NCCN Guidelines for Prostate Cancer

Ramesh Gopal, MD, PhD
Associate Professor of Radiation Oncology
MD Anderson Cancer Center
Medical Director MD Anderson Radiation Treatment Center at Presbyterian
Why Guidelines?

- To ensure that treatment is evidence based.
  - Guidelines are developed by experts based on clinical studies.
- To make treatment consistent between different physicians.
- To make it possible to detect and compare side-effects.
- To be able to compare new to old treatments and to change treatment in a consistent way.
What don’t guidelines do?

- Typically guidelines **DO NOT** require that everyone be treated the same.
- Do not restrict reasonable options.
- Do not prevent a different treatment in special circumstances.
Guidelines must be updated frequently

- To be relevant there must be a process for the guidelines to be frequently updated.
What is the NCCN?

The National Comprehensive Cancer Network® (NCCN®), is a not-for-profit alliance of 27 leading cancer centers devoted to patient care, research, and education, is dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can live better lives. Through the leadership and expertise of clinical professionals at NCCN Member Institutions, NCCN develops resources that present valuable information to the numerous stakeholders in the health care delivery system. As the arbiter of high-quality cancer care, NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers.
The NCCN

From its website

- An alliance of leading cancer centers devoted to patient care, research, and education

- Why We Exist (Our Mission)
  - To improve the quality, effectiveness, and efficiency of cancer care so that patients can live better lives

- Our Vision
  - To be the world’s leader in defining and advancing high-quality, high-value cancer care

- Our Core Values
  - The NCCN Core Values represent the principles that we, the NCCN team, strive to embrace. As representatives of leading cancer centers, we believe that by exemplifying these ideals within our organization, we can improve the quality, effectiveness, and efficiency of cancer care so that patients can live better lives.
The Member Institutions
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.
Prostate Cancer Guidelines
Life Expectancy from the SSA website

https://www.ssa.gov/OACT/STATS/table4c6.html
## NCCN Guidelines Version 2.2018
Prostate Cancer

### Risk Stratification and Staging Workup

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Clinical/pathologic features</th>
<th>Imaging†</th>
<th>Molecular testing of tumor</th>
<th>Germine testing</th>
<th>Initial therapy⁹</th>
<th>See</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low³</td>
<td>• T1cN0D0 • Gleason score 5/grade group 1 AND • PSA &lt; 10 ng/mL AND • Fewer than 3 prostate biopsy fragments/core positive, &lt;25% cancer in each fragment/core AND • PSA density &lt; 15 ng/mL³</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Consider if strong family history³</td>
<td>See PROS-4</td>
<td></td>
</tr>
<tr>
<td>Low⁰</td>
<td>• T1-2b AND • Gleason score 5/grade group 1 AND • PSA &lt; 10 ng/mL AND • Fewer than 3 prostate biopsy fragments/core positive, &lt;25% cancer in each fragment/core AND • PSA density &lt; 15 ng/mL³</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Consider if strong family history³</td>
<td>See PROS-5</td>
<td></td>
</tr>
<tr>
<td>Favorable intermediate⁰</td>
<td>• T2b-2c OR • Gleason score 3+4-7/grade group 2 OR • PSA 10-20 ng/mL • Percentage of positive biopsy cores &lt;50%</td>
<td>Bone imaging⁵ not recommended for staging • Pelvic + abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Not routinely recommended</td>
<td>Consider if strong family history³</td>
<td>See PROS-6</td>
<td></td>
</tr>
<tr>
<td>Unfavorable intermediate⁰</td>
<td>• T2b-2c OR • Gleason score 3+4-7/grade group 2 OR • PSA 10-20 ng/mL • Percentage of positive biopsy cores &lt;50%</td>
<td>Bone imaging⁵, recommended if T2 and PSA &gt;10 ng/mL • Pelvic + abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Not routinely recommended</td>
<td>Consider if strong family history³</td>
<td>See PROS-7</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>• T3a OR • Gleason score 8/grade group 4 OR Gleason score 4+5/grade group 5 OR • PSA &gt;20 ng/mL</td>
<td>Bone imaging⁵, recommended if T2 and PSA &gt;10 ng/mL • Pelvic + abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Not routinely recommended</td>
<td>Consider⁹</td>
<td>See PROS-8</td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>• T3b T4 OR • Primary Gleason pattern 5 OR • &gt;4 cores with Gleason score 8–10/grade group 4 or 5</td>
<td>Bone imaging⁵, recommended if T2 and PSA &gt;10 ng/mL • Pelvic + abdominal imaging: recommended if nomogram predicts &gt;10% probability of pelvic lymph node involvement</td>
<td>Not routinely recommended</td>
<td>Consider⁹</td>
<td>See PROS-9</td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>Any T, N1, M0</td>
<td>Already performed</td>
<td></td>
<td>Consider⁹</td>
<td>See PROS-10</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>Any T, Any N, M1</td>
<td>Already performed</td>
<td></td>
<td>Consider⁹</td>
<td>See PROS-11</td>
<td></td>
</tr>
</tbody>
</table>

