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NCCN Guidelines Panel Disclosure

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NCCN Prostate Cancer Panel Members

Summary of Guideline Updates

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Principles of Androgen Deprivation Therapy (PROS-E)
Principles of Chemotherapy/Immunotherapy (PROS-F)

Staging (ST-1)

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2012.
Summary of changes in the 3.2012 version of the Prostate Cancer Treatment guidelines from the 2.2012 version include:

Discussion

- The discussion section was updated to reflect the changes in the algorithm.

PROS-6

- “Failure of PSA to fall to undetectable” added word “levels”

PROS-F

- Changed “no visceral disease” to “no hepatic metastases”

Summary of changes in the 2.2012 version of the Prostate Cancer Treatment guidelines from the 1.2012 version include:

PROS-E (3 of 3)

- Monitor/Surveillance
  - Third bullet; changed the dose of denosumab from (120 mg SQ monthly) to 60 mg SQ every 6 months
  - Third bullet; changed the dose of zoledronic acid from 4 mg IV annually to 5 mg IV annually.
Summary of changes in the 1.2012 version of the Prostate Cancer Treatment guidelines from the 4.2011 version include:

- Following studies negative for metastases, removed bullet “antiandrogen withdrawal (if on combination androgen blockade).”
- Following studies positive for metastases:
  - removed bullet “visceral disease” following asymptomatic
  - added “docetaxel” as a category 2A recommendation with footnote s.
  - footnote s: “Although most patients without symptoms are not interested in chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or hepatic metastases despite lack of symptoms.”
  - following symptomatic, added “sipuleucel-T” as a category 2A recommendation.
- Changed footnote q, Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. Sipuleucel-T is not indicated in patients with “hepatic metastases or” life expectancy <6 months.

- External beam radiotherapy, changed the second bullet “Doses of 75.6-79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.”
- Palliative radiotherapy, changed the second bullet “Widespread bone metastases can be palliated using strontium 89 or samarium 153 with or without focal external beam radiation.”

- Optimal ADT, first bullet, added “or antagonist” to LHRH.
- Monitor/Surveillance
  - first bullet, added “including hot flashes, hot flushes, vasomotor instability.”
  - third bullet, added denosumab (120 mg SQ monthly).
INITIAL PROSTATE CANCER DIAGNOSIS

INITIAL CLINICAL ASSESSMENT

(7th Edition of the AJCC Staging Manual)

STAGING WORKUP

RECURRENT RISK

Clinically Localized:

- Very low:
  - T1c
  - Gleason score ≤6
  - PSA <10 ng/mL
  - Fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core
  - PSA density <0.15 ng/mL/g
- Low:
  - T1-T2a
  - Gleason score 2-6
  - PSA <10 ng/mL
- Intermediate:
  - T2b-T2c or Gleason score 7 or PSA 10-20 ng/mL
- High:
  - T3a or Gleason score 8-10 or PSA >20 ng/mL
- Metastatic:
  - Any T, N1
  - Any T, Any N, M1

Preferred treatment for any therapy is approved clinical trial.

- Life expectancy ≤5 y and asymptomatic
- Life expectancy >5 y or symptomatic

No further workup or treatment until symptoms except for high-risk patient

Bone scan if T1 and PSA >20 or T2 and PSA >10 or Gleason score ≥8 or T3, T4 or symptomatic

Pelvic CT or MRI if T3, T4 or T1-T2 and nomogram indicated probability of lymph node involvement >20%

Suspicious nodes → Consider biopsy

All others; no additional imaging

See Initial Therapy (PROS-2)

See Initial Therapy (PROS-3)

See Initial Therapy (PROS-4)

See Principles of Life Expectancy (PROS-A).

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. High risk factors include bulky T3-T4 disease or Gleason score 8-10.

Patients with multiple adverse factors may be shifted into the next higher risk group.

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

**Version 3.2012**

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<thead>
<tr>
<th>RECURRENCE RISK</th>
<th>EXPECTED PATIENT SURVIVAL</th>
<th>INITIAL THERAPY</th>
<th>ADJUVANT THERAPY</th>
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<tbody>
<tr>
<td>Clinically Localized:</td>
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<tr>
<td>Very Low:</td>
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<td>• T1c</td>
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<tr>
<td>• PSA &lt;10 ng/mL</td>
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<td>• Fewer than 3 prostate biopsy cores positive, ≤50% cancer in any core</td>
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<td>Low:</td>
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<td>• T1-T2a</td>
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<tr>
<td>• PSA &lt;10 ng/mL</td>
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**INITIAL THERAPY**

- **Active surveillance (category 2B)**
  - PSA at least as often as every 6 mo
  - DRE at least as often as every 12 mo
  - Repeat prostate biopsy as often as every 12 mo

**ADJUVANT THERAPY**

- **Progressive disease**
  - See Initial Clinical Assessment (PROS-1)

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**See Principles of Life Expectancy (PROS-A).**

The Panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. See NCCN Guidelines for Prostate Cancer Early Detection. Active surveillance is recommended for these subsets of patients.

**Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses.** See Principles of Active Surveillance (PROS-B).

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**See Principles of Radiation Therapy (PROS-C).**

**See Principles of Surgery (PROS-D).**

**Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.**

**Adverse laboratory/pathologic features include:**
- positive margins, seminal vesicle invasion, extracapsular extension or detectable PSA.
- Androgen deprivation therapy

**See Principles of Androgen Deprivation Therapy (PROS-E).**
**Discussion**

**RECURRENCE RISK**

**EXPECTED PATIENT SURVIVAL**

**INITIAL THERAPY**

**ADJUVANT THERAPY**

### Clinically Localized:

- **Active surveillance**
  - PSA as often as every 6 mo
  - DRE as often every 12 mo

  **Progressive disease**
  - See Initial Clinical Assessment (PROS-1)

### Intermediate:

- **T2b-T2c or Gleason score 7 or PSA 10-20 ng/mL**

  **RT** (3D-CRT/IMRT with daily IGRT)
  - ± short-term neoadjuvant/concomitant/adjuvant ADT (4-6 mo)
  - ± brachytherapy

### ≥10 y

- **Radical prostatectomy + pelvic lymph node dissection if predicted probability of lymph node metastasis ≥2%**

### <10 y

- **RT** (3D-CRT/IMRT with daily IGRT)
  - ± short-term neoadjuvant/concomitant/adjuvant ADT (4-6 mo)
  - ± brachytherapy

## ADJUVANT THERAPY

- **Undetectable PSA**
  - See Monitoring (PROS-5)

- **Detectable PSA**
  - See (PROS-6)

### Adverse features:

- **Observation** or **Androgen deprivation therapy**

### Note:

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**PROS-3**

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**NCCN Guidelines Index**

Prostate Table of Contents

Discussion
### Prostate Cancer

### Recurrence Risk

#### Clinically Localized:

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

**Locally Advanced:**
- RT \(^f\) (3D-CRT/IMRT with daily IGRT) + long-term neoadjuvant/concomitant/adjuvant ADT (2-3 y)\(^j\)
- or RT \(^f\) (3D-CRT/IMRT with daily IGRT) + brachytherapy ± short-term neoadjuvant/concomitant/adjuvant ADT (4-6 mo)
- or Radical prostatectomy\(^g\) + pelvic lymph node dissection (selected patients with no fixation)

**Very High:**
- T3b-T4

**Metastatic:**
- Any T, N1
- Any T, Any N, M1

### Initial Therapy

#### RT \(^f\) (3D-CRT/IMRT with daily IGRT) + long-term neoadjuvant/concomitant/adjuvant ADT (2-3 y)\(^j\)
- or RT \(^f\) (3D-CRT/IMRT with daily IGRT) + brachytherapy ± short-term neoadjuvant/concomitant/adjuvant ADT (4-6 mo)
- or Radical prostatectomy\(^g\) + pelvic lymph node dissection (selected patients with no fixation)

### Adjuvant Therapy

#### Adverse Features:

- Adverse features:
- RT \(^f\)
- or Observation

### See Monitoring (PROS-5)

#### Lymph Node Metastasis:

- Lymph node metastasis:
- ADT\(^j\)
- or Observation

### See Monitoring (PROS-5)

#### See Post-Radical Prostatectomy Recurrence (PROS-6)

### Note:

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*See Principles of Radiation Therapy (PROS-C).*

*See Principles of Surgery (PROS-D).*
INITIAL MANAGEMENT OR PATHOLOGY

Initial-definitive therapy

- PSA every 6-12 mo for 5 y, then every year
- DRE every year, but may be omitted if PSA undetectable

N1 or M1

- Physical exam (including DRE) + PSA every 3-6 mo

MONITORING

- PSA every 6-12 mo for 5 y, then every year
- DRE every year, but may be omitted if PSA undetectable

- Physical exam (including DRE) + PSA every 3-6 mo

RECURRENCE

- Post-radical prostatectomy
- Post-RT

- Failure of PSA to fall to undetectable levels
- Detectable PSA that increases on 2 subsequent measurements

- Rising PSA\(^m\) or Positive DRE

See Post-Radical Prostatectomy Recurrence (PROS-6)

See Post-Radiation Therapy Recurrence (PROS-7)

See Advanced Disease (PROS-8) and (PROS-9)

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

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\(m\)RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus - (1) PSA rise by 2 ng/ml or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; (2) the date of failure is determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (with no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up" to avoid the artifacts resulting from short follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature.
POST-RADICAL PROSTATECTOMY RECURRENCE

Failure of PSA to fall to undetectable levels

PSA detectable and rising on 2 or more subsequent determinations

± Bone scan
± CT/MRI
± PSADT
± Prostate bed biopsy

Studies negative for distant metastases

RT\textsuperscript{f} ± neoadjuvant/concomitant/adjuvant ADT\textsuperscript{j}
or Observation

Studies positive for distant metastases

ADT\textsuperscript{j} ± RT to site of metastases, if in weight-bearing bones, or symptomatic\textsuperscript{f}
or Observation

Progression

See Advanced Disease (PROS-8) and (PROS-9)

\textsuperscript{f}See Principles of Radiation Therapy (PROS-C).

\textsuperscript{j}See Principles of Androgen Deprivation Therapy (PROS-E).

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**POST-RADIATION THERAPY RECURRENCE**

<table>
<thead>
<tr>
<th>Candidate for local therapy:</th>
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<tbody>
<tr>
<td>• Original clinical stage T1-T2, NX or N0</td>
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<tr>
<td>• Life expectancy &gt;10 y</td>
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<tr>
<td>• PSA now &lt;10 ng/mL</td>
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</table>

<table>
<thead>
<tr>
<th>Post-RT rising PSA$^m$ or Positive DRE</th>
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<tbody>
<tr>
<td>Not a candidate for local therapy</td>
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<table>
<thead>
<tr>
<th>Prostate biopsy</th>
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<tbody>
<tr>
<td>Bone scan</td>
</tr>
<tr>
<td>± Abdominal/pelvic CT/MRI</td>
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<tr>
<td>± Endorectal MRI</td>
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<tr>
<td>± PSADT</td>
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<table>
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<tr>
<th>Observation or Radical prostatectomy$^g$ or Brachytherapy$^f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation or ADT$^i$ or Clinical trial or More aggressive work-up for local recurrence (eg, repeat biopsy, MR spectroscopy, endorectal MRI)</td>
</tr>
</tbody>
</table>

**PROS-7**

- **See Principles of Radiation Therapy (PROS-C).**
- **See Principles of Surgery (PROS-D).**
- **See Principles of Androgen Deprivation Therapy (PROS-E).**
- **RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus - (1) PSA rise by 2 ng/ml or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; (2) the date of failure is determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (with no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up" to avoid the artifacts resulting from short follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature.**

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**ADT naive (M0 or M1)**

- Orchiectomy → Relapse → Studies negative for distant metastases → **See Additional Systemic Therapy for Castration-Recurrent Prostate Cancer (PROS-9)**
  - or LHRH agonist alone ± antiandrogen ≥ 7 d to prevent testosterone flare → Relapse → Studies negative for distant metastases
  - or LHRH agonist + antiandrogen → Relapse → Studies positive for distant metastases → Consider biopsy if small cell suspected
  - or LHRH antagonist → Relapse → Studies positive for distant metastases

**Not small cell**

- **See Additional Systemic Therapy for Castration-Recurrent Prostate Cancer (PROS-9)**

**Small cell**

- Cisplatin/etoposide\(^{o,p}\) or Carboplatin/etoposide\(^{o,p}\) or Docetaxel-based regimen\(^{o,p}\)

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^nAssure castrate level of testosterone.

^oSee Principles of Chemotherapy/Immunotherapy (PROS-F).

^pSee NCCN Guidelines for Small Cell Lung Cancer.

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

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ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER (CRPC)

Studies negative for metastases → Maintain castrate serum levels of testosterone → Follow pathway below

Studies positive for metastases → Symptomatic → Yes → PSA relapse or metastases (M1)

PSA relapse or metastases (M1) → Follow pathway below

- Clinical trial (preferred)
- Observation
- Secondary hormone therapy
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole
  - Steroids
  - DES or other estrogen

Studies positive for metastases → Symptomatic → No → PSA relapse or metastases (M1)

- Clinical trial
- Secondary hormone therapy
  - Antiandrogen withdrawal
  - Ketoconazole or abiraterone acetate (category 2B)
  - Steroids
  - DES or other estrogen
- Sipuleucel-T (category 1)
- Docetaxel (category 1)
- Cabazitaxel (category 1, post-docetaxel)
- Mitoxantrone
- Mitoxantrone
- Abiraterone acetate
- Other secondary hormone therapy
  - Antiandrogen withdrawal
  - Ketoconazole
  - Steroids
  - DES or other estrogen
- Sipuleucel-T

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

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

1 See Principles of Androgen Deprivation Therapy (PROS-E).
2 See Principles of Chemotherapy/Immunotherapy (PROS-F).

Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1.
Sipuleucel-T is not indicated in patients with hepatic metastases or life expectancy <6 months.
For patients who are not candidates for docetaxel-based regimens.

