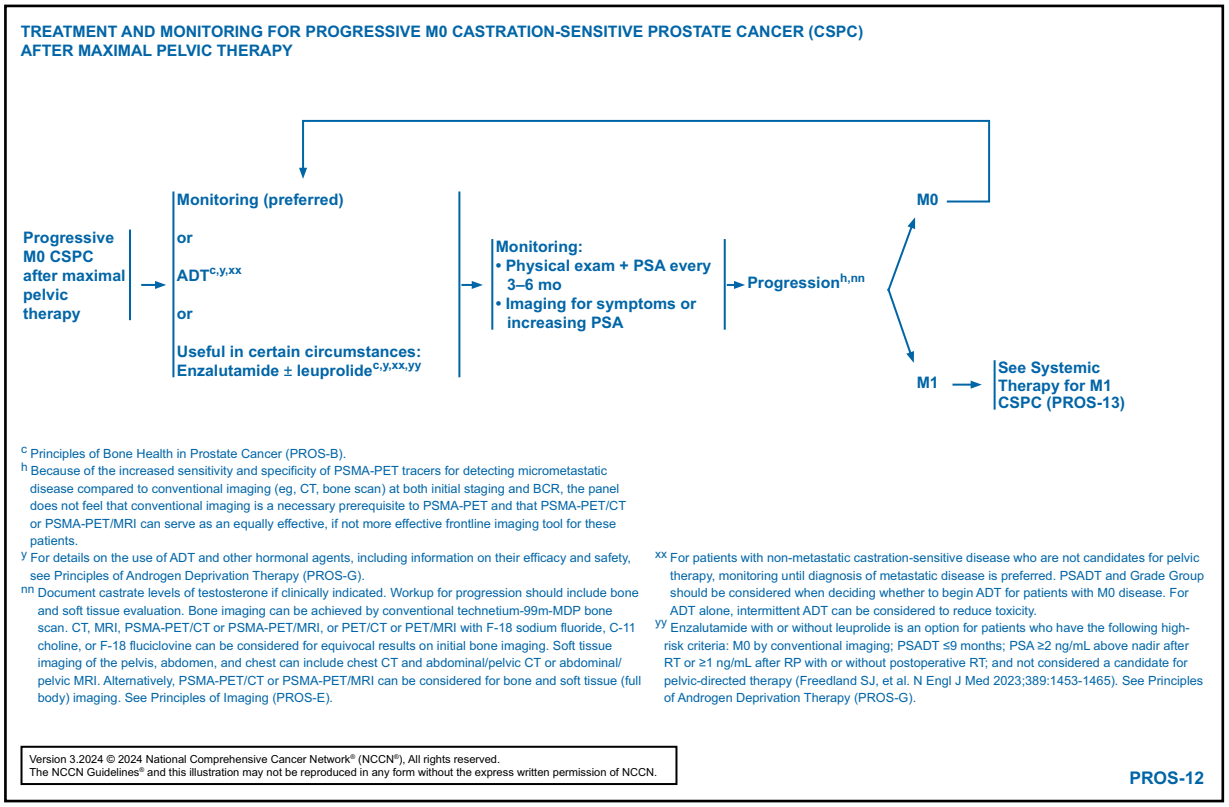


Figure 8. Treatment and monitoring for progressive M0 castration-sensitive prostate cancer (CSPC) after maximal pelvic therapy. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer, Version 3.2024 [PROS-12].

in the enzalutamide/leuprolide and placebo/leuprolide groups (11.1 vs 20.2 and 16.8 months, respectively). These differences complicate the analysis of the trial results.

Panel members noted that PSMA-PET imaging was not used in the study. At the current time, most patients undergo PSMA-PET imaging, and its use is growing. Therefore, it is hard to know which patients in practice were represented in EMBARK, creating challenges in applying the results.

Overall, however, the panel agreed that the trial demonstrates some benefit for enzalutamide in this setting, but panel members noted that many patients prefer to avoid hormone treatment and its many toxic effects for as long as possible.

The panel was supportive of adding enzalutamide with or without leuprolide as an option for patients who met the criteria of EMBARK. However, it was not immediately clear where these patients would fit within the 2023 version of the guidelines. The panel consensus was that maximal pelvic therapy should be administered before consideration of enzalutamide for these patients. Edits were therefore made to the recurrence pages (see Figures 6 and 7) to indicate that monitoring can be continued or treatment can be considered in patients who have not yet received maximal pelvic therapy. For those who have received maximal pelvic therapy, a new page was created (see Figure 8).

Overall, the panel believes that monitoring until diagnosis of metastatic disease is the preferred option for patients with nonmetastatic, biochemically recurrent, castration-sensitive disease if they are not candidates for pelvic therapy. ADT alone and enzalutamide with or without leuprolide are also options. Risk stratification based on PSADT and Grade Group should be used when deciding whether to begin hormonal therapy for this population of patients. For ADT alone, intermittent ADT can be considered to reduce toxicity.

Conclusions

For patients with newly diagnosed, nonmetastatic prostate cancer, accurate risk stratification and selection of disease management approach is critical to prevent overtreatment and undertreatment. For patents with nonmetastatic recurrent disease who have received maximal pelvic-directed therapy, monitoring until metastases are detected is the preferred approach, although certain hormonal therapies are also appropriate options, especially for patients who are at higher risk for the development of metastases. As always, shared decision-making is critical in these settings so that patient preferences can be considered along with disease characteristics that can help estimate prognosis.

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