In the late 1980s and early 1990s, the number of newly diagnosed prostate cancers in the United States increased dramatically, surpassing lung cancer as the most common cancer in men. Experts generally believe 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 (45.3% in 1999–2001 vs. 29.8% in 1989–1992; \( P < .0001 \)). The incidence of prostate cancer increased 2.0% annually from 1995 to 2001 and has since declined. In 2009, an estimated 192,280 new cases were diagnosed and prostate cancer was expected to account for 25% of new cancer cases in men. Fortunately, the age-adjusted death rates from prostate cancer have also declined (–4.1% annually from 1994 to 2001). Researchers

**Prostate Cancer Clinical Practice Guidelines in Oncology™**

James Mohler, MD; Robert R. Bahnson, MD; Barry Boston, MD; J. Erik Busby, MD; Anthony D’Amico, MD, PhD; James A. Eastham, MD; Charles A. Enke, MD; Daniel George, MD; Eric Mark Horwitz, MD; Robert P. Huben, MD; Philip Kantoff, MD; Mark Kawachi, MD; Michael Kuettel, MD, MBA, PhD; Paul H. Lange, MD; Gary MacVicar, MD; Elizabeth R. Plimack, MD, MS; Julio M. Pow-Sang, MD; Mack Roach III, MD; Eric Rohren, MD, PhD; Bruce J. Roth, MD; Dennis C. Shrieve, MD, PhD; Matthew R. Smith, MD, PhD; Sandy Srinivas, MD; Przemyslaw Twardowski, MD; and Patrick C. Walsh, MD

**Key Words**
NCCN Clinical Practice Guidelines, prostate cancer, screening, early detection, prostate-specific antigen, active surveillance, life expectancy estimation, radical prostatectomy, radiation therapy (JNCCN 2010;8:162–200)

**NCCN Categories of Evidence and Consensus**

**Category 1**: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

**Category 2A**: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

**Category 2B**: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

**Category 3**: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

**Please Note**

These guidelines are a statement of 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 representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

These guidelines are copyrighted by the 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 the NCCN © 2010.

**Disclosures for the NCCN Prostate Cancer Guidelines Panel**

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in JNCCN and online. Furthering NCCN’s commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Prostate Cancer Guidelines Panel members can be found on page 200. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit NCCN.org.
expect prostate cancer to account for 27,360 deaths in 2009.\(^1\) This comparatively low death rate suggests that, unless prostate cancer is becoming biologically less aggressive, increased public awareness with earlier detection and treatment of prostate cancer has begun to affect mortality from this prevalent cancer. However, early detection and treatment of prostate cancers that do not threaten life expectancy cause unnecessary side effects that impair quality of life, increase health care expenses, and decrease the value of PSA and digital rectal examination (DRE) as early detection tests.\(^3,4\)

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 diagnostic, staging, and treatment options. To this end, every year the NCCN convenes a panel of leading experts from the fields of urology, radiation oncology, and medical oncology at member institutions to review and update guidelines for the treatment of prostate cancer, which are available on the NCCN Web site (www.NCCN.org). The treatment algorithms and recommendations represent current evidence integrated with expert consensus regarding acceptable approaches to prostate cancer treatment rather than a universally prescribed course of therapy. Individual physicians treating individual patients with prostate cancer are expected to use independent judgment in formulating treatment decisions.

### Estimates of Life Expectancy

As a result of widespread PSA testing, most patients...
Prostate Cancer Version 1:2010

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
### Recurrence Risk

#### Expected Patient Survival

#### Initial Therapy

**Clinically Localized:**

<table>
<thead>
<tr>
<th>Very Low:</th>
<th>Low:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- T1-T2a</td>
<td>- T1-T2a</td>
</tr>
<tr>
<td>- Gleason score ≤ 6</td>
<td>- Gleason score 2-6</td>
</tr>
<tr>
<td>- PSA &lt; 10 ng/mL</td>
<td>- PSA &lt; 10 ng/mL</td>
</tr>
<tr>
<td>- Fewer than 3 biopsy cores positive, ≤ 50% cancer in each core</td>
<td>- PSA density &lt; 0.15 ng/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>&lt; 20 y</th>
<th>≤ 10 y</th>
<th>≥ 10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active surveillance (category 2B)</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td><strong>Active surveillance</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td><strong>RT</strong>&lt;sup&gt;f&lt;/sup&gt;(3D-CRT/IMRT with daily IGRT or brachytherapy)</td>
</tr>
</tbody>
</table>

- **< 20 y:**
  - PSA as often as every 6 mo
  - DRE as often as every 12 mo

- **≤ 10 y:**
  - PSA as often as every 6 mo
  - DRE as often as every 12 mo
  - Repeat prostate biopsy as often as every 12 mo

- **≥ 10 y:**
  - Radical prostatectomy<sup>i</sup> ± pelvic lymph node dissection if predicted probability of lymph node metastasis ≥ 2%
  - Adverse pathologic features:<sup>j</sup>
    - Observe or RT<sup>f</sup>
  - Lymph node metastasis:
    - Observe or ADT<sup>j</sup>

---

**Notes:**

- See Principles of Life Expectancy Estimation (page 173).
- The panel remains concerned about the problems of overtreatment related to the increased diagnosis of early prostate cancer from PSA testing (see NCCN Clinical Practice Guidelines in Oncology: Prostate Early Detection [in this issue; to view the most recent version of these guidelines, visit the NCCN Website at www.NCCN.org]). Active surveillance is preferred for this subset of patients.
- Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses. See Principles of Active Surveillance (page 173).
- See Principles of Radiation Therapy (page 174).
- See Principles of Surgery (page 175).
- Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.
- Adverse pathologic features include positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
- See Principles of Androgen Deprivation Therapy (pages 176 and 177).
### RECURRENT RISK

<table>
<thead>
<tr>
<th>EXPECTED PATIENT SURVIVAL</th>
<th>INITIAL THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically Localized:</td>
<td></td>
</tr>
</tbody>
</table>

#### < 10 y

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

- **Progressive disease**
  - See Initial Clinical Assessment (page 164).

#### > 10 y

- **Radical prostatectomy**
  - Adverse pathologic features:
    - Observation or RT.

- **Lymph node metastasis**:
  - Observation or ADT.

#### Intermediate:

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

- **Radical prostatectomy**
  - Lymph node dissection if predicted probability of lymph node metastasis ≥ 2%.

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

#### Very High:

- **T3b-T4**

- **ADT**

- **Radical prostatectomy**
  - Pelvic lymph node dissection (selected patients with no fixation).

#### High:

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

- **Lymph node metastasis**:
  - ADT or Observation.

- **Detectable PSA**
  - See Salvage Therapy (page 169).

- **Adverse pathologic features**:
  - Observation or RT.

- **Undetectable PSA**
  - See Monitoring (page 168).

- **Progressive disease**
  - See Initial Clinical Assessment (page 164).

---

**Note:**

- See Principles of Active Surveillance (page 173).
- Patients with multiple adverse factors may be shifted into the next higher-risk group.
- Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses. See Principles of Active Surveillance (page 173).
- See Principles of Radiation Therapy (page 174).
- See Principles of Surgery (page 175).
- Criteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.
- Adverse pathologic features include positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
- See Principles of Androgen Deprivation Therapy (pages 176 and 177).
- Active surveillance of intermediate- and high-risk clinically localized cancers is not recommended in patients with life expectancy > 10 years (category 1).
Prostate Cancer Version 1:2010

<table>
<thead>
<tr>
<th>RECURRENCE RISK</th>
<th>INITIAL THERAPY</th>
<th>ADJUVANT THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>High: c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>± T3a or</td>
<td>RT³ (3D-CRT/IMRT with IGRT; category 1) + long-term neoadjuvant/concomitant/adjuvant ADT (2-3 y)³</td>
<td>See Monitoring (page 168)</td>
</tr>
<tr>
<td>± Gleason score 8-10 or PSA &gt; 20 ng/mL</td>
<td>or Radical prostatectomy⁹ + pelvic lymph node dissection (selected patients with no fixation)</td>
<td>or Adverse pathologic features:¹</td>
</tr>
<tr>
<td></td>
<td>or ADT¹</td>
<td>Observation or RT¹</td>
</tr>
<tr>
<td></td>
<td>or Lymph node metastasis:</td>
<td>ADT¹ or Observation</td>
</tr>
</tbody>
</table>

