NCCN Guidelines® Insights

Prostate Cancer, Version 1.2016

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Prostate Cancer address staging and risk assessment after an initial diagnosis of prostate cancer and management options for localized, regional, and metastatic disease. Recommendations for disease monitoring, treatment of recurrent disease, and systemic therapy for metastatic castration-recurrent prostate cancer also are included. This article summarizes the NCCN Prostate Cancer Panel's most significant discussions for the 2016 update of the guidelines, which include refinement of risk stratification methods and new options for the treatment of men with high-risk and very-high-risk disease and progressive castration-naïve disease.
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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

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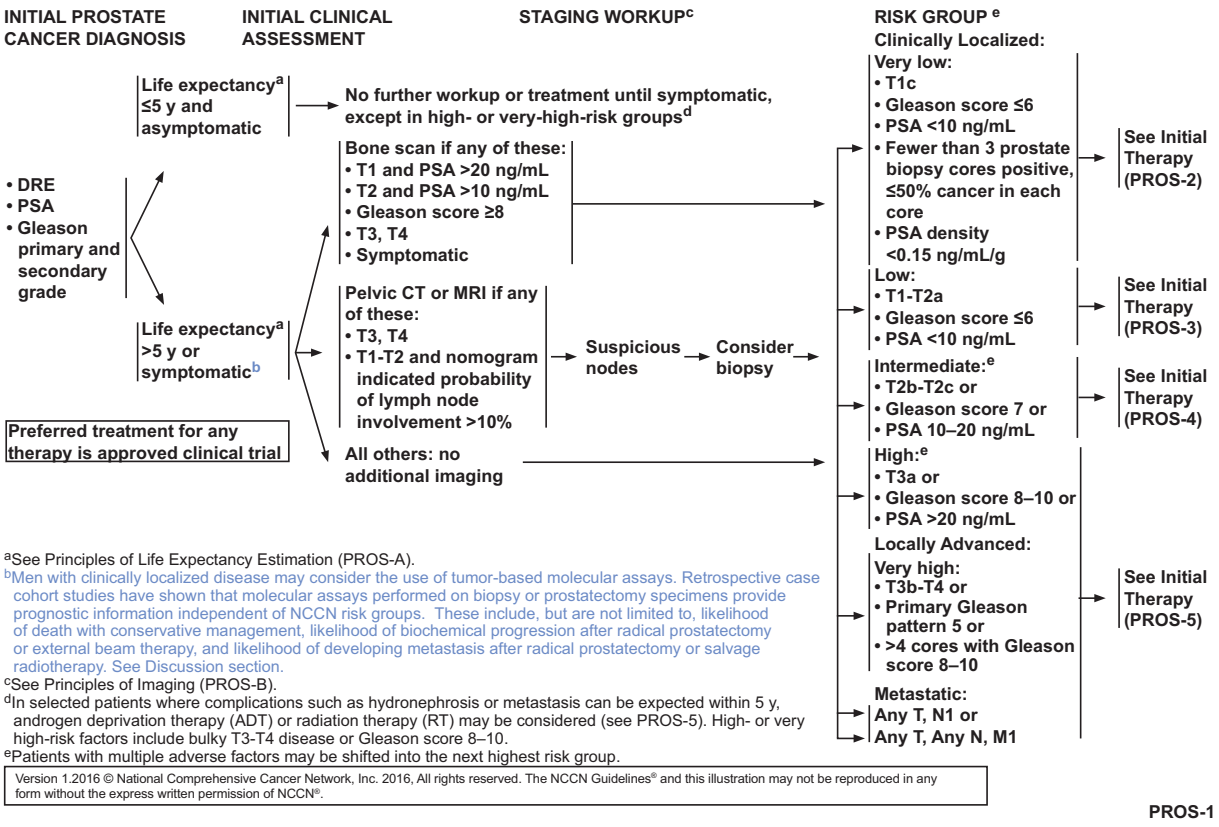


[a]See Principles of Life Expectancy Estimation (PROS-A).
[b]Men with clinically localized disease may consider the use of tumor-based molecular assays. Retrospective case cohort studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. See Discussion section.
[c]See Principles of Imaging (PROS-B).
[d]In selected patients where complications such as hydronephrosis or metastasis can be expected within 5 y, androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered (see PROS-5). High- or very high-risk factors include bulky T3-T4 disease or Gleason score 8–10.
[e]Patients with multiple adverse factors may be shifted into the next highest risk group.

