

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®)**

# **Prostate Cancer**

**Version 1.2014**

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# NCCN Guidelines Version 1.2014 Prostate Cancer

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**James L. Mohler, MD/Chair** <sup>ω</sup>  
Roswell Park Cancer Institute

**Philip W. Kantoff, MD/Vice Chair** †  
Dana-Farber/Brigham and Women's  
Cancer Center | Massachusetts General  
Hospital Cancer Center

**Andrew J. Armstrong, MD, ScM** †  
Duke Cancer Institute

**Robert R. Bahnson, MD** <sup>ω</sup>  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Michael Cohen, MD** <sup>□</sup>  
Huntsman Cancer Institute  
at the University of Utah

**Anthony Victor D'Amico, MD, PhD** §  
Dana-Farber/Brigham and Women's  
Cancer Center | Massachusetts General  
Hospital Cancer Center

**James A. Eastham, MD** <sup>ω</sup>  
Memorial Sloan-Kettering Cancer Center

**Charles A. Enke, MD** §  
Fred & Pamela Buffett Cancer Center at  
The Nebraska Medical Center

**Thomas A. Farrington**  
Prostate Health Education Network (PHEN)

**Celestia S. Higano, MD** <sup>ω</sup> †  
University of Washington/  
Fred Hutchinson Cancer Research Center/  
Seattle Cancer Care Alliance

**NCCN**  
**Maria Ho, PhD**  
**Dorothy A. Shead, MS**

**Eric Mark Horwitz, MD** §  
Fox Chase Cancer Center

**Christopher J. Kane, MD** <sup>ω</sup>  
UC San Diego Moores Cancer Center

**Mark H. Kawachi, MD** <sup>ω</sup>  
City of Hope Comprehensive  
Cancer Center

**Michael Kuettel, MD, MBA, PhD** §  
Roswell Park Cancer Institute

**Richard J. Lee, MD, PhD** †  
Dana-Farber/Brigham and Women's  
Cancer Center | Massachusetts General  
Hospital Cancer Center

**Arnold W. Malcolm, MD** §  
Vanderbilt-Ingram Cancer Center

**David Miller, MD, MPH** <sup>ω</sup>  
University of Michigan  
Comprehensive Cancer Center

**Elizabeth R. Plimack, MD, MS** †  
Fox Chase Cancer Center

**Julio M. Pow-Sang, MD** <sup>ω</sup>  
Moffitt Cancer Center

**Sylvia Richey, MD** †  
St. Jude Children's Research  
Hospital/University of Tennessee  
Health Science Center

**Mack Roach, III, MD** §  
UCSF Helen Diller Family  
Comprehensive Cancer Center

**Eric Rohren, MD, PhD** ¥  
The University of Texas  
MD Anderson Cancer Center

**Stan Rosenfeld**  
University of California San Francisco  
Patient Services Committee Chair

**Eric J. Small, MD** †  
UCSF Helen Diller Family  
Comprehensive Cancer Center

**Guru Sonpavde, MD** †  
University of Alabama at Birmingham  
Comprehensive Cancer Center

**Sandy Srinivas, MD** †  
Stanford Cancer Institute

**Cy Stein, MD, PhD** †  
City of Hope Comprehensive Cancer Center

**Seth A. Strope, MD, MPH**  
Siteman Cancer Center at Barnes-  
Jewish Hospital and Washington  
University School of Medicine

**Jonathan Tward, MD, PhD** §  
Huntsman Cancer Institute  
at the University of Utah

**Patrick C. Walsh, MD** <sup>ω</sup>  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

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[NCCN Guidelines Panel Disclosure](#)

¥Diagnostic interventional radiology  
§ Radiotherapy/Radiation oncology  
ω Urology  
† Medical oncology  
£ Supportive care, including palliative, pain management,  
pastoral care, and oncology social work  
□ Pathology  
\*Writing committee member

[NCCN Prostate Cancer Panel Members](#)

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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. ©2013.

Summary of changes in the 1.2014 version of the NCCN Guidelines for Prostate Cancer from the 4.2013 version include:

### **PROS-1**

- Life expectancy  $\leq 5$  y and asymptomatic, no further workup or treatment until symptomatic, except for high-risk patients, changed high-risk patients to *high- or very-high-risk groups*.
- Changed the header from Recurrence Risk to *Risk Group*.
- Low-risk group, changed Gleason score from 2-6 to  $\leq 6$ .
- Added footnote b: [See Principles of Imaging \(PROS-B\)](#).

### **PROS-2**

- Initial therapy, Active surveillance:
  - ▶ Changed PSA at least as often as every 6 mo to *PSA no more often than every 6 mo unless clinically indicated*.
  - ▶ Changed DRE at least as often as every 12 mo to *DRE no more often than every 12 mo unless clinically indicated*.
  - ▶ Changed Repeat prostate biopsy as often as every 12 mo to *Repeat prostate biopsy no more often than every 12 mo unless clinically indicated*.
  - ▶ Modified footnote f: “Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses.”
- Expected patient survival, changed  $\geq 10$  y to 10-20 y.
- Expected patient survival  $\geq 20$  y, initial therapy RT: removed (Daily IGRT with IMRT/3D-CRT).
- Adjuvant therapy, lymph node metastasis: changed the order of options to ADT (category 1)  $\pm$  RT (category 2B) or Observation.
- Footnote j is new: Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent.

### **PROS-4**

- Expected patient survival  $< 10$  y:
  - ▶ Replaced Active surveillance with *Observation*.
  - ▶ Added footnote j to Observation
  - ▶ Initial therapy, RT: removed (Daily IGRT with IMRT/3D-CRT)  $\pm$  short-term neoadjuvant/concomitant/adjuvant ADT (4-6 mo).
- Expected patient survival  $\geq 10$  y:
  - ▶ Initial therapy, RT: removed (Daily IGRT with IMRT/3D-CRT)  $\pm$  short-term neoadjuvant/concomitant/adjuvant ADT (4-6 mo).
  - ▶ Adjuvant therapy, lymph node metastasis: changed the order of options to ADT (category 1)  $\pm$  RT (category 2B) or Observation (category 2B).
  - ▶ Undetectable PSA, added *or nadir*.
  - ▶ Changed Detectable PSA to *PSA failure*.
  - ▶ Changed Post-radical prostatectomy recurrence to *Radical Prostatectomy Biochemical Failure*.
  - ▶ Changed Post-radiation therapy recurrence to *Radiation therapy recurrence*.

### **PROS-5**

- Initial therapy, RT: removed “(Daily IGRT with IMRT/3D-CRT) + long-term neoadjuvant/concomitant/adjuvant.”
- High-risk group, Initial therapy: RP + PLND removed (*select patients with no fixation*).
- Added footnote j to Observation.
- Changed Post-radical prostatectomy recurrence to *Radical Prostatectomy Biochemical Failure*.

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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.

[Continued on next page](#)

UPDATES



### [PROS-6](#)

- Initial management or pathology, N1 or M1, monitoring; removed (including DRE).
- Post-RP recurrence, failure of PSA to fall to undetectable levels; added (*PSA persistence*).
- Post-RP recurrence, undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations; added (*PSA recurrence*).
- Changed Post-radical prostatectomy recurrence to *Radical Prostatectomy Biochemical Failure*.

### [PROS-7](#)

- Changed Post-radical prostatectomy recurrence to *Radical Prostatectomy Biochemical Failure*.
- Failure of PSA to fall to undetectable levels; added (PSA persistence).
- Undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations; added (*PSA recurrence*).
- Changed the order of the tests.
- Added  $\pm$  C-11 choline PET.
- Following  $\pm$  bone scan added (*methylene diphosphonate [MDP] or sodium fluoride [NaF]*).
- Added footnote j to Observation.

### [PROS-8](#)

- Changed Post-radiation therapy recurrence to *Radiation Therapy Recurrence*.
- Changed the order of the tests.
- Changed prostate biopsy to *TRUS biopsy*.
- Changed endorectal MRI to *prostate MRI*.
- Added  $\pm$  C-11 choline PET.
- Added *Observation*.
- Added footnote j to Observation.

### [PROS-9](#)

- Added *Observation*.
- Added footnote j to Observation.
- Added footnote b, [See Principles of Imaging \(PROS-B\)](#).

### [PROS-10](#)

- Studies negative for *distant* metastases
- Observation *especially if PSADT  $\geq 10$  mo*
- Secondary hormone therapy, added *especially if PSADT < 10 mo*.
- Changed steroids to *corticosteroids*.
- Replaced footnote: “Frequency of imaging should be based on individual risk, age, PSADT, Gleason score, and overall health” with “[See Principles of Imaging \(PROS-B\)](#).”

### [PROS-11](#)

- Studies positive for *distant* metastases
- Added *Best supportive care* as an option for symptomatic CRPC.

### [PROS-B](#)

- This is a new page, Principles of Imaging.

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[Continued on next page](#)

UPDATES



**PROS-C 1 of 2**

- Added the following bullet: *The 2014 NCCN Guidelines for Prostate Cancer distinguishes between active surveillance and observation. Both involve at least every 6 mo monitoring but active surveillance may involve surveillance prostate biopsies. Evidence of progression will prompt conversion to potentially curative treatment in active surveillance patients, whereas monitoring continues until symptoms develop or are imminent (ie, PSA >100 ng/mL) in observation patients, who will then begin palliative ADT.*
- Modified the third bullet: Active surveillance is preferred for men with very low-risk prostate cancer and life expectancy  $\leq 20$  y. Observation is preferred for men with low-risk prostate cancer with life expectancy <10 y. [See Risk Group Criteria \(PROS-2\)](#).
- Added the following bullet: *Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or change in exam or PSA levels that suggest symptoms are imminent.*
- Modified the sixth bullet for consistency:
  - ▶ Changed PSA at least as often as every 6 mo to *PSA no more often than every 6 mo unless clinically indicated.*
  - ▶ Changed DRE at least as often as every 12 mo to *“DRE no more often than every 12 mo unless clinically indicated.”*
- Removed: Needle biopsy may be performed within 18 mo if initial prostate biopsy  $\geq 10$  cores and as often as every 12 mo.
- Modified the statement: Repeat prostate biopsies are not indicated when life expectancy is <10 y or appropriate when men are on observation.

**PROS-C 2 of 2**

- Added: *Advantages of observation:*
  - ▶ Avoidance of possible side effects of unnecessary definitive therapy and early initiation and/or continuous ADT.
- Added: *Disadvantages of observation:*
  - ▶ Risk of urinary retention or pathologic fracture without prior symptoms or concerning PSA level.

**PROS-D 1 of 2**

- Primary External Beam Radiation Therapy (EBRT):
  - ▶ Added the following bullet: *Moderately hypofractionated image-guided IMRT regimens (2.4 to 4 Gy per fraction over 4 to 6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated.*
  - ▶ Added the following bullet: *Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.”*
  - ▶ Removed: *“Treatment results appear better when disease burden is lower. Radiation should be administered before PSA exceeds 0.5 ng/mL.*
- Primary/Salvage Brachytherapy
  - ▶ First bullet: changed 4-6 mo ADT to 2-3 y neoadjuvant/concomitant/adjunct ADT.
  - ▶ Modified bullet: 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 are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, increased toxicity would be expected from the ADT and prostate size may not decline.
  - ▶ Modified bullet: High-dose rate (HDR) brachytherapy can be used alone or in combination with EBRT (40-50 Gy) instead of LDR. Commonly used boost regimens include 9.5 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions. A commonly used regimen for HDR treatment alone include 13.5 Gy x 2 fractions.

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UPDATES



### PROS-D 2 of 2

- **Post-Prostatectomy Radiation Therapy**
  - ▶ Indications for adjuvant RT include pT3 disease, positive margin(s), Gleason score 8-10, or seminal vesicle involvement. Adjuvant RT is usually given within 1 year after RP and once any operative side effects have improved/stabilized. *Added Patients with positive surgical margins and PSADT >9 mo may benefit the most.*
  - ▶ The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64 - 68 *changed to 70 Gy in standard fractionation.*
  - ▶ The defined target volumes include the prostate bed. *Added: The pelvic lymph nodes may be irradiated, but pelvic radiation is not necessary.*

### PROS-F

- **Split Timing of ADT for Advanced Disease to 2 new sections: ADT for Biochemical Failure and ADT for Metastatic Disease.**
- **ADT for Biochemical Failure:**
  - ▶ Added a new bullet: *Some patients are candidates for salvage a radiation after failed operation or RP or cryosurgery after failed radiation. Men with prolonged PSA doubling times (>12 mo) and who are older are candidates for observation. Men who choose ADT should consider intermittent ADT. A phase 3 trial that compared intermittent to continuous ADT showed that intermittent ADT was not inferior to continuous ADT with respect to survival, and quality of life was better for the intermittent ADT arm. The 7% increase in prostate cancer deaths in the intermittent ADT arm was balanced by more non-prostate cancer deaths in the continuous ADT arm.*
- **ADT for Metastatic Disease:**
  - ▶ Added a new bullet: *ADT is the gold standard for men with metastatic prostate cancer.*
  - ▶ Added a new bullet: *A phase 3 trial compared continuous ADT to intermittent ADT, but the study was statistically inconclusive for non-inferiority, however, quality of life measures for erectile function and mental health were better in the intermittent ADT arm after 3 months off ADT compared to the continuous ADT arm.*
  - ▶ Added a new bullet: *Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.*

### PROS-G

- **Added the following bullets:**
  - ▶ *Systemic chemotherapy should be reserved for men with mCRPC, in particular those who are symptomatic except when studied in a clinical trial. Certain subsets of patients with mCRPC who have more anaplastic features may benefit from earlier chemotherapy, but this has not been studied adequately in prospective trials.*
  - ▶ *Every-3-week docetaxel with or without prednisone is the preferred first-line chemotherapy treatment based on phase 3 clinical trial data for men with symptomatic mCRPC. Radium 223 has been studied in symptomatic patients who are not candidates for docetaxel-based regimens and resulted in improved overall survival. Although abiraterone and enzalutamide have not been studied in this setting, both therapies were beneficial in patients with symptoms after docetaxel and are reasonable options in this setting. Mitoxantrone and prednisone may provide palliation but have not been shown to extend survival. (See PROS-F, 3 of 4).*