Locally Advanced:

| Very high: T3b-T4 | RT³ (3D-CRT/IMRT with IGRT) + long-term neoadjuvant/concomitant/adjuvant ADT (2-3 y; category 1) | See Monitoring (page 168) |
|                  | or Radical prostatectomy⁹ + pelvic lymph node dissection (selected patients with no fixation) | or Adverse pathologic features:¹ |
|                  | or ADT¹ | Observation or RT¹ |
|                  | or Lymph node metastasis: | ADT¹ or Observation |

Metastatic:

| Any T, T1         | ADT¹ or RT³ (3D-CRT/IMRT with IGRT) + short-term neoadjuvant/concomitant/adjuvant ADT (4-6 mo)³ | See Monitoring (page 168) |

Any T, Any N, M1 → ADT¹

¹ Patients with multiple adverse factors may be shifted into the next higher-risk group.
² See Principles of Radiation Therapy (page 174).
³ See Principles of Surgery (page 175).
⁹ Adverse pathologic features include positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
¹¹ See Principles of Androgen Deprivation Therapy (pages 176 and 177).
Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
POST-RADICAL PROSTATECTOMY RECURRENCE

SALVAGE WORKUP  PRIMARY SALVAGE THERAPY

Failure of PSA to fall to undetectable levels

PSA detectable and rising on 2 or more subsequent determinations

Studies negative for metastases

± Bone scan
± CT/MRI
± PSADT
± ProstaScint
± Biopsy

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

Studies positive for metastases

ADT\textsuperscript{j} or Observation

Progression

See Systemic Therapy (page 171)

\textsuperscript{i}See Principles of Radiation Therapy (page 174).
\textsuperscript{j}See Principles of Androgen Deprivation Therapy (pages 176 and 177).
Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

© Journal of the National Comprehensive Cancer Network | Volume 8 Number 2 | February 2010
Prostate Cancer Version 1:2010

**SYSTEMIC THERAPY**

ADT naive (M0 or M1) → Orchiectomy or LHRH agonist alone ± antiandrogen → Relapse → Studies negative for metastatic disease → See Systemic Salvage Therapy for Castration-Recurrent Prostate Cancer (page 172)

ADT naive (M0 or M1) → LHRH agonist + antiandrogen → Relapse → Studies positive for metastatic disease (M1) → Consider biopsy → Neuroendocrine (with or without small cell features) → Cisplatin/etoposide or Carboplatin/etoposide or Docetaxel-based regimen

Relapse

**SYSTEMIC SALVAGE THERAPY**

Studies negative for metastatic disease → See Systemic Salvage Therapy for Castration-Recurrent Prostate Cancer (page 172)

Studies positive for metastatic disease (M1) → Consider biopsy → Neuroendocrine (with or without small cell features) → Cisplatin/etoposide or Carboplatin/etoposide or Docetaxel-based regimen

环节标记：

- **ADT** naive (M0 or M1)
- Orchiectomy
- LHRH agonist alone ± antiandrogen
- LHRH agonist + antiandrogen
- Relapse
- Studies negative for metastatic disease
- Studies positive for metastatic disease (M1)
- Consider biopsy
- Neuroendocrine (with or without small cell features)
- Cisplatin/etoposide
- Carboplatin/etoposide
- Docetaxel-based regimen

**Note:**

- Ensure castrate level of testosterone.
- See Principles of Chemotherapy (page 178).
SYSTEMIC SALVAGE THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER

Studies negative for metastases

- Clinical trial (preferred)
- Observation
- Antiandrogen withdrawal (if on combination androgen blockade)
- Secondary ADT
  - Antiandrogen
  - Adrenal enzyme inhibitor
  - Estrogen therapy

PSA relapse or metastases (M1) → Follow pathway below

Studies positive for metastases

- Docetaxel every 3 wk and steroids (category 1)
- Other docetaxel regimen
- Secondary ADT
  - Antiandrogen
  - Adrenal enzyme inhibitor
  - Estrogen therapy
- Mitoxantrone + steroids (category 1, for quality of life but not survival)\(^a\)
- Palliative RT or radionucleide for symptomatic bone metastases
- Bisphosphonates for patients with bone metastases

Clinical trial or Salvage chemotherapy or Best supportive care

\(^a\)For patients who cannot tolerate docetaxel-based regimens.
Prostate Cancer Version 1:2010

**PRINCIPLES OF LIFE EXPECTANCY ESTIMATION**

- Life expectancy estimation is critical to informed decision-making in prostate cancer early detection and treatment.
- Estimation of life expectancy is possible for groups of men but challenging for individuals.
- Life expectancy can be estimated using the Social Security Administration tables (www.ssa.gov/OACT/STATS/table4c6.html).
- Life expectancy can then be adjusted using the clinician’s assessment of overall health as follows:
  - Best quartile of health - add 50%
  - Worst quartile of health - subtract 50%
  - Middle 2 quartiles of health - no adjustment
- Example of 5-year increments of age are reproduced from NCCN Clinical Practice Guidelines in Oncology: Senior Adult Oncology for life expectancy estimation (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).

**PRINCIPLES OF ACTIVE SURVEILLANCE**

- The NCCN Prostate Cancer and Prostate Cancer Early Detection Guidelines Panels remain concerned about overdiagnosis and overtreatment of prostate cancer. The panels recommend that patients and their physicians consider active surveillance based on careful consideration of the patient’s prostate cancer risk profile, age, and health by the patient and all his physicians (urologist, radiation oncologist, medical oncologist, primary care physician).
- Active surveillance is usually appropriate for men with very low-risk prostate cancer who have life expectancy < 20 years or men with low-risk prostate cancer who have life expectancy < 10 years (See Recurrence Risk Criteria, page 165).
- Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses.
- Patients with clinically localized cancers who are candidates for definitive treatment and choose active surveillance should have regular follow-up. Follow-up should be more rigorous in younger men. Follow-up should include:
  - PSA as often as every 3 months but at least every 6 months
  - DRE as often as every 6 months but at least every 12 months
  - Needle biopsy of the prostate may be repeated within 6 months of diagnosis if initial biopsy was < 10 cores or assessment discordant (e.g., palpable tumor contralateral to side of positive biopsy)
  - Needle biopsy may be performed within 18 months if initial biopsy ≥ 10 cores
- Cancer progression may have occurred if:
  - Primary Gleason grade 4 or 5 cancer is found on repeat prostate biopsy
  - Prostate cancer is found in a greater number of prostate biopsies or occupies a greater extent of prostate biopsies
  - PSA doubling time < 3 years
- A repeat prostate biopsy is indicated for signs of disease progression by exam or PSA.
- Advantages of active surveillance:
  - Avoid possible side effects of definitive therapy that may be unnecessary
  - Quality of life/normal activities retained
  - Risk of unnecessary treatment of small, indolent cancers reduced
- Disadvantages of active surveillance:
  - Chance of missed opportunity for cure
  - Risk for 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
  - Uncertain long-term natural history of prostate cancer
**PRINCIPLES OF RADIATION THERAPY**

External Beam Radiotherapy:
- 3D conformal and intensity modulated radiation therapy (IMRT) techniques should be used. Image-guided radiation therapy (IGRT) is required if dose ≥ 78 Gy.
- Doses of 75.6 to 79 Gy in conventional 36-41 fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses between 78 and 80+ Gy provide improved PSA-assessed disease control.
- Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2-3 y (category 1).
- Patients with intermediate risk cancer may be considered for pelvic lymph node irradiation and 4-6 mo of neoadjuvant/concomitant/adjuvant ADT.
- Patients with low-risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques such as IGRT using CT, ultrasound implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.
- Evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.

Brachytherapy:
- Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers, consider combining brachytherapy with EBRT (40-50 Gy) ± 4-6 mo neoadjuvant/concomitant/adjuvant ADT. Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy; however, with the addition of EBRT and ADT, it may be effective in some patients.
- Patients with a very large or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate (TURP) are more difficult to implant and may be at increased risk for 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.
- The recommended prescribed doses for monotherapy are 145 Gy for 125-Iodine and 125 Gy for 103-Palladium. The corresponding boost doses after 40-50 Gy EBRT are 110 and 100 Gy, respectively. In addition, high dose rate (HDR) brachytherapy can be used in combination instead of lower dose.