PROS-1

NCCN Categories of Evidence and Consensus

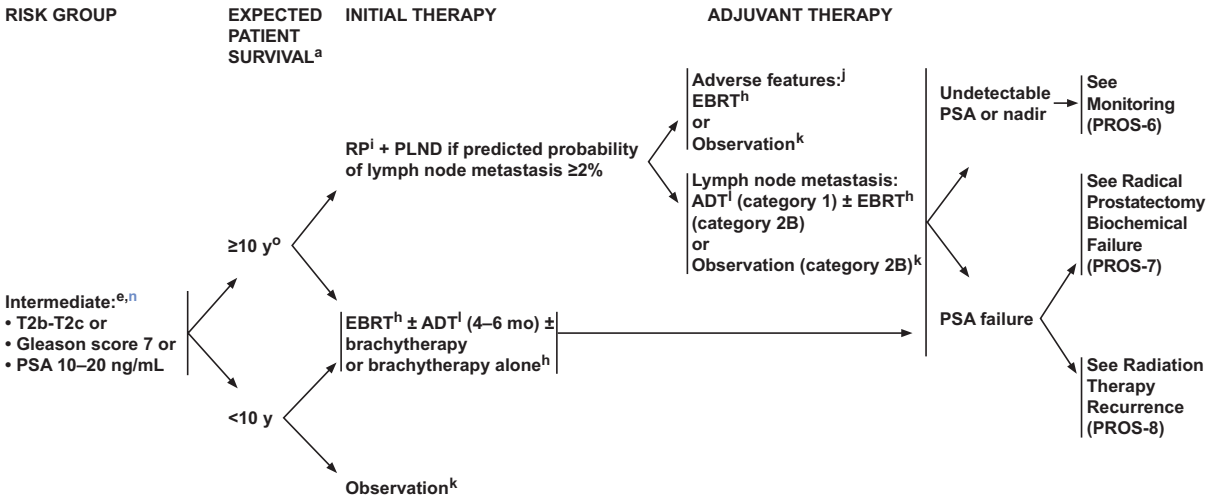
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that 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 noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Prostate cancer has surpassed lung cancer as the most common cancer in men. The increase in prostate cancer incidence has resulted primarily from prostate-specific antigen (PSA) screening that detects many early-stage prostate cancers. An estimated 220,800 new cases were diagnosed in 2015, which accounts for 26% of new cancer cases in men.[1] Fortunately, the age-adjusted death rates from prostate cancer have declined (–3.8% annually from 1994 to 2004), and researchers estimate that prostate cancer accounted for 27,540 deaths in 2015.[1] The decreasing and comparatively low death rate suggests that increased public awareness with earlier detection and treatment has affected mortality from this prevalent cancer. The alternative hypothesis is that prostate cancer is becoming biologically less aggressive, but evidence is lacking. Early detection can lead to overtreatment of prostate cancers that do not threaten life expectancy, which results in unnecessary side



[a]See Principles of Life Expectancy Estimation (PROS-A).
[e]Patients with multiple adverse factors may be shifted into the next highest risk group.
[h]See Principles of Radiation Therapy (PROS-D).
[i]See Principles of Surgery (PROS-E).
[j]Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
[k]Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[l]See Principles of Androgen Deprivation Therapy (PROS-F).
[n]Patients with favorable intermediate-risk prostate cancer (predominant Gleason grade 3 [i.e., Gleason score 3 + 4 = 7], and percentage of positive biopsy cores < 50 percent, and no more than one NCCN intermediate risk factor) may be considered for active surveillance. See Discussion section.
[o]Active surveillance of unfavorable intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).

PROS-4

effects that impair quality of life and increase health care expenditures.

The panel discussed many pertinent issues this year, which are described in this report. Changes to the guidelines are indicated with blue font in the figures.