### Note:
All recommendations are category 2A unless otherwise indicated.

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

See footnotes on next page
NCCN Guidelines Version 2.2018
Prostate Cancer

LOW RISK GROUP

EXPECTED PATIENT SURVIVAL

INITIAL THERAPY

- Active surveillance
  - PSA no more often than every 6 mo unless clinically indicated
  - DRE no more often than every 12 mo unless clinically indicated
  - Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
  - Consider mpMRI if anterior and/or aggressive cancer is suspected when PSA increases and systematic prostate biopsies are negative

ADJUVANT THERAPY

≥10 y

- EBRT or brachytherapy

RP ± PLND if predicted probability of lymph node metastasis ≥2%

<10 y

- Observation

PROGRESSIVE DISEASE

- See Initial Clinical Assessment (PROS-1)

See Monitoring for Initial Definitive Therapy (PROS-10)

Adverse feature(s) and no lymph node metastases:

- EBRT or Observation

No adverse features or lymph node metastases

Lymph node metastasis:

- ADT (category 1) ± EBRT (category 2B) or Observation

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 2.2018
Prostate Cancer

FAVORABLE INTERMEDIATE RISK GROUP
EXPECTED PATIENT SURVIVAL
INITIAL THERAPY
Active surveillance⁷
- PSA no more often than every 6 mo unless clinically indicated
- DRE no more often than every 12 mo unless clinically indicated
- Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
- Consider mpMRI if anterior and/or aggressive cancer is suspected when PSA increases and systematic prostate biopsies are negative

≥10 y
EBT³ or brachytherapy alone

<10 y
Observation¹

ADJUVANT THERAPY
• Adverse feature(s) and no lymph node metastases¹⁰
  - EBRT⁵ or Observation¹
• No adverse features or lymph node metastases
  - Observation¹
• Lymph node metastasis: ADT (category 1) or EBRT⁵ (category 2B) or Observation¹

Untreatable PSA after RP or PSA nadir¹⁰ after RT

PSA persistence/recurrence¹⁰

Progressive disease⁷
See Initial Clinical Assessment (PROS-1)
See Monitoring for Initial Definitive Therapy (PROS-10)
See Radical Prostatectomy PSA Persistence/Recurrence (PROS-11)
See Radiation Therapy Recurrence (PROS-12)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
NCCN Guidelines Version 2.2018
Prostate Cancer

REGIONAL RISK GROUP

EXPECTED PATIENT SURVIVAL

INITIAL THERAPY

EBRT§ + ADT¶ (2–3 y; category 1) ± abiraterone and prednisone

>5 y

ADT¶ ± abiraterone and prednisone

See Monitoring (PROS-10)

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 2.2018, 03/08/18 © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. The NCCN Guidelines® and this Illustration may not be reproduced in any form without the express written permission of NCCN®.

PROS-9
NCCN Guidelines Version 2.2018
Prostate Cancer

INITIAL MANAGEMENT

MONITORING

RECURRENT

See Radical Prostatectomy PSA Persistence/Recurrence (PROS-11)

See Radiation Therapy Recurrence (PROS-12)

See Systemic Therapy for Castration-Naive Disease (PROS-13)

See Systemic Therapy for M0 CRPC (PROS-14)

See Systemic Therapy for M1 CRPC (PROS-15)

PSA persistence/recurrence after RP is defined as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence).