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.
## PRINCIPLES OF SURGERY

**Pelvic Lymph Node Dissection (PLND):**
- An extended PLND will discover metastases approximately twice as often as a limited PLND. Extended PLND provides more complete staging and may cure some men with microscopic metastases; therefore, an extended PLND is preferred when PLND is performed.
- An extended PLND includes removal of all node-bearing tissue from an area 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):**
- RP is appropriate therapy for any patient with clinically localized prostate cancer that can be completely excised surgically, who has a life expectancy of ≥ 10 years, 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 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 (incontinence, loss of erection, anastomotic stricture) is high.
ADT for Clinically Localized Disease

- Neoadjuvant ADT for radical prostatectomy is strongly discouraged.
- Giving ADT before, during, and/or after radiation prolongs survival in selected radiation-managed patients.
- Studies of short-term (4-6 mo) and long-term (2-3 y) neoadjuvant ADT all have used complete androgen blockade. Whether the addition of an antiandrogen is necessary will require further studies.
- Adjuvant ADT given after completion of primary treatment is not a standard treatment at this time with the exception of selected high risk patients treated with RT (see page 166). Low-volume, high-grade prostate cancer may warrant adjuvant ADT for 4-6 mo, but 2-3 y may be considered.
- In the largest randomized trial to date using antiandrogen bicalutamide alone at high dose (150 mg), there were indications of a delay in recurrence of disease but no improvement in survival. Longer follow-up is needed.
- In one randomized trial, immediate and continuous use of ADT in men with positive nodes after RP resulted in significantly improved delay in recurrence of disease but no improvement in survival. Longer follow-up is needed.
- The side effects of continuous ADT increase with the duration of treatment.

Timing of ADT for Advanced Disease (PSA recurrence or metastatic disease)

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

Optimal ADT

- LHRH agonist (medical castration) and bilateral orchiectomy (surgical castration) are equally effective.
- Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides no proven benefit over castration alone in patients with metastatic disease.
- Antiandrogen therapy should precede or be co-administered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.
PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY (page 2 of 2)

- Antiandrogen monotherapy appears to be less effective than medical or surgical castration and should not be recommended. The side effects are different but overall less tolerable.
- No clinical data support the use of triple androgen blockade (finasteride or dutasteride with combined androgen blockade).
- Intermittent ADT may reduce side effects without altering survival compared with continuous ADT, but the long-term efficacy of intermittent ADT remains unproven.
- Patients who do not achieve adequate suppression of serum testosterone (< 50 ng/mL) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, or steroids), although the clinical benefit is not clear.

Secondary Hormonal Therapy
- The androgen receptor remains active in patients whose prostate cancer has recurred during ADT (castration-recurrent prostate cancer); thus, ADT should be continued.
- If initial ADT fails, a variety of strategies can be used that may afford clinical benefit, including antiandrogen withdrawal and administration of antiandrogens, ketoconazole, or estrogens; however, none of these has yet been shown to prolong survival in randomized clinical trials.

Monitor/Surveillance
- ADT has a variety of adverse effects, including 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 before treatment.
- Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation (www.nof.org). The National Osteoporosis Foundation guidelines include recommendations for (1) supplemental calcium (1200 mg daily) and vitamin D3 (800-1000 IU daily) for all men older than 50 years and (2) additional treatment for men when the 10 y probability of hip fracture is ≥ 3% or the 10 y probability of a major osteoporosis-related fracture is ≥ 20%. Fracture risk can be assessed using the recently released algorithm called FRAX® by the World Health Organization (www.shef.ac.uk/FRAX/index.htm). ADT should be considered “secondary osteoporosis” using the FRAX® algorithm.
- Zoledronic acid (4 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 zoledronic acid or alendronate 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 whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in men receiving ADT should differ from those for the general population is still unclear.
**PRINCIPLES OF CHEMOTHERAPY**

- Patients with advanced prostate cancer should be encouraged to participate in clinical trials and referred early to a medical oncologist.
- Systemic chemotherapy should be reserved for patients with castration-recurrent metastatic prostate cancer except when studied in clinical trials.
- Based on phase III data, every-3-wk docetaxel and prednisone is the preferred first-line chemotherapy treatment. Alternative regimens include every-3-wk docetaxel and estramustine, weekly docetaxel and prednisone, and every-3-wk mitoxantrone and prednisone.
- Docetaxel-based regimens have been shown to confer a survival benefit in 2 phase III studies:
  - **SWOG 9916** compared docetaxel plus estramustine to mitoxantrone plus prednisone. Median survival for the docetaxel arm was 17 vs. 15.6 mo for the mitoxantrone arm ($P = .01$).\(^1\)
  - **TAX 327** compared 2 docetaxel schedules (weekly and every-3-wk) to mitoxantrone and prednisone. Median survival for the every-3-wk docetaxel arm was 19.2 vs. 16.3 mo for the mitoxantrone arm ($P = .009$).\(^2\)
- Only regimens using docetaxel on an every-3-wk schedule showed 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.
- Patients who failed taxotere chemotherapy should be encouraged to participate in clinical trials. Mitoxantrone has limited activity in that setting and no chemotherapy regimen to date has shown improved survival or quality of life. For patients who have not shown definitive evidence of progression on prior docetaxel therapy, retreatment with this agent can be attempted.
- In men with castration-recurrent prostate cancer and bone metastases, zoledronic acid every 3-4 wk is recommended to prevent disease-related skeletal complications, including pathologic fractures, spinal cord compression, and the need for surgery or radiation therapy to bone. Treatment should be initiated at reduced dose in men with impaired renal function (estimated creatinine clearance 30-60 mL/min) and is not recommended for men with baseline creatinine clearance < 30 mL/min.
- The optimal duration of zoledronic acid in men with castration-recurrent prostate cancer is undefined.
- Clinical trials are in progress to define the potential role of zoledronic acid in men with androgen-stimulated prostate cancer and bone metastases.

---


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, and radiotherapy.

Estimates of life expectancy have emerged as a key determinant of treatment decision-making, particularly when considering active surveillance (see Principles of Active Surveillance, page 180). Although estimating life expectancy for groups of men is possible, extrapolating these estimates to individual patients is more difficult. Life expectancy can be estimated using the Minnesota Metropolitan Life Insurance Table or Social Security Administration Period Life Table. The life expectancy can then be adjusted by adding or subtracting 50%, depending on whether the physician believes the patient is in the healthiest or unhealthiest quartile, respectively.

For example, according to the Social Security Administration Period Life Table, the life expectancy for a 65-year-old American man is 16.05 years. If judged to be in the upper quartile of health, a life expectancy of 24 years is assigned. If judged to be in the lower quartile of health, life expectancy of 8 years is assigned. Thus, treatment recommendations could change dramatically using the NCCN guidelines, depending on whether the man is judged to be in either very poor or excellent health. The algorithm (page 173) suggests that life expectancy should be estimated using the Social Security Administration tables and modified further according to the clinician’s assessment of overall health. Examples of 5-year increments of age are reproduced from the NCCN Clinical Practice Guidelines in Oncology: Senior Adult Oncology (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Other prognostic indices have been researched but are more difficult to use clinically. For example, Lee et al. developed a prognostic index for 4-year mortality based on information that combines both comorbid and functional measures. These investigators identified 12 independent predictors of mortality, including 2 demographic measures (i.e., age and sex), 6 comorbid conditions (including body mass index), and difficulty with 4 functional variables.

Nomograms and Predictive Models
Optimal treatment of prostate cancer requires assessment of risk: how likely is a given cancer to be confined to the prostate or to spread to the regional lymph nodes? How likely is the cancer to progress or metastasize after treatment? How likely is salvage with adjuvant radiation after an unsuccessful radical prostatectomy? Prostate cancers are best characterized by clinical (TNM) stage determined based on DRE, Gleason score in the biopsy specimen, and serum PSA level. Imaging studies (ultrasound, MRI) have been investigated intensively but have not been accepted as essential adjuncts to staging.

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

The Partin tables were the first prediction method to achieve widespread use for counseling men with clinically localized prostate cancer. The tables combine clinical stage, biopsy Gleason grade, and preoperative PSA level to predict pathologic stage, assigned as 1 of 4 mutually exclusive groups: 1) organ-confined, 2) extracapsular (i.e., extraprostatic) extension, 3) seminal vesicle invasion, or 4) lymph node metastasis. The tables give the probability (95% CIs) 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, a nomogram can be devised that incorporates the interactive effects of multiple prognostic factors to make accurate predictions about stage and prognosis for individual.
Principles of 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 high prevalence of prostate cancer on autopsy of the prostate, the high frequency of positive prostate biopsies in men with normal DRE and serum PSA values, contrast between the incidence and mortality rates of the malignancy, and need to treat an estimated 48 men with screen-detected prostate cancer or 100 men with low-risk prostate cancer to prevent one death from the disease has fueled debate about the need to diagnose and treat every American man who has prostate cancer. The best models of prostate cancer detection and progression estimate that 23% to 42% of all screen-detected cancers in the United States are overtreated and that PSA detection was responsible for up to 6.9 years of lead-time bias. The panel has responded to these evolving data with careful consideration of which men should be recommended for active surveillance: men with very low–risk prostate cancer and life expectancy estimated as less than 20 years or those with low-risk cancer and life expectancy estimated as less than 10 years.