Risk Stratification

Management approaches for locoregional prostate cancer include surgery, radiotherapy, active surveillance (actively monitoring disease, with curative-intent intervention if cancer progresses), observation (monitoring disease, with palliative therapy for symptoms) and androgen deprivation therapy (ADT). Making the critical decisions regarding management approach requires careful assignment of patients to risk groups, which depends on the clinical T stage as determined by digital rectal examination (DRE) and radiologic results, Gleason score and extent of cancer in the biopsy specimens, and serum PSA level.[2–4] Nomograms and an estimate of life expectancy are other key determinants of primary management options in these men.[5–20] Although risk groups, life expectancy estimates, and nomograms help inform decisions, uncertainty about the risk of disease progression persists. American men continue to underselect active surveillance, and their physicians may underrecommend it, likely as a result of uncertainty.[21] For men who choose treatment over active surveillance, further difficult decisions must be made regarding the use of adjuvant treatment and/or treatment of recurrent disease.

Additional prognostic information from tumor-based molecular assays and more refined risk stratification, both discussed herein, may encourage appropriate men to choose active surveillance and avoid the side effects of treatment that is likely unneces-

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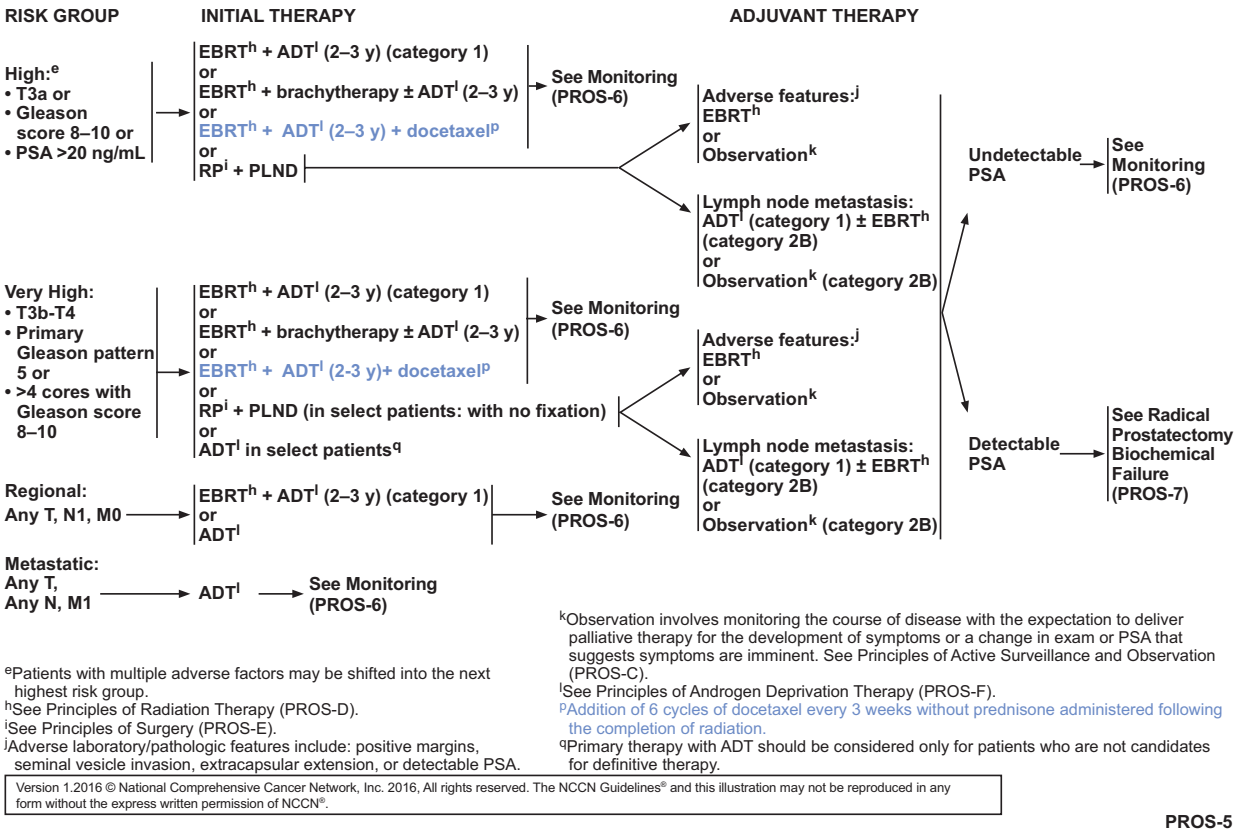