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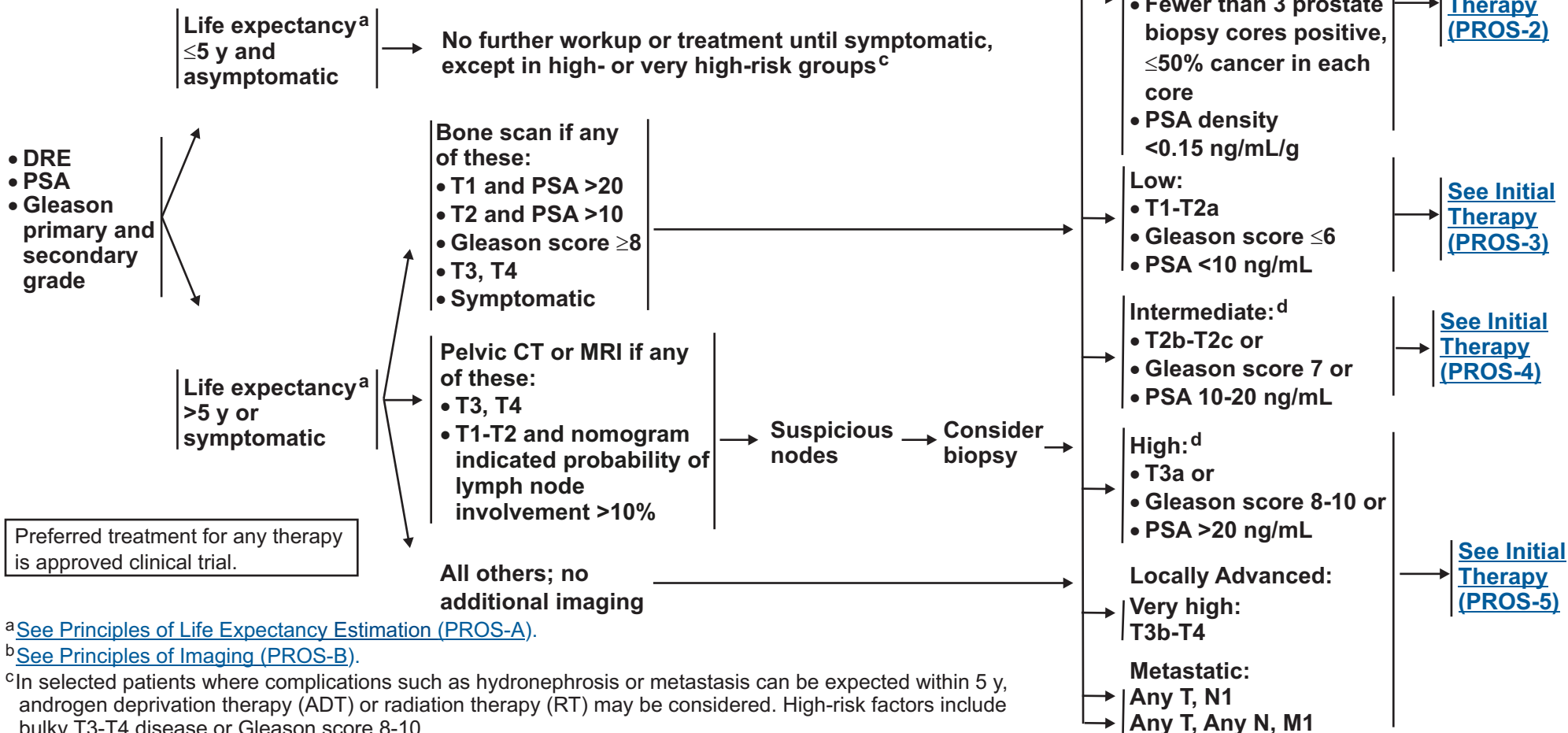
## Prostate Cancer

### INITIAL PROSTATE CANCER DIAGNOSIS

### INITIAL CLINICAL ASSESSMENT

### STAGING WORKUP<sup>b</sup>

### RISK GROUP Clinically Localized:



Preferred treatment for any therapy is approved clinical trial.

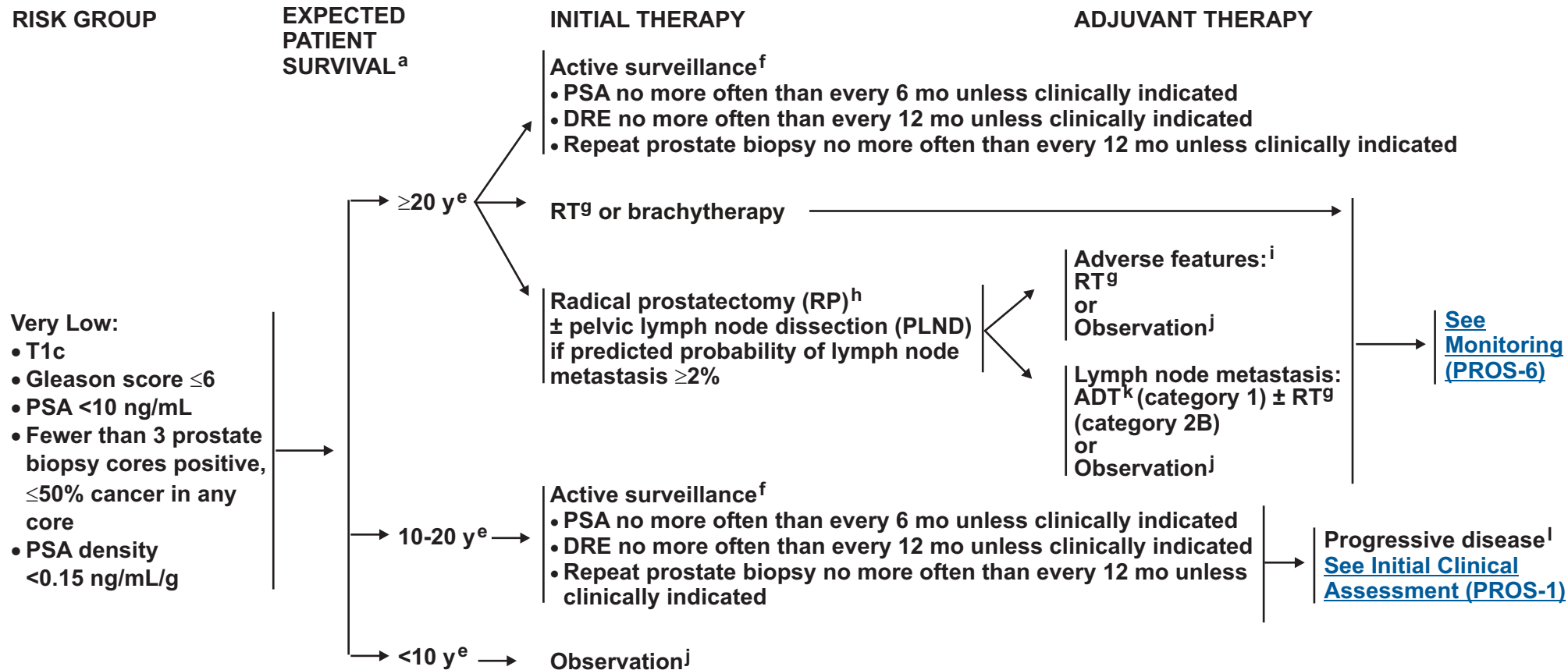
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# NCCN Guidelines Version 1.2014

## Prostate Cancer



<sup>a</sup>See [Principles of Life Expectancy Estimation \(PROS-A\)](#).

<sup>e</sup>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.

<sup>f</sup>Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See [Principles of Active Surveillance and Observation \(PROS-C\)](#).

<sup>g</sup>See [Principles of Radiation Therapy \(PROS-D\)](#).

<sup>h</sup>See [Principles of Surgery \(PROS-E\)](#).

<sup>i</sup>Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

<sup>j</sup>Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See [Principles of Active Surveillance and Observation \(PROS-C\)](#).

<sup>k</sup>See [Principles of Androgen Deprivation Therapy \(PROS-F\)](#).

<sup>l</sup>Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.

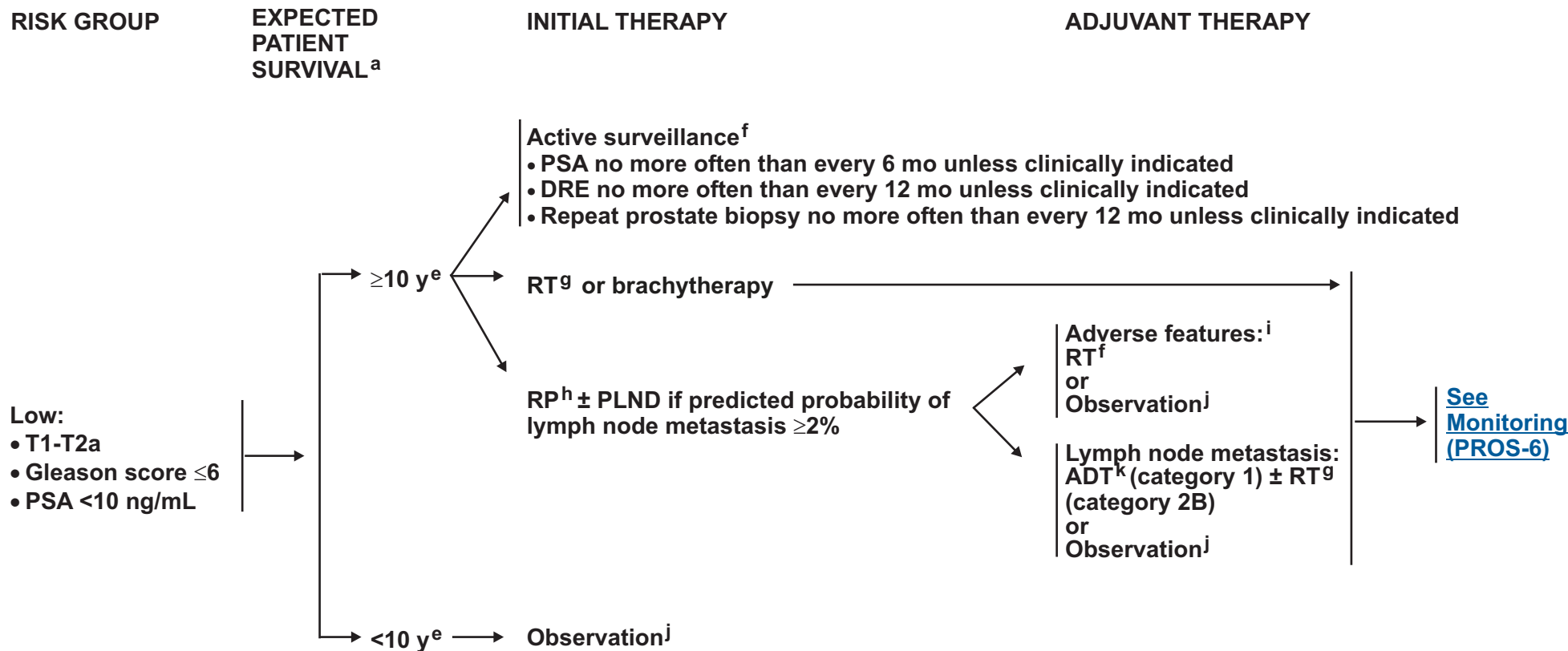
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## Prostate Cancer



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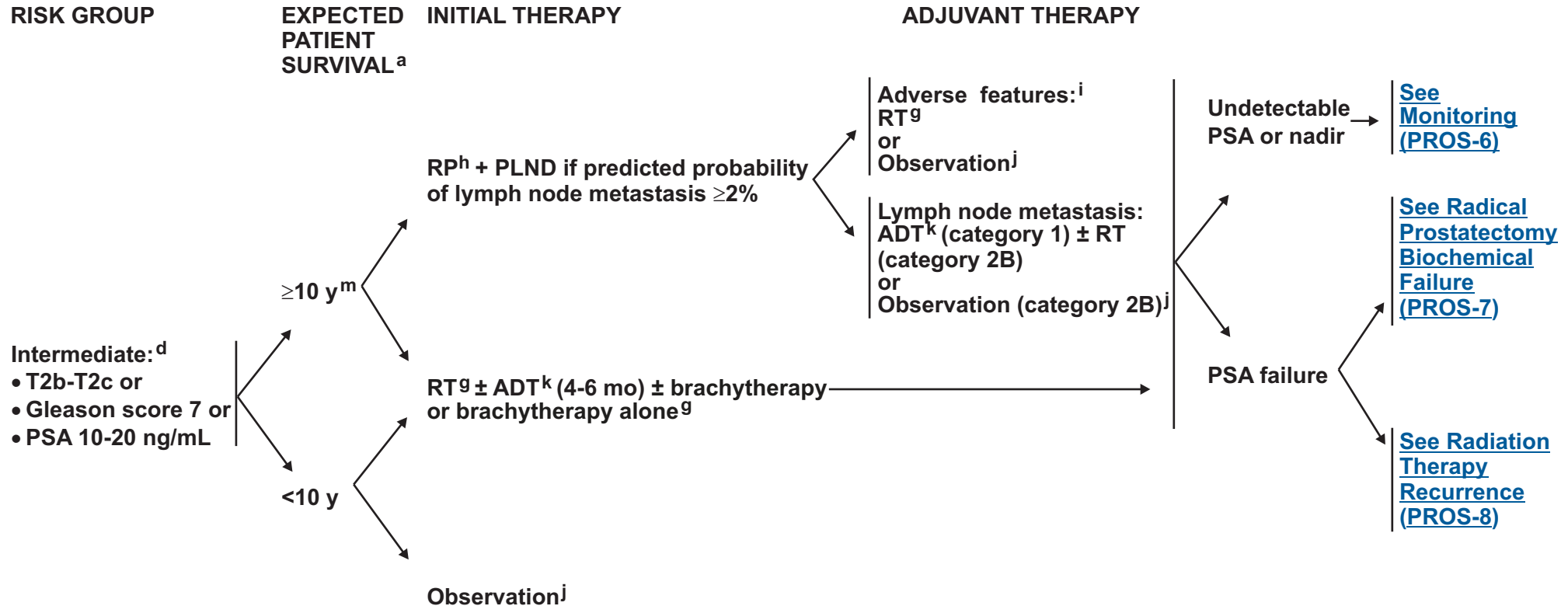
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## Prostate Cancer



<sup>a</sup>See [Principles of Life Expectancy Estimation \(PROS-A\)](#).

<sup>d</sup>Patients with multiple adverse factors may be shifted into the next highest risk group.

<sup>g</sup>See [Principles of Radiation Therapy \(PROS-D\)](#).

<sup>h</sup>See [Principles of Surgery \(PROS-E\)](#).

<sup>i</sup>Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

<sup>j</sup>Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See [Principles of Active Surveillance and Observation \(PROS-C\)](#).

<sup>k</sup>See [Principles of Androgen Deprivation Therapy \(PROS-F\)](#).

<sup>l</sup>Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.

<sup>m</sup>Active surveillance of intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).

