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# NCCN Prostate Cancer Panel Members

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ω Urology
† Medical oncology
£ Supportive Care including Palliative, Pain management, Pastoral care and Oncology social work
¥ Patient advocacy
*Writing committee member
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**NCCN Prostate Cancer Panel Members**

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Summary of the Guidelines updates

Highlights of major changes in the 2007 version of the Prostate Cancer Treatment guidelines from the 2005 version include:

- **PROS-2**
  - Changed the terminology from androgen ablation to androgen deprivation therapy throughout the guidelines.
  - Changed the recommendation for pelvic lymph node dissection if predicted probability of lymph node metastasis is ≥ 3% to ≥ 7%.

- **PROS-3**
  - High risk of recurrence: Androgen deprivation therapy is recommended at least 2 y, previously it was 2-3 y.

- **PROS-4**
  - Life expectancy ≥ 10 y: PSA as often as every 3 mo, DRE as often as every 6 mo, and repeat prostate biopsy as often as annually.
  - Life expectancy < 10 y: PSA, DRE, prostate biopsy may be done less frequently.

- **PROS-5**
  - Salvage workup includes ± bone scan, ± biopsy, ± CT/MRI, ± ProstaScint.
  - Depending on probability of benefit from RT and Gleason score primary salvage therapy may include RT, androgen deprivation therapy or observation.

- **PROS-7**
  - Systemic therapy, consideration of antiandrogen for ≥ 10 d for flare has been changed to ≥ 7 d.
  - Bisphosphonate treatment recommendation was revised to consider for prevention of skeletal related events.

**PROS-A - Principles of Life Expectancy Estimation** is new to the guideline

**PROS-C - Principles of Expectant Management**

- Cancer progression may have occurred if:
  - Primary Gleason grade 4 or 5 cancer is found upon repeat prostate biopsy.
  - Prostate cancer is found in a greater number of prostate biopsies or occupies a greater extent of prostate biopsies.
  - PSA doubling time < 3 y or PSA velocity is > 0.75.

**PROS-D - Principles of Radiation Therapy**

- External beam radiotherapy section:
  - Patients with intermediate risk cancer may be considered for pelvic lymph node irradiation and 4-6 mo neoadjuvant ± adjuvant ADT.
  - Patients with low risk cancer should not receive pelvic lymph node irradiation or ADT.

**PROS-E - Principles of Surgery**

- Pelvic lymph node dissection was revised and clarified. New recommendations added include use of open, laparoscopic or robotic technique.
- Radical prostatectomy was updated. It is recommended that high volume surgeons in high volume centers generally provide better outcomes. Laparoscopic and robot assisted radical prostatectomy are used commonly. In experienced hands, the results of these approaches appear comparable to open surgical approaches.
Summary of the Guidelines updates (continued)

- **PROS-F - Principles of Hormonal Therapy**
  - Neoadjuvant androgen deprivation therapy for radical prostatectomy is strongly discouraged.
  - Giving ADT before, during and/or after radiation prolongs survival in selected radiation managed patients.
  - 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.
  - Men who are osteopenic/osteoporotic should be strongly considered for bisphosphonate therapy with zoledronic acid, pamidronate, alendronate, raloxifene or toremifene.

- **PROS-G - Principles of Chemotherapy**
  - Docetaxel-based regimens are now the standard of care for first-line treatment in this group of patients.
  - Bisphosphonate therapy should be considered in patients with castration-recurrent metastatic prostate cancer since it may prevent skeletal-related events and improve bone mineral density. Bisphosphonate therapy can cause renal insufficiency and mandibular osteonecrosis in men with dental disease.
  - Bisphosphonate therapy does not have a role in oncologic treatment of men with newly diagnosed, advanced prostate cancer although clinical trials are in progress.
INITIAL PROSTATE CANCER DIAGNOSIS

INITIAL CLINICAL ASSESSMENT

STAGING WORKUP
(TNM staging refers to 2002 Classification)

RECURRENT RISK

Clinically Localized:

Low: T1-T2a and Gleason score 2-6 and PSA < 10 ng/mL

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

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

Locally Advanced:
Very high:
T3b-T4

Metastatic:
Any T, N1

Any T, Any N, M1

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

---

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

---

See Principles of Life Expectancy (PROS-A).