[e]Patients with multiple adverse factors may be shifted into the next highest risk group.
[h]See Principles of Radiation Therapy (PROS-D).
[i]See Principles of Surgery (PROS-E).
[j]Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
[k]Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[l]See Principles of Androgen Deprivation Therapy (PROS-F).
[p]Addition of 6 cycles of docetaxel every 3 weeks without prednisone administered following the completion of radiation.
[q]Primary therapy with ADT should be considered only for patients who are not candidates for definitive therapy.

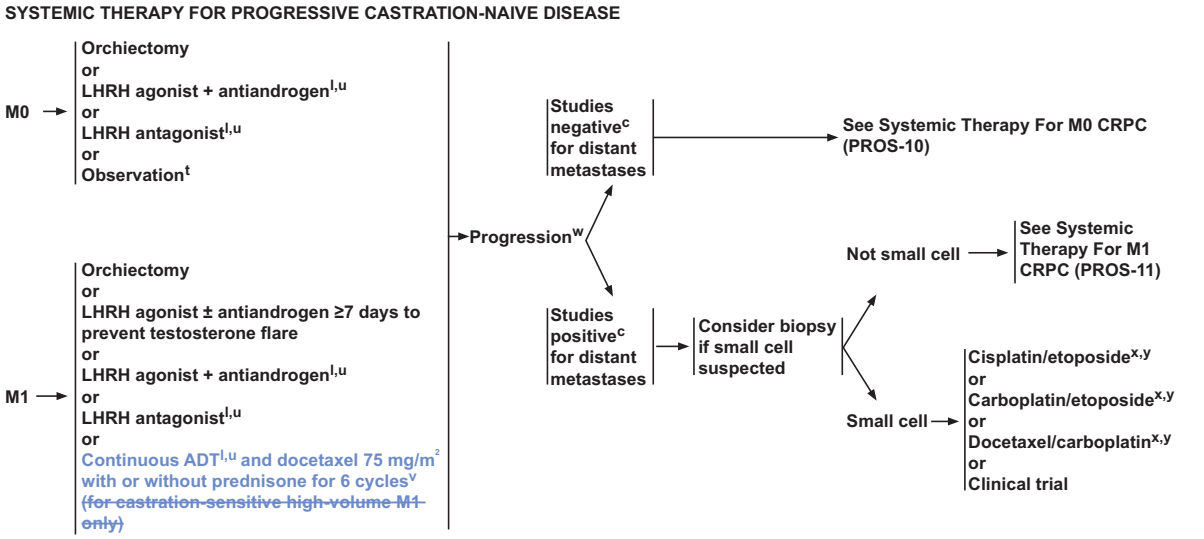
PROS-5

sary, and may enable patients to make optimal decisions regarding adjuvant or subsequent treatment.

Tumor-Based Molecular Assays

Several tissue-based molecular assays have been developed in an effort to improve decision-making in men with newly diagnosed prostate cancer who are considering active surveillance, and in treated men who are considering adjuvant therapy or therapy for recurrences. Uncertainty about the risk of disease progression can be reduced if such molecular assays can accurately and reproducibly provide prognostic or predictive information beyond NCCN risk group assignment and currently available life-expectancy tables and nomograms. Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN risk groups, that include likelihood of death with conservative management, likelihood of biochemical recurrence after surgery or radiotherapy, and likelihood of developing metastasis after surgery or salvage radiotherapy.[22–26] No randomized controlled trials have studied the utility of these tests. Several of these assays are clinically available, and 3 have received positive reviews by the Molecular Diagnostic Services Program (MolDX) and are likely to be covered by CMS (Centers for Medicare & Medicaid Services). Several other tests are under development, and the use of these assays is likely to increase in the coming years.