However, the panel recognizes the uncertainty associated with estimating the chance of competing causes of death, the definition of very low–or low-risk prostate cancer, the ability to detect disease progression without compromising chance of cure, and the chance and consequences of treatment side effects. Epstein et al. introduced clinical criteria to predict pathologically “insignificant” prostate cancer. According to these investigators, insignificant prostate cancer is identified by clinical stage T1c, biopsy Gleason score 6 or less, the presence of disease in fewer than 3 biopsy cores, 50% or less prostate cancer involvement in any core, and PSA density less than 0.15 ng/mL/g.

Despite the usefulness of these criteria, physicians are cautioned against basing treatment decisions solely on them. Studies have shown that as many as 8% of cancers that qualified as insignificant using the Epstein criteria were not organ-confined based on postsurgical findings. A new nomogram may be better. Although many variations on this definition have been proposed (reviewed by Bastian et al.), the panel reached consensus that insignificant...
cant prostate cancer, especially when detected early using serum PSA, poses little threat to men with a life expectancy of less than 20 years. The confidence that Americans with very low-risk prostate cancer have a very small risk for 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.\(^\text{38}\)

Active surveillance is considered the best option for patients with low-risk cancers or a short life expectancy. Recently, Lu-Yao et al.\(^\text{39}\) reported that among patients who chose active surveillance, those diagnosed between 1992 and 2002 showed up to a 74% reduction in disease-specific mortality compared with those diagnosed in earlier periods when PSA testing was uncommon. The role of active surveillance should increase with the shift toward earlier-stage diagnosis attributed to PSA testing. However, results from randomized or cohort studies comparing this deferral strategy with immediate treatment are mixed, partly because of heterogeneity within the patient populations (reviewed by Sanda and Kaplan\(^\text{40}\)). For example, a cohort of 3331 participants showed no difference in the rate of metastases or disease-specific death at mean 7.7 years follow-up,\(^\text{41}\) whereas a randomized trial in 695 patients showed a relative risk of 0.65 for both 12-year disease-specific mortality (95% CI, 0.45–0.94; \(P = .03\)) and distant metastases (CI, 0.47–0.88; \(P = .006\)) for those managed with active surveillance versus radical prostatectomy.\(^\text{42}\) A recent clinical case presentation and poll with 3720 votes underscore the ongoing debate on the pros and cons of active surveillance and the difficulty in pinpointing the optimal strategy for low-risk disease.\(^\text{43,44}\) However, patients with high-risk disease have a better 5-year overall and disease-specific survival with active intervention than with observation until symptomatic,\(^\text{45}\) and these patients should not be observed unless they are aged and/or in poor health.

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

Patients and physicians involved in active surveillance must be aware that the PSA is likely to rise and 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 their decision to defer treatment. Trigger points for intervention based on PSA, histologic progression, or clinical progression have been used,\(^\text{46–48}\) although whether these trigger points will ultimately be validated remains uncertain.

Patients must commit to a regular schedule of follow-up, which includes DRE and PSA, and may include repeat prostate needle biopsies, at frequencies outlined in the algorithm (page 173). Cancer progression is suggested if a Gleason grade of 4 or 5 is found on repeat biopsy, the prostate cancer is found in a greater number or occupies a greater extent of prostate biopsies, or the PSA doubling time is less than 3 years. In these situation, the NCCN guideline panel recommends treatment in most men.

Advantages of active surveillance include 1) avoiding the side effects of definitive therapy that may be unnecessary; 2) retaining quality of life and normal activities; 3) avoiding unnecessary treatment of small indolent cancers; and 4) decreasing initial costs. Disadvantages are 1) chance of missed opportunity for cure; 2) possible cancer progression or metastasis before treatment; 3) possible need to use more complex treatment with greater side effects for larger, more-aggressive cancers; 4) possibility that nerve sparing at subsequent prostatectomy will be more difficult, which may reduce the chance of potency preservation after surgery; 5) increased patient anxiety of living with an untreated cancer;\(^\text{49}\) 6) need for frequent medical examinations and periodic prostate biopsies; 7) uncertain long-term natural history of untreated prostate cancer; and 8) undetermined timing and value of periodic imaging studies. Studies are in progress to develop trigger points for deciding when to start treatment with curative intent after initially choosing active surveillance.

Principles of RT

External-Beam RT

External-beam RT is one of the principle treatment options for clinically localized prostate cancer. The 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
Prostate Cancer

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 to 70 Gy because of 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. Three-dimensional conformal RT (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 for late effects. The second-generation 3D technique, intensity-modulated radiation therapy (IMRT), is now state-of-the-art and required.

These techniques have permitted safer dose escalation, and results of randomized trials suggest that dose escalation is associated with improved biochemical outcomes. Kuban et al. recently published an updated analysis on their dose-escalation trial of 301 patients with stage T1b to T3 prostate cancer. With a median follow-up reaching 8.7 years, the authors reported superior freedom from biochemical failure in the group randomized to 78 Gy compared with 70 Gy (78% vs. 59%; \( P = .004 \)). The difference was even greater among patients with initial PSA greater than 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 Gy in 36 to 41 conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Intermediate- and high-risk patients should receive doses between 75 and 80 Gy. For higher doses (> 75 Gy), daily prostate localization using daily image-guided radiation therapy (IGRT) is essential for target margin reduction and treatment accuracy. Imaging techniques, including ultrasound, implanted fiducials, electromagnetic targeting and tracking, and endorectal balloon, can be helpful in improving oncolgic cure rates and minimizing complications.

One of the key aspects of RT planning includes identifying which patients will benefit from inclusion of pelvic lymph node irradiation and androgen deprivation therapy (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. Evidence has emerged from randomized trials supporting the use of adjuvant/salvage RT after radical prostatectomy in men with adverse pathologic features or detectable PSA (see Very High Risk for Recurrence, page 190).

External-beam RT for prostate cancer shows several distinct advantages over surgical therapy. RT avoids complications associated with surgery, 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. This therapy includes a very low risk for urinary incontinence and stricture, and a good chance of short-term preservation of erectile function. 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. However, the addition of ADT increases the risk for erectile dysfunction.

The disadvantages of external-beam RT include a treatment course of 8 to 9 weeks; up to 50% of patients have some temporary bladder or bowel symptoms during treatment; it is associated with a low but definite risk for protracted rectal symptoms from radiation proctitis; and the risk for erectile dysfunction increases over time. In addition, if the cancer recurs, salvage surgery is associated with a higher risk for complications than primary surgical therapy.

Contraindications to RT include prior pelvic irradiation, active inflammatory disease of the rectum, or a permanent indwelling Foley catheter. Relative contraindications include very low–capacity bladder, chronic moderate or severe diarrhea, bladder outlet obstruction requiring a suprapubic catheter, and inactive ulcerative colitis.

**Brachytherapy**

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

The advantage of brachytherapy is that the treatment is completed in 1 day with little time lost from normal activities. In appropriate patients, the cancer-control rates appear comparable to surgery (> 90%) for low-risk tumors with medium-term follow-up. In addition, the risk for incontinence is minimal in patients without a previous transurethral resection of the prostate (TURP), and erectile function is preserved in the short-term.

Disadvantages of brachytherapy include the requirement for general anesthesia and the risk for acute urinary retention. Frequently, irritative voiding symptoms may persist for as long as 1 year after implantation. The risk for incontinence is greater after TURP because of acute retention and bladder neck contractures, and many patients develop progressive erectile dysfunction over several years.

Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers, brachytherapy may be combined with external-beam RT (40–50 Gy) with or without neoadjuvant ADT, but the complication rate increases. Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy; however, with the addition of external-beam RT and ADT, brachytherapy may be effective in selected patients. D'Amico et al. studied a cohort of 1342 patients with PSA greater than 20 ng/mL and disease of clinical stage T3/T4 and/or Gleason score 8 to 10. Addition of either external-beam RT or ADT to brachytherapy did not confer an advantage over brachytherapy alone, but the use of all 3 reduced prostate cancer–specific mortality compared with use of brachytherapy alone (adjusted hazard ratio [HR], 0.32; 95% CI, 0.14–0.73).