Although most patients without symptoms are not interested in chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or hepatic metastases despite lack of symptoms.
PRINCIPLES OF LIFE EXPECTANCY ESTIMATION

- Life expectancy estimation is critical to informed decision-making in prostate cancer early detection and treatment.
- Estimation of life expectancy is possible for groups of men but challenging for individuals.
- Life expectancy can be estimated using the Social Security Administration tables (www.ssa.gov/OACT/STATS/table4c6.html)
- Life expectancy can then be adjusted using the clinicians assessment of overall health as follows:
  - Best quartile of health - add 50%
  - Worst quartile of health - subtract 50%
  - Middle two quartiles of health - no adjustment
- Example of 5 y increments of age are reproduced from NCCN Guidelines for Senior Adult Oncology for life expectancy estimation.¹

PRINCIPLES OF ACTIVE SURVEILLANCE

- The NCCN Prostate Cancer Panel and the NCCN Prostate Cancer Early Detection Panel (See NCCN Guidelines for Prostate Cancer Early Detection) remain concerned about over-diagnosis and overtreatment of prostate cancer. The Panel recommends that patients and their physicians (urologist, radiation oncologist, medical oncologist, primary care physician) consider active surveillance based on careful consideration of the patient’s prostate cancer risk profile, age, and health.
- Active surveillance is usually appropriate for men with very low-risk prostate cancer when life expectancy <20 y or men with low-risk prostate cancer when life expectancy <10 y. See Recurrence Risk Criteria (PROS-2)
- Active surveillance involves actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses.
- Patients with clinically localized cancers who are candidates for definitive treatment and choose active surveillance should have regular follow up. Follow up should be more rigorous in younger men than older men. Follow up should include:
  - PSA as often as every 3 mo but at least every 6 mo
  - DRE as often as every 6 mo but at least every 12 mo
  - Needle biopsy of the prostate should be repeated within 6 mo of diagnosis if initial biopsy was <10 cores or assessment discordant (eg, palpable tumor contralateral to side of positive biopsy)
  - A repeat prostate biopsy should be considered if prostate exam changes or PSA increases, but neither parameter is very reliable for detecting prostate cancer progression.
  - Needle biopsy may be performed within 18 mo if initial prostate biopsy ≥10 cores and as often as every 12 months. Repeat prostate biopsies are not indicated after age 75 y or when life expectancy <10 y.
- A repeat prostate biopsy should be considered as often as annually to assess for disease progression because PSA kinetics may not be reliable as monitoring parameters to determine progression of disease.
- PSA doubling time appears unreliable for identification of progressive disease that remains curable.
- Cancer progression may have occurred if:
  - Gleason grade 4 or 5 cancer is found upon repeat prostate biopsy
  - Prostate cancer is found in a greater number of prostate biopsies or occupies a greater extent of prostate biopsies.
- Advantages of active surveillance:
  - Avoid possible side effects of definitive therapy that may be unnecessary
  - Quality of life/normal activities potentially less affected
  - Risk of unnecessary treatment of small, indolent cancers reduced
- Disadvantages of active surveillance:
  - Chance of missed opportunity for cure
  - Risk of progression and/or metastases
  - Subsequent treatment may be more complex with increased side effects
  - Nerve sparing may be more difficult, which may reduce chance of potency preservation after surgery
  - Increased anxiety
  - Requires frequent medical exams and periodic biopsies, which are not without complications
  - Uncertain long-term natural history of prostate cancer

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

External Beam Radiotherapy:
- 3D conformal and IMRT (intensity modulated radiation therapy) techniques should be employed. Image-guided radiation therapy (IGRT) is required if dose ≥78 Gy.
- Doses of 75.6-79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.
- Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2-3 y (category 1).
- Patients with intermediate-risk cancer may be considered for pelvic lymph node irradiation and 4-6 mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with low-risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques such as IGRT using CT, ultrasound implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.
- Evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.

Brachytherapy:
- Permanent low-dose rate (LDR) brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers consider combining brachytherapy with EBRT (40-50 Gy) ± 4-6 mo neoadjuvant/comcomitant/adjuvant ADT. Patients with high-risk cancers may be treated with a combination of EBRT (40-50 Gy) and brachytherapy ± 4-6 mo neoadjuvant/comcomitant/adjuvant ADT.
- Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate (TURP) are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant androgen deprivation therapy may be used to shrink the prostate to an acceptable size.
- Post-implant dosimetry should be performed to document the quality of the implant.
- The recommended prescribed doses for LDR monotherapy are 145 Gy for 125-Iodine and 125 Gy for 103-Palladium. The corresponding boost dose after 40-50 Gy EBRT are 110 Gy and 90-100 Gy, respectively.
- High-dose rate (HDR) brachytherapy can be used in combination with EBRT (40-50 Gy) instead of LDR. Commonly used boost regimens include 9.5-10.5 Gy x 2 fractions, 5.5-7.5 Gy x 3 fractions, and 4.0-6.0 Gy x 4 fractions.

Palliative Radiotherapy:
- 800 cGy as a single dose should be used instead of 3000 cGy in 10 fractions for non-vertebral metastases.
- Widespread bone metastases can be palliated using strontium 89 or samarium 153 with or without focal external beam radiation.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Pelvic Lymph Node Dissection (PLND):
- An extended PLND will discover metastases approximately twice as often as a limited PLND. Extended PLND provides more complete staging and may cure some men with microscopic metastases, therefore, an extended PLND is preferred when PLND is performed.
- An extended PLND includes removal of all node-bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.
- A PLND can be excluded in patients with < 2% predicted probability of nodal metastases by nomograms, although some patients with lymph node metastases will be missed.
- PLND can be performed using an open, laparoscopic or robotic technique.

Radical Prostatectomy:
- RP is appropriate therapy for any patient with clinically localized prostate cancer that can be completely excised surgically, who has a life expectancy of 10 years or more and no serious co-morbid conditions that would contraindicate an elective operation.
- High volume surgeons in high volume centers generally provide better outcomes.
- Laparoscopic and robot-assisted radical prostatectomy are used commonly. In experienced hands, the results of these approaches appear comparable to open surgical approaches.
- Blood loss can be substantial with radical prostatectomy but can be reduced by careful control of the dorsal vein complex and periprostatic vessels.
- Urinary incontinence can be reduced by preservation of urethral length beyond the apex of the prostate and avoiding damage to the distal sphincter mechanism. Bladder neck preservation may decrease the risk of incontinence. Anastomotic strictures increase the risk of long-term incontinence.
- Recovery of erectile function is directly related to age at radical prostatectomy, preoperative erectile function and the degree of preservation of the cavernous nerves. Replacement of resected nerves with nerve grafts has not been shown beneficial. Early restoration of erections may improve late recovery.
- Salvage radical prostatectomy is an option for highly selected patients with local recurrence after EBRT, brachytherapy, or cryotherapy in the absence of metastases, but the morbidity (incontinence, loss of erection, anastomotic stricture) is high.
Androgen deprivation therapy (ADT) for Clinically Localized Disease
- Neoadjuvant ADT for radical prostatectomy is strongly discouraged.
- Giving ADT before, during and/or after radiation prolongs survival in selected radiation managed patients.
- Studies of short-term (4-6 mo) and long-term (2-3 y) neoadjuvant ADT all have used complete androgen blockade. Whether the addition of an antiandrogen is necessary will require further studies.
- Adjutant ADT given after completion of primary treatment is not a standard treatment at this time with the exception of selected high-risk patients treated with radiation therapy (See PROS-3). Low volume, high-grade prostate cancer may warrant adjuvant ADT for 4-6 mo but 2-3 y may be considered.
- In the largest randomized trial to date using antiandrogen bicalutamide alone at high dose (150 mg), there were indications of a delay in recurrence of disease but no improvement in survival. Longer follow-up is needed.
- In one randomized trial, immediate and continuous use of ADT in men with positive nodes following radical prostatectomy resulted in significantly improved overall survival compared to men who received delayed ADT. Therefore, such patients should be considered for immediate ADT.
- The side effects of continuous ADT increase with the duration of treatment.

Timing of ADT for Advanced Disease (PSA recurrence or metastatic disease)
- The timing of ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, and the short and long-term side effects of ADT.
- A significant proportion of these patients will ultimately die of their disease; their prognosis is best approximated by the absolute level of PSA, the rate of change in the PSA level (PSA “doubling time”), and the initial stage, grade, and PSA level at the time of definitive therapy.
- Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early ADT is not clear, treatment should be individualized until definitive studies are done. Patients with an elevated PSA (>50 ng/mL) and/or a shorter PSA doubling time (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.
- Treatment should begin immediately in the presence of tumor-related symptoms or overt metastases (category 1). Earlier ADT will delay the appearance of symptoms and of metastases, but it is not clear whether earlier ADT will prolong survival. The complications of long-term ADT have not been adequately documented.

Optimal ADT
- LHRH agonist or antagonist (medical castration) and bilateral orchiectomy (surgical castration) are equally effective.
- Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides no proven benefit over castration alone in patients with metastatic disease.
- Antiandrogen therapy should precede or be co-administered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.
Antiangen monotherapy appears to be less effective than medical or surgical castration and should not be recommended. The side effects are different but overall less tolerable.

No clinical data support the use of triple androgen blockade (finasteride or dutasteride with combined androgen blockade).

Intermittent ADT may reduce side effects without altering survival compared to continuous ADT but the long term efficacy of intermittent ADT remains unproven.

Patients who do not achieve adequate suppression of serum testosterone (less than 50 ng/dl) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, or steroids), although the clinical benefit is not clear.

Secondary Hormonal Therapy

Androgen receptor activation and autocrine/paracrine androgen synthesis are potential mechanisms of recurrence of prostate cancer during ADT (castration-recurrent prostate cancer [CRPC]). Thus castrate levels of testosterone should be maintained while additional therapies are applied.

A variety of strategies can be employed that may afford clinical benefit if initial ADT has failed, which include anti-androgen withdrawal, administration of anti-androgens (bicalutamide, nilutamide, flutamide), administration of adrenal/paracrine androgen synthesis inhibitors (ketoconazole or abiraterone acetate), or the use of estrogens, such as diethylstilbestrol (DES); however, none of these agents have yet demonstrated a prolongation in overall survival in the pre-chemotherapy setting.

Abiraterone acetate with low-dose prednisone prolongs overall survival among men with metastatic CRPC who have been treated previously with docetaxel, as demonstrated in a randomized, placebo-controlled phase III trial. Statistically significant improvements in time to progression, tumor response and PSA also were observed. Thus, the administration of abiraterone acetate (1000 mg per day without food) with prednisone (5 mg twice daily) is a reasonable treatment option after docetaxel has failed. Side effects of abiraterone acetate that require ongoing monitoring include hypertension, hypokalemia, peripheral edema, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.

Abiraterone acetate also can be considered for men with metastatic CRPC who are not candidates for chemotherapy. Use of abiraterone acetate in patients who have not received prior docetaxel is based on single-arm, phase 2 clinical trial data. A phase III placebo-controlled trial in the pre-docetaxel setting has been completed; results are not yet available. Until those results are available, docetaxel remains the standard of care for CRPC patients refractory to secondary hormone therapy who are candidates for chemotherapy.
Monitor/Surveillance

- ADT has a variety of adverse effects including hot flashes, hot flushes, vasomotor instability, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease. Patients and their medical providers should be advised about these risks prior to treatment.

- Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation (www.nof.org). The National Osteoporosis Foundation guidelines include recommendations for (1) supplemental calcium (1200 mg daily) and vitamin D3 (800-1000 IU daily) for all men over age 50 y and (2) additional treatment for men when the 10 y probability of hip fracture is ≥ 3% or the 10 y probability of a major osteoporosis-related fracture is ≥20%. Fracture risk can be assessed using the recently released algorithm called FRAX® by the World Health Organization (www.shef.ac.uk/FRAX/index.htm). ADT should be considered “secondary osteoporosis” using the FRAX® algorithm.

- Denosumab (60 mg SQ every 6 mo), zoledronic acid (5 mg IV annually) and alendronate (70 mg PO weekly) increase bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either denosumab, zoledronic acid or alendronate sodium is recommended when the absolute fracture risk warrants drug therapy.

- Screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended in men receiving ADT. These medical conditions are common in older men and it remains uncertain whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in men receiving ADT should differ from the general population.
Men with advanced prostate cancer should be encouraged to participate in clinical trials and referred early to a medical oncologist. Systemic chemotherapy should be reserved for men with castration-recurrent metastatic prostate cancer except when studied in clinical trials. Every 3-week docetaxel and prednisone is the preferred first-line chemotherapy treatment based upon phase 3 clinical trial data for men with symptomatic castration-recurrent prostate cancer. Symptomatic patients who are not candidates for docetaxel-based regimens could be treated with mitoxantrone and prednisone. Men with castration-recurrent metastatic prostate cancer who are symptomatic should be considered for chemotherapy. Men with less advanced disease may consider immunotherapy. - Sipuleucel-T has been shown in a Phase 3 clinical trial to extend mean survival from 21.7 mo in the control arm to 25.8 mo in the treatment arm, which constitutes a 22% reduction in mortality risk. - Sipuleucel-T is well tolerated; common complications include chills, pyrexia, and headache. - Sipuleucel-T may be considered for men with castration-recurrent metastatic prostate cancer who have:
  ◦ good performance status (ECOG 0-1)
  ◦ estimated life expectancy >6 mo
  ◦ no hepatic metastases
  ◦ no or minimal symptoms

Only regimens utilizing docetaxel on an every 3 week schedule demonstrated beneficial impact on survival. The duration of therapy should be based on the assessment of benefit and toxicities. In the pivotal trials establishing survival advantage of docetaxel-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted. Rising PSA should not be used as the sole criteria for progression. Assessment of response should incorporate clinical and radiographic criteria.

Men who have failed docetaxel-based chemotherapy should be encouraged to participate in clinical trials. However, cabazitaxel with prednisone has been shown in a randomized phase 3 study to prolong overall survival, progression-free survival, and PSA and radiologic responses when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second line setting. Selection of patients without severe neuropathy and adequate liver, kidney, and bone marrow function is necessary, given the high risk of neutropenia and other side effects in this population, with consideration of prophylactic granulocyte growth factor injections.

Mitoxantrone has not demonstrated a survival improvement in this post-docetaxel setting but remains a palliative therapeutic option, particularly in men who are not candidates for cabazitaxel therapy. No chemotherapy regimen to date has demonstrated improved survival or quality of life following cabazitaxel, and trial participation should be strongly encouraged. Outside of a clinical trial, several systemic agents have shown palliative benefits in single arm studies. Treatment decisions should be individualized based on comorbidities and functional status. Finally, for patients who have not demonstrated definitive evidence of progression on prior docetaxel therapy, retreatment with this agent can be attempted.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
In men with castration-recurrent prostate cancer who have bone metastases, denosumab and zoledronic acid have been shown to prevent disease-related skeletal complications, which include fracture, spinal cord compression, or the need for surgery or radiation therapy to bone.