In selected patients where complications such as hydronephrosis or metastasis can be expected within 5 y, hormonal treatment or radiation therapy may be considered. High risk factors include bulky T3-T4 disease or Gleason score 8-10.

See Nomogram Tables I-IV (PROS-B). These tables were developed to represent trends in presentation and pathologic stage for men newly diagnosed with clinically localized prostate cancer. Clinicians can use these nomograms to counsel individual patients and help them make important decisions regarding their disease.

---

a See Principles of Life Expectancy (PROS-A).
b In selected patients where complications such as hydronephrosis or metastasis can be expected within 5 y, hormonal treatment or radiation therapy may be considered. High risk factors include bulky T3-T4 disease or Gleason score 8-10.
c See Nomogram Tables I-IV (PROS-B). These tables were developed to represent trends in presentation and pathologic stage for men newly diagnosed with clinically localized prostate cancer. Clinicians can use these nomograms to counsel individual patients and help them make important decisions regarding their disease.
**Prostate Cancer**

**RECURRENT RISK**

**EXPECTED PATIENT SURVIVAL**

<table>
<thead>
<tr>
<th>Clinically Localized:</th>
<th>INITIAL THERAPY</th>
<th>ADJUVANT THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: T1-T2a and Gleason score 2-6 and PSA &lt; 10 ng/mL</td>
<td>Expectant management or RT (3D-CRT or brachytherapy)</td>
<td>If radical prostatectomy and positive margins, observe or RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10 y</td>
<td>Expectant management or RT (3D-CRT or brachytherapy)</td>
<td>If radical prostatectomy and lymph node metastasis, observe or androgen deprivation therapy</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy ± pelvic lymph node dissection if predicted probability of lymph node metastasis is ≥ 7%</td>
<td>See Surveillance (PROS-4)</td>
</tr>
<tr>
<td>≥ 10 y</td>
<td>Radical prostatectomy ± pelvic lymph node dissection if predicted probability of lymph node metastasis is ≥ 7%</td>
<td></td>
</tr>
<tr>
<td>Intermediate:* T2b-T2c or Gleason score 7 or PSA 10-20 ng/mL</td>
<td>Expectant management or RT (3D-CRT ± brachytherapy) ± pelvic lymph node dissection if predicted probability of lymph node metastasis is ≥ 7%</td>
<td></td>
</tr>
<tr>
<td>≥ 10 y</td>
<td>Radical prostatectomy + pelvic lymph node dissection if predicted probability of lymph node metastasis is ≥ 7%</td>
<td></td>
</tr>
</tbody>
</table>

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

**ADJUVANT THERAPY**

- If radical prostatectomy and positive margins, observe or RT
- If radical prostatectomy and lymph node metastasis, observe or androgen deprivation therapy

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See Principles of Life Expectancy (PROS-A).

See Principles of Radiation Therapy (PROS-D).

See Principles of Surgery (PROS-E).

See Principles of Hormonal Therapy (PROS-F).
<table>
<thead>
<tr>
<th>RECURRENCE RISK</th>
<th>INITIAL THERAPY</th>
<th>ADJUVANT THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>High:*</td>
<td>Androgen deprivation therapy(^h) (at least 2 y) + RT(^f) (3D-CRT) (category 1) or RT(^f) (3D-CRT ± concurrent short-term androgen deprivation therapy(^h)) (selected patients with a single adverse high risk factor) or Radical prostatectomy (selected patients: low volume, no fixation(^i) + pelvic lymph node dissection)</td>
<td>Positive margins: • Observation or • RT(^f)</td>
</tr>
<tr>
<td>T3a or Gleason score 8-10 or PSA &gt; 20 ng/mL</td>
<td></td>
<td>Lymph node metastasis: • Androgen deprivation therapy(^h) or • Expectant management(^e)</td>
</tr>
<tr>
<td>Locally Advanced:</td>
<td>RT(^f) (3D-CRT) + androgen deprivation therapy(^h) (category 1) or Androgen deprivation therapy(^h)</td>
<td>Undetectable PSA → See Surveillance (PROS-4)</td>
</tr>
<tr>
<td>Very high: T3b-T4</td>
<td></td>
<td>Detectable PSA → See Salvage Therapy (PROS-5)</td>
</tr>
<tr>
<td>Metastatic:</td>
<td>Androgen deprivation therapy(^h) or RT(^f) (3D-CRT) + androgen deprivation therapy(^h)</td>
<td>See Surveillance (PROS-4)</td>
</tr>
<tr>
<td>Any T, N1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any T, Any N, M1</td>
<td>Androgen deprivation therapy(^h)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{e}\) Expectant management involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses or if symptoms become imminent. See Principles of Expectant Management (PROS-C).