The review of these guidelines by NCCN Member Institutions that preceded the 2016 panel meeting led to requests by several reviewers to review footnote "b," which stated, "Men with clinically localized disease could consider use of a tumor-based molecular assay to stratify better risk of adverse pathology at radical prostatectomy or chance of biochemical recurrence or disease-specific mortality after radical prostatectomy." The reviewers requested



[c]See Principles of Imaging (PROS-B).
[l]See Principles of Androgen Deprivation Therapy (PROS-F).
[t]Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[u]Intermittent ADT can be considered for men with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-F)
[v]High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low volume disease have less certain benefit from early treatment with docetaxel combined with ADT.
[w]Assure castrate level of testosterone.
[x]See Principles of Immunotherapy and Chemotherapy (PROS-G).
[y]See NCCN Guidelines for Small Cell Lung Cancer.

PROS-9

more guidance about use of these tests to include an expanded discussion of the number of emerging molecular tests, the FDA-clearance status of the various tests, their possible associated risks, and examples of when molecular testing may improve upon the usual risk stratifications.

The panel engaged in a long discussion regarding molecular testing. Many panel members expressed their excitement regarding the potential benefits of these tests, and many said they currently order them for their patients. However, the panel also discussed the data supporting the clinical utility of these tests and emphasized several points. First, no randomized clinical trial has yet assessed the clinical utility of these tests. Second, no test has been shown to be predictive of prostate cancer–specific outcomes in response to various management strategies. Finally, no head-to-head comparisons of these assays have been performed. Still, the panel pointed to data suggesting that test results may encourage men to choose active surveillance and thus reduce overtreatment. In one study, results from a molecular test on initial biopsy specimens from untreated men with newly diagnosed prostate cancer changed management in 48% of cases.[27] Of these, 72% of men and their physicians (34% of the initial population) chose to reduce treatment, and 27% (13% of the initial population) chose to increase treatment. In addition, results of retrospective studies suggest that molecular testing can have prognostic value. For example, one study showed the cumulative incidence of metastasis 5 years after adjuvant radiation in men with pT3 disease or positive margins to be 0%, 9%, and 29% for those with low, average, and high genomic classifier scores, respectively (P=.002).[28]

In summary, although molecular test results can provide additional guidance to patients, only limited data on prostate cancer–specific survival are available, and whether patient outcomes are improved with use of these tests is unclear. Furthermore, the

panel cannot recommend any particular molecular test over another, because of the lack of comparison data. Therefore, the panel believes that any of these tests may be considered to aid management decisions, but they are not required for standard of care at this time. The panel modified the footnote on PROS-1 (page 21) to read, "Men with clinically localized disease may consider the use of tumor-based molecular assays. Retrospective case cohort studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam radiation therapy (EBRT), and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy."

In addition, the panel added Table 1 to the discussion section of the guidelines to provide an overview of each clinically available molecular test, populations in which each test has been studied, outcomes reported for each test, and references supporting this work. The panel also included information regarding the review of these tests, which can be expensive, by MolDX. The panel also noted that the molecular biomarker tests listed in Table 1 have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be performed, the panel believes that men with clinically localized disease may consider the use of tumor-based molecular assays at this time. Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of men with prostate cancer.

Favorable Intermediate-Risk Prostate Cancer

The NCCN Guidelines for Prostate Cancer incorporate a risk stratification scheme based on clinical T stage, Gleason score, and PSA level to assign patients to risk groups. These risk groups are used to select the appropriate options that should be considered and to predict the probability of biochemical failure after definitive local therapy.[2] Risk group stratification has been published widely and validated, and provides a better basis for treatment recommendations than clinical stage alone.[3,4]

However, the panel recognizes that heterogeneity exists within each risk group. For example, an analysis of 12,821 patients showed that men assigned to the intermediate-risk group by clinical stage (T2b–T2c) had a lower risk of recurrence than men categorized according to Gleason score (7) or PSA level (10–20 ng/mL).[29] Men placed in the high-risk group by clinical stage (T3a) had a similar trend of superior recurrence-free survival compared with those assigned by Gleason score (8–10) or PSA level (>20 ng/mL), although the difference did not reach statistical significance.