- When compared to zoledronic acid, denosumab was shown to be superior in prevention of skeletal-related events.
- Choice of agent may depend on underlying co-morbidities, whether the patient has been treated with zoledronic acid previously, logistics, and/or cost considerations.
  - Zoledronic acid is given intravenously every 3-4 weeks. The dose is based on the serum creatinine obtained just prior to each dose and must be adjusted for impaired renal function. Zoledronic acid is not recommended for creatinine clearance <30 mL/min.
  - Denosumab is given subcutaneously every 4 weeks. Although renal monitoring is not required, denosumab is not recommended in patients with creatinine clearance <30 mL/min. When creatinine clearance is <60 mL/min the risk for severe hypocalcemia increases. Even in patients with normal renal function, hypocalcemia is seen twice as often with denosumab than zoledronic acid and all patients on denosumab should be treated with vitamin D and calcium with periodic monitoring of serum calcium levels.
- Osteonecrosis of the jaw is seen with both agents; risk is increased in patients who have tooth extractions, poor dental hygiene, or a dental appliance.
- The optimal duration of therapy for either denosumab or zoledronic acid remains uncertain.
- The toxicity profile of denosumab when denosumab is used in patients who have been treated with zoledronic acid remains uncertain.
- Clinical trials are in progress that assess a role for zoledronic acid or denosumab in men beginning androgen deprivation therapy for bone metastases.
### Table 1. TNM Staging System For Prostate Cancer

#### Primary Tumor (T)

**Clinical**

<table>
<thead>
<tr>
<th>T Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically inapparent tumor neither palpable nor visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor incidental histologic finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor incidental histologic finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor identified by needle biopsy (e.g., because of elevated PSA)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor confined within prostate*</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor involves one-half of one lobe or less</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor involves more than one-half of one lobe but not both lobes</td>
</tr>
<tr>
<td>T2c</td>
<td>Tumor involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends through the prostatic capsule **</td>
</tr>
<tr>
<td>T3a</td>
<td>Extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor invades the seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder, levator muscles, and/or pelvic wall.</td>
</tr>
</tbody>
</table>

**Note:** Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

**Note:** Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

**Pathologic (pT)**

<table>
<thead>
<tr>
<th>pT Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2</td>
<td>Organ confined</td>
</tr>
<tr>
<td>pT2a</td>
<td>Unilateral, involving one-half of one side or less</td>
</tr>
<tr>
<td>pT2b</td>
<td>Unilateral, involving more than one-half of one side but not both sides</td>
</tr>
<tr>
<td>pT2c</td>
<td>Bilateral disease</td>
</tr>
<tr>
<td>pT3</td>
<td>Extracapsular extension</td>
</tr>
<tr>
<td>pT3a</td>
<td>Extracapsular extension or microscopic invasion of the bladder neck**</td>
</tr>
<tr>
<td>pT3b</td>
<td>Seminal vesicle invasion</td>
</tr>
<tr>
<td>pT4</td>
<td>Invasion of bladder, rectum</td>
</tr>
</tbody>
</table>

*Note: There is no pathologic T1 classification.

**Note:** Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

#### Regional Lymph Nodes (N)

**Clinical**

<table>
<thead>
<tr>
<th>N Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes were not assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in regional lymph node(s)</td>
</tr>
</tbody>
</table>

**Pathologic**

<table>
<thead>
<tr>
<th>pN Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNX</td>
<td>Regional nodes not sampled</td>
</tr>
<tr>
<td>pN0</td>
<td>No positive regional nodes</td>
</tr>
<tr>
<td>pN1</td>
<td>Metastases in regional nodes(s)</td>
</tr>
</tbody>
</table>

#### Distant Metastasis (M)*

<table>
<thead>
<tr>
<th>M Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Non-regional lymph node(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone(s)</td>
</tr>
<tr>
<td>M1c</td>
<td>Other site(s) with or without bone disease</td>
</tr>
</tbody>
</table>

*Note: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.

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ANATOMIC STAGE/PROGNOSTIC GROUPS *

<table>
<thead>
<tr>
<th>Group</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>PSA</th>
<th>Gleason</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1a-c</td>
<td>N0</td>
<td>M0</td>
<td>PSA &lt; 10</td>
<td>Gleason ≤ 6</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>PSA &lt; 10</td>
<td>Gleason ≤ 6</td>
</tr>
<tr>
<td></td>
<td>T1a-2a</td>
<td>N0</td>
<td>M0</td>
<td>PSA X</td>
<td>Gleason X</td>
</tr>
<tr>
<td>IIA</td>
<td>T1a-c</td>
<td>N0</td>
<td>M0</td>
<td>PSA &lt; 20</td>
<td>Gleason 7</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
<td>PSA &lt; 20</td>
<td>Gleason ≤ 6</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>PSA &lt; 20</td>
<td>Gleason ≤ 7</td>
</tr>
<tr>
<td></td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>PSA X</td>
<td>Gleason X</td>
</tr>
<tr>
<td>IIIB</td>
<td>T2c</td>
<td>N0</td>
<td>M0</td>
<td>Any PSA</td>
<td>Any Gleason</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>PSA ≥ 20</td>
<td>Any Gleason</td>
</tr>
<tr>
<td></td>
<td>T1-2</td>
<td>N0</td>
<td>M0</td>
<td>Any PSA</td>
<td>Gleason ≥ 8</td>
</tr>
<tr>
<td>III</td>
<td>T3a-b</td>
<td>N0</td>
<td>M0</td>
<td>Any PSA</td>
<td>Any Gleason</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>Any PSA</td>
<td>Any Gleason</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td>Any PSA</td>
<td>Any Gleason</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any PSA</td>
<td>Any Gleason</td>
</tr>
</tbody>
</table>

*Note: When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

Histopathologic Grade (G)

Gleason score is recommended because as the grading system of choice, it takes into account the inherent morphologic heterogeneity of prostate cancer, and several studies have clearly established its prognostic value. A primary and a secondary pattern (the range of each is 1–5) are assigned and them summed to yield a total score. Scores of 2–10 are thus theoretically possible. The vast majority of newly diagnosed needle biopsy detected prostate cancers are graded Gleason score 6 or above. (If a single pattern of disease is seen, it should be reported as both grades. For example, if a single focus of Gleason pattern 3 disease is seen, it is reported as Gleason score 3 + 3 = 6.) In a radical prostatectomy, if a tertiary pattern is present, it is commented upon but not reflected in the Gleason score. It is recommended that radical prostatectomy specimens should be processed in an organized fashion where a determination can be made of a dominant nodule or separate tumor nodules. If a dominant nodule/s is present, the Gleason score of this nodule should be separately mentioned as this nodule is often the focus with highest grade and/or stage of disease.

Gleason X
Gleason score cannot be processed
Well differentiated (slight anaplasia)
Gleason ≤ 6
Moderately differentiated (moderate anaplasia)
Gleason 7
Poorly differentiated/undifferentiated (marked anaplasia)
Gleason 8-10

Histopathologic Type

This classification applies to adenocarcinomas and squamous carcinomas, but not to sarcoma or transitional cell carcinoma of the prostate. Adjectives used to describe adenocarcinomas can include mucinous, signet ring cell, ductal, and neuroendocrine including small cell carcinoma. Transitional cell (urothelial) carcinoma of the prostate is classified as a urethral tumor. There should be histologic confirmation of the disease.

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Discussion

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.

Overview

In the late 1980s and early 1990s, the number of newly diagnosed prostate cancers in U.S. men increased dramatically, and prostate cancer surpassed lung cancer as the most common cancer in men. It is generally accepted that these changes resulted from prostate-specific antigen (PSA) screening that detected many early-stage prostate cancers. For example, the percentage of patients with low-risk disease has increased to 45% in 1999-2001 from 30% in 1989-1992 ($P < .0001$). The incidence of prostate cancer increased 2% annually from 1995 to 2001, and has since declined. An estimated 241,740 new cases will be diagnosed in 2012, accounting for 29% of new cancer cases in men in 2012. Fortunately, the age-adjusted death rates from prostate cancer have also declined (-4.1% annually from 1994 to 2001). Researchers estimated prostate cancer to account for 28,170 deaths in 2012. This comparatively low death rate suggests that unless prostate cancer is becoming biologically less aggressive, increased public awareness with earlier detection and treatment has begun to affect mortality from this prevalent cancer. However, early detection and treatment of prostate cancers that do not threaten life expectancy results in unnecessary side effects, which impair quality of life and health care expenses, while decreasing the value of PSA and digital rectal exam as early detection tests (see below).

To properly identify and manage patients with prostate cancer or any other malignancy, physicians must have an in-depth understanding of the natural history and the diagnostic, staging and treatment options. To this end, an NCCN guideline panel of leading experts from the fields of urology, radiation oncology, and medical oncology at member institutions developed guidelines for the treatment of prostate cancer. The panel representing NCCN member institutions reviews and updates the prostate guidelines every year, which are available on the NCCN web site (www.nccn.org). The treatment algorithms and recommendations represent current evidence integrated with expert consensus regarding acceptable approaches to prostate cancer treatment rather than a universally prescribed course of therapy. Individual physicians treating individual men with prostate cancer are expected to use independent judgment in formulating specific treatment decisions.

Estimates of Life Expectancy

As a result of widespread PSA testing, most patients are diagnosed with asymptomatic, clinically localized cancer. The combination of Gleason score, PSA level, and stage can effectively stratify patients into categories associated with different probabilities of achieving a cure. However, in addition to considering the probability of cure, the choice of initial treatment is influenced greatly by estimated life
expectancy, comorbidities, potential therapy side effects, and patient preference. The primary management options for initial therapy for clinically localized prostate cancer include active surveillance, radical prostatectomy or radiotherapy.

Estimates of life expectancy have emerged as a key determinant of treatment decision-making, particularly when considering active surveillance (see below). While it is possible to estimate life expectancy for groups of men, it is more difficult to extrapolate these estimates to an individual patient. Life expectancy can be estimated using the Minnesota Metropolitan Life Insurance Tables or the Social Security Administration Life Insurance Tables. The life expectancy can then be adjusted for individual patients by adding or subtracting 50% based upon whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively. As an example, the Social Security Administration Life Expectancy for a 65 year old American man is 16.05 years. If judged to be in the upper quartile of health, a life expectancy of 24 years is assigned. If judged to be in the lower quartile of health, life expectancy of 8 years is assigned. Thus, treatment recommendations could change dramatically using the NCCN guidelines if a 65 year old man was judged to be in either very poor or excellent health. Life expectancy should be estimated using the Social Security Administration Tables and modified further by a clinician’s assessment of overall health. Examples of 5 year increments of age are reproduced from the NCCN Senior Adult Oncology Guidelines. Other prognostic indices have been researched but are more difficult to employ clinically. For example, Lee and colleagues developed a prognostic index for 4 year mortality based on information that combines both comorbid and functional measures. Twelve independent predictors of mortality were identified, including 2 demographic measures (i.e. age and sex), 6 comorbid conditions (including body mass index), and difficulty with 4 functional variables.

Nomograms and Predictive Models

Optimal treatment of prostate cancer requires assessment of risk: how likely is a given cancer to be confined to the prostate or to spread to the regional lymph nodes? How likely is the cancer to progress or metastasize after treatment? How likely is salvage by adjuvant radiation after an unsuccessful radical prostatectomy? Prostate cancers are best characterized by clinical (TNM) stage determined by digital rectal examination (DRE), Gleason score in the biopsy specimen, and serum PSA level. Imaging studies (ultrasound, MRI) have been investigated intensively but have yet to be accepted as essential adjuncts to staging.

Predicting prognosis is essential for patient decision-making, treatment selection, and adjuvant therapy. These NCCN Guidelines incorporate a risk stratification scheme that uses a minimum of stage, grade, and PSA to assign patients to risk groups. These risk groups are used to select the appropriate options that should be considered for treatment and to predict the probability of biochemical failure (i.e., probability of a rising PSA, which is also termed biochemical recurrence or PSA failure) after definitive local therapy. This risk group stratification has been published widely and validated, and it provides a better basis for treatment recommendations than clinical stage alone.

The Partin tables were the first prediction method to achieve widespread use for counseling men with clinically localized prostate cancer. The tables combine clinical stage, biopsy Gleason grade, and preoperative PSA level to predict pathologic stage, assigned as one of four mutually exclusive groups: (1) organ confined; (2) extracapsular (i.e., extraprostatic) extension; (3) seminal vesicle invasion; or (4) lymph node metastasis. The tables give the probability (95%
confidence intervals) that a patient with a certain clinical stage, Gleason score, and PSA will have a cancer of each pathologic stage.

To quantify risk more accurately, one can devise a nomogram that incorporates the interactive effects of multiple prognostic factors to make accurate predictions about stage and prognosis for the individual patient. A nomogram is any predictive instrument that takes a set of input data (variables) and makes predictions about an outcome. Nomograms predict more accurately for the individual patient than risk groups, because they combine the relevant prognostic variables, regardless of value. With risk group assignment, a cancer could be considered intermediate risk or high risk based on a single adverse prognostic factor. With nomograms, discordant values (e.g., high PSA but low Gleason sum and clinical stage) can be incorporated into a more accurate prediction. With any model, the more clinically relevant information that is used in the calculation of time to PSA failure, the more accurate the result.

Nomograms can be used to inform treatment decision-making for men contemplating active surveillance, radical prostatectomy, neurovascular bundle preservation or omission of pelvic lymph node dissection during radical prostatectomy, brachytherapy or external beam radiation therapy (EBRT). Biochemical progression-free survival can be reassessed post-operatively using age, diagnostic serum PSA, and pathologic grade and stage. Potential success of adjuvant or salvage radiation therapy after unsuccessful radical prostatectomy can be assessed using a nomogram.

None of the current models predict with perfect accuracy, and only some of these models predict metastasis and cancer-specific death. New independent prognostic factors are being developed. Given the competing causes of mortality, many men who sustain PSA failure will not live long enough either to develop clinical evidence of distant metastases or to die from prostate cancer. Those with a short PSA doubling time are at greatest risk of death. Not all PSA failures are clinically relevant; thus, PSA doubling time may be a more useful measure of risk of death. Further refinement of the patient’s risk of recurrent cancer is being investigated currently using molecular markers and other radiologic evaluations of the prostate. However, these approaches remain investigational and are not available currently or validated for routine application. The NCCN guideline panel recommends that NCCN risk categories are used to begin the discussion of options for the treatment of clinically localized prostate cancer and nomograms be used to provide additional and more individualized information.