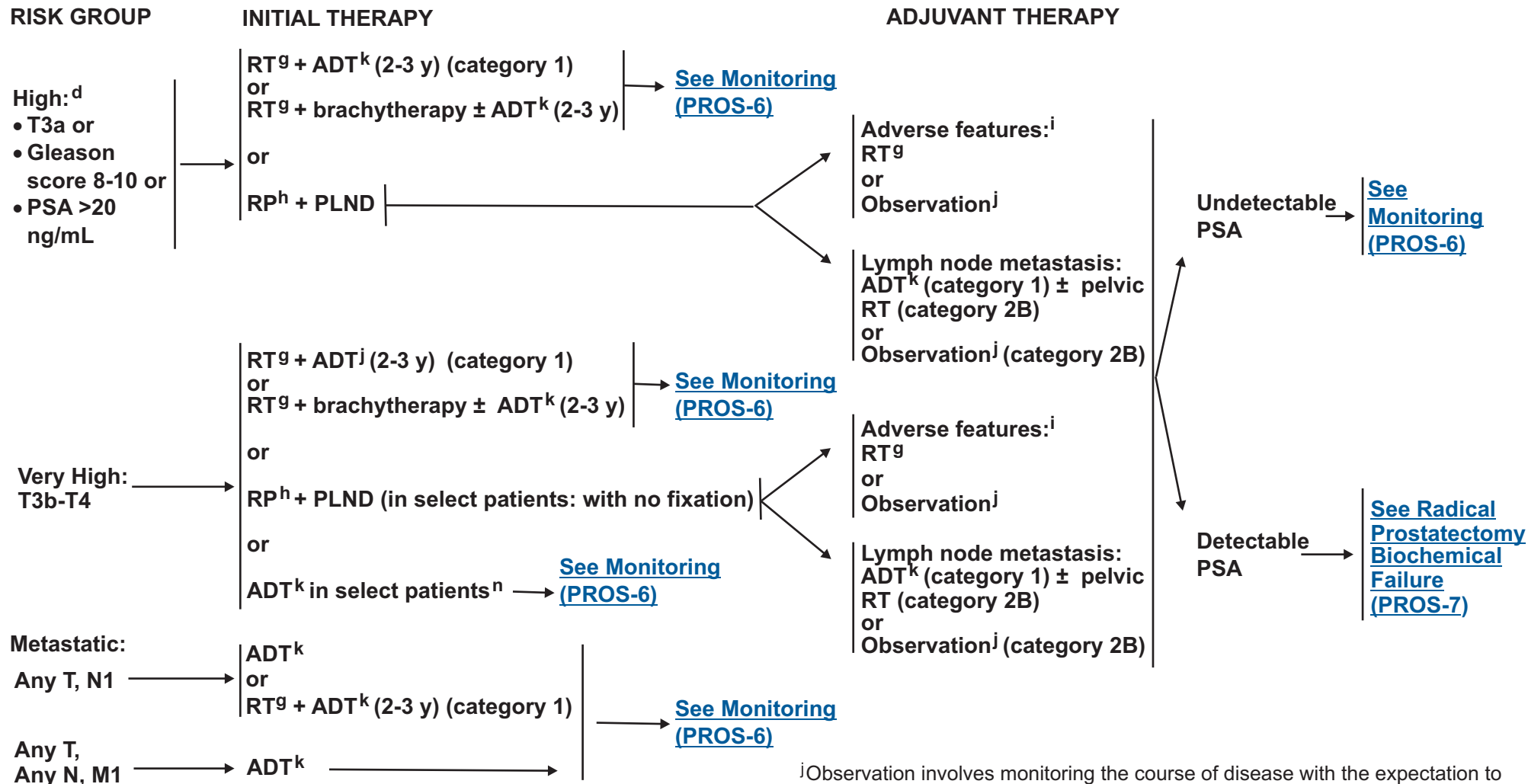
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## Prostate Cancer



<sup>d</sup>Patients with multiple adverse factors may be shifted into the next highest risk group.

<sup>g</sup>See Principles of Radiation Therapy (PROS-D).

<sup>h</sup>See Principles of Surgery (PROS-E).

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<sup>k</sup>See Principles of Androgen Deprivation Therapy (PROS-F).

<sup>n</sup>Primary therapy with ADT should be considered only for patients who are not candidates for definitive therapy.

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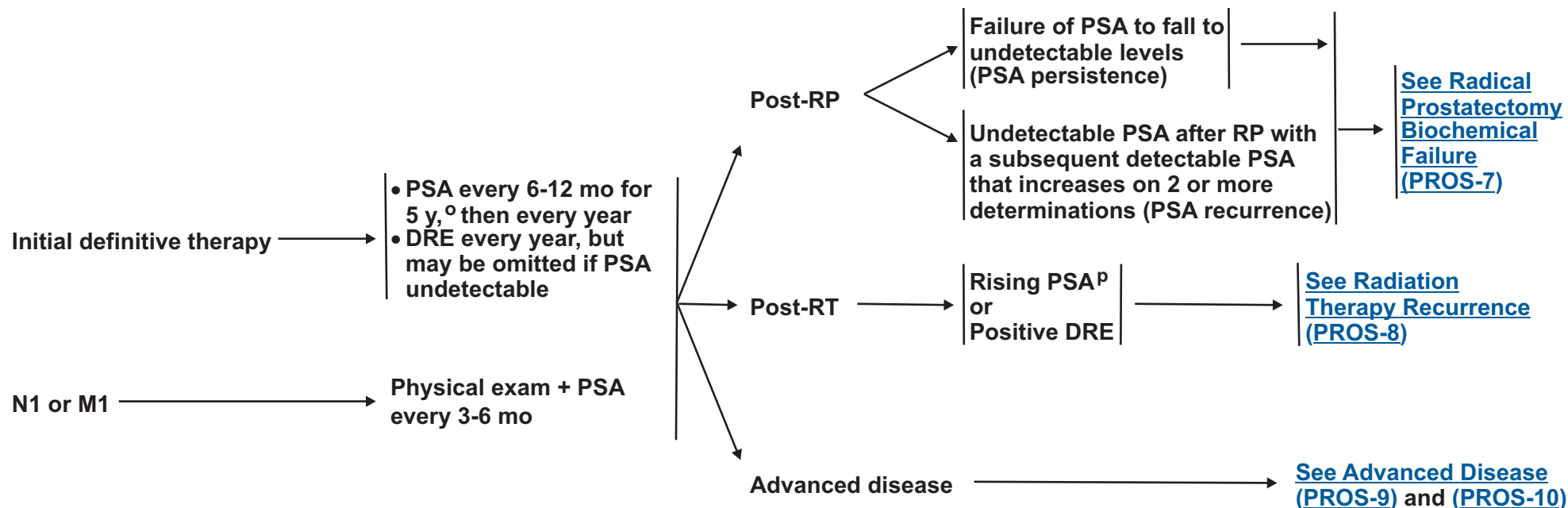


# NCCN Guidelines Version 1.2014 Prostate Cancer

## INITIAL MANAGEMENT OR PATHOLOGY

## MONITORING

## RECURRENCE



<sup>o</sup>PSA as frequently as every 3 mo may be necessary to clarify disease status, especially in high-risk men.

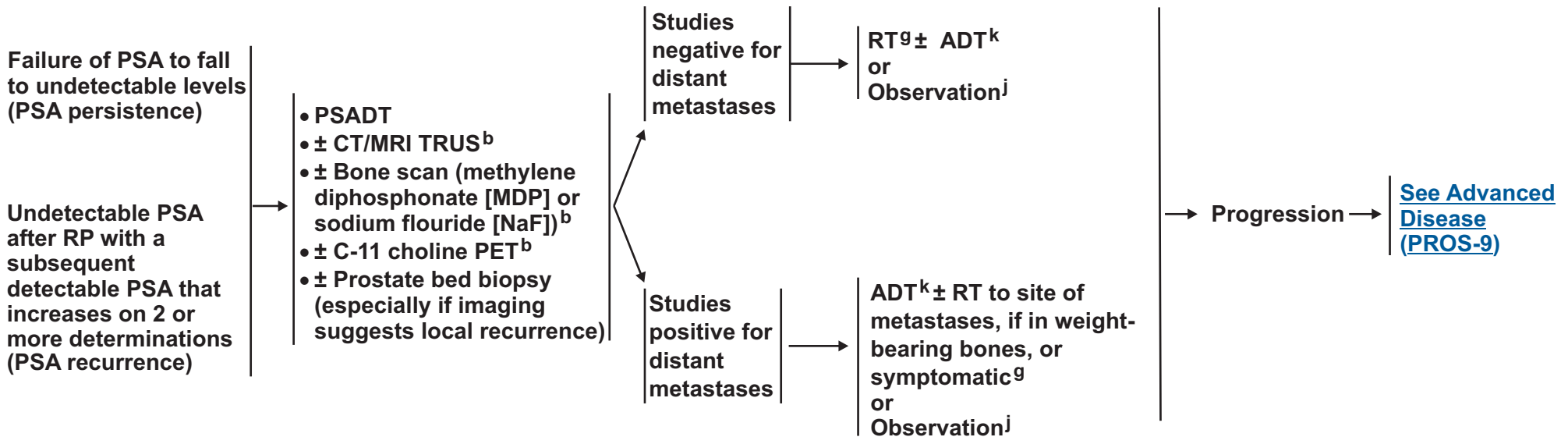
<sup>p</sup>RTOG-ASTRO (Radiation Therapy Oncology Group-American Society for Therapeutic Radiology and Oncology) Phoenix Consensus-1) PSA rise by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and 2) the date of failure is determined "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.

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**RADICAL PROSTATECTOMY BIOCHEMICAL FAILURE**



<sup>b</sup> See Principles of Imaging (PROS-B).

<sup>g</sup> See Principles of Radiation Therapy (PROS-D).

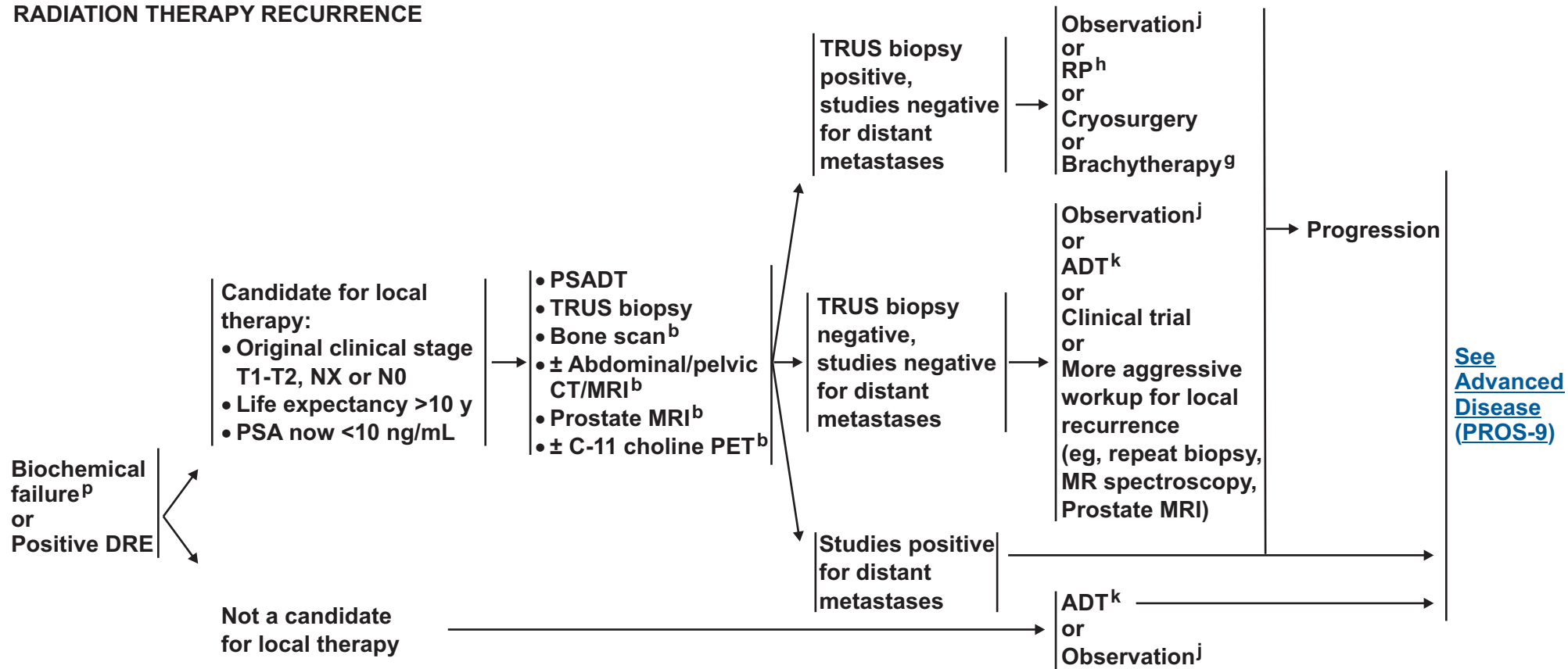
<sup>j</sup> Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent See Principles of Active Surveillance and Observation (PROS-C).

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### RADIATION THERAPY RECURRENCE



<sup>b</sup> See Principles of Imaging (PROS-B).

<sup>g</sup> See Principles of Radiation Therapy (PROS-D).

<sup>h</sup> See Principles of Surgery (PROS-E).

<sup>j</sup> Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent See Principles of Active Surveillance and Observation (PROS-C).

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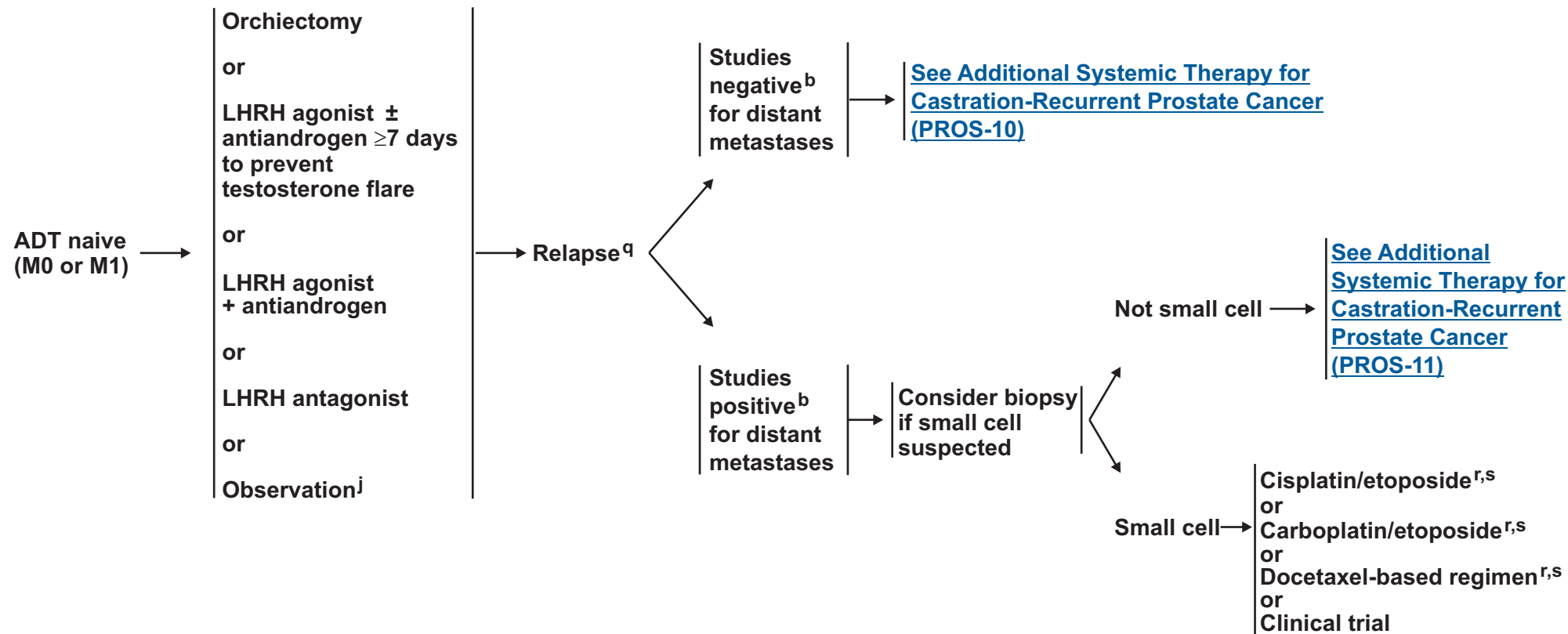
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### ADVANCED DISEASE: SYSTEMIC THERAPY



<sup>b</sup> See Principles of Imaging (PROS-B).