\(^{f}\) See Principles of Radiation Therapy (PROS-D).

\(^{g}\) See Principles of Surgery (PROS-E).

\(^{h}\) See Principles of Hormonal Therapy (PROS-F).

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**Prostate Cancer**

**INITIAL MANAGEMENT OR PATHOLOGY**

- **Expectant management**
  - Life expectancy ≥ 10 y
  - Life expectancy < 10 y

- **Initial-definitive therapy**
  - N1 or M1

**SURVEILLANCE**

- PSA as often as every 3 mo
- DRE as often as every 6 mo
- Repeat prostate biopsy as often as annually
- PSA, DRE, prostate biopsy may be done less frequently

**RECURRENT**

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

**SURVEILLANCE**

- Failure of PSA to fall to undetectable levels
- Detectable PSA that increases on 2 subsequent measurements
  - Post-radical prostatectomy
  - Post-RT
  - Rising PSA
    - or Positive DRE
    - Rising PSA and/or blastic bone metastases and/or other metastases
  - Disseminated
    - Visceral or lytic bone metastases and low PSA

**INITIAL MANAGEMENT**

- OR PATHOLOGY
  - See Primary Salvage Therapy (PROS-6)
  - See Systemic Therapy (PROS-7)

---

\(a\)Expectant management involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses or if symptoms become imminent. See Principles of Expectant Management (PROS-C).

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

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

---

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
HIGH PROBABILITY OF BENEFIT FROM RT:
- Gleason score ≤ 7, PreRT PSA ≤ 2, positive margins
- or
- Gleason score ≤ 7, PreRT PSA ≤ 2, negative margins, PSADT > 10 months
- or
- Gleason score 8-10, PreRT PSA ≤ 2, positive margins, PSADT > 10 months

LOWER PROBABILITY OF BENEFIT FROM RT:
- Seminal vesicle invasion
- Lymph node metastases
- Not in one of above categories

Distant metastases

Androgen deprivation therapy

RT

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

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

See Principles of Radiation Therapy (PROS-D).
See Principles of Hormonal Therapy (PROS-F).
SALVAGE WORKUP

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

Post RT rising PSA or Positive DRE

Not a candidate for local therapy

Biopsy positive, no metastases
- Bone scan ± Abd/pelvic CT ± MRI ± ProstaScint

Positive studies for metastases

Surgery in selected cases or Local therapy (Clinical trial preferred)

Androgen deprivation therapy or Observation

Observation or Androgen deprivation therapy

PRIMARY SALVAGE THERAPY

See Systemic Therapy (PROS-7)

\textsuperscript{9}See Principles of Hormonal Therapy (PROS-F).

\textsuperscript{j}The American Society for Therapeutic Radiology and Oncology (ASTRO) Definition defined PSA failure as (1) a rise by 2 ng/ml or more above the nadir PSA be considered the standard definition for biochemical failure after EBRT with or without HT; (2) the date of failure be determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (with no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up". To avoid the artifacts resulting from short follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition would allow comparisons with a large existing body of literature.

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**Prostate Cancer**

**SYSTEMIC THERAPY**

- Disseminated disease
- Blastic bone and/or other metastases and rising PSA

**SYSTEMIC SALVAGE THERAPY**

- Orchietomy or LHRH agonist alone ± antiandrogen for ≥ 7 d for testosterone flare or LHRH agonist + antiandrogen

- Antiandrogen or Second-line hormonal therapy: ketoconazole ± glucocorticoids, or estrogens

- Clinical assessment

**Visceral or lytic bone metastasis and low PSA or Rapidly progressing soft tissue masses**

**Biopsy**

- Not neuroendocrine (with or without small cell features)
- Neuroendocrine (with or without small cell features)

**Follow above pathway for blastic bone and/or other metastases**

- Cisplatin/etoposide or Carboplatin/etoposide

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**See Principles of Hormonal Therapy (PROS-F)**

**See Principles of Chemotherapy (PROS-G)**

^Assure castrate level of testosterone.