Active Surveillance

Active surveillance (also referred to as observation, watchful waiting, expectant management or deferred treatment) involves actively monitoring the course of the disease with the expectation to intervene if the cancer progresses. The advantages of active surveillance include (1) avoiding the side effects of definitive therapy that may not be necessary; (2) quality of life and normal activities are retained; (3) small indolent cancers do not receive unnecessary treatment; and (4) decreased initial costs. The disadvantages of active surveillance are (1) chance of missed opportunity for cure; 2) the cancer may progress or metastasize before treatment; (3) treatment of a larger, more aggressive cancer may be more complex with greater side effects; 4) nerve sparing at subsequent prostatectomy may be more difficult, which may reduce the chance of potency preservation after surgery; 5) the increased anxiety of living with an untreated cancer; (6) the requirement for frequent medical examinations and periodic prostate biopsies; (7) the uncertain long-term natural history of untreated
prostate cancer; and (8) the timing and value of periodic imaging studies have not been determined.

The high prevalence of prostate cancer upon autopsy of the prostate, the high frequency of positive prostate biopsies in men with normal digital rectal exams and serum PSA values, the contrast between the incidence and mortality rates of the malignancy, and the need to treat an estimated 37 men with screen-detected prostate cancer or 100 men with low-risk prostate cancer to prevent one death from the disease has fueled the debate about the need to diagnose and treat every man who has prostate cancer. The controversy regarding over-treatment of prostate cancer and the value of prostate cancer early detection has been informed further by publication of the Goteborg study, a subset of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Many believe that this study best approximates proper use of PSA for early detection since it was population-based and involved a 1:1 randomization of 20,000 men who received PSA every 2 years and used thresholds for prostate biopsy of PSA > 3 and > 2.5 since 2005. The follow-up of 14 years is longer than the European study as a whole (9 years) and Prostate, Lung, Colorectal, and Ovarian (PLCO) (11.5 years). Prostate cancer was diagnosed in 12.7% of the screened group compared to 8.2% of the control group. Prostate cancer mortality was 0.5% in the screened group and 0.9% in the control group, which gave a 40% absolute cumulative risk reduction of prostate cancer death (compared to ERSPC 20% and PLCO 0%). Most impressively, 40% of the patients were initially managed by active monitoring and 28% were still on active surveillance at the time these results were analyzed. To prevent a prostate cancer death, 12 men would need to be diagnosed and treated as opposed to the ERSPC as a whole where 37 needed to be treated. Thus, early detection when applied properly should reduce prostate cancer mortality. However, that reduction comes at the expense of over-treatment that may occur in as many as 50% of men treated for PSA-detected prostate cancer.

The best models of prostate cancer detection and progression estimate that 23% to 42% of all U.S. screen-detected cancers are overtreated and that PSA detection was responsible for up to 12.3 years of lead-time bias. The NCCN guideline panel responded in 2010 to these evolving data with careful consideration of which men should be recommended active surveillance – men with very low risk prostate cancer and life expectancy estimated < 20 years or men with low risk prostate cancer and life expectancy estimated < 10 years. However, the NCCN guideline panel recognizes the uncertainty associated with the estimation of chance of competing causes of death, the definition of very low or low risk prostate cancer, the ability to detect disease progression without compromising chance of cure, and the chance and consequences of treatment side effects.

Epstein et al introduced clinical criteria to predict pathologically “insignificant” prostate cancer. According to Epstein et al., insignificant prostate cancer is identified by: clinical stage T1c, biopsy Gleason score ≤ 6, the presence of disease in fewer than 3 biopsy cores, and ≤ 50% prostate cancer involvement in any core, and PSA density < 0.15 ng/mL/g. Despite the usefulness of these criteria, physicians are cautioned against using these as the sole decision maker. Studies have shown that as many as 8% of cancers that qualified as being insignificant using the Epstein criteria were not organ-confined based on postsurgical findings. A new nomogram may be better. Although many variations upon this definition have been proposed (reviewed by Bastian et al), a consensus of the NCCN guideline panel was reached that insignificant prostate cancer, especially when detected early using serum PSA, poses little threat to men with life
expectancy < 20 years. The confidence that Americans with very low risk prostate cancer have a very small risk of prostate cancer death is enhanced by lead time bias introduced by PSA early detection that ranges from an estimated 12.3 years in a 55 year old man to 6 years in a 75 year old man.43

Active surveillance is considered the best option for patients with low-risk cancers or for patients with a short life expectancy. Recently, Lu-Yao and colleagues48 reported that among patients who chose active surveillance, there was up to 74% reduction in disease-specific mortality for patients diagnosed between 1992 and 2002 compared to those diagnosed in earlier periods, when PSA testing was uncommon. The role for active surveillance should increase with the shift towards earlier-stage diagnosis attributed to PSA testing. However, results from randomized or cohort studies comparing this deferral strategy with immediate treatment are mixed, partly due to heterogeneity of the patient populations (reviewed by Sanda and Kaplan49). For example, a cohort of 3,331 participants showed no difference in the rate of metastases or disease-specific death at a mean 7.7 years follow-up,50 while a randomized trial in 695 patients with early disease demonstrated reduced risk of death with radical prostatectomy compared to active surveillance.51, 52

Ultimately, a recommendation for active surveillance must be based on careful individualized weighing of a number of factors: life expectancy, disease characteristics, general health condition, potential side effects of treatment, and patient preference.

Patients and physicians involved in active surveillance must be aware that the PSA is likely to rise and that the tumor may grow with time. Patients should not be under the impression that the tumor will remain stable indefinitely and must be prepared to reevaluate the decision to defer treatment. Trigger points for intervention based on PSA, histologic progression, or clinical progression have been used.53-55 The NCCN guideline panel recommends treatment in most men who demonstrate a Gleason grade of 4 or 5 on repeat biopsy, cancer in a greater number of prostate biopsies or greater extent of prostate biopsies, or if the PSA doubling time is less than 3 years. Whether these trigger points will ultimately be validated or not remains uncertain.

The 2011 NCCN guideline update clarified the content of an active surveillance program. PSA should be measured at least as often as every 6 months, digital rectal exam should be performed at least as often as every 12 months, and a needle biopsy may be repeated as often as every 12 months. Each of the major observation series has used different criteria for reclassification.53, 56-59 Reclassification criteria have been met by 23% of men with a median follow-up of 7 years in the Toronto experience,57 33% of men with a median follow-up of 3 years in the Johns Hopkins experience,59 and 16% of men with a median follow-up of 3.5 years in the UCSF experience56 (Table 1). Uncertainty regarding reclassification criteria and the desire to avoid missing an opportunity for cure have driven several reports in the past year that have dealt with the validity of commonly used reclassification criteria. The Toronto group demonstrated that a PSA trigger point of PSA doubling time < 3 years could not be improved upon by using a PSA threshold of 10 or 20, PSA doubling time calculated in various ways, or PSA velocity > 2 ng/ml/yr.60 The Johns Hopkins group used biopsy-demonstrated reclassification to Gleason pattern 4 or 5 or increased tumor volume on biopsy as their only criteria for reclassification. Of 290 men on an annual prostate biopsy program, 35% demonstrated reclassification at a median follow-up of 2.9 years.61 Unfortunately, neither PSA doubling time (AUC 0.59) nor PSA velocity (AUC 0.61) was associated with prostate biopsy reclassification. Both groups have
concluded that PSA kinetics cannot replace regular prostate biopsy although treatment of most men who demonstrate reclassification on prostate biopsy prevents evaluation of biopsy reclassification as a criterion for treatment or reduction of survival.

The Toronto group published on 5 patients who died of prostate cancer in their experience of more than 450 men. These 3 deaths led to them to revise their criteria for offering men active surveillance since each of these 3 men probably had metastatic disease at the time of entry onto active surveillance. In 450 men followed a median of 6.8 years, overall survival was 78.6% and prostate cancer-specific survival was 92.2%. Of the 30% (n=145) men who progressed, 8% were from increase in Gleason score, 14% were for PSA doubling time < 3 years, 1% were for development of a prostate nodule, and 3% were for anxiety. One hundred and thirty-five of these 145 men were treated; 35 by radical prostatectomy, 90 by radiation therapy with or without androgen deprivation therapy, and 10 with androgen deprivation therapy alone. Follow-up is available for 110 of these men and 5-year biochemical progression-free survival is only 62% for those undergoing radical prostatectomy and 43% for those undergoing radiation. By comparison, among 192 men on active surveillance who underwent delayed treatment at a median of 2 years after diagnosis in the Johns Hopkins experience, 5-year biochemical progression-free survival was 96% for those undergoing surgery and 75% for those undergoing radiation. These experiences contrast with the UCSF experience where 74 men who progressed on active surveillance and underwent radical prostatectomy were compared with 148 men who were matched by clinical parameters. The two groups were similar by pathological Gleason grade, pathological stage, and margin positivity. All men treated by radical prostatectomy after progression on active surveillance had freedom from biochemical progression at median follow-up 37.5 months, compared to 97% of men in the primary radical prostatectomy group at median follow-up 35.5 months.

The panel believes there is an urgent need for further clinical research regarding the criteria for recommending active surveillance, the criteria for reclassification on active surveillance and the schedule for active surveillance especially as it pertains to prostate biopsies, which unfortunately come within an increasing burden. The most recent literature suggests that as many as 7% of men undergoing prostate biopsy will suffer an adverse event, those with urinary tract infection were often fluoroquinolone resistant, and radical prostatectomy may become technically challenging after multiple sets of biopsies especially as it pertains to potency preservation.

**Radiation Therapy**

**External Beam Radiation Therapy**

EBRT is one of the principle treatment options for clinically localized prostate cancer. The NCCN guideline panel consensus was that modern RT and surgical series show similar progression-free survival in low-risk patients treated with radical prostatectomy or RT, although studies of surgical outcomes generally have longer follow-up.

Over the past several decades, RT techniques have evolved to allow higher doses of radiation to be administered safely. For example, standard 2-dimensional planning techniques used until the early 1990s limited total doses to 67-70 Gy due to acute and chronic toxicities. In the 1990s, 3-dimensional (3D) planning techniques were developed that reduced the risk of acute toxicities and hence allowed treatment with higher doses. 3D-CRT uses computer software to integrate CT images of the patients’ internal anatomy in the treatment position, which allows the volume receiving the high radiation dose to "conform" more
exactly to the shape of the prostate. 3D-CRT allows higher cumulative doses to be delivered with lower risk of late effects.\textsuperscript{25, 64-66} The second generation 3D technique, intensity-modulated radiation therapy (IMRT), significantly reduces the risk of gastrointestinal toxicities compared to 3D-CRT.\textsuperscript{67, 68} Daily prostate localization using image-guided radiation therapy (IGRT) is essential for target margin reduction and treatment accuracy. Imaging techniques, including ultrasound, implanted fiducials, electromagnetic targeting and tracking, or endorectal balloon, can be helpful in improving cure rates and minimizing complications.

These techniques have permitted safer dose escalation, and results of randomized trials suggested that dose escalation is associated with improved biochemical outcomes.\textsuperscript{69-72} Kuban et al\textsuperscript{72} recently published an updated analysis on their dose-escalation trial of 301 patients with stage T1b to T3 prostate cancer. With a median follow-up reaching 8.7 years, the authors reported superior freedom from biochemical or clinical failure in the group randomized to 78 Gy compared to 70 Gy (78\% vs 59\%, \( P = 0.004 \)). The difference was even greater among patients with initial PSA > 10 ng/mL (78\% vs 39\%, \( P = 0.001 \)). In light of these findings, the conventional 70 Gy is no longer considered adequate. A dose of 75.6-79.2 Gy in conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Intermediate-risk and high-risk patients should receive doses up to 81.0 Gy.\textsuperscript{67, 73, 74}

One of the key aspects of RT planning includes identifying which patients will benefit from inclusion of pelvic lymph node irradiation and ADT. Patients with high-risk cancers are candidates for pelvic lymph node irradiation (78-80+ Gy) and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2-3 years or 4-6 months if they have a single high risk adverse factor. Patients with intermediate risk cancer may be considered for pelvic lymph node irradiation and 4-6 months of neoadjuvant/concomitant/adjuvant ADT. Patients with low risk cancers should not receive either pelvic lymph node radiation or ADT. Evidence from randomized trials has emerged that supports the use of adjuvant/salvage RT after radical prostatectomy in men with adverse laboratory or pathologic features or detectable PSA (See Section “Adjuvant therapy for high/very high risk of recurrence”).

EBRT for prostate cancer shows several distinct advantages over surgical therapy. RT avoids complications associated with surgery, such as bleeding and transfusion-related effects as well as risks associated with anesthesia, such as myocardial infarction and pulmonary embolus. 3D-conformal and IMRT techniques are available widely in community practice and are possible for patients over a wide range of ages. This therapy includes a very low risk of urinary incontinence and stricture as well as a good chance of short-term preservation of erectile function.\textsuperscript{75} Combined with ADT, radiation offers a survival benefit in locally advanced cancer, because treatments may eradicate extensions of tumor beyond the margins of the prostate.\textsuperscript{76} However, the addition of ADT increases the risk for erectile dysfunction.\textsuperscript{77}

The disadvantages of EBRT include a treatment course of 8 to 9 weeks. Up to 50\% of patients have some temporary bladder or bowel symptoms during treatment, there is a low but definite risk of protracted rectal symptoms from radiation proctitis, and the risk of erectile dysfunction increases over time.\textsuperscript{75, 77} In addition, if the cancer recurs, salvage surgery is associated with a higher risk of complications than primary surgical therapy.\textsuperscript{78} Contraindications to RT include prior pelvic irradiation, active inflammatory disease of the rectum or a permanent indwelling Foley catheter. Relative contraindications include very low capacity bladder, chronic moderate or severe diarrhea, bladder outlet
obstruction requiring a suprapubic catheter, and inactive ulcerative colitis.

Proton Therapy
Proton beams can be used as an alternative radiation source. Theoretically, protons may reach deeply-located tumors with less damage to surrounding tissues. However, proton therapy is not recommended for routine use at this time, since clinical trials have not yet yielded data that demonstrates superiority to, or equivalence of, proton beam and conventional external beam for treatment of prostate cancer.

