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-naive disease. 

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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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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.

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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. 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. 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
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. Nomograms and an estimate of life expectancy are other key determinants of primary management options in these men. 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. 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 unnessec-
RISK GROUP

High:
- T3a or
- Gleason score 8–10 or
- PSA >20 ng/mL

Very High:
- T3b-T4
- Primary Gleason pattern 5 or
- >4 cores with Gleason score 8–10

Regional:
- Any T, N1, M0
- ADT

Metastatic:
- Any T, Any N, M1
- ADT

INITIAL THERAPY

EBRT + ADT (2-3 y) (category 1)
or EBRT + brachytherapy ± ADT (2-3 y)
or EBRT + ADT (2-3 y) + docetaxel
or RP + PLND

ADJUVANT THERAPY

See Monitoring (PROS-6)

Adverse features:
EBRT or Observation

Lymph node metastasis:
ADT (category 1) ± EBRT (category 2B)
or Observation (category 2B)

See Monitoring (PROS-6)

Undetectable PSA
See Radical Prostatectomy Biochemical Failure (PROS-7)

Detectable PSA

Regional:
Any T, N, M0
- ADT

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...
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. 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 (\(P=.002\)).

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. Risk group stratification has been published widely and validated, and provides a better basis for treatment recommendations than clinical stage alone.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

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

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.
In this trial, 562 evalu-
34-
32,33
35–37
Informed decision-making, and use close monitoring
cer, but should be approached with caution, include
men with favorable intermediate-risk prostate can-
lance can be considered. As delineated in footnote
“n,” they defined “favorable” as predominant Glea-
son 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 favor-
able intermediate-risk prostate cancer as men with
NCCN low-risk prostate cancer except for Gleason
secondary pattern 4 in a single biopsy. The panel be-
lieves that active surveillance may be considered for
men with favorable intermediate-risk prostate can-
cer, 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.

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 interme-
diate-risk prostate cancer were treated with radiation
with or without neoadjuvant and concurrent ADT.
Multivariate analysis revealed that primary Gleason
pattern 4, percentage of positive biopsy cores of 50
or greater, and presence of more than 1 interme-
diate-risk factor (ie, T2b–c, PSA 10–20 ng/mL, Glea-
son score 7) were significant predictors of increased
incidence of distant metastasis. The authors then
used these factors to separate the patients into un-
favorable and favorable intermediate-risk groups and
determined that the unfavorable intermediate-risk
group had worse PSA recurrence-free survival, dis-
tant metastasis, and prostate cancer–specific mortal-
ity than the favorable intermediate-risk group.

The panel decided to define a favorable interme-
diate-risk subset of patients for whom active surveil-
ance can be considered. As delineated in footnote

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 pan-
el 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 evalu-
able men with nonmetastatic disease classified as
high- or very-high-risk received radiation and ADT
or radiation and ADT with docetaxel and predni-
sone 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 \( P=0.03 \)). 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 \( P=0.05 \)). 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 pa-
tients who are fit for chemotherapy.

Treatment of Progressive,
Castration-Naive Disease

The 2015 version of the guidelines added systemic
therapy options for men with progressive castration-
aive 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.\textsuperscript{19} 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.\textsuperscript{10} 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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

**References**


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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