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. Implantation may be more difficult for these patients, and they have an increased risk for side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size. Postimplant dosimetry should be performed to document the quality of the implant. The recommended prescribed doses for monotherapy are 145 Gy for $^{125}$Iodine and 125 Gy for $^{103}$Palladium. After 40- to 50-Gy external-beam RT, the corresponding boost doses are 110 and 100 Gy, respectively.

**Proton Therapy**

Proton beams can be used as an alternative radiation source. Theoretically, protons may reach deeply located tumors with less damage to surrounding tissues. However, proton therapy is currently not recommended for routine use, because clinical trials have not yet yielded data showing its superiority or equivalence to conventional external-beam RT for treating prostate cancer.

**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 using a short course of radiation. A short course of 800 cGy in one fraction is as effective and less costly than delivering 3000 cGy in 10 fractions. Most patients should be managed with a single fraction of 800 cGy for nonvertebral metastases based on therapeutic guidelines from the American College of Radiology.

Radiopharmaceuticals are an effective and appropriate option for patients with widespread metastatic disease, particularly if they are no longer candidates for effective chemotherapy. Because many patients have multifocal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Radiopharmaceuticals developed for the treatment of painful bone metastases most commonly used for prostate cancer include strontium-89 (${}^{89}$Sr) and Samarium-153 (${}^{153}$Sm).
Principles of Surgical Therapy

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 patients with low-grade prostate cancer experience a cancer-specific death after 20 years of follow-up. Stephenson et al. reported a low 15-year prostate cancer–specific mortality of 12% in patients who underwent radical prostatectomy (5% for low-risk patients), although whether the favorable prognosis is from the effectiveness of the procedure or the low lethality of cancers detected in the PSA era is unclear. Long-term cancer control has been achieved in most patients with the retropubic and perineal approaches; high-volume surgeons in high-volume centers generally provide superior outcomes. Laparoscopic and robot-assisted radical prostatectomy are used commonly and considered comparable to conventional approaches in experienced hands. In a recent cohort study using US Surveillance, Epidemiology, and End Results (SEER) Medicare-linked data on 8837 patients, minimally invasive surgery was associated with shorter length of hospital stay, less need for blood transfusions, and fewer surgical complications compared with open surgery, but rates of incontinence and erectile dysfunction were higher. Oncologic outcome assessed using additional therapies was similar.

Return of urinary continence after surgery may be improved by preserving the urethra beyond the prostatic apex and by avoiding damage to the distal sphincter mechanism. Anastomotic strictures that increase the risk for long-term incontinence are less frequent with modern surgical techniques. Recovery of erectile function is related directly to the degree of preservation of the cavernous nerves, age at surgery, and preoperative erectile function. Improvement in urinary function was also seen with nerve-sparing techniques. For patients undergoing wide resection of the neurovascular bundles, replacement of resected nerves with nerve grafts does not appear effective. Early pharmacologic stimulation of erection may improve late recovery of sexual function. Salvage radical prostatectomy may be considered an option for highly selected patients with local recurrence after external-beam RT, brachytherapy, or cryotherapy in the absence of metastases; however, the morbidity (e.g., incontinence, loss of erections, anastomotic stricture) is high.

Pelvic Lymph Node Dissection
The decision to perform PLND should be guided by the probability of nodal metastases. The panel chose 2% as the cutoff for PLND because this avoids 47.7% of PLNDs at a cost of missing 12.1% of positive lymph nodes. PLND should be performed using an extended technique. An extended PLND includes removal of all node-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. A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly because of the elimination of microscopic metastases. PLND can be performed safely laparoscopically, robotically, or open, and complication rates should be similar for all approaches.

Principles of ADT
ADT is commonly used for treating prostate cancer. ADT can be accomplished using a luteinizing hormone–releasing hormone (LHRH) agonist (medical castration) or bilateral orchiectomy (surgical castration), which are equally effective. Combined androgen blockade (medical or surgical castration combined with an antiandrogen) or triple androgen blockage (finasteride or dutasteride, antiandrogen, plus medical or surgical castration) provides no proven benefit over castration alone. In patients with overt metastases who are at risk for developing symptoms associated with the flare in testosterone with initial LHRH agonist alone, antiandrogen therapy should precede or be coadministered with LHRH agonist and continued in combination for at least 7 days. Patients who do not show adequate suppression of serum testosterone (< 50 ng/mL) with medical or surgical castration can be considered for...
additional hormonal manipulation (with estrogens, antiandrogens, or steroids), although the clinical benefit is not clear.

Several alternative treatment regimens to continuous ADT have undergone limited study. Intermittent ADT is a widely used approach to reduce side effects and does not alter survival compared with continuous ADT, but its long-term efficacy remains unproven because large Intergroup studies comparing intermittent and continuous ADT (SWOG 9346 and NCI Canada PR7) are still ongoing. Antiandrogen monotherapy seems to be less effective than medical or surgical castration, with the possible exception of patients without overt metastases (M0). Antiandrogen monotherapy may be associated with an increased chance of death in patients with localized disease undergoing active surveillance. The side effects are different from those associated with ADT, but antiandrogen monotherapy is considered less tolerable overall.

ADT is used routinely in conjunction with definitive RT in patients with high-risk clinically localized disease or locally advanced disease. In this setting, ADT before, during, and after RT prolongs survival in selected patients. ADT is also used routinely for metastatic disease. Earlier ADT will delay the appearance of symptoms and metastases, but whether earlier ADT will prolong survival is not clear. The complications of long-term ADT have not been documented adequately.

Patients with a rising PSA level and no symptomatic or clinical evidence of cancer after definitive treatment present a therapeutic dilemma regarding the role of ADT; some will ultimately die of their cancer. Their prognosis is best approximated by 1) the absolute level of PSA; 2) the rate of change in the PSA level over time (PSA “doubling time”); and 3) the initial stage, grade, and PSA level at definitive therapy. Therefore, 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- and long-term side effects of ADT. Although early sustained ADT is acceptable, an alternative is close observation until progression of cancer, at which time appropriate therapeutic options may be considered. Earlier ADT may be better than delayed therapy, although the definitions of early and late (i.e., what level of PSA) remain controversial. Because the benefit of ADT is unclear, treatment should be individualized until definitive studies are completed. Patients with an elevated PSA (> 50 ng/mL) and/or a shorter PSA doubling time (rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.

Studies on the benefit of adjuvant ADT in patients with positive pelvic lymph nodes reveal mixed findings. Messing et al. randomly assigned patients who were found to have positive lymph nodes at radical prostatectomy to immediate ADT (n = 47) or observation (n = 51). 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 questioned, however. The results of a meta-analysis caused the ASCO guidelines to recommend against ADT for lymph node metastatic prostate cancer. A recent cohort analysis of 731 men failed to show a survival benefit associated with ADT initiated within 4 months of radical prostatectomy compared with observation.

Antiandrogen monotherapy after completion of primary treatment has also been investigated as an adjuvant therapy in patients with early prostate cancer as a strategy to reduce progression or recurrence. The Early Prostate Cancer (EPC) trial was the largest prostate cancer trial to date and evaluated bicalutamide, 150 mg daily, as adjuvant therapy in 8113 patients with prostate cancer who were managed with watchful waiting, radiotherapy, or radical prostatectomy. The original study was published in 2001, with additional analyses in 2004, and the 7.4-year follow-up was published in 2006. Patients with either localized (T1–2, N0) or locally advanced prostate cancer (T3–4, any N, or any T, N+) were enrolled. The primary end points were progression-free and overall survival. The authors reported that patients with localized disease did not seem to derive clinical benefit from added bicalutamide. However, adding bicalutamide, 150 mg, 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. In this subset, all patients had undergone either prostatectomy or radiotherapy; patients with positive pelvic nodes were not included. Patients were randomized to re-
Prostate Cancer

cieve either adjuvant bicalutamide, 150 mg daily, or placebo for 2 years. With a median follow-up of 7.7 years, few clinical events occurred in either group, and no differences in the primary end points of progression-free or overall survival were seen. However, bicalutamide significantly increased the time to PSA progression. 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.

Finally, ADT has been used commonly as primary therapy for early-stage, low-risk disease, especially in the elderly. In a cohort study of 19,271 elderly men with localized prostate cancer (T1–T2), Lu-Yao et al. reported no survival benefit in those receiving ADT compared with those undergoing observation alone. Therefore, placing elderly patients with prostate cancer on ADT should not be routine practice.

**Adverse Effects of ADT**

ADT has various adverse effects, including 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 aware of these risks before treatment.