Stereotactic Body Radiotherapy
The relatively slow proliferation rate of prostate cancer is reflected in a low α/β ratio, most commonly reported between 1 and 4. These values are similar to that for the rectal mucosa. Since the α/β ratio for prostate cancer is similar to or lower than the surrounding tissues responsible for most of the toxicity reported with radiation therapy, appropriately designed radiation treatment fields and schedules using hypofractionated regimens should result in similar cancer control rates without an increased risk of late toxicity. Stereotactic body radiotherapy (SBRT) delivers highly conformal, high dose radiation in 5 or fewer treatment fractions, that is possible to do safely only with precise delivery. Single institution series with median follow-up as long as 5 years report that biochemical progression-free survival is 90-100% and early toxicity (bladder, rectal, and quality of life) is similar to other standard radiation techniques. Longer follow-up and prospective multi-institutional data are required to evaluate longer term results especially since late toxicity theoretically could be worse in hypofractionated regimens compared to conventional fractionation (1.8 to 2.0 Gy per fraction).

Brachytherapy
Brachytherapy involves placing radioactive sources into the prostate tissue. Most centers use permanent implants, where the sources are implanted into the prostate and gradually lose their radioactivity. Because of the short range of the irradiation emitted from these low-energy sources, adequate dose levels can be delivered to the cancer within the prostate, whereas excessive irradiation of the bladder and rectum can be avoided. Very high doses are not possible with brachytherapy, because the radiation is delivered at a much slower dose rate than with EBRT, which reduces biological effectiveness. Current brachytherapy techniques attempt to improve the radioactive seed placement and radiation dose distribution. Prostate brachytherapy as monotherapy has become a popular treatment option for early, clinically organ-confined prostate cancer (cT1c–T2a, Gleason grade 2-6, PSA < 10 ng/mL).

The advantage of brachytherapy is that the treatment is completed in 1 day with little time lost from normal activities. In appropriate patients, the cancer-control rates appear comparable to surgery (over 90%) for low-risk tumors with medium-term follow up. In addition, the risk of incontinence is minimal in patients without a previous transurethral resection of the prostate (TURP), and erectile function is preserved in the short term. Disadvantages of brachytherapy include the requirement for general anesthesia and the risk of acute urinary retention. Frequently, irritative voiding symptoms may persist for as long as 1 year after implantation. The risk of incontinence is greater after TURP because of acute retention and bladder neck contractures, and many patients develop progressive erectile dysfunction over several years. IMRT causes less acute and late genitourinary toxicity and similar freedom from biochemical failure compared with an iodine-125 or palladium-103 permanent seed implant.
Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers, brachytherapy may be combined with EBRT (45 Gy) with or without neoadjuvant ADT, but the complication rate increases.\textsuperscript{89, 90} Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy; however, with the addition of EBRT and ADT, brachytherapy may be effective in selected patients. D'Amico and colleagues studied a cohort of 1,342 patients with PSA over 20 ng/mL and clinical T3/T4 and/or Gleason score 8-10 disease.\textsuperscript{91} Addition of either EBRT or ADT to brachytherapy did not confer an advantage over brachytherapy alone. But the use of all three reduced prostate cancer-specific mortality compared to brachytherapy alone (adjusted HR = 0.32; 95% CI, 0.14-0.73). Sathya et al\textsuperscript{92} randomized 104 patients with locally advanced tumor to brachytherapy plus EBRT or EBRT alone. At a median follow-up of 8.2 years, the combination arm had significantly lower biochemical failure rates (29% vs 61%; HR = 0.42; P = 0.0024) and postradiation biopsy positivity (24% vs 51%; OR = 0.30; P = 0.015). Overall survival was similar.

By combining EBRT with high dose rate (HDR) brachytherapy, one can safely escalate radiation doses in patients with intermediate or high risk prostate cancer.\textsuperscript{93-96} Two groups have observed a lower risk of urinary frequency, urgency, and rectal pain with HDR brachytherapy compared with low dose rate (LDR) brachytherapy (permanent seed implant).\textsuperscript{97, 98} Moreover, Vargas et al\textsuperscript{99} reported that HDR brachytherapy results in a lower risk of erectile dysfunction than LDR brachytherapy.

Patients with very large or very small prostates, symptoms of bladder outlet obstruction (high International Prostate Symptom Score), or a previous TURP are not ideal candidates for brachytherapy. For these patients, implantation may be more difficult and there is an increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size. Post-implant dosimetry should be performed to document the quality of the implant.\textsuperscript{100} The recommended prescribed doses for monotherapy are 145 Gy for \textsuperscript{125}Iodine and 125 Gy for \textsuperscript{103}Palladium. After 40 to 50 Gy EBRT, the corresponding boost doses are 110 and 100 Gy, respectively.

**Palliative Radiation**

Radiation is an effective means of palliating bone metastases from prostate cancer. Recent studies have confirmed the common practice in Canada and Europe of managing prostate cancer with bone metastases with a short course of radiation. A short course of 8 Gy x 1 is as effective as and less costly than 30 Gy in 10 fractions.\textsuperscript{101} In a randomized trial of 898 patients with bone metastases, grade 2-4 acute toxicity was observed less often in the 8-Gy arm (10%) than the 30-Gy arm (17%) (P=0.002); however, the retreatment rate was higher in the 8-Gy group (18%) than the 30-Gy group (9%) (P<0.001).\textsuperscript{102} Most patients should be managed with a single fraction of 8 Gy for non-vertebral metastases based on therapeutic guidelines from the American College of Radiology.\textsuperscript{103}

Radiopharmaceuticals are an effective and appropriate option for patients with wide-spread metastatic disease, particularly if they are no longer candidates for effective chemotherapy.\textsuperscript{103} Since many patients have multi-focal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Radiopharmaceuticals developed for the treatment of painful bone metastases most commonly used for prostate cancer include Strontium-89 (\textsuperscript{89}Sr) and Samarium-153 (\textsuperscript{153}Sm).\textsuperscript{104}
Surgery

Radical Prostatectomy

Radical prostatectomy is appropriate therapy for any patient whose tumor is clinically confined to the prostate. However, because of potential perioperative morbidity, radical prostatectomy should be reserved for patients whose life expectancy is 10 years or more. This recommendation is consistent with data showing that fewer than 10% of low-grade patients with prostate cancer experience a cancer-specific death after 20 years of follow up. Stephenson and colleagues reported a low 15-year prostate cancer-specific mortality of 12% in patients who underwent radical prostatectomy (5% for low risk patients), although it is unclear whether the favorable prognosis is due to the effectiveness of the procedure or the low lethality of cancers detected in the PSA era.

Long-term cancer control has been achieved in most patients with both the retropubic and the perineal approaches; high volume surgeons in high volume centers generally provide superior outcomes. Laparoscopic and robot-assisted radical prostatectomy are used commonly and are considered comparable to conventional approaches in experienced hands. In a cohort study using US Surveillance, Epidemiology, and End Results (SEER) Medicare-linked data on 8837 patients, minimally invasive surgery compared to open surgery was associated with shorter length of hospital stay, less need of blood transfusions, and fewer surgical complications, but rates of incontinence and erectile dysfunction were higher. Oncologic outcome assessed by use of additional therapies was similar. A meta-analysis on 19 observational studies (n=3893) reported less blood loss and lower transfusion rates with minimally invasive techniques than with open surgery. Risk of positive surgical margins was the same.

Return of urinary continence after surgery may be improved by preserving the urethra beyond the prostatic apex and by avoiding damage to the distal sphincter mechanism. Anastomotic strictures that increase the risk of long-term incontinence are less frequent with modern surgical techniques. Recovery of erectile function is related directly to the degree of preservation of the cavernous nerves, age at surgery, and preoperative erectile function. Improvement in urinary function was also seen with nerve-sparing techniques. For patients undergoing wide resection of the neurovascular bundles, replacement of resected nerves with nerve grafts does not appear effective.

Pelvic Lymph Node Dissection (PLND)

The decision to perform PLND should be guided by the probability of nodal metastases. The NCCN guideline panel chose 2% as the cutoff for PLND since this avoids 47.7% of PLNDs at a cost of missing 12.1% of positive lymph nodes.

PLND should be performed using an extended technique. An extended PLND includes removal of all node baring tissue from an area bounded by the external iliac vein anteriorly, the pelvic side wall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally. Removal of more lymph nodes has been associated with an increased likelihood of finding lymph node metastases, thereby providing more complete staging. A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to the elimination of microscopic metastases. PLND can be performed safely laparoscopically, robotically, or open, and complication rates should be similar for the three approaches.
Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) is commonly used in the treatment of prostate cancer. ADT can be accomplished using bilateral orchiectomy (surgical castration) or a luteinizing-hormone releasing hormone (LHRH, also known as gonadotropin-releasing hormone or GnRH) agonist or antagonist (medical castration), which are equally effective. In patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone, antiandrogen therapy should precede or be co-administered with LHRH agonist and be continued in combination for at least 7 days.\textsuperscript{122, 123}

The LHRH antagonists are a newer class of ADT available to prostate cancer patients. Unlike LHRH agonists that initially stimulate LHRH receptors before leading to hypogonadism, LHRH antagonists rapidly and directly inhibit the release of androgens. Therefore, no initial flare is associated with these agents and no co-administration of antiandrogen is necessary. Degarelix is the first LHRH antagonist approved by the Food and Drug Administration (FDA) in 2008 for treatment of men with advanced prostate cancer. The pivotal trial was a randomized open-label study of 610 patients.\textsuperscript{124} Three regimens were assessed: 240 mg degarelix for one month followed by monthly maintenance doses of 80 mg or 160 mg, or monthly 7.5 mg leuprolide. Degarelix and leuprolide achieved the same level of testosterone suppression; 96% of patients receiving degarelix had testosterone $\leq 50$ ng/dL within 3 days. However, due to its site of injection (subcutaneous), degarelix was associated with significantly more injection-site reactions than leuprolide (40% vs $< 1\%$).

Medical or surgical castration combined with an antiandrogen is known as combined androgen blockade (CAB). While no prospective randomized studies have demonstrated a survival advantage with CAB over the serial use of an LHRH agonist and an anti-androgen, meta-analysis data suggest that non-cyproterone acetate anti-androgens such as bicalutamide may provide an incremental relative improvement in overall survival by 5-20% over LHRH agonist monotherapy.\textsuperscript{125, 126} Triple androgen blockage (finasteride or dutasteride, antiandrogen, plus medical or surgical castration) provides no proven benefit over castration alone. Antiandrogen monotherapy appears to be less effective than medical or surgical castration and is not routinely used as primary ADT. The side effects are different than ADT but antiandrogen monotherapy is considered less tolerable overall.

ADT is primarily administered (neoadjuvant/concomitant/adjuvant) in combination with radiation in localized or locally advanced prostate cancers and as primary systemic therapy in advanced disease. In the community, ADT has also been used commonly as primary therapy for early stage, low risk disease especially in the elderly. This practice has been challenged by a large cohort study of 19,271 elderly men with T1-T2 tumors.\textsuperscript{127} No survival benefit was found in patients receiving ADT compared to observation alone. Placing elderly patients with early prostate cancer on ADT should not be routine practice.

While ADT is routinely added to primary radiation for localized and locally advanced disease (see “NCCN Recommendations” for discussion under different risk categories), neoadjuvant or adjuvant ADT generally confers no added benefit in men who have undergone radical prostatectomy.\textsuperscript{128} The role of adjuvant ADT after surgery is restricted to cases with positive pelvic lymph nodes. Studies in this area reveal mixed findings. Messing and colleagues randomly assigned patients to immediate ADT or observation who were found to have positive lymph nodes at the time of radical prostatectomy.\textsuperscript{129} At a median follow-up of 11.9 years, those receiving immediate ADT had a significant improvement in overall survival (HR = 1.84; 95% CI, 1.01-
The results of this trial have been called into question. A meta-analysis resulted in a recommendation against ADT for pathologic lymph node metastatic prostate cancer in the ASCO guidelines.\textsuperscript{130} A cohort analysis of 731 men with positive nodes failed to demonstrate a survival benefit of ADT initiated within 4 months of radical prostatectomy compared to observation.\textsuperscript{131}

Antiandrogen monotherapy after completion of primary treatment has also been investigated as an adjuvant therapy in patients with localized or locally advanced prostate cancer. The Early Prostate Cancer (EPC) was the largest prostate cancer trial ever undertaken and evaluated daily bicalutamide as adjuvant therapy in 8,113 patients with prostate cancer who were managed with watchful waiting, radiotherapy or radical prostatectomy.\textsuperscript{132} At a median follow up of 7.4 years, patients with localized disease did not appear to derive clinical benefit from added bicalutamide. However, adding bicalutamide to standard care improved progression-free survival in patients with locally advanced prostate cancer, irrespective of primary therapy.

The results of the North American component of this trial have been reported separately.\textsuperscript{133} In this subset, all patients had undergone either prostatectomy or radiotherapy; patients with positive pelvic nodes were not included. Patients were randomized to receive either adjuvant 150 mg daily bicalutamide or placebo for 2 years. Bicalutamide significantly increased the time to PSA progression but not survival. The authors concluded that the data does not support a benefit of adjuvant bicalutamide in patients with early prostate cancer. The authors also note that these results were not consistent with the results reported for the trial as a whole.

Patients with a rising PSA level and with no symptomatic or clinical evidence of cancer following definitive treatment present a therapeutic dilemma regarding the role of ADT. Some of these patients will ultimately die of their cancer. Timing of ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient and physician anxiety, and the short-term and long-term side effects of ADT. Although early, sustained ADT is acceptable, an alternative is close observation until progression of cancer, at which time appropriate therapeutic options may be considered. Earlier ADT may be better than delayed therapy, although the definitions of early and late (i.e., what level of PSA) remain controversial. Because the benefit of ADT is unclear,\textsuperscript{130} treatment should be individualized until definitive studies are completed. Patients with an elevated PSA and/or a shorter PSA doubling time (rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.

Intermittent ADT is a widely used approach in advanced disease to reduce side effects. Two large intergroup studies are comparing the efficacy of intermittent and continuous ADT (Southwest Oncology Group [SWOG] 9346 and National Cancer Institute [NCI] Canada PR7).