<sup>j</sup> Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent See Principles of Active Surveillance and Observation (PROS-C).

<sup>q</sup> Assure castrate level of testosterone.

<sup>r</sup> See Principles of Immunotherapy and Chemotherapy (PROS-G).

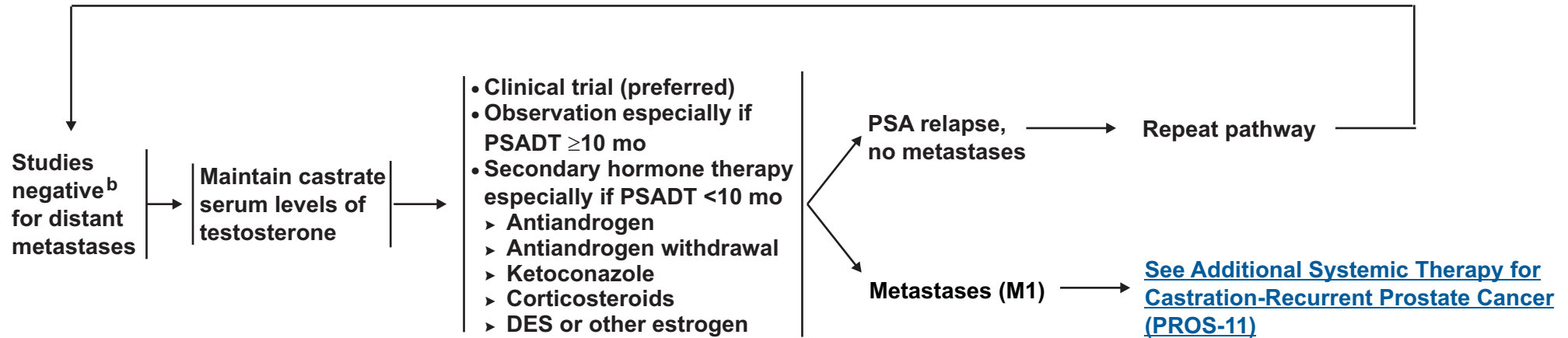
<sup>s</sup> See NCCN Guidelines for Small Cell Lung Cancer.

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### ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER

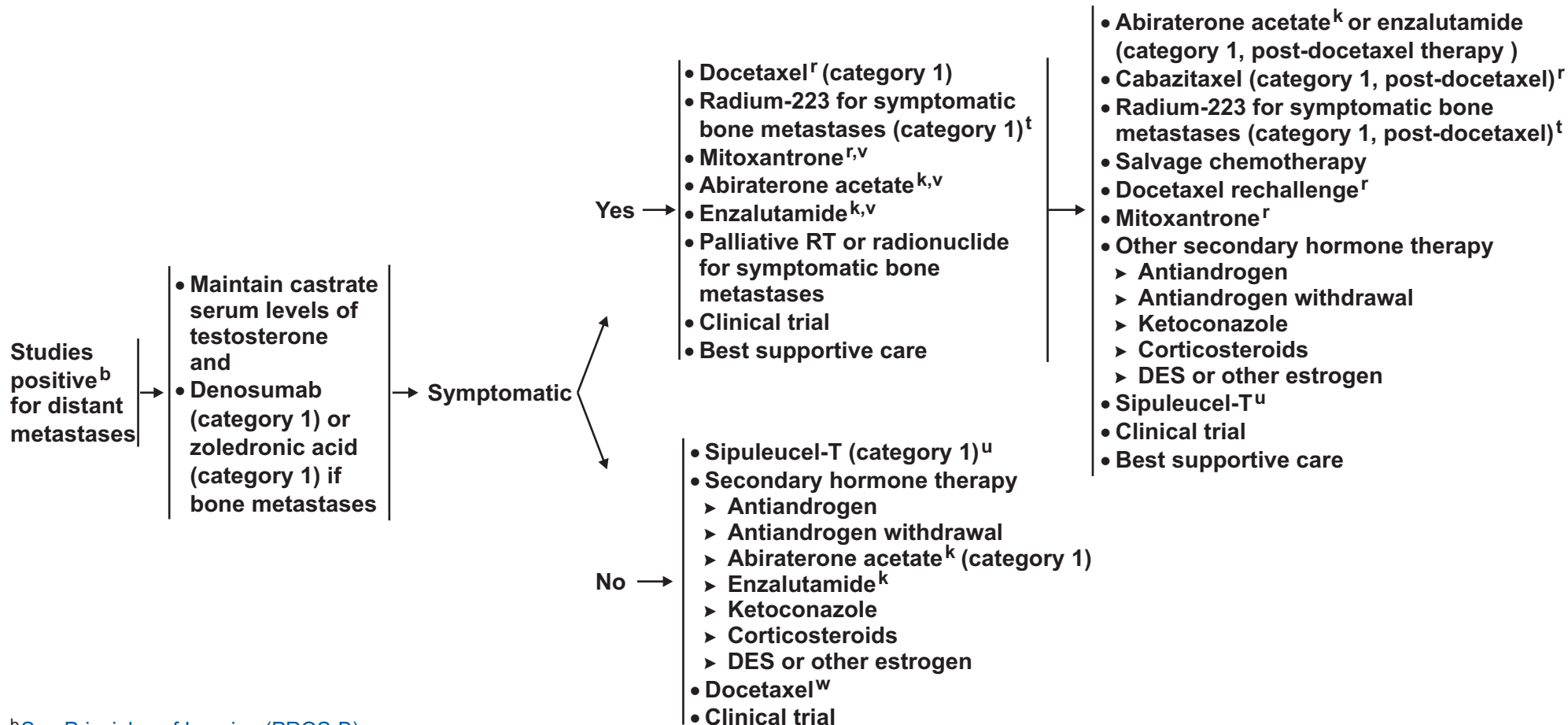


<sup>b</sup>[See Principles of Imaging \(PROS-B\)](#).

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**ADVANCED DISEASE: ADDITIONAL SYSTEMIC THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER**



<sup>b</sup>See Principles of Imaging (PROS-B)

<sup>k</sup>See Principles of Androgen Deprivation Therapy (PROS-F).

<sup>r</sup>See Principles of Immunotherapy and Chemotherapy (PROS-G).

<sup>t</sup>Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).

<sup>u</sup>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.

<sup>v</sup>For patients who are not candidates for docetaxel-based regimens.

<sup>w</sup>Although most patients without symptoms are not treated with 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.

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### 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](http://www.ssa.gov/OACT/STATS/table4c6.html)).
- Life expectancy can then be adjusted using the clinician's 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-year increments of age are reproduced from the [NCCN Guidelines for Senior Adult Oncology](#) for life expectancy estimation.<sup>1</sup>

<sup>1</sup>Howard DH. Life expectancy and the value of early detection. J Health Econ 2005;24:891-906.

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### PRINCIPLES OF IMAGING

#### Goals of Imaging

- Imaging is performed for the detection and characterization of disease in order to guide appropriate management.
- Imaging studies should be performed based on the best available clinical evidence and not influenced by business or personal interests of the care provider.
- Imaging techniques can evaluate anatomic or functional parameters.
  - Anatomic imaging techniques include plain film radiographs, ultrasound, CT, and MRI.
  - Functional imaging techniques include radionuclide bone scan, PET, and advanced MR techniques, such as spectroscopy and diffusion-weighted imaging (DWI).

#### Efficacy of Imaging

- The utility of imaging for men with early biochemical failure after RP depends on risk group prior to operation, pathologic Gleason grade and stage, PSA, and PSA doubling time (PSADT) after recurrence. Low and intermediate risk groups with low serum PSAs postoperatively have a very low risk of positive bone scans or CT scans.
- Frequency of imaging should be based on individual risk, age, PSADT, Gleason score, and overall health.
- Bone scans are rarely positive in asymptomatic men with PSA <10 ng/mL.

#### Plain Radiography

- Plain radiography can be used to evaluate symptomatic regions in the skeleton and is particularly useful for evaluation of risk for pathologic fracture. However, conventional plain x-rays will not detect a bone lesion until nearly 50% of the mineral content of the bone is lost or gained.

#### Ultrasound

- Ultrasound uses high-frequency sound waves to image small regions of the body.
  - Standard ultrasound imaging provides anatomic information.
  - Vascular flow can be assessed using Doppler ultrasound techniques.
- Endorectal ultrasound is used to guide transrectal biopsies of the prostate.
- Endorectal ultrasound can be considered for patients with suspected recurrence after RP.
- Advanced ultrasound techniques for imaging of the prostate and for differentiation between prostate cancer and prostatitis are under evaluation.

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### PRINCIPLES OF IMAGING

#### Bone Scan

- Radionuclide bone scan (also termed skeletal scintigraphy) is a nuclear medicine technique to evaluate for osseous metastatic disease.
  - A radioactive compound with affinity for bone matrix is injected and allowed to localize skeletal structures.
  - Sites of increased uptake imply accelerated bone turnover, and may indicate metastatic disease.
  - Osseous metastatic disease may be diagnosed based on the overall pattern of activity, or in conjunction with anatomic imaging.
- The primary bone scan techniques are:
  - Conventional bone scan performed using 99mTc-medronate and a gamma camera, either using planar imaging or 3-D imaging with single photon emission CT (SPECT).
  - PET bone scan performed using 18F-NaF and a PET scanner.
  - Additive value may be obtained from both techniques when imaging is performed using a hybrid imaging device (SPECT/CT, or PET/CT), which allows registration of SPECT or PET radiotracer localization on CT anatomy.
- Bone scan is indicated in the initial evaluation of patients at high risk for skeletal metastases.
  - T1 disease and PSA  $\geq 20$ , T2 disease and PSA  $\geq 10$ , Gleason score  $\geq 8$ , or T3/T4 disease
  - Any stage disease with symptoms suggestive of osseous metastatic disease
- Bone scan can be considered for the evaluation of the post-prostatectomy patient when there is failure of PSA to fall to undetectable levels, or when there is undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more subsequent determinations.
- Bone scan can be considered for the evaluation of patients with a rising PSA or positive DRE after RT if the patient is a candidate for additional local therapy.

#### Computed Tomography

- CT provides a high level of anatomic detail, and may detect gross extracapsular disease, nodal metastatic disease, and visceral metastatic disease.
  - CT is generally not sufficient to evaluate the prostate gland itself.
- CT may be performed with or without oral and intravenous contrast, and CT technique should be optimized to maximize diagnostic utility while minimizing radiation dose to the patient.
- CT is used for initial staging in select patients ([PROS-1](#))
  - T3 or T4 disease
  - Patients with T1 or T2 disease and nomogram indicated probability of lymph node involvement  $>10\%$  may be candidates for pelvic imaging, but the level of evidence is low.
- CT may be considered in patients after RP when PSA fails to fall to undetectable levels or when an undetectable PSA becomes detectable and increases on 2 or more subsequent determinations, or after RT for rising PSA or positive DRE if the patient is a candidate for additional local therapy.

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### PRINCIPLES OF IMAGING

#### Magnetic Resonance Imaging

- The strengths of MRI include high soft tissue contrast and characterization, multiparametric image acquisition, multiplanar imaging capability, and advanced computational methods to assess function.
  - ▶ MRI can be performed with or without the administration of intravenous contrast material
  - ▶ Resolution of MR images in the pelvis can be augmented with the use of an endorectal coil
- Standard MRI techniques can be considered for initial evaluation of high-risk patients.
  - ▶ T3 or T4 disease
  - ▶ Patients with T1 or T2 disease and nomogram indicated probability of lymph node involvement >10% may be candidates for pelvic imaging, but the level of evidence is low.
- MRI may be considered in patients after RP when PSA fails to fall to undetectable levels or when an undetectable PSA becomes detectable and increases on 2 or more subsequent determinations, or after RT for rising PSA or positive DRE if the patient is a candidate for additional local therapy
- Advanced MRI techniques (endorectal MRI, MR perfusion/diffusion, contrast enhancement, and MR spectroscopy) may provide additional information in certain clinical settings, such as rising PSA or positive DRE after RT in the setting of a negative prostate biopsy. Application of this technology may be particularly useful in men being considered for local salvage therapy

#### Positron Emission Tomography/Computed Tomography

- PET/CT using choline tracers may identify sites of metastatic disease in men with biochemical recurrence after primary treatment failure
  - ▶ Other choline radiotracers are under evaluation.
  - ▶ Further study is needed to determine the best use of choline PET/CT imaging in patients with prostate cancer.
- Oncologic PET/CT is performed typically using 8F-fluorodeoxyglucose (FDG), a radioactive analog of glucose.
  - ▶ In certain clinical settings, the use of FDG-PET/CT may provide useful information, but its routine use is not recommended at this time.
  - ▶ Data on the utility of FDG-PET/CT in patients with prostate cancer is limited.