During the institutional review for the 2016 update of the NCCN Guidelines for Prostate Cancer, reviewers raised questions about the heterogeneity of the intermediate-risk group and what the observed variation in outcomes might mean for management decisions. In particular, the panel considered the following questions: Should active surveillance be considered an option for men with intermediate-risk disease? Should active surveillance be considered an option for a subset of patients with intermediate-risk disease and a favorable profile? How should such a favorable subset be defined?

The panel approached these questions by first reviewing the literature on outcomes of active surveillance of men with intermediate-risk prostate cancer. In the PIVOT trial, men with localized prostate cancer and life expectancy of 10 years or more were randomized to radical prostatectomy or observation.[30] Of the 120 participants with intermediate-risk disease who were randomized to observation, only 13 died from prostate cancer, a nonsignificant difference compared with 6 prostate cancer deaths in 129 participants with intermediate-risk disease in the resection arm (hazard ratio [HR], 0.50; 95% CI, 0.21–1.21; P=.12). The median 10-year follow-up and less-than-average health of men in the PIVOT study suggest only men with competing risks may safely be offered active surveillance. In a single-arm prospective cohort study, men with low-risk (75% of the study population) or intermediate-risk (25%) prostate cancer were managed with active surveillance, and intervention was offered for progression.[31] The 10- and 15-year actuarial cause-specific survival rates were 98.1% and 94.3 %, respectively, for the entire cohort; the authors did not report outcomes

Table 1 Clinically Available Tissue-Based Tests for Prostate Cancer Prognosis

Test	Platform	Populations Studied	Outcome Reported (Test Independently Predicts)	References	Molecular Diagnostic Services Program Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post RP, adverse pathology/high-risk features	Metastasis Prostate cancer–specific mortality	28,43–52	Cover post RP for (1) pT2 with positive margins; (2) any pT3 disease; (3) increasing PSA (above nadir)
		Post RP, biochemical recurrence	Metastasis Biochemical failure		
		Post RP, adjuvant or salvage radiotherapy	Metastasis		
Ki-67	IHC	Biopsy, intermediate- to high-risk treated with RT	Metastasis	53–56	Not recommended
		Biopsy, conservatively managed (active surveillance)	Prostate cancer–specific mortality		
Oncotype DX	Quantitative RT-PCR for 12 prostate cancer–related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	Non–organ-confined pT3 or Gleason grade 4 disease on RP	26,57	Cover post biopsy for NCCN very-low-risk and low-risk prostate cancer at diagnosis with a 10- to 20-y life expectancy
Prolaris	Quantitative RT-PCR for 31 cell cycle–related genes and 15 housekeeping controls	TURP, conservatively managed (active surveillance)	Prostate cancer–specific mortality	22–25,58,59	Cover post biopsy for NCCN very-low-risk and low-risk prostate cancer at diagnosis with at least a 10-y life expectancy
		Biopsy, conservatively managed (active surveillance)	Prostate cancer–specific mortality		
		Biopsy, localized prostate cancer	Biochemical recurrence Metastasis		
		Biopsy, intermediate-risk treated with RT	Biochemical failure		
		RP, node-negative localized prostate cancer	Biochemical recurrence		
ProMark	Multiplex immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	Non–organ-confined pT3 or Gleason pattern 4 disease on RP	60	Not reviewed
PTEN	Fluorescence in situ hybridization or IHC	TURP, conservatively managed (active surveillance)	Prostate cancer–specific mortality	61–63	Not recommended
		Biopsy, Gleason grade 3+3	Upgrading to Gleason pattern 4 on RP		
		RP, high-risk localized disease	Biochemical recurrence		

Abbreviations: FFPE, formalin-fixed, paraffin-embedded; IHC, immunohistochemistry; PSA, prostate-specific antigen; RP, radical prostatomy; RT, radiation therapy; RT-PCR, reverse transcription polymerase chain reaction; TURP, transurethral resection of the prostate.

separately for low-risk and intermediate-risk subgroups. At the time of publication, only 15 of 993 patients had died of prostate cancer; an additional 13 men developed metastatic disease, and only 27% of the cohort received eventual treatment. Other prospective studies of active surveillance that included men with intermediate-risk prostate cancer resulted in prostate cancer–specific survival rates of 100% for the full cohorts.[32,33] The panel interpreted these data to show that a subset of men with intermediate-risk prostate cancer may be considered for active surveillance, although longer-term follow-up is needed in these and other studies to increase confidence about the risks and benefits of active surveillance in this population.