**Abiraterone Acetate**

In April 2011, the FDA approved the androgen synthesis inhibitor, abiraterone acetate, in combination with low dose prednisone for the treatment of men with metastatic castration-recurrent prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel. Autocrine and/or paracrine androgen synthesis is known to be enhanced in the tumor microenvironment during ADT in many men, and abiraterone acetate inhibits a key enzyme, cytochrome P450 c17 (lyase, hydroxylase), that metabolizes testosterone/dihydrotestosterone from weak adrenal androgens.\textsuperscript{134}

FDA approval was based on the results of a phase III, randomized, placebo-controlled trial in men with metastatic CRPC previously treated
with docetaxel-containing regimens.\textsuperscript{135} Patients were randomized to receive either abiraterone acetate 1000 mg orally once daily (N=797) or placebo once daily (N=398), and both arms received daily prednisone. The study was unblinded after a pre-specified interim demonstrated a statistically significant improvement in overall survival in patients receiving abiraterone acetate. The median survival was 14.8 vs. 10.9 months in the abiraterone and placebo arm, respectively (HR 0.646; 95% CI, 0.54-0.77; P < 0.0001).\textsuperscript{135} Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone acetate.

The most common adverse reactions seen with abiraterone acetate/prednisone (>5%) were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia or upper respiratory tract infection. The most common adverse drug reactions resulting in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase, urosepsis, or cardiac failure (each in < 1% of patients taking abiraterone). The most common electrolyte imbalances in patients receiving abiraterone were hypokalemia (28%) and hypophosphatemia (24%).

Adverse Effects of Androgen Deprivation Therapy
ADT has a variety of adverse effects including hot flashes, hot flushes, vasomotor instability, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease. In general, the side effects of continuous ADT increase with the duration of treatment. Patients and their medical providers should be advised about these risks prior to treatment.

Bone Health during Androgen Deprivation Therapy
Osteoporosis is an important but under-appreciated problem in men worldwide.\textsuperscript{136} In the United States, 2 million men have osteoporosis and another 12 million are at risk for the disease. Hypogonadism, chronic glucocorticoid therapy, and alcohol abuse are the major causes of acquired osteoporosis in men.

ADT is associated with greater risk for clinical fractures. In large population-based studies, for example, ADT was associated with a 21-54% relative increase in fracture risk.\textsuperscript{137-139} Longer treatment duration conferred greater fracture risk. Age and comorbidity were also associated with higher fracture incidence. ADT increases bone turnover and decrease bone mineral density,\textsuperscript{140-143} a surrogate for fracture risk. Bone mineral density of the hip and spine decreases by approximately 2-3% per year during initial therapy. Most studies have reported that bone mineral density continues to decline steadily during long-term therapy. ADT significantly decreases muscle mass,\textsuperscript{144} and treatment-related sarcopenia appears to contribute to frailty and increased risk of falls in older men.

Screening and treatment for osteoporosis are recommended according to guidelines for the general population from the National Osteoporosis Foundation.\textsuperscript{145} The National Osteoporosis Foundation guidelines include recommendations for (1) supplemental calcium (1,200 mg daily) and vitamin D3 (800-1,000 IU daily) for all men over age 50 years, and (2) additional treatment for men when the 10-year probability of hip fracture is \(\geq 3\%\) or the 10-year probability of a major osteoporosis-related fracture is \(\geq 20\%\). Fracture risk can be assessed using the algorithm FRAX\textsuperscript{®}, recently released by the World Health Organisation.\textsuperscript{146} ADT should be considered “secondary osteoporosis” using the FRAX\textsuperscript{®} algorithm.
Several small randomized controlled trials have demonstrated that bisphosphonates increase bone mineral density, a surrogate for fracture risk, during ADT. In a 12-month multicenter placebo-controlled study of 106 men with prostate cancer, intravenous zoledronic acid every 3 months increased bone mineral density of the hip and spine by a difference of 3.9% and 7.8%, respectively.147 Similar results have been reported with annual zoledronic acid.148 In a randomized, controlled trial of 112 men with prostate cancer, alendronate increased bone mineral density of the hip and spine by 2.3% and 5.1% after 12 months.149 In 2011, the FDA approved denosumab, a novel human monoclonal antibody targeting the receptor activator of NF-κB ligand (RANKL), as a treatment to prevent bone loss and fractures during ADT. Approval was based on a phase III study that randomized 1,468 non-metastatic prostate cancer patients undergoing ADT to either biannual denosumab or placebo. At 24 months, denosumab increased bone mineral density by 6.7% and reduced fractures (1.5% vs. 3.9%) compared to placebo.150 Denosumab also was approved for prevention of skeletal-related events in patients with bone metastasis (see “Chemotherapy and Immunotherapy” section).

Currently, treatment with denosumab (60 mg every 6 months), zoledronic acid (5 mg IV annually), or alendronate (70 mg PO weekly) is recommended when the absolute fracture risk warrants drug therapy.

**Diabetes and Cardiovascular Disease**

In a landmark population-based study, ADT was associated with higher incidence of diabetes and cardiovascular disease.151 After controlling for other variables, including age and comorbidity, ADT with a GnRH agonist was associated with a greater risk for new diabetes (HR 1.44; P < 0.001), coronary artery disease (HR 1.16; P < 0.001), and myocardial infarction (HR 1.11; P = 0.03). Studies that have evaluated the potential relationship between ADT and cardiovascular mortality produced mixed results.151-158

Several mechanisms may contribute to a greater risk for diabetes and cardiovascular disease during ADT. ADT increases fat mass and decreases lean body mass.144, 159, 160 ADT with a GnRH agonist increases fasting plasma insulin levels161, 162 and decreases insulin sensitivity.163 ADT also increases serum levels of cholesterol and triglycerides.161, 164

Cardiovascular disease and diabetes are leading causes of morbidity and mortality in the general population. Based on the observed adverse metabolic effects of ADT and the association between ADT and higher incidence of diabetes and cardiovascular disease, screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended for men receiving ADT. Whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in men receiving ADT should differ from those of the general population remains uncertain.

**Chemotherapy and Immunotherapy**

Recent research has expanded the therapeutic options for patients with metastatic CRPC depending on the presence or absence of symptoms. Currently, four systemic agents have demonstrated improvements in overall survival in this setting: docetaxel, sipuleucel-T, cabazitaxel, and abiraterone acetate. Abiraterone acetate has been discussed under the section “Androgen Deprivation Therapy”.

**Docetaxel**

Two randomized phase III studies have evaluated docetaxel-based regimens in symptomatic or rapidly progressive disease (TAX 327 and SWOG 9916).165-167 TAX 327 compared docetaxel (every three weeks...
or weekly) plus prednisone to mitoxantrone plus prednisone in 1,006 men. Every 3-week docetaxel resulted in higher median overall survival than mitoxantrone (18.9 vs. 16.5 months; \( P = .009 \)). This survival benefit was maintained at extended follow-up. The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared to mitoxantrone plus prednisone. Docetaxel is FDA-approved for metastatic CRPC.

**Sipuleucel-T**

In April 2010, sipuleucel-T became the first in a new class of cancer immunotherapeutic agents to be approved by the Food and Drug Administration (FDA). This autologous cancer “vaccine” involves collection of the white blood cell fraction containing antigen-presenting cells from each patient, exposure of the cells to the prostatic acid phosphatase - granulocyte macrophage colony-stimulating factor (PAP-GM-CSF recombinant fusion protein), and subsequent reinfusion of the cells into the patient. The pivotal study was a phase III, multi-center, randomized, double-blind trial (D9902B). Five hundred and twelve patients with minimally symptomatic or asymptomatic metastatic CRPC were randomized 2:1 to receive sipuleucel-T or placebo. Median survival in the vaccine arm was 25.8 months compared to 21.7 months in the control arm. Sipuleucel-T treatment resulted in a 22% reduction in mortality risk (HR = 0.78; 95% CI, 0.61-0.98; \( P = 0.03 \)). Common complications included mild to moderate chills (54.1%), pyrexia (29.3%) and headache (16.0%), which were mostly transient.

**Cabazitaxel**

In June 2010, the FDA approved the semi-synthetic taxane derivative cabazitaxel for men with metastatic CRPC previously treated with a docetaxel-containing regimen based on results of an international randomized phase III trial. In the study, 755 men with progressive metastatic CRPC were randomized to receive cabazitaxel 25 mg/m\(^2\) or mitoxantrone 12 mg/m\(^2\), each with daily prednisone. A 2.4 month improvement in overall survival was demonstrated with cabazitaxel compared to mitoxantrone (HR 0.72, \( P <0.0001 \)). The improvement in survival was balanced against a higher toxic death rate with cabazitaxel (4.9% vs. 1.9%), which was due, in large part, to differences in rates of sepsis and renal failure. Febrile neutropenia was observed in 7.5% of cabazitaxel-treated men vs. 1.3% of mitoxantrone-treated men. The incidences of severe diarrhea (6%), fatigue (5%), nausea/vomiting (2%), anemia (11%), and thrombocytopenia (4%) also were higher in cabazitaxel-treated men, which indicated the need for vigilance and treatment or prophylaxis in this setting to prevent febrile neutropenia.

**Agents Related to Bone Health in CRPC**

Zoledronic acid is an intravenous bisphosphonate. In a multicenter study, 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases randomized to intravenous zoledronic acid every 3 weeks or placebo. At 15 months, fewer men in the zoledronic acid 4 mg group than men in the placebo group had SREs (33% vs. 44%; \( P = .02 \)), which met the primary endpoint of the study. An update at 24 months also revealed an increase in the median time to first skeletal-related event (488 days vs. 321 days; \( P = .01 \)). No significant differences were found in overall survival. Other bisphosphonates are not known to be effective for the prevention of disease-related skeletal complications.

Denosumab is a subcutaneously administered fully human monoclonal antibody that binds to and inhibits RANK ligand, thereby blunting osteoclast function and delaying generalized bone resorption and local bone destruction. Denosumab was compared to zoledronic acid in a randomized, double-blind placebo-controlled study in men with CRPC. The absolute incidence of SREs was similar in the two
groups, however the median time to first SRE was delayed by 3.6 months by denosumab compared to zoledronic acid (20.7 vs. 17.1 months, \( P = .0002 \) for non-inferiority, \( P = .008 \) for superiority). The rates of important SREs with denosumab was similar to zoledronic acid and included spinal cord compression (3% vs. 4%), need for radiation (19% vs. 21%), and pathological fracture (14% vs. 15%).

Treatment-related toxicities reported for zoledronic acid and denosumab were similar and included hypocalcemia (more common with denosumab 13% vs. 6%), arthralgias, and osteonecrosis of the jaw (ONJ, 1%-2% incidence). Most, but not all, patients who develop ONJ have preexisting dental problems.\(^{173}\)

**NCCN Recommendations**

**Initial Prostate Cancer Diagnosis**

Initial suspicion of prostate cancer is based on an abnormal digital rectal examination (DRE) or an elevated PSA level. A PSA value of 4.0 ng/mL or less is considered normal; however, 15% of men with this “normal” PSA will have prostate cancer and 2% will have high-grade cancer. In fact, there is no PSA level below which cancer has not been detected; a few men with PSA values of 0.5 ng/mL or less have had high-grade prostate cancer on diagnostic biopsies.\(^{32}\) A separate NCCN guideline panel has written additional guidelines for prostate cancer early detection (see NCCN Prostate Cancer Early Detection Guidelines). Definitive diagnosis requires biopsies of the prostate, usually performed by the urologist using a needle under transrectal ultrasound guidance. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Clinical staging is based on the TNM 2009 classification from the AJCC (American Joint Committee on Cancer) Staging Manual, 7th edition.\(^{174}\) However, NCCN treatment recommendations are based on risk stratification (see below) rather than AJCC prognostic grouping. The goals of NCCN treatment guidelines are to optimize cancer survival while minimizing treatment-related morbidity.

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The NCCN guideline panel is in favor of pathology synoptic reports from the College of American Pathologists (CAP).\(^{175}\)

On January 1, 2004, the Commission on Cancer (COC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, pathologists should familiarize themselves with these documents. The CAP protocols comply with the COC requirements.

**Initial Clinical Assessment and Staging Evaluation**

Patients are stratified at diagnosis for initial treatment recommendations based on anticipated life expectancy of the individual patient and on whether they are symptomatic from the cancer.

For patients with a life expectancy of less than 5 years and without clinical symptoms, further workup or treatment may be delayed until symptoms develop. If high-risk factors (bulky T3-T4 cancers or Gleason score 8-10) for developing hydronephrosis or metastases are present, ADT or radiation therapy (RT) may be considered. Patients with advanced cancer may be candidates for observation if the risks and complications of therapy are judged to be greater than the benefit in terms of prolonged life or improved quality of life.
For symptomatic patients and/or those with a life expectancy of greater than 5 years, a bone scan is appropriate for patients with any of the following: 1) T1 disease with PSA over 20 ng/mL or T2 disease with PSA over 10 ng/mL; 2) a Gleason score of 8 or higher; 3) T3 to T4 tumors or symptomatic disease. Pelvic computed tomography (CT) or magnetic resonance imaging (MRI) scanning is recommended if there is T3 or T4 disease, or T1 or T2 disease and a nomogram indicates that there is greater than 20% chance of lymph node involvement, although staging studies may not be cost effective until the chance of lymph node positivity reaches 45%. Biopsy should be considered for further evaluation of suspicious nodal findings. For all other patients, no additional imaging is required for staging.

Following the staging work up, patients are categorized according to their recurrence risk into those with clinically localized disease at low, intermediate and high risk of recurrence, or those with locally advanced at very high risk of recurrence, or those with metastatic disease.

**Low Risk of Recurrence**

As defined by the NCCN guidelines, patients with low risk for biochemical recurrence include those with tumors stage T1 to T2a, low Gleason score (≤ 6), and serum PSA level below 10 ng/mL. Although 40% of men older than 50 years of age harbor prostate cancer, only 1 in 4 present clinically, and only 1 in 14 will die of a prostate cancer-specific death. Therefore, active surveillance is recommended for men with low-risk prostate cancer and life expectancy less than 10 years. Evidence for this approach is supported by data showing that the 5 to 10-year cancer-specific mortality is very low for most prostate cancers except those that are poorly differentiated.

If the patient’s life expectancy is 10 years or more, the treatment recommendations also include radical prostatectomy with or without a pelvic lymph node dissection if the predicted probability of pelvic lymph node involvement is 2% or greater. A study by Johansson and colleagues assessed the long-term natural history of untreated, early-stage prostate cancer in 223 patients during 21 years of follow-up. They found that most prostate cancers diagnosed at an early stage have an indolent course; however, local tumor progression and aggressive metastatic disease may develop in the long term. The mortality rate was significantly higher after 15 years of follow-up when compared with the first 5 years. Their findings support early radical prostatectomy, especially among patients with an estimated life expectancy exceeding 15 years. Radiation therapy using either 3D-CRT/IMRT with daily IGRT or brachytherapy is another option. Surgery, EBRT and brachytherapy carry different side effects profile that will likely influence decision-making. An analysis of 475 men treated for localized disease revealed higher rates of incontinence and lower likelihood of regaining baseline sexual function, but lower rates of bowel dysfunction, after prostatectomy than after radiation.