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**PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION**

- 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 over-treatment of prostate cancer. The Panel recommends that patients and their physicians (ie, 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.
- The 2014 NCCN Guidelines for Prostate Cancer distinguish between active surveillance and observation. Both involve at least every-6-month monitoring but active surveillance may involve surveillance prostate biopsies. Evidence of progression will prompt conversion to potentially curative treatment in active surveillance patients, whereas monitoring continues until symptoms develop or are eminent (ie, PSA >100 ng/mL) in observation patients, who will then begin palliative ADT.
- Active surveillance is preferred for men with very low-risk prostate cancer and life expectancy  $\leq 20$  y. Observation is preferred for men with low-risk prostate cancer with life expectancy <10 y. [See Risk Group Criteria \(PROS-2\)](#).
- Active surveillance involves actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses.
- Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or change in exam or PSA levels that suggest symptoms are imminent.
- Patients with clinically localized prostate 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 in older men. Follow-up should include:
  - PSA no more often than every 6 mo unless clinically indicated
  - DRE no more often than every 12 mo unless clinically indicated
  - 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.
  - A repeat prostate biopsy should be considered as often as annually to assess for disease progression, because PSA kinetics may not be as reliable as monitoring parameters to determine progression of disease.
  - Repeat prostate biopsies are not indicated when life expectancy is less than 10 y or appropriate when men are on observation.
  - PSADT appears unreliable for identification of progressive disease that remains curable. Although multi-parametric MRI is not recommended for routine use, it may be considered if PSA rises and systematic prostate biopsy is negative to exclude the presence of an anterior cancer.
- 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

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### PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **Advantages of active surveillance:**
  - ▶ **Avoidance of 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**
- **Advantages of observation:**
  - ▶ **Avoidance of possible side effects of unnecessary definitive therapy and early initiation and/or continuous ADT**
- **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**
- **Disadvantages of observation:**
  - ▶ **Risk of urinary retention or pathologic fracture without prior symptoms or concerning PSA level.**

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### PRINCIPLES OF RADIATION THERAPY

#### Primary External Beam Radiation Therapy (EBRT)

- Highly conformal RT techniques should be used to treat prostate cancer.
- Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate ( $\pm$  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.
- Moderately hypofractionated image-guided IMRT regimens (2.4 to 4 Gy per fraction over 4-6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated.
- Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.
- 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 to 3 y (category 1).
- Patients with intermediate-risk cancer may be considered for pelvic lymph node irradiation and 4- to 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 of IGRT using CT, ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.

#### Primary/Salvage 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)  $\pm$  4- to 6-mo neoadjuvant/concomitant/adjuvant ADT. Patients with high-risk cancers may be treated with a combination of EBRT (40-50 Gy) and brachytherapy  $\pm$  2 to 3 y-neoadjuvant/concomitant/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 are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, increased toxicity would be expected from ADT and prostate size may not decline.
- Post-implant dosimetry must be performed to document the quality of the implant.
- The recommended prescribed doses for LDR monotherapy are 145 Gy for Iodine-125 and 125 Gy for Palladium-103. The corresponding boost doses after 40 to 50 Gy EBRT are 110 Gy and 90 to 100 Gy, respectively.
- High-dose rate (HDR) brachytherapy can be used alone or in combination with EBRT (40-50 Gy) instead of LDR. Commonly used boost regimens include 9.5 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions. A commonly used regimen for HDR treatment alone includes 13.5 Gy x 2 fractions.
- Permanent LDR or temporary HDR brachytherapy can be used as treatment for a local recurrence following EBRT or primary brachytherapy. Radiation dose depends on the original primary external beam dose and ranges from 100 to 110 Gy for LDR and 9 to 12 Gy x 2 fractions for HDR.

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### PRINCIPLES OF RADIATION THERAPY

#### Post-Prostatectomy Radiation Therapy

- Evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.
- Indications for adjuvant RT include pT3 disease, positive margin(s), Gleason score 8-10, or seminal vesicle involvement. Adjuvant RT is usually given within 1 year after RP and once any operative side effects have improved/stabilized. Patients with positive surgical margins and PSADT >9 mo may benefit the most.
- Indications for salvage RT include an undetectable PSA that becomes detectable and then increases on 2 subsequent measurements. Treatment is most effective when pre-treatment PSA is <1 ng/mL and PSADT is slow.
- The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64-70 Gy in standard fractionation.
- The defined target volumes include the prostate bed. The pelvic lymph nodes may be irradiated, but pelvic radiation is not necessary.

#### Radiopharmaceutical Therapy

- Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in men who have CRPC with symptomatic bone metastases, but no visceral metastases. Radium-223 differs from beta-emitting agents, such as samarium 153 and strontium 89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3-4 hematologic toxicity (2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at a low risk.
- Radium-223 is administered intravenously once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.
- Prior to the initial dose, patients must have absolute neutrophil count  $\geq 1.5 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , and hemoglobin  $\geq 10g/dL$ .
- Prior to subsequent doses, patients must have absolute neutrophil count  $\geq 1 \times 10^9/L$  and platelet count  $\geq 50 \times 10^9/L$  (per label, although this may be too low in practice). Radium-223 should be discontinued if a delay of 6 to 8 weeks does not result in the return of blood counts to these levels.
- Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms are likely related to the fact that radium-223 is predominantly eliminated by fecal excretion.
- At the present time, except on a clinical trial, radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression.
- Concomitant use of denosumab or zoledronic acid does not interfere with the beneficial effects of radium-223 on survival.

#### 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.

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### PRINCIPLES OF SURGERY

#### Pelvic Lymph Node Dissection:

- 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 bound 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% predicated 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 an appropriate therapy for any patient with clinically localized prostate cancer that can be completely excised surgically, who has a life expectancy of  $\geq 10$  years, and has no serious comorbid conditions that would contraindicate an elective operation.
- High-volume surgeons in high-volume centers generally provide better outcomes.
- Laparoscopic and robot-assisted RP are used commonly. In experienced hands, the results of these approaches appear comparable to open surgical approaches.
- Blood loss can be substantial with RP, 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 RP, preoperative erectile function, and the degree of preservation of the cavernous nerves. Replacement of resected nerves with nerve grafts has not been shown to be beneficial. Early restoration of erections may improve late recovery.
- Salvage RP is an option for highly selected patients with local recurrence after EBRT, brachytherapy, or cryotherapy in the absence of metastases, but the morbidity (ie, incontinence, loss of erection, anastomotic stricture) is high.

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### PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

#### ADT for Localized Disease

- Neoadjuvant ADT for RP is strongly discouraged outside of a clinical trial.
- 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.
- 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 RP resulted in significantly improved overall survival compared to men who received delayed ADT. Therefore, such patients should be considered for immediate ADT.
- Many of the side effects of continuous ADT are cumulative over time on ADT.

#### ADT for Biochemical Failure

- 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.
- Most patients will have a good 15-year prognosis, but their prognosis is best approximated by the absolute level of PSA, the rate of change in the PSA level (PSADT), 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 a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.
- Some patients are candidates for salvage after biochemical failure, which may include radiation after failed operation or RP or cryosurgery after failed radiation.
- Men with prolonged PSA doubling times (>12 mo) and who are older are candidates for observation.
- Men who choose ADT should consider intermittent ADT. A phase 3 trial that compared intermittent to continuous ADT showed that intermittent ADT was not inferior to continuous ADT with respect to survival, and quality of life was better for the intermittent ADT arm. The 7% increase in prostate cancer deaths in the intermittent ADT arm was balanced by more non-prostate cancer deaths in the continuous ADT arm.

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### PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

#### ADT for Metastatic Disease

- ADT is the gold standard for men with metastatic prostate cancer.
- A phase 3 trial compared continuous ADT to intermittent ADT, but the study was statistically inconclusive for non-inferiority, however, quality of life measures for erectile function and mental health were better in the intermittent ADT arm after 3 months off ADT compared to the continuous ADT arm.
- Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.

#### 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 modest to no benefit over castration alone in patients with metastatic disease.
- Antiandrogen therapy should precede or be coadministered 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.
- Antiandrogen monotherapy appears to be less effective than medical or surgical castration and should not be recommended. The side effects are different but overall more tolerable.
- No clinical data support the use of triple androgen blockade (finasteride or dutasteride with combined androgen blockade).
- 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 remains uncertain. The optimal level of serum testosterone decline has yet to be defined.

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### PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

#### Secondary Hormonal Manipulation

- **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.**
- **Once the tumor becomes resistant to initial ADT, there are a variety of options that may afford clinical benefit. The available options are based on whether the patient has evidence of metastases by imaging, non-metastatic CRPC vs. metastatic CRPC (mCRPC), and whether or not the patient is symptomatic.**
- **In the setting in which patients are docetaxel-naive and have no or minimal symptoms, administration of secondary hormonal manipulations including addition of, or switching to, a different anti-androgen (flutamide, bicalutamide, nilutamide, enzalutamide), addition of adrenal/paracrine androgen synthesis inhibitors (ketoconazole, abiraterone), or use of an estrogen, such as DES, can be considered.**
- **In a randomized controlled trial in the setting of mCRPC prior to docetaxel chemotherapy, abiraterone (1000 mg daily on an empty stomach) and low-dose prednisone (5 mg BID) compared to prednisone alone improved radiographic progression-free survival (rPFS), time to initiation of chemotherapy, time to onset or worsening of pain, and time to deterioration of performance status. There was a trend toward improvement in overall survival. Use of abiraterone and prednisone in this setting is a category 1 recommendation. The side effects of abiraterone that require ongoing monitoring include hypertension, hypokalemia, peripheral edema, atrial fibrillation, congestive heart failure, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.**
- **In uncontrolled studies of docetaxel-naive men, enzalutamide (160 mg daily) resulted in significant PSA declines, but the use of enzalutamide in the setting is category 2A until the results of the completed randomized, controlled trial in this setting are reported. The side effects of enzalutamide that require long-term monitoring include fatigue, diarrhea, hot flashes, headache, and seizures (reported in 0.9% of men on enzalutamide).**
- **Both randomized trials of abiraterone and enzalutamide in the pre-docetaxel setting were conducted in men who had no or minimal symptoms due to mCRPC. How these agents compare to docetaxel for pain palliation in this population of patients is not clear. Both drugs have palliative effects in the post-docetaxel setting. Abiraterone is approved in this setting and has a category 1 recommendation. Enzalutamide awaits approval in this setting. Both drugs are suitable options for men who are not good candidates to receive docetaxel.**
- **In the post-docetaxel CRPC population, enzalutamide and abiraterone plus prednisone have been shown to extend survival in randomized, controlled trials. Therefore, each agent has a category 1 recommendation.**
- **Evidence-based guidance on the sequencing of these agents in either pre- or post-docetaxel remains unavailable.**

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### PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

#### Monitor/Surveillance

- ADT has a variety of adverse effects including hot flashes, loss of libido and erectile dysfunction, shrinkage of penis and testicles, loss of muscle mass and strength, fatigue, depression, hair loss, 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](http://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 >50 y of age; and 2) additional treatment for men when the 10-y probability of hip fracture is  $\geq 3\%$  or the 10-y probability of a major osteoporosis-related fracture is  $\geq 20\%$ . Fracture risk can be assessed using FRAX®, the algorithm recently released by WHO. ADT should be considered “secondary osteoporosis” when using the FRAX® algorithm. Treatment options to increase bone density, a surrogate for fracture risk, include denosumab (60 mg SQ every 6 mo), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly).
- A baseline DEXA scan should be obtained before starting therapy in men at increased risk for fracture based on FRAX® screening. A follow-up DEXA scan after 1 year of therapy is recommended by the International Society for Clinical Densitometry, although there is no consensus on the optimal approach to monitoring the effectiveness of drug therapy. Use of biochemical markers of bone turnover to monitor response to therapy is not recommended.
- The serum level of 25-hydroxy vitamin D and average daily dietary intake of vitamin D will assist the nutritionist in making a patient-specific recommendation for vitamin D supplementation. There are currently no guidelines on how often to monitor vitamin D levels. However, for those who require monitoring with DEXA scans, it makes sense to check the serum vitamin D level at the same time.
- 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.

**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 IMMUNOTHERAPY AND CHEMOTHERAPY

- Men with advanced prostate cancer should be encouraged to participate in clinical trials and referred early to a medical oncologist.
- Men with asymptomatic or minimally symptomatic mCRPC 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
- Systemic chemotherapy should be reserved for men with mCRPC, in particular those who are symptomatic except when studied in a clinical trial. Certain subsets of patients with mCRPC who have more anaplastic features may benefit from earlier chemotherapy, but this has not been studied adequately in prospective trials.
- Every 3-week docetaxel with or without prednisone is the preferred first-line chemotherapy treatment based on phase 3 clinical trial data for men with symptomatic mCRPC. Radium-223 has been studied in symptomatic patients who are not candidates for docetaxel-based regimens and resulted in improved overall survival. Although abiraterone and enzalutamide have not been studied in this setting, both therapies were beneficial in patients with symptoms after docetaxel and are reasonable options in this setting. Mitoxantrone and prednisone may provide palliation but have not been shown to extend survival. ([See PROS-F, 3 of 4](#)).
- 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.

[Continue on the next page](#)

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### PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

- **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.**
- **In men with CRPC 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 RT 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 comorbidities, whether the patient has been treated with zoledronic acid previously, logistics, and/or cost considerations.**
    - ◊ **Zoledronic acid is given intravenously every 3 to 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. Patients should be referred for dental evaluation before starting either zoledronic acid or denosumab. If invasive dental procedures are required, bone-targeted therapy should be withheld until the dentist indicates that the patient has healed completely from all dental procedure(s).**
  - ▶ **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 ADT for bone metastases.**

**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.



**Table 1.**  
**TNM Staging System For Prostate Cancer**

**Primary Tumor (T)**

**Clinical**

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

\*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)\***

<b>pT2</b>	Organ confined
<b>pT2a</b>	Unilateral, involving one-half of one side or less
<b>pT2b</b>	Unilateral, involving more than one-half of one side but not both sides
<b>pT2c</b>	Bilateral disease
<b>pT3</b>	Extraprostatic extension
<b>pT3a</b>	Extraprostatic extension or microscopic invasion of the bladder neck**
<b>pT3b</b>	Seminal vesicle invasion
<b>pT4</b>	Invasion of bladder, rectum

\*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**

<b>NX</b>	Regional lymph nodes were not assessed
<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Metastasis in regional lymph node(s)

**Pathologic**

<b>PNX</b>	Regional nodes not sampled
<b>pN0</b>	No positive regional nodes
<b>pN1</b>	Metastases in regional nodes(s)

**Distant Metastasis (M)\***

<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis
<b>M1a</b>	Non-regional lymph node(s)
<b>M1b</b>	Bone(s)
<b>M1c</b>	Other site(s) with or without bone disease

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

[Continue](#)

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### ANATOMIC STAGE/PROGNOSTIC GROUPS \*

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA < 10	Gleason ≤ 6
	T2a	N0	M0	PSA < 10	Gleason ≤ 6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA < 20	Gleason 7
	T1a-c	N0	M0	PSA ≥ 10 < 20	Gleason ≤ 6
	T2a	N0	M0	PSA < 20	Gleason ≤ 7
	T2b	N0	M0	PSA < 20	Gleason ≤ 7
IIB	T2b	N0	M0	PSA X	Gleason X
	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥ 20	Any Gleason
III	T1-2	N0	M0	Any PSA	Gleason ≥ 8
	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

\*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 Type

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

### 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 then 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 ≤ 6**