See Principles of Chemotherapy (PROS-G).
PRINCIPLES OF LIFE EXPECTANCY ESTIMATION

- Life expectancy estimation is critical to informed decision-making in prostate cancer early detection and treatment.
- Estimation of life expectancy is possible for groups of men but challenging for individuals.
- Life expectancy can be estimated using the Social Security Administration tables (www.ssa.gov/OACT/STATS/table4c6.html)
- Life expectancy can then be adjusted using the clinicians assessment of overall health as follows:
  - Best quartile of health - add 50%
  - Worst quartile of health - subtract 50%
  - Middle two quartiles of health - no adjustment
- Example of 5-year increments of age are reproduced from NCCN Senior Adult Oncology Guidelines for life expectancy estimation.
Staging nomogram to predict the probability (95% confidence intervals) of each, mutually exclusive pathological stage from the preoperative clinical stage, biopsy Gleason score, and serum PSA level (ng/mL). Reproduced with permission from Partin et al. Urology (2001)¹.

**TABLE I. Clinical Stage T1c (nonpalpable, PSA elevated) (page 1 of 6)**

<table>
<thead>
<tr>
<th>PSA Range (ng/mL)</th>
<th>Pathologic Stage</th>
<th>Gleason Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-4</td>
</tr>
<tr>
<td>0-2.5</td>
<td>Organ confined</td>
<td>95 (89-99)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>5 (1-11)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
<tr>
<td>2.6-4.0</td>
<td>Organ confined</td>
<td>92 (82-98)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>8 (2-18)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
<tr>
<td>4.1-6.0</td>
<td>Organ confined</td>
<td>90 (78-98)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>10 (2-22)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
<tr>
<td>6.1-10.0</td>
<td>Organ confined</td>
<td>87 (73-97)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>13 (3-27)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
<tr>
<td>&gt; 10.0</td>
<td>Organ confined</td>
<td>80 (61-95)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>20 (5-39)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
</tbody>
</table>


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

Continued on next page
### TABLE II. Clinical Stage T2a (palpable < ½ of one lobe) (page 2 of 6)

<table>
<thead>
<tr>
<th>PSA Range (ng/mL)</th>
<th>Pathologic Stage</th>
<th>Gleason Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-4</td>
</tr>
<tr>
<td>0-2.5</td>
<td>Organ confined</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td></td>
</tr>
<tr>
<td>2.6-4.0</td>
<td>Organ confined</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td></td>
</tr>
<tr>
<td>4.1-6.0</td>
<td>Organ confined</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
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<tr>
<td></td>
<td>Lymph node (+)</td>
<td></td>
</tr>
<tr>
<td>6.1-10.0</td>
<td>Organ confined</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
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</tr>
<tr>
<td>&gt; 10.0</td>
<td>Organ confined</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td></td>
</tr>
</tbody>
</table>

Continued on next page
### TABLE III. Clinical Stage T2b (palpable > ½ of one lobe, not on both lobes) (page 3 of 6)

<table>
<thead>
<tr>
<th>PSA Range (ng/mL)</th>
<th>Pathologic Stage</th>
<th>Gleason Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-4</td>
</tr>
<tr>
<td>0-2.5</td>
<td>Organ confined</td>
<td>88  (73-97)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>12 (3-27)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
<tr>
<td>2.6-4.0</td>
<td>Organ confined</td>
<td>80 (61-95)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>20 (5-39)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
<tr>
<td>4.1-6.0</td>
<td>Organ confined</td>
<td>75 (55-93)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>25 (7-45)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
<tr>
<td>6.1-10.0</td>
<td>Organ confined</td>
<td>69 (47-91)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>31 (9-53)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
<tr>
<td>&gt; 10.0</td>
<td>Organ confined</td>
<td>57 (35-86)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>43 (14-65)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>-----</td>
</tr>
</tbody>
</table>


**Note:** All recommendations are category 2A unless otherwise indicated. 
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### TABLE IV. Clinical Stage T2c (palpable on both lobes) (page 4 of 6)