The panel next considered data to inform the definition of favorable versus unfavorable subsets of patients with intermediate-risk prostate cancer. In a retrospective study, 1,024 patients with intermediate-risk prostate cancer were treated with radiation with or without neoadjuvant and concurrent ADT.[34] Multivariate analysis revealed that primary Gleason pattern 4, percentage of positive biopsy cores of 50 or greater, and presence of more than 1 intermediate-risk factor (ie, T2b–c, PSA 10–20 ng/mL, Gleason score 7) were significant predictors of increased incidence of distant metastasis. The authors then used these factors to separate the patients into unfavorable and favorable intermediate-risk groups and determined that the unfavorable intermediate-risk group had worse PSA recurrence-free survival, distant metastasis, and prostate cancer–specific mortality than the favorable intermediate-risk group.

The panel decided to define a favorable intermediate-risk subset of patients for whom active surveillance can be considered. As delineated in footnote "n," they defined "favorable" as predominant Gleason grade 3 (ie, Gleason score 3+4=7), percentage of positive biopsy cores less than 50, and no more than 1 NCCN intermediate-risk factor (see PROS-4, page 22). Other members more simply define favorable intermediate-risk prostate cancer as men with NCCN low-risk prostate cancer except for Gleason secondary pattern 4 in a single biopsy. The panel believes that active surveillance may be considered for men with favorable intermediate-risk prostate cancer, but should be approached with caution, include informed decision-making, and use close monitoring for progression. Further research is needed to confirm the safety of this approach.

Treatment of High-Risk and Very-High-Risk Localized Disease

Docetaxel has been shown to prolong survival in the metastatic castration-recurrent/resistant prostate cancer (mCRPC) setting.[35–37] During this year's panel discussion, a panelist asked the group to consider adding docetaxel as an initial therapy option for patients in the high-risk and very-high-risk groups based on emerging data suggesting that the early use of docetaxel may result in an overall survival (OS) benefit for these men.

The panel discussed the results of the phase III RTOG 0521 trial that were presented at the 2015 ASCO annual meeting.[38] In this trial, 562 evaluable men with nonmetastatic disease classified as high- or very-high-risk received radiation and ADT or radiation and ADT with docetaxel and prednisone after the completion of radiation. The 4-year OS rates were 89% for the control arm and 93% for the docetaxel arm (HR, 0.68; 95% CI, 0.44–1.03; 1-sided P=.03). The 5-year disease-free survival rates were 66% and 73% for the control and docetaxel groups, respectively (HR, 0.76; 95% CI, 0.57–1.00; 2-sided P=.05). The survival benefit of docetaxel was small, and some panelists criticized the use of 1-sided statistical analysis. In addition, the panel noted that the analysis is premature, with few deaths to date. Still, many panel members use this strategy or at least discuss it with their fit patients. Others even claimed they would use docetaxel for themselves in this setting. Thus, the panel voted unanimously to add this as an option, mainly based on consensus and the expectation that stronger data on this strategy are likely to emerge in the future.

The panel thus concluded that EBRT + ADT + docetaxel is a reasonable option in appropriate men with high-risk and very-high-risk disease, and they added it on PROS-5 (see page 23).The panel noted that this strategy should only be considered for patients who are fit for chemotherapy.

Treatment of Progressive, Castration-Naïve Disease

The 2015 version of the guidelines added systemic therapy options for men with progressive castration-naïve prostate cancer. Docetaxel combined with ADT was an option for men with high-volume

metastatic disease based on results from the phase III ECOG 3805 trial, also known as CHAARTED.[39] CHAARTED randomized 790 men with metastatic, androgen-stimulated prostate cancer to docetaxel plus ADT or ADT alone. The patients in the combination arm experienced a longer OS than those in the ADT arm (57.6 vs 44.0 months; HR, 0.61; 95% CI, 0.47–0.80; *P*<.001). Subgroup analysis showed that the survival benefit was more pronounced in the 65% of participants with high-volume disease (HR, 0.60; 95% CI, 0.45–0.81; *P*<.001). Men with low-volume disease in CHAARTED may have derived a survival benefit from the inclusion of docetaxel (HR, 0.60; 95% CI, 0.32–1.13; *P*=.11), although median OS was not reached for either arm, and the number of patients was low.