Osteoporosis is an important but underappreciated problem in men worldwide. 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. Long-term 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, which is 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, and treatment-related sarcopenia seems to contribute to frailty and increased risk for falls in older men.

Screening and treatment for osteoporosis are recommended according to guidelines for the general population from the National Osteoporosis Foundation (www.nofo.org). These guidelines include recommendations for 1) supplemental calcium (1200 mg daily) and vitamin D (800–1000 IU daily) for all men older than 50 years, and 2) additional treatment for men when the 10-year probability of hip fracture is 3% or greater or the 10-year probability of a major osteoporosis-related fracture is 20% or greater. Fracture risk can be assessed using the algorithm FRAX®, recently released by the WHO (www.shef.ac.uk/FRAX/index.htm). ADT should be considered “secondary osteoporosis” using the FRAX® algorithm.

Limited evidence exists about fracture prevention during ADT. Several small, randomized, controlled trials have shown that bisphosphonates increase bone mineral density, a surrogate for fracture risk, during ADT. Intravenous pamidronate significantly decreased biochemical markers of bone turnover and increased bone mineral density of the hip and spine in men undergoing gonadotropin-releasing hormone (GnRH) agonist therapy. 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. Similar results have been reported with annual zoledronic acid. 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%, respectively, after 12 months. Currently, treatment with either zoledronic acid (4 mg, intravenously annually) or alendronate (70 mg, orally weekly) is recommended when the absolute fracture risk warrants drug therapy.

Two large randomized controlled trials of novel agents to prevent bone loss and fractures during ADT were completed recently. One study showed increased bone mineral density and reduced incidence of fractures with biannual denosumab, a novel human monoclonal antibody targeted against receptor activator of NF-kB ligand (RANKL). The other study evaluated toremifene, a selective estrogen receptor modulator. Interim reports of the ongoing trial showed improvements in bone density and lipid profiles in patients in the toremifene arm compared with the placebo arm.
In a landmark population-based study, ADT was associated with higher incidence of diabetes and cardiovascular disease. After controlling for other variables, including age and comorbidity, ADT with a GnRH agonist was associated with a greater risk for newly diagnosed diabetes (HR, 1.44; \( P < .001 \)), coronary artery disease (HR, 1.16; \( P < .001 \)), and myocardial infarction (HR, 1.11; \( P = .03 \)). A subsequent large population-based study also reported a significant association between ADT and greater incidence of cardiovascular morbidity. Studies that have evaluated the potential relationship between ADT and cardiovascular mortality produced mixed results.

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

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 undergoing 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.

**Algorithms**

**Initial Prostate Cancer Diagnosis**

Initial suspicion of prostate cancer is based on an abnormal DRE or 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. A separate NCCN panel has written additional guidelines for the early detection of prostate cancer (see NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection) [in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org].

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 2002 classification from the American Joint Committee on Cancer (AJCC; see the staging table, available online, in these guidelines, at www.NCCN.org [ST-1]).

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 help pathologists provide clinically useful and relevant information. The panel is in favor of using pathology synoptic reports from the College of American Pathologists (CAP).

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 their anticipated life expectancy and 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 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 T1 to T2 disease who also have a PSA greater than 20 ng/mL or a Gleason score of 8 or higher. Patients with T3 to T4 or
symptomatic disease should also have a bone scan. Pelvic CT or MRI scanning is recommended if the patient has T3 or T4 disease, or T1 or T2 disease and their nomogram indicates they have a greater than 20% chance of lymph node involvement, although staging studies may not be cost-effective until the chance of lymph node positivity reaches 45%. Biopsy should be considered for further evaluation of suspicious nodal findings. For all other patients, no additional imaging is required for staging.

After the staging workup, patients are categorized according to their recurrence risk into those with clinically localized disease at low, intermediate, and high risk for recurrence; those with locally advanced disease at very high risk for recurrence; or those with metastatic disease.

**Low Risk for Recurrence:** As defined by the guidelines, patients with low risk for biochemical recurrence include those with stage T1 to T2a tumors, low Gleason score (2–6), and serum PSA level less than 10 ng/mL. Although 40% of men older than 50 years harbor prostate cancer, only 1 in 4 present clinically, and only 1 in 14 will die of prostate cancer. Therefore, active surveillance is recommended for men with low-risk prostate cancer and life expectancy less than 10 years. Evidence for this approach is supported by data showing that the 5- to 10-year cancer-specific mortality is very low for most prostate cancers except those that are poorly differentiated.

If the patient’s life expectancy is 10 years or more, the treatment recommendations also include radical prostatectomy with or without a pelvic lymph node dissection if the predicted probability of pelvic lymph node involvement is 2% or greater. A study by Johansson et al. assessed the long-term natural history of untreated, early-stage prostate cancer in 223 patients during 21 years of follow-up. They found that most prostate cancers diagnosed at an early stage have an indolent course; however, local tumor progression and aggressive metastatic disease may develop in the long term. The mortality rate was significantly higher after 15 years of follow-up when compared with the first 5 years. Their findings support early radical prostatectomy, especially among patients with an estimated life expectancy exceeding 15 years.

Radiation therapy using either 3D-CRT/IMRT with daily IGRT or brachytherapy is another option. Surgery, external-beam RT, and brachytherapy have different side effect profiles that will likely influence decision-making. An analysis of 475 men treated for localized disease showed higher rates of incontinence and lower likelihood of regaining baseline sexual function, but lower rates of bowel dysfunction, after prostatectomy than after radiation.

ADT as a primary treatment for localized prostate cancer does not improve survival and is not recommended by the panel. Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that damages tumor tissue through local freezing. Based on different definitions of biochemical failure, the reported 5-year biochemical disease-free rate after cryotherapy ranged from 65% to 92% in low-risk patients. However, this technique is not recommended as primary therapy because of lack of data from long-term studies for comparison with radiation and radical prostatectomy.

**Very Low Risk for Recurrence:** The panel remains concerned about the problems of overtreatment related to the increased frequency of diagnosis of prostate cancer from widespread use of PSA levels for early detection or screening (see NCCN Prostate Cancer Early Detection Guidelines [in this issue; to view the most recent version, visit www.NCCN.org]). 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 of less than 20 years should undergo active surveillance. Incorporating 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 regarding the balance of risks and benefits of an active surveillance strategy and the lack of high level evidence that will eventually be available from ongoing clinical trials.

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

**Intermediate Risk for Recurrence:** As defined by these 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 patients with a life expectancy of less than 10 years, active surveillance remains a reasonable option. Johansson et al.\(^\text{132}\) observed that only 13% of men developed metastases 15 years after diagnosis of T0 to T2 disease and only 11% had died of prostate cancer. Treatment options include RT and radical prostatectomy. External-beam RT (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. Another option is radical prostatectomy with pelvic lymph node dissection unless the predicted probability of lymph node metastasis is less than 2%.

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 with watchful waiting in a randomized trial of 695 patients with early-stage prostate cancer (mostly T2).\(^\text{42}\) With a median follow-up of 11 years, those assigned to the radical prostatectomy group had significant improvements in disease-specific mortality, overall mortality, and risk for metastasis and local progressions. The results of this trial offer high-quality evidence to support radical prostatectomy as a treatment option.

External-beam RT (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. Three randomized trials\(^\text{89,115,133}\) have evaluated whether 4 to 6 months of ADT prolongs survival when added to external-beam RT. RTOG 8610\(^\text{115}\) consisted of nearly all high-risk patients, whereas TROG 9601\(^\text{89}\) and DFCI 95096\(^\text{133}\) included approximately 20% and 60% of men with intermediate-risk prostate cancer. Both an overall and cancer-specific survival benefit was noted in DFCI 95096,\(^\text{133}\) which had the highest proportion of men with intermediate-risk prostate cancer, whereas a cancer-specific survival benefit only was noted in TROG 9601\(^\text{89}\) and RTOG 8610.\(^\text{133}\) Because none of these studies examined men with intermediate-risk disease only, 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 external-beam RT or radical surgery as measured by biochemical-free survival for patients who showed a component of Gleason pattern 4 or 5 cancer, or a serum PSA value greater than 10 ng/mL.\(^\text{9}\)

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

**High Risk for 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 panel to be at high risk for recurrence after definitive therapy. Patients with multiple adverse factors may be shifted into the very high-risk category. The preferred treatment for this group is 3D-CRT/IMRT with daily IGRT in conjunction with long-term ADT; ADT alone is insufficient (category 1).\(^\text{134}\) In particular, patients with low-volume, high-grade tumors warrant aggressive local radiation combined with typically 2 to 3 years of ADT.