<table>
<thead>
<tr>
<th>PSA Range (ng/mL)</th>
<th>Pathologic Stage</th>
<th>Gleason Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-4</td>
</tr>
<tr>
<td><strong>Organ confined</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2.5</td>
<td>Extraprostatic extension</td>
<td>86 (71-97)</td>
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<tr>
<td></td>
<td>Seminal vesicle (+)</td>
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<tr>
<td></td>
<td>Lymph node (+)</td>
<td></td>
</tr>
<tr>
<td><strong>2.6-4.0</strong></td>
<td>Extraprostatic extension</td>
<td>78 (58-94)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td></td>
</tr>
<tr>
<td><strong>4.1-6.0</strong></td>
<td>Extraprostatic extension</td>
<td>73 (52-93)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td></td>
</tr>
<tr>
<td><strong>6.1-10.0</strong></td>
<td>Extraprostatic extension</td>
<td>67 (45-91)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td></td>
</tr>
<tr>
<td><strong>&gt; 10.0</strong></td>
<td>Extraprostatic extension</td>
<td>54 (32-85)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td></td>
</tr>
</tbody>
</table>


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Optimal treatment of prostate cancer requires assessment of risk: how likely is a given cancer to be confined to the prostate or spread to the regional lymph nodes? How likely is the cancer to progress or metastasize after treatment? Prostate cancers are best characterized by their clinical (TNM) stage determined by DRE, Gleason grade in the biopsy specimen, and serum PSA level. Imaging studies (ultrasound, MRI) have been intensively investigated but have yet to be accepted as essential adjuncts to staging. Each of the key characteristics predicts pathologic stage and prognosis, but more accurate prediction can be achieved by combining the individual factors into risk groups, which are easily remembered but contain a heterogeneous population of patients. To quantify risk more accurately, one can devise a nomogram that incorporates the effects of multiple prognostic factors to make predictions about pathologic stage and prognosis for the individual patient. A nomogram is a predictive instrument that takes a set of input data (variables) and makes predictions about an outcome.

The most widely used nomogram in prostate cancer is an algorithm that combines clinical stage, biopsy Gleason grade, and preoperative PSA level to predict pathologic stage, assigned as one of four mutually exclusive groups: organ-confined, extracapsular extension, seminal vesicle invasion, or lymph node metastasis (see PROS-A)\(^1\). The tables give the probability (95% confidence intervals) that a patient with a certain clinical stage, Gleason score, and PSA will have a cancer of each pathological stage. These staging tables are widely used in clinical practice and are an accurate way of predicting the probability of positive lymph nodes (see PROS-1). In addition, estimates of pathologic stage are also important in treatment planning.

Predicting pathologic stage is important in clinical decision-making and may help determine the need for more intensive therapy, ie, high-dose, 3-D conformal external beam irradiation therapy rather than lower dose radiotherapy, or modifying surgical technique to resect a neurovascular bundle. But pathologic stage is only a proxy for prognostic and does not predict success with a given form of treatment. Predicting prognosis is essential for patient decision-making, treatment selection, and adjuvant therapy. These NCCN Guidelines incorporate a risk stratification scheme that uses stage, grade, and PSA to assign patients to risk groups that predict the probability of biochemical failure after definitive local therapy (see PROS-1, PROS-2 and PROS-3)\(^2\). This risk group stratification has been widely published and validated, and it provides a better basis for treatment recommendations than clinical stage alone\(^3\).

Nomograms have also been developed to predict biochemical failure (probability of a rising PSA) after radical prostatectomy\(^4,5\), external beam radiation therapy\(^6\), and brachytherapy\(^7\). Nomograms predict more accurately for the individual patient than risk groups, because they combine the relevant prognostic variables, regardless of value\(^6\). With risk group assignment, a cancer could be considered intermediate- or high-risk based on a single adverse prognostic factor. With nomograms, discordant values (eg, high PSA but low Gleason sum and clinical stage) can be incorporated into a more accurate prediction. With any model, the more clinically relevant information that is used in the calculation of time to PSA failure, the more accurate the result. Risk stratification schemas and validated nomograms are available for predicting 2-year freedom from recurrence following surgery\(^2\) or external beam radiation\(^2\), and 5-year freedom from recurrence following surgery\(^4,8\), external beam radiation,\(^6\) or brachytherapy\(^7\). After surgery, there are models that include pathological stage to predict 7-year freedom from recurrence\(^9\).
None of the current models predict outcome with perfect accuracy, and only some of these models predict metastases and cancer specific death. New independent prognostic factors are being developed. Given the competing causes of mortality, many men who sustain PSA failure will not live long enough to develop clinical evidence of distant metastases or suffer death from cancer. Those with a short PSA doubling time are at greatest risk. The next generation of nomograms will incorporate pre- and post-treatment variables to predict important clinical endpoints.