ADT as a primary treatment for localized prostate cancer does not improve survival and is not recommended by the NCCN guideline panel.

Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that achieves damage to tumor tissue through local freezing. Based on different definitions of biochemical failure, the reported 5-year biochemical disease-free rate following cryotherapy ranged from 65% to 92% in low-risk patients. However, this technique is not recommended as primary therapy due to lack of data from long-term studies for comparison with radiation and radical prostatectomy.
Very Low Risk of Recurrence

The NCCN guideline panel remains concerned about the problems of over-treatment related to the increased frequency of diagnosis of prostate cancer from widespread use of PSA for early detection or screening (see NCCN Prostate Cancer Early Detection Guidelines). Given the potential side effects of definitive therapy, men whose prostate cancers meet the criteria for very low risk and have an estimated life expectancy < 20 years should undergo active surveillance. Incorporation of a modification of the Epstein criteria in patient assessment is recommended to help recognize these clinically insignificant tumors for which surveillance is preferable. This guideline is a category 2B recommendation, which reflects the ongoing debate on the balance of risks and benefits of an active surveillance strategy and the lack of high level evidence that will result eventually from ongoing clinical trials. For patients who meet the very low risk criteria but who have a life expectancy of 20 years or above, the panel agreed that active surveillance, radiotherapy, or radical prostatectomy are all viable options.

Panelists also emphasized the importance in differentiating patients under active surveillance for different reasons. Men of older age or serious comorbidity will likely die of other causes. Since the prostate cancer will never be treated for cure, observation for as long as possible is a reasonable option based on physician’s discretion. Contrastingly, the goal of active surveillance for younger men with seeming indolent cancer is to defer treatment and their potential side effects. Because these patients have a long life expectancy, they should be followed closely and treatment should start promptly should the cancer progress so as not to miss the chance for cure.

Intermediate Risk of Recurrence

As defined by the NCCN guidelines, the intermediate-risk category includes patients with any T2b to T2c cancer, Gleason score of 7, or PSA value of 10 to 20 ng/mL. Patients with multiple adverse factors may be shifted into the high-risk category.

For these patients with a life expectancy of less than 10 years, active surveillance remains a reasonable option. Johansson and colleagues observed that only 13% of men developed metastases 15 years after diagnosis of T0-T2 disease and only 11% had died from prostate cancer. RT is the alternative option. EBRT (3D-CRT/IMRT with daily IGRT with or without brachytherapy) may include neoadjuvant/concomitant/adjuvant ADT. ADT should be given as short term therapy for 4 to 6 months.

Treatment options for patients with an expected survival of 10 years or more include RT and radical prostatectomy. Radical prostatectomy should include a pelvic lymph node dissection if the predicted probability of lymph node metastasis is 2% or greater. Radical prostatectomy was compared to watchful waiting in a randomized trial of 695 patients with early stage prostate cancer (mostly T2). With a median follow up of 11 years, those assigned to the radical prostatectomy group had significant improvements in disease specific mortality, overall mortality and risk of metastasis and local progressions. The results of this trial offer high quality evidence to support radical prostatectomy as a treatment option.

EBRT (3D-CRT/IMRT with daily IGRT with or without brachytherapy) with or without 4 to 6 months of neoadjuvant/concomitant/adjuvant ADT is another treatment option. Overall and cancer-specific survival improved with the addition of short-term ADT to radiation in three randomized trials containing 20% to 60% of men with intermediate-risk...
prostate cancer (Tran Tasman Radiation Oncology Group [TROG] 9601, Dana Farber Cancer Institute [DFCI] 95096, Radiation Therapy Oncology Group [RTOG] 9408). Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly high-risk men (RTOG 8610). Overall, the addition of short course ADT to RT in men with intermediate-risk disease is a viable option.

Brachytherapy as monotherapy is not recommended for this group of men. Risk stratification analysis has shown that brachytherapy alone is inferior to EBRT or radical surgery as measured by biochemical-free survival for patients who showed (1) a component of Gleason pattern 4 or 5 cancer, or (2) a serum PSA value greater than 10 ng/mL.

Active surveillance is not recommended for those with a life expectancy of greater than 10 years (category 1).

High Risk of Recurrence

Men with prostate cancer that is clinically localized stage T3a, Gleason score 8 to 10, or PSA level greater than 20 ng/mL are categorized by the NCCN guideline panel to be at high risk of recurrence after definitive therapy. Patients with multiple adverse factors may be shifted into the very high-risk category. Patients with high-risk disease have a better 5-year overall and disease-specific survival with active intervention than with observation until symptomatic and thus should be treated unless life expectancy is 5 years or less.

There are several treatment options for patients with high-risk disease. The preferred treatment is 3D-CRT/IMRT with daily IGRT in conjunction with long-term ADT (category 1); ADT alone is insufficient. In particular, patients with low volume, high grade tumor warrant aggressive local radiation combined with typically 2-3 years of ADT. Two randomized phase III trials evaluated long-term ADT with or without radiation in mostly T3 patients. Another study randomized 415 patients to EBRT alone or EBRT plus 3-year ADT. In a fourth study (RTOG 8531), 977 patients with T3 disease treated with RT were randomized to adjuvant ADT or ADT at relapse. In all four studies, the combination group showed improved disease-specific and overall survival compared to single-modality treatment.

Increasing evidence favors long-term over short-term neoadjuvant/concurrent/adjuvant ADT in high-risk patients. The RTOG 9202 trial included 1,521 patients with T2c-T4 prostate cancer who received 4 months of ADT before and during RT. They were randomized to no further treatment or an additional 2 years of ADT. At 10 years, the long-term group is superior for all end points except overall survival. A subgroup analysis of patients with Gleason score 8-10 found an advantage in overall survival for long-term ADT (32% vs 45%, P = 0.0061). The European Organization for Research and Treatment of Cancer (EORTC) 22961 trial also showed superior survival when 2.5 years of ADT was added to RT given with 6 months of ADT in 970 patients, mostly with T2c-T3, N0 disease. In a secondary analysis of RTOG 8531 that mandated lifelong ADT, those who adhered to the protocol had better survival than those who discontinued ADT within 5 years.

There are emerging data that associate lower biochemical failure rates with the addition of brachytherapy to EBRT in patients at high risk. An analysis on a cohort of 12,745 high-risk patients found treatment with brachytherapy or brachytherapy plus EBRT to lower cancer-specific mortality compared to EBRT alone. The combination of EBRT and brachytherapy, with or without ADT, is now listed as a primary treatment option. However, the optimal duration of ADT in this setting remains unclear.
Radical prostatectomy with pelvic lymph node dissection remains an option in selected patients with no fixation to adjacent organs. For patients with Gleason scores of 8 or greater, a 36% progression-free survival rate has been reported after radical prostatectomy.\(^{196}\)

**Very High Risk of Recurrence**

Patients at very high risk of recurrence are defined by the NCCN guidelines as those with clinical stage T3b to T4 (locally advanced). The options for this group include: (1) a combination of 3D-CRT/IMRT with daily IGRT and long-term ADT (category 1), (2) EBRT plus brachytherapy with or without ADT, (3) radical prostatectomy plus pelvic lymphadenectomy in selected patients with no fixation to adjacent organs, or (4) ADT (for patients not eligible for definitive therapy only). The three randomized trials that demonstrated survival benefits with the combination of RT and long-term ADT in high-risk disease also included patients under this category.\(^{187-189}\)

**Metastatic Disease**

ADT or radiation plus neoadjuvant/concomitant/adjuvant ADT (2-3 years) are available options for patients with N1 disease on presentation.\(^{187, 188}\) The EORTC 30846 trial randomized 234 treatment-naïve node-positive patients to immediate versus delayed ADT.\(^{197}\) At 13 years, the authors report similar survival between the two arms, although the study was not powered to show non-inferiority.

ADT is recommended for patients with M1 cancer.

**Active Surveillance**

Those electing active surveillance with life expectancy of 10 years or more might benefit from definitive local therapy if the cancer progresses. Therefore, appropriate surveillance includes a PSA determination as often as every 3 months but at least every 6 months, a DRE as often as every 6 months but at least every 12 months, and a repeat prostate biopsy as often as annually. If the patient initially had a 10 to 12 core biopsy, repeat needle biopsy may be performed within 18 months. Surveillance may be less intense for those with a life expectancy < 10 years; PSA and DRE may be done less frequently (as often as every 6-12 months) and follow-up prostate biopsies are rarely necessary.

Repeat biopsy is recommended to determine whether higher-grade elements are evolving although the risks appear small\(^{198}\), which may influence prognosis and, hence, the decision to continue active surveillance or to proceed to definitive local therapy. After an initial repeat biopsy, subsequent biopsies may be performed at the observing physician’s discretion. Treatment of all men who developed Gleason pattern 4 on annual prostate biopsies has thus far avoided a prostate cancer death among 769 men in the Johns Hopkins study.\(^{59}\) However, whether treatment of all who progress to Gleason pattern 4 was necessary remains uncertain. Studies remain in progress to identify the best trigger points, after choosing deferred treatment, when interventions with curative intent may still be reliably successful. The criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression. If progressive disease is detected, the patient may require RT or radical prostatectomy.

**Monitoring after Treatment**

For patients initially treated with intent to cure, a serum PSA level should be measured every 6 to 12 months for the first 5 years and then rechecked annually. When prostate cancer recurred after radical prostatectomy, Pound and colleagues found that 45% of patients experienced recurrence within the first 2 years, 77% within the first 5
years, and 96% by 10 years. Because local recurrence may result in substantial morbidity and can, in rare cases, occur in the absence of a PSA elevation, an annual DRE is also appropriate to monitor for prostate cancer recurrence as well as for colorectal cancer. Similarly, after RT, the monitoring of serum PSA levels is recommended every 6 months for the first 5 years and then annually and a DRE is recommended annually. The clinician may opt to omit the DRE if PSA levels remain undetectable.

For patients presenting with nodal positive or metastatic disease, the intensity of clinical monitoring is determined by the response to initial ADT, radiotherapy, or both. Follow-up evaluation of these patients should include a history and physical examination, DRE, and PSA determination every 3 to 6 months.

Patients being treated with either medical or surgical ADT are at risk for having or developing osteoporosis. A baseline bone mineral density study should be considered in this group of patients. Supplementation is recommended using calcium (500 mg) and vitamin D (400 IU). Men who are osteopenic/osteoporotic should be considered for bisphosphonate therapy.

Adjuvant or Salvage Therapy after Radical Prostatectomy

Most patients who have undergone a radical prostatectomy are cured of prostate cancer. However, some men will suffer pathologic or biochemical failure. Selecting men appropriately for adjuvant or salvage radiation is difficult. However, recently published trials provide high level evidence that can be used to counsel patients more appropriately. Thompson and colleagues reported the results of the SWOG 8794 trial enrolling 425 men with extraprostatic cancer treated with radical prostatectomy. Patients were randomized to receive either adjuvant RT or usual care and follow-up has reached a median of 12.6 years. The initial study report revealed that adjuvant RT reduced the risk of PSA relapse and disease recurrence. An update reported improved 10-year biochemical failure-free survival for high risk patients (seminal vesicle positive) receiving post-prostatectomy adjuvant radiation compared to observation (36% vs. 12%, P = 0.001). Most recently, SWOG 8794 has demonstrated improved overall and metastasis-free survival. Another randomized trial conducted by the EORTC compared post-prostatectomy observation and adjuvant RT in 1,005 patients. All patients had extraprostatic extension and/or positive surgical margins. The 5-year biochemical progression-free survival significantly improved with RT compared to observation for patients with positive surgical margins (78% vs. 49%), but benefit was not seen for patients with negative surgical margins. Recently, a German study by Wiegel et al reported results on 268 patients. All participants had pT3 disease and undetectable PSA levels after radical prostatectomy. Post-operative radiation improved 5-year biochemical progression-free survival compared to observation alone (72% vs. 54%; HR = 0.53; 95% CI, 0.37-0.79). Collectively, these trial results suggest that continued follow-up of these series of patients may show a survival advantage.

Based on these results, adjuvant RT after recuperation from surgery (usually within 6 months) is likely beneficial in men with adverse laboratory or pathologic features including positive margin, seminal vesicle invasion, and/or extracapsular extension. Positive surgical margins are especially unfavorable if diffuse (>10 mm margin involvement or ≥3 sites of positivity) or associated with persistent serum levels of PSA. If adjuvant RT is considered, it should be administered before the PSA exceeds 1.5 ng/mL. Adjuvant ADT should be considered for patients with positive lymph nodes found during surgery. However, the survival advantage reported for early and continuous ADT has been refuted by more recent reports. Therefore,
observation is recommended until a detectable PSA develops, at which time clinical trials or ADT should be considered.

Several retrospective studies have assessed the prognostic value of various combinations of pretreatment PSA levels, Gleason scores, PSA doubling time and the presence or absence of positive surgical margins. A large retrospective review of 501 patients who received salvage radiotherapy for detectable and increasing PSA after prostatectomy showed that the predictors of progression were Gleason score 8-10, pre-RT PSA level greater than 2 ng/mL, seminal vesicle invasion, negative surgical margins and a PSA doubling time of 10 months or less. However, separation of men into those likely to have local recurrence versus systemic disease and hence response to postoperative radiation has proven not possible for individual patients using clinical and pathologic criteria. Unfortunately, delivery of adjuvant or salvage RT becomes both therapeutic and diagnostic – PSA response indicates local persistence/recurrence. Delayed biochemical recurrence requires restaging and a new nomogram may prove useful to predict response but it has not yet been validated.

Men who suffer a biochemical recurrence following prostatectomy fall into three groups: (1) those whose PSA level fails to fall to undetectable levels after surgery, (2) those who achieve an undetectable PSA after surgery with a subsequent detectable PSA level that increases on two or more laboratory determinations, or (3) the occasional, otherwise stable case with persistent but very low PSA level attributed to slow metabolism or residual benign tissue. Group (3) does not require further workup until PSA rises. Since PSA elevation alone does not necessarily lead to clinical failure, the workup for (1) and (2) focuses on the assessment of distant metastases. The specific tests depend on the clinical history, but potentially include bone scan, biopsy of the prostate bed, PSA doubling time assessment, and CT/MRI. Bone scans are appropriate when patients develop symptoms or when the PSA level is increasing rapidly. In one study, the probability of a positive bone scan for a patient not on ADT after radical prostatectomy was less than 5% unless the PSA increased to 40 to 45 ng/mL. If there is little suspicion of distant metastasis during biochemical recurrence, primary salvage therapy involves radiation with or without neoadjuvant/concomitant/adjuvant ADT. When there is proven or high suspicion for distant metastases, ADT alone becomes the main salvage treatment. Radiation alone is not recommended but may be given to the site of metastasis or symptoms (such as weight-bearing bones) in addition to ADT in specific cases such as skeletal involvement. Observation remains acceptable for select patients. In all cases, the form of primary or secondary systemic therapy should be based on the hormonal status of the patient.