Increasing evidence favors long-over short-term neoadjuvant/concurrent/adjuvant ADT in high-risk patients. The RTOG 92-02 trial included 1521 patients with T2c to T4 prostate cancer who received 4 months of ADT before and during RT.\(^\text{135}\) They were randomized to no further treatment or an additional 2 years of ADT. At 10 years, the long-term group is superior for all end points except overall survival. A subgroup analysis of patients with Gleason score 8 to 10 found an advantage in overall survival for long-term ADT (32% vs. 45%; \(P = .0061\)). The EORTC 22961 trial also showed superior survival when 2.5 years of ADT was added to RT given with 6 months of ADT in 970 patients, mostly with T2c to T3, N0 disease.\(^\text{136}\)

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
Very High Risk for Recurrence: Patients at very high risk for recurrence are defined by these guidelines as those with clinical stage T3b to T4 (locally advanced). The options for this group include either 1) a combination of 3D-CRT/IMRT with daily IGRT and short-term ADT (category 1), 2) radical prostatectomy plus pelvic lymphadenectomy in selected patients with no fixation to adjacent organs, or 3) ADT.

Metastatic Disease: ADT or radiation plus short-term neoadjuvant/concomitant/adjuvant ADT are available options for patients with N1 disease, but only ADT is recommended for patients with M1 cancer.

Active Surveillance
Those electing active surveillance with a 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 is not necessary for at least 18 months (see page 173). Surveillance may be less intense for those with a life expectancy less than 10 years; PSA and DRE may be performed less frequently (as often as every 6–12 months) and follow-up prostate biopsies are rarely necessary.

Repeat biopsy is recommended to determine whether higher-grade elements are evolving although the risks appear small, which may influence prognosis and, hence, the decision to continue active surveillance or proceed to definitive local therapy. After an initial repeat biopsy, subsequent biopsies may be performed at the observing physician’s discretion. Studies remain in progress to identify appropriate trigger points for progression in patients who choose deferred treatment when interventions with curative intent may still be reliably successful. The criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression. If progressive disease is detected, the patient may require RT or radical prostatectomy.

Monitoring After Treatment
For patients initially treated with intent to cure, a serum PSA level should be measured every 6 to 12 months for the first 5 years and then rechecked annually. When prostate cancer recurred after radical prostatectomy, Pound 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. Because local recurrence may result in substantial morbidity and can, rarely, occur in the absence of a PSA elevation, an annual DRE is also appropriate to monitor for prostate cancer recurrence, as well as colorectal cancer. Similarly, after RT, monitoring serum PSA levels is recommended every 6 months for the first 5 years and then annually, and a DRE is recommended at least annually.

For patients presenting with locally advanced or metastatic disease, the intensity of clinical monitoring is determined by the response to initial ADT, radiation therapy, or both. Follow-up evaluation of these patients should include a history and physical examination, DRE, and PSA determination every 6 to 12 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 these patients. Supplementation is recommended using calcium (500 mg) and vitamin D (400 IU). Men who are osteopenic/osteoporotic should be considered for bisphosphonate therapy.

Adjuvant or Salvage Therapy After Radical Prostatectomy
Most patients who have undergone a radical prostatectomy are cured of prostate cancer. However, some men will experience pathologic or biochemical failure. Selecting men appropriately for adjuvant or salvage radiation is difficult. 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. The initial study report showed that adjuvant RT reduced the risk for PSA relapse and disease recurrence. An update reported improved 10-year biochemical failure-free survival for high-risk patients (seminal vesicle positive) undergoing postprostatectomy adjuvant radiation compared with observation (36% vs. 12%; \( P = .001 \)). Most
recently, SWOG 8794 showed improved overall and metastasis-free survival.\(^{140}\)

Another randomized trial conducted by the EORTC\(^{143}\) compared postprostatectomy 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 with 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.\(^{144}\) reported results on 268 patients. All participants had pT3 disease and undetectable PSA levels after radical prostatectomy. Postoperative radiation improved 5-year biochemical progression-free survival compared with 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 patients may show a survival advantage.

Based on these results, adjuvant RT after recuperation from surgery is likely beneficial in men with adverse pathologic features, including positive margin, seminal vesicle invasion, and/or extracapsular extension. Positive surgical margins are especially unfavorable if diffuse (> 10 mm margin involvement or ≥ 3 sites of positivity) or associated with persistent serum levels of PSA. If adjuvant RT is considered, it should be administered before the PSA exceeds 1.5 ng/mL. Adjuvant ADT should be considered for patients with positive lymph nodes found during surgery. However, the survival advantage reported for early and continuous ADT\(^{90}\) has been refuted by more recent reports.\(^{93,92}\) Therefore, observation is recommended until a detectable PSA develops, at which time clinical trials or ADT should be considered.

Several retrospective studies have assessed the prognostic value of various combinations of pretreatment PSA levels, Gleason scores, PSA doubling time, and the presence or absence of positive surgical margins.\(^{145–149}\) A large retrospective review of 501 patients who underwent salvage radiotherapy for detectable and increasing PSA after prostatectomy\(^{148}\) 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 margin, and a PSA doubling time of 10 months or less. However, separation of men into those likely to experience local recurrence versus systemic disease, and hence response to postoperative radiation, has not been possible for individual patients using clinical and pathologic criteria.\(^{150}\) Unfortunately, delivery of adjuvant or salvage RT becomes both therapeutic and diagnostic: PSA response indicates local persistence/recurrence. Delayed biochemical recurrence requires restaging, and a new nomogram\(^{13,24}\) may prove useful to predict response, but it has not yet been validated.

Men who experience a biochemical recurrence following prostatectomy fall into 2 groups: those whose PSA level fails to fall to undetectable levels after surgery, and those who have an undetectable PSA after surgery with a subsequent detectable PSA level that increases on 2 or more laboratory determinations. Because PSA elevation alone does not necessary lead to clinical failure,\(^{151}\) the workup for these groups focuses on the assessment of distant metastases (see page 169). The specific tests depend on the clinical history, but potentially include a bone scan, biopsy, PSA doubling time assessment, CT/MRI, or radioimmunologic scintigraphy (i.e., ProstaScint scan). Bone scans are appropriate when patients develop symptoms or their PSA level is increasing rapidly. In one study, the probability of a positive bone scan for a patient not undergoing ADT after radical prostatectomy was less than 5% unless the PSA increased to 40 to 45 ng/mL.\(^{152}\)

If there is little suspicion of distant metastasis during biochemical recurrence, primary salvage therapy involves radiation with or without neoadjuvant/concomitant/adjuvant ADT. When there is proven or high suspicion for distant metastases, radiation is unlikely to be useful and ADT alone becomes the main salvage treatment. 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 (see page 170).

**Postirradiation Recurrence:** According to the 2006 Phoenix definition revised by the American Society for Radiation Oncology (ASTRO) and the Radiation Therapy Oncology Group in Phoenix,\(^{153}\) 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 external-beam RT with or without neoadjuvant ADT therapy. The date of failure should be deter-
mined “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 or T2, a life expectancy of greater than 10 years, and a current PSA of less than 10 ng/mL. Workup includes a prostate biopsy, bone scan, and additional tests as clinically indicated, such as an abdominal/pelvic CT, MRI, or a radioimmunologic scintigraphy (i.e., ProstaScint scan).

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

A negative biopsy after postradiation 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.

Patients with positive study results indicating metastatic disease or those who are not initial candidates for local therapy should be observed or treated with ADT (see page 170).

**Systemic Therapy**

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.

Longer concomitant use of antiandrogen with an LHRH agonist, commonly known as combined androgen blockade (CAB), is an acceptable option. CAB provides no proven benefit over castration alone in patients with metastatic disease.

Neuroendocrine differentiation should be considered in patients who do not experience response to ADT. Those with an initial Gleason score of 9 or 10 are especially at risk. Thus, a biopsy of accessible lesions should be considered to identify patients with neuroendocrine differentiation who are managed with subsequent cytotoxic chemotherapy, such as cisplatin/etoposide or carboplatin/etoposide.

**Systemic Salvage Therapy**

Patients relapsing after primary ADT with castration-recurrent prostate cancer should undergo a laboratory assessment to assure a castrate level of testosterone. Several options for systemic salvage therapy should be considered based on metastasis status. For patients without signs of metastasis (M0), clinical trial is the preferred choice and observation is the second option. For patients who have undergone CAB, the antiandrogen should be discontinued to exclude an antiandrogen withdrawal response. Secondary hormonal therapy is also feasible in M0 patients because the androgen receptor may remain active. This can be achieved using an antiandrogen (for patients who initially underwent medical or surgical castration), ketoconazole (adrenal enzyme inhibitor) with or without glucocorticoids, or estrogens/progesterone. However, none of these strategies has yet been shown to prolong survival in randomized clinical trials. Supportive care should be provided to all patients.