**Gleason 7**

**Gleason 8-10**

#### Gleason score cannot be processed

Well differentiated (slight anaplasia)

Moderately differentiated (moderate anaplasia)

Poorly differentiated/undifferentiated (marked anaplasia)

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# NCCN Guidelines Version 1.2014 Prostate Cancer

## Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 07/26/13

### 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.**

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## 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 from 30% in the period from 1989 to 1992 ( $P < .0001$ ) to 45% in the period from 1999 to 2001.<sup>1</sup> 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.<sup>2,3</sup> Fortunately, the age-adjusted death rates from prostate cancer have also declined (-4.1% annually from 1994 to 2001). Researchers have estimated prostate cancer to account for 28,170 deaths in 2012.<sup>2</sup> 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 result in unnecessary side effects, which impair quality of life and health care expenses, while decreasing the value of PSA and digital rectal exam (DRE) 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 Guidelines Panel of leading experts from the fields of urology, radiation oncology, and medical oncology at NCCN 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](http://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.<sup>4</sup> 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.<sup>5</sup> 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, a 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<sup>4</sup> and modified further by a clinician's assessment of overall health. Examples of 5-year increments of age are reproduced from the NCCN Guidelines for Senior Adult Oncology. Other prognostic indices have been researched but are more difficult to employ clinically. For example, Lee et al. developed a prognostic index for 4-year mortality based on information that combines both comorbid and functional measures.<sup>6</sup> Twelve independent predictors of mortality were identified, including 2 demographic measures (ie, age, 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 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 (ie, probability of a rising PSA, which is also termed *biochemical recurrence* or *PSA failure*) after definitive local therapy.<sup>7</sup> This risk group stratification has been published widely and validated, and it provides a better basis for treatment recommendations than clinical stage alone.<sup>8,9</sup>

The Partin tables<sup>10,11</sup> 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 (ie, extraprostatic) extension; 3) seminal vesicle invasion; or 4) lymph node metastasis.<sup>11</sup> 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 (eg, 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,<sup>12</sup> radical prostatectomy,<sup>13-15</sup> neurovascular bundle preservation<sup>16-18</sup> or omission of pelvic lymph node dissection (PLND) during radical prostatectomy,<sup>19</sup> brachytherapy,<sup>13,20,21</sup> or external beam radiation therapy (EBRT).<sup>13,22</sup> Biochemical progression-free survival can be reassessed postoperatively using age, diagnostic serum PSA, and pathologic grade and stage.<sup>6,23</sup> Potential success of adjuvant or salvage radiation therapy (RT) after unsuccessful radical prostatectomy can be assessed using a nomogram.<sup>13,24</sup>

None of the current models predict with perfect accuracy, and only some of these models predict metastasis<sup>6,13,25,26</sup> and cancer-specific death.<sup>15,27</sup> New independent prognostic factors are being developed.<sup>28</sup> 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.<sup>29</sup> 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 Guidelines Panel recommends that NCCN risk categories be used to begin the discussion of options for the treatment of clinically localized prostate cancer, and that 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) retaining quality of life and normal activities; 3) ensuring that small indolent cancers do not receive unnecessary treatment; and 4) decreased initial costs. The disadvantages of active surveillance include: 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;<sup>30</sup> 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.

### Rationale

The high prevalence of prostate cancer upon autopsy of the prostate,<sup>31</sup> the high frequency of positive prostate biopsies in men with normal DREs and serum PSA values,<sup>32</sup> 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<sup>33,34</sup> or 100 men with low-risk prostate cancer<sup>35</sup> 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<sup>33-39</sup> has been informed further by publication of the Goteborg study, a subset of the

European Randomized Study for Screening of Prostate Cancer (ERSPC).<sup>40</sup> 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.<sup>41</sup>

The best models of prostate cancer detection and progression estimate that 23% to 42% of all U.S. screen-detected cancers are overtreated<sup>42</sup> and that PSA detection was responsible for up to 12.3 years of lead-time bias.<sup>43</sup> The NCCN Guidelines 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 cancer and life expectancy estimated <10 years. However, the NCCN Guidelines 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.

### Application

Epstein et al. introduced clinical criteria to predict pathologically “insignificant” prostate cancer.<sup>44</sup> 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, ≤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.<sup>23,45</sup> A new nomogram may be better.<sup>46</sup> Although many variations upon this definition have been proposed (reviewed by Bastian, et al.<sup>47</sup>), a consensus of the NCCN Guidelines 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.<sup>43</sup>

Active surveillance is considered the best option for patients with low-risk cancers or for patients with a short life expectancy. Lu-Yao et al.<sup>48</sup> 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 Kaplan<sup>49</sup>). For example, a study that randomly assigned 731 men with localized disease to radical prostatectomy or observation reported no difference in overall or disease-specific mortality,<sup>50</sup> while another randomized trial in 695 patients with early disease demonstrated reduced risk of death with surgical intervention compared to active surveillance.<sup>51</sup>

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. For example, Liu et al. conducted a simulation model on 200,000 men with low-risk prostate cancer managed with active surveillance or radical prostatectomy to calculate quality-adjusted life expectancy, life expectancy, prostate cancer-specific mortality, and years of treatment side effects.<sup>52</sup> Men 65 years of age and of average health were used as a comparator group. Operation produced 0.3 additional years of life expectancy, 1.6 additional years of incontinence or impotence, and an absolute decrease of 4.9% in prostate cancer-specific mortality compared to active surveillance. The authors concluded that age, health status, and patient preference affect the choice between active surveillance and surgery, and older age and poorer health status should favor active surveillance.

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.<sup>53-55</sup> The NCCN Guidelines Panel recommends treatment in most men who demonstrate a Gleason grade of 4 or 5 on repeat biopsy, have cancer in a greater number or greater extent of prostate biopsies, or have a PSA doubling time of less than 3 years. Whether these trigger points will ultimately be validated or not remains uncertain. However, the field appears to be moving toward consensus as more clinical series are reported and prospective clinical trials enroll patients.<sup>56</sup>

### Surveillance Program and Reclassification Criteria

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, DRE 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.<sup>53,57-60</sup> Reclassification criteria have been met by 23% of men with a median follow-up of 7 years in the Toronto experience,<sup>58</sup> 33% of men with a median follow-up of 3 years in the Johns Hopkins experience,<sup>60</sup> and 16% of men with a median follow-up of 3.5 years in the UCSF experience<sup>57</sup> (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.<sup>61</sup> 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.<sup>62</sup> 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 3 patients who died of prostate cancer in their experience with 450 men.<sup>58</sup> 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 for a median of 6.8 years, overall survival was 78.6% and prostate cancer-specific survival was 92.2%.<sup>58</sup> Of the 30% (n=145) of men who progressed, 8% were from an 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 RT with or without androgen deprivation therapy (ADT), and 10 with ADT 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,<sup>60</sup> 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 pathologic Gleason grade, pathologic stage, and margin positivity. All men treated by radical prostatectomy after progression on active

surveillance had freedom from biochemical progression at median follow-up of 37.5 months, compared to 97% of men in the primary radical prostatectomy group at median follow-up of 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,<sup>37</sup> those with urinary tract infection are often fluoroquinolone-resistant,<sup>63</sup> and radical prostatectomy may become technically challenging after multiple sets of biopsies, especially as it pertains to potency preservation.<sup>64</sup>

## Radiation Therapy

### External Beam Radiation Therapy

EBRT is one of the principle treatment options for clinically localized prostate cancer. The NCCN Guidelines 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 conformal radiation therapy (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.<sup>25,65-67</sup> The second-generation 3D technique, intensity-modulated radiation therapy (IMRT), significantly reduces the risk of gastrointestinal toxicities compared to 3D-CRT.<sup>68,69</sup> IMRT is the preferred technique over 3D-CRT; IMRT increases treatment cost<sup>70</sup> but appears to decrease rates of salvage therapy without increasing side effects, especially when applied to patients with high-risk disease.<sup>71</sup> Daily prostate localization using image-guided radiation therapy (IGRT) is essential with either 3D-CRT or IMRT 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 have suggested that dose escalation is associated with improved biochemical outcomes.<sup>72-75</sup> Kuban et al.<sup>75</sup> published an 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%,  $P = .001$ ). In light of these findings, the conventional 70 Gy is no longer considered adequate. A dose of 75.6 to 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.<sup>68,76,77</sup>

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 to 3 years or 4 to 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 to 6 months of neoadjuvant/concomitant/adjuvant ADT. Patients with low-risk cancers should not receive either pelvic lymph node radiation or ADT.

EBRT of the primary prostate tumor shows several distinct advantages over surgical therapy. RT avoids complications associated with radical prostatectomy, such as bleeding and transfusion-related effects and risks associated with anesthesia, such as myocardial infarction and pulmonary embolus. 3D-CRT and IMRT techniques are widely available in community practice and are possible for patients over a wide range of ages. EBRT includes a low risk of urinary incontinence and stricture as well as a good chance of short-term preservation of erectile function.<sup>78</sup> 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.<sup>79</sup> However, the addition of ADT increases the risk for erectile dysfunction.<sup>80</sup>

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.<sup>78,80</sup> In addition, if the cancer recurs, salvage radical prostatectomy is associated with a higher risk of complications than primary radical prostatectomy.<sup>81</sup> Contraindications to RT include prior pelvic irradiation, active inflammatory disease of the

rectum, or a permanent indwelling Foley catheter. Relative contraindications include very low bladder capacity, chronic moderate or severe diarrhea, bladder outlet obstruction requiring a suprapubic catheter, and inactive ulcerative colitis.

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 *Adjuvant or salvage therapy after radical prostatectomy*).

### Proton Therapy

Proton beams can be used as an alternative radiation source.<sup>82</sup> The costs associated with proton beam facility construction and proton beam treatment are high.<sup>83</sup> However, theoretically, protons may reach deeply located tumors with less damage to surrounding tissues. A single center report of prospectively collected quality-of-life data 3 months, 12 months, and >2 years after treatment revealed significant problems with incontinence, bowel dysfunction, and impotence.<sup>84</sup> Perhaps most concerning is that only 28% of men with normal erectile function maintained normal erectile function after therapy. Two comparisons between men treated with proton beam therapy and EBRT show similar early toxicity rates.<sup>83,84</sup> Therefore, proton therapy is not recommended for routine use at this time, since clinical trials have not yet yielded data that demonstrate 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  $\alpha/\beta$  ratio,<sup>85</sup> most commonly reported between 1 and 4. These values are similar to that for the rectal mucosa. Since the  $\alpha/\beta$  ratio for prostate cancer is similar to or lower than the surrounding tissues responsible for most of the toxicity reported with RT, 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, which are safe to administer only with precise delivery.<sup>86</sup> Single institution series with median follow-up as long as 5 years<sup>87-91</sup> 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.<sup>85-91</sup> 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 (1.8-2.0 Gy per fraction).

### Brachytherapy

Brachytherapy is used traditionally for low-risk cases since earlier studies found it less effective than EBRT for high-risk disease.<sup>9,92</sup> However, increasing evidence suggests that technical advancements in brachytherapy may provide a role for contemporary brachytherapy in high-risk localized and locally advanced prostate cancer.<sup>93</sup> Brachytherapy involves placing radioactive sources into the prostate tissue. There are currently two methods of prostate brachytherapy: low dose-rate (LDR) and high dose-rate (HDR).

#### LDR Brachytherapy

LDR brachytherapy consists of placement of permanent seed implants in the prostate. The short range of the radiation emitted from these low-energy sources allows delivery of adequate dose levels 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.

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.<sup>94</sup> 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.<sup>80</sup> 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.<sup>95,96</sup>

Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers (cT1c–T2a, Gleason grade 2-6, PSA <10 ng/mL). For intermediate-risk cancers, brachytherapy may be combined with EBRT (45 Gy) with or without neoadjuvant ADT, but the complication rate increases.<sup>97,98</sup> Patients with high-risk cancers are generally considered poor candidates for permanent 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.<sup>99</sup> The recommended prescribed doses for monotherapy are 145 Gy for iodine-125 and 125 Gy for palladium-103.

### **HDR Brachytherapy**

HDR brachytherapy, which involves temporary insertion of a radiation source, is a newer approach that provides a “boost” dose in addition to EBRT for patients at high risk of recurrence. Combining EBRT (40-50 Gy) and HDR brachytherapy allows dose escalation while minimizing acute or late toxicity in patients with high-risk localized or locally advanced cancer.<sup>100-103</sup> Studies have demonstrated reduced risk of recurrence with the addition of brachytherapy to EBRT.<sup>104-106</sup> An analysis of a cohort of 12,745 high-risk patients found that treatment with brachytherapy (HR, 0.66; 95% CI, 0.49-0.86) or brachytherapy plus EBRT (HR, 0.77; 95% CI, 0.66-0.90) lowered disease-specific mortality compared to EBRT alone.<sup>107</sup> Common boost doses include 9.5 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, or 4.0 to 6.0 Gy x 4 fractions.

Addition of ADT to brachytherapy and EBRT is common for patients at high risk of recurrence. The outcome of trimodality treatment is excellent, with 9-year progression-free survival and disease-specific survival reaching 87% and 91%, respectively.<sup>108,109</sup> However, it is unclear whether the ADT component contributes to outcome improvement. D’Amico et al. studied a cohort of 1342 patients with PSA over 20 ng/mL and clinical T3/T4 and/or Gleason score 8 to 10 disease.<sup>110</sup> Addition of either EBRT or ADT to brachytherapy did not confer an advantage over brachytherapy alone. The use of all three modalities reduced prostate cancer-specific mortality compared to brachytherapy alone (adjusted HR, 0.32; 95% CI, 0.14-0.73). Other analyses did not find an improvement in failure rate when ADT was added to brachytherapy and EBRT.<sup>111,112</sup>

Two groups have observed a lower risk of urinary frequency, urgency, and rectal pain with HDR brachytherapy compared with LDR brachytherapy (permanent seed implant).<sup>113,114</sup> Vargas et al.<sup>115</sup> reported that HDR brachytherapy results in a lower risk of erectile dysfunction than LDR brachytherapy.

### Radiopharmaceutical Therapy

In May 2013, the Food and Drug Administration (FDA) approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This first-in-class radiopharmaceutical was approved for treatment of metastatic castration-recurrent prostate cancer (CRPC) in patients with symptomatic bone metastases and no known visceral metastatic disease. Approval was based on clinical data from a multicenter, phase III, randomized trial including 921 men with symptomatic CRPC, 2 or more bone metastases, and no known visceral disease.<sup>116</sup> Fifty-seven percent of the patients received prior docetaxel and all patients received best supportive care. Patients were randomized in a 2:1 ratio to 6 monthly radium-223 intravenous injections or placebo. Compared to placebo, radium-223 significantly improved overall survival (median 14.9 months vs. 11.3 months; HR, 0.70; 95% CI, 0.058–0.83;  $P < .001$ ) and prolonged time to first skeletal-related event (SRE) (median 15.6 months vs. 9.8 months). Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, 13% anemia), likely due to the short range of radioactivity.<sup>116</sup> Fecal elimination of the agent led to generally mild non-hematological side effects, which included nausea, diarrhea, and vomiting.