A reviewer questioned whether upfront docetaxel should be considered for men with low-volume metastatic disease based on the CHAARTED results. Other reviewers requested that the panel consider data from the STAMPEDE trial and how it might affect the recommendation for the use of upfront docetaxel in the castration-naïve setting. The STAMPEDE trial, a multi-arm, multistage phase III trial, included patients with both M0 and M1 castration-naïve prostate cancer starting initial ADT.[40] The extent of metastatic disease was not evaluated in the 1,087 men with M1 disease, but the median OS for all patients with M1 disease was 5.4 years in the ADT/docetaxel arm versus 3.6 years in the ADT arm (a difference of 1.8 years between groups compared with a 1.1-year difference in CHAARTED). The results of the M1 population of STAMPEDE seem to confirm the survival advantage of adding docetaxel to ADT seen in CHAARTED, but the trial has not completed peer review.

Panel members brought up the European GETUG-AFU 15 trial, which compared ADT versus ADT + docetaxel in this population but did not find a survival benefit (median OS, 58.9 vs 54.2 months; HR, 1.01; 95% CI, 0.75–1.36).[41] Retrospective subset analyses from this trial showed that participants with high-volume metastatic disease derived a nonsignificant 20% reduction in the risk of death, whereas no reduction was seen in the low-volume subgroup.[42] However, the GETUG trial was small (n=385), and panel members believe it was underpowered for the subset analysis. Some panelists pointed out that CHAARTED is underpowered for the low-volume subset, because of the low number of deaths to date. In contrast, the panel discussed the strong statistical power of STAMPEDE (n=2,962), which showed a clear survival advantage to the upfront chemotherapy approach, even if the trial is not yet mature. Many panel members therefore expressed their hesitation to deny this approach to men with low-volume disease.

The final panel decision was to include the option of ADT with docetaxel for all men with progressive metastatic castration-naïve prostate cancer, but to include information in the footnote regarding the less certain benefit for men with low-volume disease (PROS-9, page 24). The panel believes that fit men should be informed about the lower level of evidence regarding low-volume M1 disease and should be offered it as an option. The panel reemphasized their belief that docetaxel should not be offered to men with progressive castration-naïve prostate cancer and no metastases based on results of preplanned subgroup analysis of the STAMPEDE trial that showed no OS benefit for participants with M0 disease.[40]

Conclusions

The major changes to the guidelines this year included efforts to better define risk for men with localized prostate cancer and help them make optimal decisions regarding management approach. The panel hopes these changes can help reduce the problem of overtreatment of prostate cancer by encouraging appropriate men to choose active surveillance. At the other end of the spectrum of disease, the panel recommended consideration of docetaxel in men undergoing EBRT for high-risk or very-high-risk localized disease and in men with low-volume metastatic castration-naïve disease (previously only recommended for high-volume disease). Although data in this area are still maturing, the panel believes the evidence to date is compelling enough to include the option of earlier docetaxel so as not to deny patients the opportunity for this potentially beneficial approach.

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Posttest Questions

1. A 64-year-old man has been diagnosed with T2a prostate cancer. His PSA is 7 ng/mL and his Gleason grade is 3 + 3 = 6. Which of the following might help him decide whether to undergo treatment?
   a. An estimation of life expectancy
   b. A nomogram
   c. A tumor-based molecular assay
   d. All of the above
2. True or False: The 2016 NCCN Guidelines for Prostate Cancer include the option for active surveillance in a subset of men with intermediate-risk prostate cancer who fit a favorable profile.
3. Docetaxel is NOT considered part of an appropriate treatment plan for which of the following prostate cancer settings:
   a. High-risk localized disease
   b. Very-high-risk localized disease
   c. Nonmetastatic progressive castration-naïve disease
   d. Low-volume M1 progressive castration-naïve disease
   e. High-volume M1 progressive castration-naïve disease