1 RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus: 1) PSA increase by 2 ng/ml or more above the nadir PSA is the standard definition for PSA persistence/recurrence after EBRT with or without HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/ml, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

2 PSA as frequently as every 3 mo may be necessary to clarify disease status, especially in high-risk men.

N1 on ADT or Localized on observation

• Physical exam + PSA every 3–6 mo
• Bone imaging1 for symptoms and as often as every 6–12 mo

Post-RP

Post-EBRT

Progression1 to metastatic disease without PSA persistence/recurrence

Progression2,3 to metastatic disease with PSA persistence/recurrence

N1M0

M1

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Radical Prostatectomy PSA Persistence/Recurrence

PSA persistence/recurrence

- PSA DT
  - Consider:
    - Chest x-ray or chest CT
    - Bone imaging
    - Abdominal/pelvic CT or MRI and/or TRUS
  - C-11 choline or F-18 fluoroavaine PET/CT or PET/MRI
  - Decipher molecular assay (category 2B)
  - Prostate bed biopsy (especially if imaging suggests local recurrence)

Studies negative for distant metastases

- EBRT ± ADT or Observation

Progression

Studies positive for distant metastases

- Observation

Progression

- ADT ± EBRT to site of metastases, if in weight-bearing bone or symptomatic

See Systemic Therapy for Castration-Naive Disease (PROS-13)

See Systemic Therapy for M1 CRPC (PROS-14)

Note: All recommendations are category 2A unless otherwise indicated.

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

PROS-11
RADIATION THERAPY RECURRENT

Candidate for local therapy:
- Original clinical stage T1-T2, NX or N0
- Life expectancy >10 y
- PSA now <10 ng/mL

PSA persistence/recurrence or Positive DRE

Not a candidate for local therapy

Bone imaging

Observation

TRUS biopsy positive, studies negative for distant metastases
- PSADT
- Chest x-ray or chest CT
- Bone imaging
- Prostate MRI
- TRUS biopsy

Observation

TRUS biopsy negative, studies negative for distant metastases
- Abdominal/pelvic CT/MRI
- C-11 choline or F-18 fluocitovine PET/CT or PET/MRI

Studies positive for distant metastases

ADT (especially if bone scan positive) or Observation

Progression

See Systemic Therapy for Castration-Naive Disease (PROS-13)

See Systemic Therapy for M0 CRPC (PROS-14)

See Systemic Therapy for M1 CRPC (PROS-15)

Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluocitovine PET/CT or PET/MRI for further soft tissue evaluation of F-18 sodium fluoride PET/CT for further bone evaluation. See Principles of Imaging (PROS-6) and Discussion.

The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had noadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.


Histologic confirmation is recommended whenever feasible due to significant rates of false positivity.
NCCN Guidelines Version 2.2018
Prostate Cancer

SYSTEMIC THERAPY FOR CASTRATION-NAIVE DISEASE

M0
- Physical exam + PSA every 3–6 mo
- Bone imaging1 for symptoms and as often as every 6–12 mo

M1
- ADT1 and docetaxel 75 mg/m² for 6 cycles2a (category 1)
- ADT1 and abiraterone1 with prednisone (category 1)

Studies negative for distant metastases
See Systemic Therapy for M0 CRPC (PROS-14)

Studies positive for distant metastases
See Systemic Therapy for M1 CRPC (PROS-15)

Notes:
1. ADT: Androgen Deprivation Therapy
2. See Principles of Androgen Deprivation Therapy (PROS-F).
3. 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).
4. Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 flucloxacil PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation. See Principles of Imaging (PROS-B) and Discussion.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
**SYSTEMIC THERAPY FOR M0 CASTRATION-RESISTANT PROSTATE CANCER (CRPC)**

1. **Studies negative for distant metastases**
   - **Continue ADT to maintain castrate serum levels of testosterone (<50 ng/dL)**

2. **Observation**
   - **Observation** especially if PSA < 10 (m0)
   - **Apalectamide** especially if PSA < 10 (category 1)
   - **Other secondary hormone therapy** especially if PSA < 10 (mo)

3. **PSA increasing**
   - **No metastases (M0)**
     - **Change or maintain current treatment and continue monitoring**
   - **Metastases (M1)**
     - **Yes → Imaging**
     - **Imaging**

4. **Maintain current treatment and continue monitoring**

---

1. **See Principles of Androgen Deprivation Therapy (PROS-E)**
2. **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).**
3. **Workup for progression should include chest x-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT or PET/MRI or F-18 fluoride PET/CT or PET/MRI for further soft tissue evaluation or F-18 sodium fluoride PET/CT for further bone evaluation. See Principles of Imaging (PROS-B) and Discussion.**

---

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Other sites

- Similarly to what we have seen, NCCN Guidelines are available for other situations and disease sites.