### 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.<sup>117</sup> 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%) ( $P = .002$ ); however, the retreatment rate was higher in the 8-Gy group (18%) than in the 30-Gy group (9%) ( $P < .001$ ).<sup>118</sup> 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.<sup>119</sup>

Beta-emitting radiopharmaceuticals are an effective and appropriate option for patients with wide-spread metastatic disease, particularly if they are no longer candidates for effective chemotherapy.<sup>119</sup> Since many patients have multifocal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Unlike the alpha-emitting agent radium-223, beta-emitters confer no survival advantage and are palliative. Radiopharmaceuticals developed for the treatment of painful bone metastases most commonly used for prostate cancer include strontium-89 (89Sr) and samarium-153 (153Sm).<sup>120</sup>

### 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.<sup>121,122</sup> Stephenson et al.<sup>15</sup> 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.<sup>123,124</sup> Laparoscopic and robot-assisted radical prostatectomy are used commonly and are considered comparable to conventional approaches in experienced hands.<sup>125,126</sup> Minimally invasive techniques have added costs to treatment of clinically localized prostate cancer.<sup>70</sup> Reports of outcomes—quality of life and oncologic—that evaluated robot-assisted radical prostatectomy early in its adoption raised concerns. In a cohort study using U.S. 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 for blood transfusions, and fewer surgical complications, but rates of incontinence and erectile dysfunction were higher.<sup>127</sup> Oncologic outcome of a robotic versus open approach was similar when assessed by use of additional therapies<sup>127</sup> or rate of positive surgical margins,<sup>128</sup> although longer follow-up is necessary. A meta-analysis on 19 observational studies (n=3893) reported less blood loss and lower transfusion rates with minimally invasive techniques than with open operation.<sup>128</sup> Risk of positive surgical margins was the same. Two recent meta-analyses showed a statistically significant advantage in favor of a robotic approach compared to an open approach in 12-month urinary continence (OR, 1.53; 95% CI 1.04-2.25;  $P = .03$ )<sup>129</sup> and potency recovery (OR, 2.84; 95% CI 1.46-5.43;  $P = .002$ ).<sup>130</sup>

Return of urinary continence after operation may be improved by preserving the urethra beyond the prostatic apex and by avoiding damage to the distal sphincter mechanism. Bladder neck preservation

may allow more rapid recovery of urinary control.<sup>131</sup> 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.<sup>132</sup> For patients undergoing wide resection of the neurovascular bundles, replacement of resected nerves with nerve grafts does not appear to be effective.<sup>133</sup>

### Pelvic Lymph Node Dissection

The decision to perform PLND should be guided by the probability of nodal metastases. The NCCN Guidelines 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.<sup>134</sup>

PLND should be performed using an extended technique.<sup>135,136</sup> An extended PLND includes removal of all node-bearing 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.<sup>137-139</sup> A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to the elimination of microscopic metastases.<sup>138,140-142</sup> PLND can be performed safely laparoscopically, robotically, or open, and complication rates should be similar for the three approaches.



### 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 coadministered with LHRH agonist and be continued in combination for at least 7 days.<sup>143,144</sup>

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 coadministration of antiandrogen is necessary. Degarelix was the first LHRH antagonist approved by the FDA in 2008 for treatment of men with advanced prostate cancer. The pivotal trial was a randomized open-label study of 610 patients.<sup>145</sup> 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% to 20% over LHRH agonist monotherapy.<sup>146,147</sup> 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.<sup>148</sup> 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.<sup>149</sup> The role of adjuvant ADT after surgery is restricted to cases with positive pelvic lymph nodes. Studies in this area reveal mixed findings. Messing et al. randomly assigned patients to immediate ADT or observation who were found to have positive lymph nodes at the time of radical prostatectomy.<sup>150</sup> 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, 1.01-3.35). 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.<sup>151</sup> 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.<sup>152</sup>

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 8113 patients with prostate cancer who were managed with watchful waiting, radiotherapy, or radical prostatectomy.<sup>153</sup> 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.<sup>154</sup> 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 do 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 (ie, what level of PSA) remain controversial. Because the benefit of ADT is unclear,<sup>151</sup> 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 to reduce ADT side effects. This approach was demonstrated to be non-inferior to continuous ADT with respect to overall survival for patients with non-metastatic biochemical recurrence after RT in a randomized trial (n=1386).<sup>155</sup> Two large intergroup studies are comparing the efficacy of intermittent and continuous ADT in the advanced disease setting (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 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.<sup>156,157</sup>

FDA approval in the post-docetaxel setting was based on the results of a phase III, randomized, placebo-controlled trial (COU-AA-301) in men with metastatic CRPC previously treated with docetaxel-containing

regimens.<sup>158,159</sup> 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. In the final analysis, the median survival was 15.8 vs. 11.2 months in the abiraterone and placebo arm, respectively (HR, 0.74; 95% CI, 0.64-0.86;  $P < .0001$ ).<sup>159</sup> Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone acetate.<sup>159,160</sup>

FDA approval in the pre-docetaxel setting occurred December 10, 2012 and was based on a randomized phase 3 trial of abiraterone acetate and prednisone (n=546) versus prednisone alone (n=542) in men with asymptomatic or minimally symptomatic, metastatic CRPC.<sup>161</sup> Most men in this trial were not taking narcotics for cancer pain and none had visceral metastatic disease or prior ketoconazole exposure. The co-primary endpoint of radiographic progression-free survival was improved by treatment from 8.3 to 16.5 months (HR, 0.53;  $P < .001$ ). Overall survival was improved by treatment after 333 mortality events were reported, from 27.2 months to not reached (HR, 0.75;  $P = .01$ ), but this did not meet pre-specified statistical significance. Key secondary endpoints of time to symptomatic deterioration, time to chemotherapy initiation, time to pain progression, and PSA progression-free survival were significantly improved with abiraterone treatment, and PSA declines (62% vs. 24% with >50% decline) and radiographic responses (36% vs. 16% RECIST responses) were more common. Thus, abiraterone acetate has level 1 evidence to support its use in the pre-docetaxel setting for men with asymptomatic or minimally symptomatic, metastatic CRPC. Its use in men with visceral disease or with symptomatic disease pre-docetaxel is reasonable but has not been

assessed formally in a controlled trial or compared with docetaxel chemotherapy. In symptomatic men who are not candidates for docetaxel, abiraterone acetate is recommended.

The most common adverse reactions seen with abiraterone acetate/prednisone (>5%) were fatigue (39%); back or joint discomfort (28%-32%); peripheral edema (28%); diarrhea, nausea, or constipation (22%); hypokalemia (17%); hypophosphatemia (24%); atrial fibrillation (4%); muscle discomfort (14%); hot flushes (22%); urinary tract infection; cough; hypertension (22%, severe hypertension in 4%); urinary frequency and nocturia; dyspepsia; or upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase (11%-12%), or cardiac disorders (heart failure, arrhythmias, and myocardial infarction in 19%, serious in 6%). Thus, monitoring of liver function, potassium and phosphate levels, and blood pressure readings on a monthly basis at least initially is warranted during abiraterone acetate/prednisone therapy. Symptom-directed assessment for cardiac disease also is warranted, particularly in patients with pre-existing cardiovascular disease.

### Enzalutamide

On August 31, 2012, the FDA approved enzalutamide (formerly known as MDV3100) for treatment of men with metastatic CRPC who had received prior docetaxel chemotherapy. Approval was based on the results of the AFFIRM randomized, phase 3, placebo-controlled trial.<sup>162</sup> This trial randomized 1199 men to enzalutamide or placebo in a 2:1 ratio and the primary endpoint was overall survival. Median survival was improved with enzalutamide from 13.6 to 18.4 months (HR, 0.63;  $P < .001$ ). Survival was improved in all subgroups analyzed, which included men with poor performance status, high or low PSA values, visceral



metastases, significant pain, and more than 2 prior chemotherapy regimens. Secondary endpoints also were improved significantly, which included the proportion of men with >50% PSA decline (54% vs. 2%), radiographic response (29% vs. 4%), radiographic progression-free survival (8.3 vs. 2.9 months), and time to first SRE (16.7 vs. 13.3 months). Quality of life measured using validated surveys was improved with enzalutamide compared to placebo. Adverse events were mild, and included fatigue (34% vs. 29%), diarrhea (21% vs. 18%), hot flushes (20% vs. 10%), headache (12% vs. 6%), and seizures (0.6% vs. 0%). The incidence of cardiac disorders did not differ between the arms. Enzalutamide is dosed 160 mg daily.

Patients in the AFFIRM study were maintained on GnRH agonist/antagonist therapy and could receive bone supportive care medications. The seizure risk in the enzalutamide FDA label was 0.9% versus 0.6% in the manuscript.<sup>162,163</sup> Thus, enzalutamide represents a new treatment option for men in the post-docetaxel metastatic CRPC setting and is a reasonable choice in men who are not candidates for chemotherapy. Level 1 evidence to support the routine use of enzalutamide in the pre-docetaxel setting may derive from the results of the PREVAIL phase 3 randomized study, which completed accrual in 2012. There is evidence of clinical activity from uncontrolled studies of enzalutamide in the pre-chemotherapy metastatic CRPC setting.<sup>164</sup>

### 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.<sup>165</sup> 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% to 54% relative increase in fracture risk.<sup>166-168</sup> Longer treatment duration conferred greater fracture risk. Age and comorbidity were also associated with higher fracture incidence. ADT increases bone turnover and decreases bone mineral density,<sup>169-172</sup> a surrogate for fracture risk. Bone mineral density of the hip and spine decreases by approximately 2% to 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,<sup>173</sup> and treatment-related sarcopenia appears to contribute to frailty and increased risk of falls in older men.

The NCCN Guidelines Panel recommends screening and treatment for osteoporosis according to guidelines for the general population from the National Osteoporosis Foundation.<sup>174</sup> The National Osteoporosis Foundation guidelines include: 1) supplemental calcium (1200 mg daily) and vitamin D3 (800-1000 IU daily) for all men older than 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®, recently released by WHO.<sup>175</sup> ADT should be considered “secondary osteoporosis” using the FRAX® 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.<sup>176</sup> Similar results have been reported with annual zoledronic acid.<sup>177</sup> 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.<sup>178</sup> In 2011, the FDA approved denosumab, a novel human monoclonal antibody targeting the receptor activator of NF- $\kappa$ B ligand (RANKL), as a treatment to prevent bone loss and fractures during ADT. Approval was based on a phase III study that randomized 1468 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.<sup>179</sup> Denosumab also was approved for prevention of SREs in patients with bone metastasis (see *Chemotherapy and Immunotherapy*).

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. A baseline dual-energy x-ray absorptiometry (DEXA) scan before start of therapy and a follow-up DEXA scan after one year of therapy is recommended by the International Society for Clinical Densitometry to monitor response. Use of biochemical markers of bone turnover is not recommended. There are no existing guidelines on the optimal frequency of vitamin D testing, but vitamin D levels can be measured when DEXA scans are obtained.

### **Diabetes and Cardiovascular Disease**

In a landmark population-based study, ADT was associated with higher incidence of diabetes and cardiovascular disease.<sup>180</sup> 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;  $P < .001$ ), coronary artery disease (HR, 1.16;  $P < .001$ ), and myocardial infarction (HR, 1.11;  $P = .03$ ). Studies that have evaluated the potential relationship between ADT and cardiovascular mortality produced mixed results.<sup>180-187</sup>

Several mechanisms may contribute to a greater risk for diabetes and cardiovascular disease during ADT. ADT increases fat mass and decreases lean body mass.<sup>173,188,189</sup> ADT with a GnRH agonist increases fasting plasma insulin levels<sup>190,191</sup> and decreases insulin sensitivity.<sup>192</sup> ADT also increases serum levels of cholesterol and triglycerides.<sup>190,193</sup>

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, six agents have demonstrated improvements in overall survival in this setting: docetaxel, sipuleucel-T, cabazitaxel, enzalutamide, abiraterone acetate, and radium-223 dichloride.



Abiraterone acetate and enzalutamide has been discussed under the section *Androgen Deprivation Therapy*. Radium-223 has been discussed under the section *Radiation Therapy, Radiopharmaceutical Therapy*.

### Docetaxel

Two randomized phase III studies have evaluated docetaxel-based regimens in symptomatic or rapidly progressive disease (TAX 327 and SWOG 9916).<sup>194-196</sup> TAX 327 compared docetaxel (every three weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1006 men.<sup>195</sup> 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.<sup>196</sup> The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared to mitoxantrone plus prednisone.<sup>194</sup> 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 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, multicenter, randomized, double-blind trial (D9902B).<sup>197</sup> 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;  $P = .03$ ). 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.<sup>198</sup> In the study, 755 men with progressive metastatic CRPC were randomized to receive cabazitaxel 25 mg/m<sup>2</sup> or mitoxantrone 12 mg/m<sup>2</sup>, each with daily prednisone. A 2.4 month improvement in overall survival was demonstrated with cabazitaxel compared to mitoxantrone (HR, 0.72;  $P < .0001$ ). 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 were randomized to intravenous zoledronic acid every 3 weeks or placebo.<sup>199</sup> 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 SRE (488 days vs. 321 days;  $P = .01$ ).<sup>200</sup> 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.<sup>201</sup> 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 were similar to zoledronic acid and included spinal cord compression (3% vs. 4%), need for radiation (19% vs. 21%), and pathologic 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.<sup>202</sup>

## NCCN Recommendations

### Initial Prostate Cancer Diagnosis

Initial suspicion of prostate cancer is based on an abnormal 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.<sup>32</sup> A separate NCCN Guidelines Panel has written

additional guidelines for prostate cancer early detection (see [NCCN Guidelines for Prostate Cancer Early Detection](#)). 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 Staging Manual, 7<sup>th</sup> edition.<sup>203</sup> 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 Guidelines Panel is in favor of pathology synoptic reports from the College of American Pathologists (CAP).<sup>204</sup>

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 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;<sup>205</sup> 2) a Gleason score of 8 or higher; 3) T3 to T4 tumors or symptomatic disease. Pelvic CT or MRI scanning is recommended if there is T3 or T4 disease, or if T1 or T2 disease and a nomogram indicate that there is greater than 10% chance of lymph node involvement, although staging studies may not be cost effective until the chance of lymph node positivity reaches 45%.<sup>206</sup> Biopsy should be considered for further evaluation of suspicious nodal findings. For all other patients, no additional imaging is required for staging. NCCN panelists voiced concern about inappropriate use of PET imaging in the community setting. FDG or fluoride PET is considered investigational at this time and should not be ordered outside of a registry (<http://www.cancerpetregistry.org/>).