**Post-irradiation Recurrence**

According to the 2006 Phoenix definition revised by ASTRO and the Radiation Therapy Oncology Group in Phoenix, a rise in PSA by 2 ng/mL or more above the nadir PSA (defined as the lowest PSA achieved) is the current standard definition for biochemical failure after EBRT with or without neoadjuvant ADT therapy. The date of failure should be determined “at call” and not backdated. To avoid the artifacts resulting from short follow-up, the reported date of control should be listed as 2 years short of the median follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition would allow comparisons with a large existing body of literature.

Further work up is indicated in patients who are considered candidates for local therapy. These patients include those with original clinical stage T1-2, a life expectancy of greater than 10 years, and a current
PSA of less than 10 ng/mL\textsuperscript{214} Work up includes a prostate biopsy, bone scan, and additional tests as clinically indicated, such as an abdominal/pelvic CT, MRI, or PSA doubling time assessment.

Options for primary salvage therapy for those with positive biopsy but low suspicion of metastases to distant organs include observation or salvage prostatectomy in selected cases. Morbidity (including incontinence, erectile dysfunction, and bladder neck contracture) remains significantly higher than when radical prostatectomy is used as initial therapy.\textsuperscript{215} Other options for localized interventions include cryotherapy\textsuperscript{216} and brachytherapy (reviewed by Allen et al\textsuperscript{217}). Treatment, however, needs to be individualized based upon the patient's risk of progression, the likelihood of success, and the risks involved with the therapy.

A negative biopsy following post-radiation biochemical recurrence poses clinical uncertainties. Observation, ADT, or enrolling in clinical trials are viable options. Alternatively, the patients may undergo more aggressive workup, such as repeat biopsy, MR spectroscopy, and/or endorectal MRI.\textsuperscript{218, 219}

Patients with positive study results indicating distant metastatic disease or patients who are not initial candidates for local therapy should be observed or treated with ADT.

**Androgen Deprivation Therapy for Advanced Disease**
ADT using medical or surgical castration is the most common form of systemic therapy. In patients with radiographic evidence of metastases who are treated with LHRH agonist alone, "flare" in serum LH (luteinizing hormone) and testosterone levels may occur within the first several weeks after therapy is initiated, which may worsen the existing disease. Thus, LHRH agonist is often used in conjunction with antiandrogen for at least 7 days to diminish ligand binding to the androgen receptor. LHRH antagonist therapy does not require short-term antiandrogen. CAB is an acceptable option.\textsuperscript{125, 126} The ASCO guidelines\textsuperscript{130} on ADT use suggest that a balanced risk/benefit discussion at the time of ADT initiation should include potential risks and benefits of CAB with an LHRH agonist and bicalutamide if tolerated. This combination therapy may lead to additional costs and side effects, and prospective randomized evidence is lacking to inform on this decision further at this time.

**CRPC**
Patients relapsing after primary ADT with CRPC should receive a laboratory assessment to assure a castrate level of testosterone. A number of options for systemic therapy should be considered based on metastasis status.

**CRPC without Signs of Metastasis**
For patients without signs of distant metastasis (M0), clinical trial is the preferred choice. Observation is another option, as is secondary hormone therapy since the androgen receptor may remain active. For patients who have undergone CAB, the antiandrogen should be discontinued to exclude an "antiandrogen withdrawal response."\textsuperscript{220, 221} This can be achieved using an antiandrogen (for patients who initially received medical or surgical castration), ketoconazole (adrenal enzyme inhibitor), steroids, diethylstilbestrol (DES) or other estrogens.\textsuperscript{222, 223} However, none of these strategies has yet been shown to prolong survival in randomized clinical trials in men who have not yet received docetaxel-based chemotherapy.

**Small Cell Carcinoma of the Prostate**
Small cell carcinoma of the prostate should be considered in patients who no longer respond to ADT and test positive for metastases. Those
with an initial Gleason score of 9 or 10 are especially at risk. These relatively rare tumors are typically associated with low PSA levels despite large metastatic burden and visceral disease. Thus, a biopsy of accessible lesions should be considered to identify patients with small cell histomorphologic features. These cases may be managed by cytotoxic chemotherapy, such as cisplatin/etoposide, carboplatin/etoposide, or a docetaxel-based regimen. Physicians should consult the NCCN Small Cell Lung Cancer Guidelines since the behavior of small cell carcinoma of the prostate is similar to that of small cell carcinoma of the lung. Of note, small cell carcinomas of the prostate are distinct from neuroendocrine prostate cancers; the latter histology may be more common and should not alter treatment.

Prevention of Skeletal-related Events in CRPC
In men with CRPC and bone metastases, zoledronate every 3-4 weeks or denosumab 120 mg every 4 weeks is recommended to prevent or delay disease-associated skeletal related events (SREs) (category 1 recommendation). SREs include pathological fractures, spinal cord compression, surgery or radiation therapy to bone. The optimal duration of zoledronate or denosumab in men with CRPC and bone metastases remains unclear.

Oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce the risk of ONJ. Supplemental calcium and vitamin D treatment is recommended to prevent hypocalcemia in patients receiving either denosumab or zoledronate.

Monitoring of creatinine clearance is required for zoledronate to guide dosing. Zoledronate should be dose reduced in men with impaired renal function (estimated creatinine clearance 30-60 ml/min), and held for creatinine clearance <30 ml/min. Denosumab may be administered to men with impaired renal function, including men on hemodialysis, although the risk for severe hypocalcemia and hypophosphatemia is greater in this population, and the dose, schedule, and safety of denosumab for this group is not yet defined. A single study of 55 patients with creatinine clearance < 30 ml/min or on hemodialysis evaluated the use of a 60-mg dose of denosumab. Hypocalcemia should be corrected before starting denosumab and serum calcium monitoring is required for denosumab and recommended for zoledronate, with appropriate repletion as needed.

Clinical research continues on the prevention or delay of disease spread to bone. In a phase III randomized trial involving 1,432 patients with non-metastatic CRPC at high risk of bone involvement, denosumab was reported to delay bone metastasis by 4 months compared to placebo. However, overall survival did not improve and this specific indication for denosumab was not approved by the FDA.

Systemic Therapy for Metastatic CRPC
For metastatic CRPC patients without symptoms, sipuleucel-T is a category 1 recommendation based on phase III randomized trial evidence for those who have good performance level (ECOG 0-1) and at least 6 months of estimated life expectancy. Clinicians and patients should be aware that the usual markers of benefit (decline in PSA, improvement in bone or CT scans) are not seen usually and therefore benefit to the individual patient cannot be ascertained using currently available testing. Treatment subsequent to sipuleucel-T treatment should proceed as clinically indicated, particularly in the occurrence of symptoms. Secondary ADT (including abiraterone acetate designated as category 2B in this setting), docetaxel, and participation in clinical trials are viable alternatives to sipuleucel-T. Although docetaxel is not commonly used for asymptomatic patients, it may be considered for
those who are showing signs of rapid progression or liver involvement (category 2A in this setting).

In the case of symptomatic disease, every 3-week docetaxel and prednisone is the preferred first-line chemotherapy treatment (category 1 in this setting).\textsuperscript{165-167} PSA rise alone does not define docetaxel failure. If clinical progression is not apparent, the patient may benefit from continued chemotherapy. The addition of estramustine to docetaxel has been shown to increase side effects without enhancing efficiency and is not recommended.\textsuperscript{232}

For symptomatic patients who cannot tolerate docetaxel, mitoxantrone may provide palliative benefit. The traditional option of glucocorticoids and EBRT for symptomatic bone metastases remains available for patients with focal pain or impending pathologic fractures. The use of systemic radiotherapy with either strontium-89 or samarium-153 occasionally benefits patients with widely metastatic, painful, skeletal involvement that is not responding to palliative chemotherapy or systemic analgesia and who are not candidates for localized EBRT.\textsuperscript{104} The risk of bone marrow suppression, which might influence the ability to provide additional systemic chemotherapy, should be considered before this therapy is initiated. Clinical trial enrollment is another option. The NCCN acknowledges that some men with metastatic CRPC are not candidates for docetaxel chemotherapy. In these men, abiraterone acetate with prednisone may be an appropriate therapy, given its survival and palliative benefit and reasonable toxicity profile (category 2B in this setting). However, its routine use in the pre-docetaxel setting should be discouraged until high-level evidence from an ongoing randomized study of abiraterone acetate and prednisone vs. prednisone in this setting has been reported. This trial has completed accrual, and initial results are expected soon.

**Second-line Systemic Therapy**

Currently, no consensus exists for the best additional therapy following docetaxel failure in metastatic CRPC patients. Options include abiraterone acetate (category 1), cabazitaxel (category 1), salvage chemotherapy, docetaxel rechallenge, mitoxantrone, secondary ADT, sipuleucel-T, and participation in clinical trials.

Abiraterone acetate has demonstrated clinical benefit and thus represents a new standard of care after failure of docetaxel chemotherapy for metastatic CRPC (category 1). Abiraterone acetate should be given with oral prednisone 5 mg twice daily. It should be taken in a fasting state due to higher levels of drug exposure when taken with food to abrogate signs of mineralocorticoid excess that can result from the treatment. These signs can include hypertension, hypokalemia, and peripheral edema. Serum electrolytes should be monitored closely during therapy.

The NCCN panel included cabazitaxel as an option for second-line therapy after docetaxel failure for patients with symptomatic metastatic CRPC. This recommendation is category 1 based on randomized phase III study data, however, extension of survival is relatively short and side effects are relatively high. Physicians should follow current guidelines for prophylactic white blood cell growth factor use, particularly in this heavily pre-treated, high risk population. In addition, supportive care should include anti-emetics (including prophylactic anti-histamines, H2 antagonists, and steroids prophylaxis), and symptom-directed anti-diarrheal agents. Cabazitaxel has not been tested in patients with hepatic dysfunction and therefore should not be used in these patients. Cabazitaxel should be stopped upon clinical disease progression or intolerance.
The decision to initiate therapy with abiraterone acetate with prednisone or cabazitaxel with prednisone in the post-docetaxel CRPC setting should be based on the available high-level evidence of safety, efficacy, and tolerability of these agents and the application of this evidence to an individual patient. There are no randomized trials comparing these two agents, and there are currently no predictive models or biomarkers that are able to identify patients who are likely to benefit from either approach. Choice of therapy is based largely on clinical considerations which include patient preferences. The NCCN recommends that patients be monitored closely with radiologic imaging (CT, bone scan), PSA tests, and clinical exams for evidence of progression. In cases where PSA or bone scan changes may indicate flare rather than true clinical progression, therapy should be continued until clinical progression or intolerability. The sequential use of these agents is reasonable in a patient who remains a candidate for further systemic therapy.

NCCN panelists agreed that docetaxel rechallenge may be useful in some patients (category 2A instead of category 1 in this setting). Mitoxantrone remains a palliative treatment option for men who are not candidates for taxane-based therapy based on older randomized studies showing improved palliative responses and duration of palliative benefit. While limited evidence suggests potential palliative benefits with mitoxantrone and a variety of chemotherapeutic or hormonal agents, no randomized studies have demonstrated improved survival with these agents after docetaxel failure. Treatment with these agents could be considered after an informed discussion between the physician and an individual patient about treatment goals and risks/side effects and alternatives, which must include best supportive care.

In the recent phase III sipuleucel-T trial, 18.2% of patients had received prior chemotherapy, including docetaxel, since eligibility requirements included no chemotherapy for 3 months and no steroids for 1 month prior to enrollment. Further, these men too were asymptomatic or minimally symptomatic. In a subset analysis, both those who did and those who did not receive prior chemotherapy (and otherwise met eligibility criteria) benefited from sipuleucel-T treatment. The panel included sipuleucel-T as an option after failure of or treatment with chemotherapy (category 2A instead of category 1 in this setting). However, patients with rapidly progressing disease, liver metastasis, or life expectancy less than 6 months should not be considered for sipuleucel-T. Clinical trial enrollment is encouraged for all men with metastatic CRPC, given the limited improvements in outcomes seen with approved systemic options.

**Summary**

The intention of these guidelines is to provide a framework on which to base treatment decisions. Prostate cancer is a complex disease, with many controversial aspects of management and with a dearth of sound data to support treatment recommendations. Several variables (including life expectancy, disease characteristics, predicted outcomes, and patient preferences) must be considered by the patient and physician in tailoring prostate cancer therapy to the individual patient.
### Table 1. Active surveillance experience in North America

<table>
<thead>
<tr>
<th>Center</th>
<th>Toronto(^{57})</th>
<th>Johns Hopkins(^{53, 58, 59})</th>
<th>UCSF(^{56})</th>
</tr>
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<tbody>
<tr>
<td>No. patients</td>
<td>450</td>
<td>769</td>
<td>531</td>
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<tr>
<td>Age (yr)</td>
<td>70</td>
<td>66</td>
<td>63</td>
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<tr>
<td>Follow-up (mo)</td>
<td>82</td>
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<td>43</td>
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<td>Overall survival</td>
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<td>98%</td>
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<tr>
<td>CSS</td>
<td>97%</td>
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<tr>
<td>Treatment</td>
<td>30%</td>
<td>33%</td>
<td>24%</td>
</tr>
</tbody>
</table>

**Reason for reclassification**

<table>
<thead>
<tr>
<th></th>
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<th>Johns Hopkins(^{53, 58, 59})</th>
<th>UCSF(^{56})</th>
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<tr>
<td>Grade change</td>
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<tr>
<td>PSA increase</td>
<td>14%*</td>
<td>-</td>
<td>26%(^{†})</td>
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<tr>
<td>Positive node</td>
<td>1%</td>
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<td>Anxiety</td>
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<td>9%</td>
<td>8%</td>
</tr>
</tbody>
</table>

CSS = cancer-specific survival

* PSA doubling time < 3 years

† PSA velocity >0.75 ng/mL/y
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