Systemic salvage therapy for patients with metastatic prostate cancer (M1) includes bisphosphonates plus systemic chemotherapy, secondary hormonal therapy, or systemic RT using samarium or strontium (see page 178). Two phase III studies (SWOG 9916 and TAX 327) showed that docetaxel-based regimens conferred a survival benefit and established that every-3-week docetaxel and steroids is the preferred first-line chemotherapy treatment in these patients. 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 ef-
ficiency and is not recommended.\textsuperscript{167}

Mitoxantrone with prednisone has been shown to provide palliative benefit in patients with painful bony metastases from castration-recurrent prostate cancer. However, its impact on survival as second-line therapy after docetaxel has not been determined. The traditional option of glucocorticoids and external-beam RT for symptomatic bone metastases remains available for patients with focal pain or impending pathologic fractures. The use of systemic RT with either \textsuperscript{90}Sr or \textsuperscript{153}Sm 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, external-beam RT.\textsuperscript{67} The risk for bone marrow suppression, which might influence the ability to provide additional systemic chemotherapy, should be considered before this therapy is initiated.

Currently, no consensus exists for the best additional therapy after docetaxel failure in patients with metastases; clinical trial enrollment is encouraged. Two vaccines under development have been reported in abstract form only to show improved survival in randomized controlled trials of men with castration-recurrent prostate cancer.\textsuperscript{168,169}

**Bisphosphonates and Prostate Cancer**

In men with castration-recurrent prostate cancer and bone metastases, zoledronic acid every 3 to 4 weeks is recommended to prevent disease-related skeletal complications, including pathologic fractures, spinal cord compression, surgery, or RT to bone (category 1). Other bisphosphonates are not known to be effective for preventing disease-related skeletal complications.

In a pivotal multicenter study, 643 men with castration-recurrent prostate cancer and asymptomatic or minimally symptomatic bone metastases were assigned randomly to intravenous zoledronic acid (4 or 8 mg, every 3 weeks) or placebo.\textsuperscript{170} All men continued ADT (bilateral orchiectomies or treatment with a GnRH agonist) throughout the study and received additional antineoplastic therapy at the discretion of the investigator. The primary study end point was the proportion of men who experienced one or more skeletal-related event (pathologic fracture, spinal cord compression, surgery, or RT to bone, or change in antineoplastic treatment to treat bone pain) by 15 months. Adverse renal events prompted 2 study amendments. In the first amendment, the infusion time for zoledronic acid was increased from 5 to 15 minutes. In the second amendment, the zoledronic dose in the 8-mg treatment group was reduced to 4 mg, serum creatinine monitoring was implemented before each dose, and the primary efficacy assessment became the comparison of the 4-mg group versus placebo.

At 15 months, fewer men in the group receiving 4 mg of zoledronic acid had skeletal-related events than in the placebo group (33\% vs. 44\%; \textit{P} = .02). An update at 24 months also showed an increase in the median time to first skeletal-related event (488 vs. 321 days; \textit{P} = .01).\textsuperscript{171} No significant differences were found in overall survival. Based on the results of this study, zoledronic acid (4 mg, intravenously every 3–4 weeks) was approved to treat men with prostate cancer metastatic to bone and disease progression despite first-line ADT.

Zoledronic acid should be initiated at a reduced dose in men with impaired renal function (estimated creatinine clearance 30–60 mL/min). Treatment is not recommended for men with baseline creatinine clearance less than 30 mL/min. The optimal duration of zoledronic acid in men with castration-recurrent prostate cancer and bone metastases is undefined. Zoledronic acid and other bisphosphonates are associated with increased risk for osteonecrosis of the jaw (ONJ). Most patients who develop ONJ have preexisting dental problems.\textsuperscript{172,173} Oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce risk for ONJ.\textsuperscript{174}

Clinical trials are in progress to define the potential role of zoledronic acid in men with newly diagnosed prostate cancer and bone metastases. Zoledronic acid or other bisphosphonates have not been shown to prevent bone metastases. Ongoing large, randomized, controlled trials are evaluating the role of denosumab, a novel human monoclonal antibody targeted against RANKL, for preventing and treating bone metastases in men with prostate cancer.

**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 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 patients and physicians when tailoring prostate cancer therapy to the individual patient.

References
Prostate Cancer


101. Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral


Prostate Cancer


## Individual Disclosures for the NCCN Prostate Cancer Panel

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support</th>
<th>Advisory Boards, Speakers Bureau, Expert Witness, or Consultant</th>
<th>Patent, Equity, or Royalty</th>
<th>Other</th>
<th>Date Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robert R. Bahnson, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/6/09</td>
</tr>
<tr>
<td>Barry Boston, MD</td>
<td>BEST</td>
<td>Bayer HealthCare; Onyx Pharmaceuticals, Inc.; Pfizer Inc.; and sanofi-aventis U.S.</td>
<td>None</td>
<td>None</td>
<td>10/28/09</td>
</tr>
<tr>
<td>J. Erik Busby, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/6/09</td>
</tr>
<tr>
<td>Anthony D’Amico, MD, PhD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>James A. Eastham, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>Charles A. Enke, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>10/13/09</td>
</tr>
<tr>
<td>Daniel George, MD</td>
<td>Roche Laboratories, Inc.</td>
<td>Genentech, Inc.; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Pharmacia Corp; and sanofi-aventis U.S.</td>
<td>None</td>
<td>None</td>
<td>12/17/09</td>
</tr>
<tr>
<td>Eric Mark Horwitz, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/9/09</td>
</tr>
<tr>
<td>Robert P. Huben, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/6/09</td>
</tr>
<tr>
<td>Phillip Kantoff, MD</td>
<td>Dendreon Corporation</td>
<td>Amgen Inc.; Merck &amp; Co., Inc.; Novartis Pharmaceuticals Corporation; BIND Biosciences, Inc.; Cougar Biotechnology, Inc.; Forest Pharmaceuticals, Inc.; Gerson Lehrman Group, Inc; Guidepoint Global; and Tokia</td>
<td>None</td>
<td>None</td>
<td>12/30/09</td>
</tr>
<tr>
<td>Mark Kawachi, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>10/16/09</td>
</tr>
<tr>
<td>Michael Kuettel, MD, PhD, MBA</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>Paul H. Lange, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>Gary MacVicar, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>James Mohler, MD</td>
<td>Roswell Park Cancer Institute</td>
<td>None</td>
<td>None</td>
<td>Androbiosys, Inc.</td>
<td>8/18/09</td>
</tr>
<tr>
<td>Elizabeth R. Plimack, MD, MS</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>Julio M. Pow-Sang, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>12/1/09</td>
</tr>
<tr>
<td>Mack Roach III, MD</td>
<td>GlaxoSmithKline; and NCI, U-56</td>
<td>CareCore National LCC; and Molecular Insight, TROFEX</td>
<td>None</td>
<td>None</td>
<td>1/7/10</td>
</tr>
<tr>
<td>Eric Rohren, MD, PhD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
<tr>
<td>Bruce J. Roth, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/8/09</td>
</tr>
<tr>
<td>Dennis C. Shrieve, MD, PhD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>9/28/09</td>
</tr>
<tr>
<td>Matthew R. Smith, MD, PhD</td>
<td>Amgen Inc.; Novartis Pharmaceuticals Corporation; and GTX Incorporated</td>
<td>Amgen Inc.; Novartis Pharmaceuticals Corporation; Ferring Pharmaceuticals; and GTx Inc</td>
<td>None</td>
<td>Cougar Biotechnology</td>
<td>9/7/09</td>
</tr>
<tr>
<td>Sandy Srinivas, MD</td>
<td>None</td>
<td>Amgen Inc.; Novartis Pharmaceuticals Corporation; and sanofi-aventis U.S.</td>
<td>None</td>
<td>None</td>
<td>7/6/09</td>
</tr>
<tr>
<td>Przemyslaw Twardowski, MD</td>
<td>None</td>
<td>AstraZeneca Pharmaceuticals LP</td>
<td>None</td>
<td>None</td>
<td>7/2/09</td>
</tr>
<tr>
<td>Patrick C. Walsh, MD</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>7/1/09</td>
</tr>
</tbody>
</table>

The NCCN guidelines staff have no conflicts to disclose.