The staging workup is used to categorize patients according to their recurrence risk into those with clinically localized disease at very low, low, intermediate, or 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 ( $\leq 6$ ), 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.<sup>121,122,207</sup>

If the patient's life expectancy is 10 years or more, the treatment recommendations also include radical prostatectomy with or without a PLND if the predicted probability of pelvic lymph node involvement is 2% or greater. A study by Johansson et al. assessed the long-term natural history of untreated, early-stage prostate cancer in 223 patients during 21 years of follow-up.<sup>208</sup> 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. RT using either 3D-CRT/IMRT with daily IGRT or brachytherapy is another option. Surgery, EBRT, and brachytherapy carry different side effect profiles 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.<sup>209</sup>

ADT as a primary treatment for localized prostate cancer does not improve survival and is not recommended by the NCCN Guidelines Panel.<sup>148</sup>



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.<sup>210</sup> A recent report suggests that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer.<sup>211</sup> A study by Donnelly et al.<sup>212</sup> randomly assigned 244 men with T2 or T3 disease to either cryotherapy or RT. All patients received neoadjuvant ADT. There was no difference in 3-year overall or disease-free survival. Patients who received cryotherapy reported poorer sexual function.<sup>213</sup> For patients with locally advanced cancer, cryoablation was associated with lower 8-year biochemical progression-free rate compared to EBRT in a small trial of 62 patients, although disease-specific and overall survival were similar.<sup>214</sup> At this time, cryotherapy is not recommended as routine primary therapy for localized prostate cancer due to lack of long-term data from long-term studies for comparison with radiation and radical prostatectomy.

The panel feels similarly about other emerging focal therapies. High intensity focused ultrasound (HIFU) and vascular-targeted photodynamic (VTP) therapies,<sup>215</sup> like cryotherapy, warrant further study. These treatments and active surveillance, RT and radical prostatectomy will all benefit from improved prostate imaging. Multiparametric MRI shows promise and a recent consensus conference should help with standardization of techniques and reporting.<sup>216</sup>

### Very Low Risk of Recurrence

The NCCN Guidelines 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 Guidelines for Prostate Cancer Early Detection](#)). 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 et al.<sup>217</sup> 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 PLND 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),<sup>218</sup> and results were updated recently.<sup>51</sup> With a median follow-up of 12.8 years, those assigned to the radical prostatectomy group had significant improvements in disease-specific mortality, overall mortality, and risk of metastasis and local progression. Overall, 15 men needed to be treated to avert one death; that number fell to 7 for men younger than 65 years of age. 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).<sup>219-221</sup> Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly high-risk men (RTOG 8610).<sup>182</sup> 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.<sup>9</sup>

Active surveillance is not recommended for those with a life expectancy of >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 Guidelines 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,<sup>222</sup> 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 to 3 years of ADT. Two randomized phase III trials evaluated long-term ADT with or without radiation in mostly T3 patients.<sup>223,224</sup> Another study randomized 415 patients to EBRT alone or EBRT plus 3-year ADT.<sup>225</sup> In a fourth study (RTOG



8531), 977 patients with T3 disease treated with RT were randomized to adjuvant ADT or ADT at relapse.<sup>226</sup> 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 1521 patients with T2c-T4 prostate cancer who received 4 months of ADT before and during RT.<sup>227</sup> They were randomized to no further treatment or an additional 2 years of ADT. At 10 years, the long-term group was superior for all endpoints 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%,  $P = .0061$ ). The European Organization for Research and Treatment of Cancer (EORTC) 22961 trial also showed superior survival when 2.5 years of ADT were added to RT given with 6 months of ADT in 970 patients, mostly with T2c-T3, N0 disease.<sup>228</sup> 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.<sup>229</sup>

There are emerging data that associate lower biochemical failure rates with the addition of brachytherapy to EBRT in patients at high risk.<sup>104,105</sup> 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.<sup>107</sup> The combination of EBRT and brachytherapy, with or without ADT (typically 2-3 years), is now listed as a primary treatment option. However, the optimal duration of ADT in this setting remains unclear.

Radical prostatectomy with PLND 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.<sup>230</sup>

### 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.<sup>223-225</sup>

### Metastatic Disease

ADT or RT of the primary tumor plus neoadjuvant/concomitant/adjuvant ADT (2-3 years) are available options for patients with N1 disease on presentation.<sup>223,224</sup> The EORTC 30846 trial randomized 234 treatment-naïve, node-positive patients to immediate versus delayed ADT.<sup>231</sup> 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. Multiparametric MRI may be considered to exclude the presence of anterior cancer if the PSA level rises and systematic prostate biopsy remains negative.<sup>216</sup> However, multiparametric MRI is not recommended for routine use. PSA doubling time is not considered reliable enough to be used alone to detect disease progression.<sup>56</sup>

Repeat biopsy is recommended to determine whether higher-grade elements are evolving although the risks appear small,<sup>232</sup> 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.<sup>60</sup> 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;<sup>56</sup> 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. PSA testing every 3 months may be required for men at high risk of recurrence. When prostate cancer recurred after radical prostatectomy, Pound et al. found that 45% of patients experienced recurrence within the first 2 years, 77% within the first 5 years, and 96% by 10 years.<sup>233</sup> 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

#### Adjuvant Therapy

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 et al. 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.<sup>234</sup> The initial study report revealed that adjuvant RT reduced the risk of PSA relapse and disease recurrence.<sup>235</sup> 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%;  $P = .001$ ).<sup>236</sup> Another randomized trial conducted by the EORTC<sup>237</sup> compared post-prostatectomy observation and adjuvant RT in 1005 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.<sup>238</sup> All participants had pT3 disease and undetectable PSA levels after radical prostatectomy. Postoperative 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 radical prostatectomy (usually within one year) 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  $\geq 3$  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. Retrospective data showed that whole pelvic radiation is superior over prostate bed radiation in terms of biochemical recurrence-free survival.<sup>239</sup>

There are several management options if positive lymph nodes are found during radical prostatectomy. The patient may be observed until a detectable PSA develops. ADT may be administered although the survival advantage reported for early and continuous ADT<sup>150</sup> has been refuted by more recent reports.<sup>151,152</sup> ADT plus pelvic radiation is a third option (category 2B). This is based on retrospective data demonstrating improved biochemical recurrence-free survival and cancer-specific survival with post-prostatectomy RT and ADT compared to adjuvant ADT alone in 250 patients with lymph node metastases.<sup>240</sup>

#### **Biochemical Recurrence**

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.<sup>241-245</sup> A large retrospective review of 501 patients who received salvage radiotherapy for detectable and increasing PSA after radical prostatectomy<sup>244</sup> showed that the predictors of progression were Gleason score 8 to 10, pre-RT PSA level greater than 2 ng/mL, seminal vesicle invasion, negative surgical margins, and PSA doubling times 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.<sup>246</sup> 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 nomogram<sup>13,24</sup> may prove useful to predict response, but it has not been validated.



Men who suffer a biochemical recurrence following radical prostatectomy fall into three groups: 1) those whose PSA level fails to fall to undetectable levels after radical prostatectomy (persistent disease); 2) those who achieve an undetectable PSA after radical prostatectomy with a subsequent detectable PSA level that increases on two or more subsequent laboratory determinations (recurrent disease); or 3) the occasional case with persistent but low PSA levels attributed to slow PSA metabolism or residual benign tissue. To date, there is no consensus definition of a threshold level of PSA below which PSA is truly “undetectable.” Group 3 does not require further evaluation until PSA rises. Since PSA elevation alone does not necessary lead to clinical failure,<sup>247</sup> the workup for 1 and 2 must include an evaluation for 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/ultrasound. 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.<sup>248</sup> A prostate bed biopsy may be helpful when imaging suggests local recurrence.

If there is little suspicion of distant metastasis during biochemical recurrence, primary salvage therapy involves radiation with or without neoadjuvant/concomitant/adjuvant ADT. Treatment is most effective when pre-treatment PSA level is below 0.5 ng/mL<sup>24</sup> and, paradoxically, may be most beneficial when the PSA doubling time is fast.<sup>24,246</sup> However, most men with prolonged PSA doubling time may be observed safely.<sup>249</sup> 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,<sup>250</sup> 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 workup 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.<sup>251</sup> Workup 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.<sup>252</sup> Morbidity (including incontinence, erectile dysfunction, and bladder neck contracture) remains significantly higher than when radical prostatectomy is used as initial therapy.<sup>252,253</sup> Overall and cancer-specific 10-year survival ranged from 54% to 89% and 70% to 83%, respectively.<sup>252</sup> Other options for localized interventions include cryotherapy<sup>254</sup> and brachytherapy

(reviewed by Allen et al.<sup>255</sup>). Treatment, however, needs to be individualized based upon the patient's risk of progression, the likelihood of success, and the risks involved with salvage 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.<sup>256,257</sup>

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.<sup>144</sup> LHRH antagonist therapy does not require short-term antiandrogen. CAB is an acceptable option.<sup>146,147</sup> The ASCO guidelines<sup>151</sup> 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.

### Castration-Recurrent Prostate Cancer

Patients who recur during primary ADT with CRPC should receive a laboratory assessment to assure a castrate level of testosterone. In addition, imaging tests may be indicated to monitor for signs of distant metastases. Factors affecting the frequency of imaging include individual risk, age, PSA velocity, Gleason grade, and overall patient health.

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.”<sup>258,259</sup> 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.<sup>260,261</sup> 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.<sup>262</sup> Thus, a biopsy of accessible lesions should be considered to identify patients with small cell histomorphologic features.<sup>263</sup> These cases may be managed



by cytotoxic chemotherapy, such as cisplatin/etoposide, carboplatin/etoposide, or a docetaxel-based regimen.<sup>264,265</sup> Physicians should consult the [NCCN Guidelines for Small Cell Lung Cancer](#) 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, zoledronic acid every 3 to 4 weeks or denosumab 120 mg every 4 weeks is recommended to prevent or delay disease-associated SREs (category 1 recommendation). SREs include pathologic fractures, spinal cord compression, surgery, or RT to bone. The optimal duration of zoledronic acid 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.<sup>266</sup> If invasive dental surgery is necessary, therapy should be deferred until the dentist confirms that the patient has healed completely from the dental procedure. Supplemental calcium and vitamin D treatment is recommended to prevent hypocalcemia in patients receiving either denosumab or zoledronic acid.

Monitoring of creatinine clearance is required for zoledronic acid to guide dosing. Zoledronic acid 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.<sup>267</sup> Denosumab may be administered to men with impaired renal function, including men on hemodialysis; however, the risk for severe hypocalcemia and hypophosphatemia is greater in this population, and the dose, schedule,

and safety of denosumab for this group has not yet been defined. A single study of 55 patients with creatinine clearance less than 30 mL/min or on hemodialysis evaluated the use of a 60 mg dose of denosumab.<sup>268</sup> Hypocalcemia should be corrected before starting denosumab, and serum calcium monitoring is required for denosumab and recommended for zoledronic acid, 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 1432 patients with non-metastatic CRPC at high risk of bone involvement, denosumab was reported to delay bone metastasis by 4 months compared to placebo.<sup>269</sup> 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 usually seen, 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. Abiraterone acetate/prednisone is another category 1 option. Other secondary ADT (including enzalutamide), 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).<sup>194-196</sup> 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.<sup>270</sup> Radium-223 is a category 1 first-line option for patients with symptomatic bone metastases and no known visceral disease. Hematologic evaluation should be performed according to the FDA label before treatment initiation and before each subsequent dose.<sup>271</sup> Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial has the potential for additive myelosuppression. Radium-223 can be used with denosumab or a bisphosphonate.

Mitoxantrone may provide palliative benefit for symptomatic patients who cannot tolerate docetaxel. Abiraterone acetate has not been assessed formally in symptomatic men with CRPC prior to docetaxel. Therefore, its use in these patients is a category 2A recommendation. Use of abiraterone also is reasonable for men who are not candidates for docetaxel or who decline chemotherapy. Enzalutamide alone is also an appropriate option, given its survival and palliative benefit and reasonable toxicity profile. Randomized study of this agent in the pre-docetaxel setting is ongoing.

The use of systemic radiotherapy with either 89Sr or 153Sm 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.<sup>120</sup> 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.

### **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), enzalutamide (category 1), cabazitaxel (category 1), radium-223 (category 1), salvage chemotherapy, docetaxel rechallenge, mitoxantrone, secondary ADT, sipuleucel-T, and participation in clinical trials.

Both abiraterone acetate/prednisone<sup>158,159</sup> and enzalutamide<sup>162</sup> have independently demonstrated clinical benefit and thus represent a new standard of care after failure of docetaxel chemotherapy for metastatic CRPC (category 1), provided these agents were not used pre-docetaxel. 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 and blood pressure should be monitored closely during therapy. Patients receiving enzalutamide have no restrictions for food intake and concurrent prednisone is permitted but not required.<sup>162</sup>

The NCCN Guidelines 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 antiemetics (including prophylactic antihistamines, H2 antagonists, and steroids prophylaxis), and symptom-directed antidiarrheal 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.

Radium-223 is a category 1 second-line treatment option for patients with symptomatic bone metastases. However, the agent is not recommended if visceral metastasis is detected or if the patient is receiving concurrent docetaxel rechallenge or other salvage chemotherapy. Clinicians should follow instructions in the FDA label on hematologic evaluation before each injection.

The decision to initiate therapy with abiraterone acetate with prednisone, enzalutamide, cabazitaxel with prednisone, or radium-223 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. Prior exposures to these agents should be considered. There are no data on the sequential efficacy of these agents in men with metastatic CRPC, and there are some data to suggest cross-resistance between abiraterone and enzalutamide. There are no randomized trials comparing these agents, and there are currently no predictive models or biomarkers that are able to identify patients who are likely to benefit from any of these agents. Choice of therapy is based largely on clinical considerations, which include patient preferences, prior treatment, presence or absence of visceral disease, and symptoms. NCCN recommends that patients be monitored closely with radiologic imaging (ie, 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.<sup>272</sup> 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). Some patients with metastatic CRPC may be deemed unsuitable for taxane chemotherapy; such patients could be considered for radium-223 or a second-line hormonal agent. In addition, 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.<sup>197</sup> Further, these men also 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**

Center	Toronto <sup>58</sup>	Johns Hopkins <sup>53,59,60</sup>	UCSF <sup>57</sup>
No. patients	450	769	531
Age (yr)	70	66	63
Median follow-up (mo)	82	36	43
Overall survival	68%	98%	98%
Cancer-specific survival	97%	100%	100%
Conversion to treatment	30%	33%	24%
<b>Reason for treatment</b>			
Gleason grade change	8%	14%	38%
PSA increase	14%*	-	26%†
Positive lymph node	1%	-	-
Anxiety	3%	9%	8%
* PSA doubling time <3 years			
† PSA velocity >0.75 ng/mL/year			



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