PRINCIPLES OF EXPECTANT MANAGEMENT

- Expectant management 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 expectant management should have regular follow up:
  - DRE and PSA every 6 mo for life expectancy ≥ 10 ys and every 6-12 mo for life expectancy < 10 ys
  - Needle biopsy of the prostate may be repeated within 6 mo of diagnosis if initial biopsy was < 10 cores or assessment discordant (eg, palpable tumor contralateral to side of positive biopsy)
  - Needle biopsy may be performed within 18 mo if > 10 cores obtained initially, then periodically.
- Cancer progression may have occurred if:
  - Primary Gleason grade 4 or 5 cancer is found upon repeat prostate biopsy
  - Prostate cancer is found in a greater number of prostate biopsies or occupies a greater extent of prostate biopsies
  - PSA doubling time < 3 yr or PSA velocity is > 0.75.
- A repeat prostate biopsy is indicated for signs of disease progression by exam or PSA.
- Advantages of expectant management:
  - 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 is reduced.
- Disadvantages of expectant management:
  - Chance of missed opportunity for cure
  - Risk of progression and/or metastases
  - Subsequent treatment may be more intense 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.

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

**External Beam Radiotherapy:**
- 3D conformal or IMRT (intensity modulated radiation therapy) techniques should be employed.
- Doses of 70-75 Gy in 35-41 fractions to the prostate (± seminal vesicles for part of the therapy) appear to be appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses between 75-80 Gy appear to provide improved PSA-assessed disease control.
- Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant ± adjuvant androgen deprivation therapy for a total of 2-3 y or 4-6 mo if they have only a single high risk adverse factor.
- Patients with intermediate risk cancer may be considered for pelvic lymph node irradiation and 4-6 mo neoadjuvant ± adjuvant ADT.
- Patients with low risk cancer should not receive pelvic lymph node irradiation or ADT.
- If target (PTV) margins are reduced, such as for doses above 75 Gy, extra attention to daily prostate localization, with techniques such as ultrasound, implanted fiducials, or an endorectal balloon, is indicated.

**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) ± neoadjuvant androgen deprivation therapy. Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy; however, with the addition of EBRT and androgen deprivation therapy, it may be effective in select patients.
- Patients with a large prostate (> 60 gm) or small prostate (<15-20 gm), symptoms of bladder outlet obstruction (IPSS score > 15), or a previous transurethral resection of the prostate (TURP) are not appropriate candidates because of increased risk of urinary morbidity. Neoadjuvant androgen deprivation therapy may be used to shrink the prostate to an acceptable size.
- Post-implant dosimetry should be performed to document the quality of the implant.
- The recommended prescribed doses for monotherapy are 145 Gy for 125-Iodine and 125 Gy for 103-Palladium. The corresponding boost dose after 40-50 Gy EBRT are 110 Gy and 100 Gy, respectively.

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**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Pelvic Lymph Node Dissection (PLND):

- An extended PLND includes removal of all node-bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.
- A limited PLND includes removal of all node-bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the obturator nerve posteriorly, Cooper's ligament distally, and the internal iliac vein proximally.
- 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.
- Dissection of nodes anterior and lateral to the external iliac vessels is associated with an increased risk of lymphedema and is discouraged. Extended PLND compared to limited PLND increases the risk of lymphedema after external beam radiation therapy. In addition, an extra peritoneal dissection is preferred if EBRT is anticipated.
- A PLND can be excluded in patients with < 7% 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.
- An extra peritoneal dissection is preferred if EBRT is anticipated.

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 or more and no serious co-morbid conditions that would contraindicate an elective operation.
- High volume surgeons in high volume centers generally provide better outcomes.
- Laparoscopic and robot-assisted radical prostatectomy are used commonly. In experienced hands, the results of these approaches appear comparable to open surgical approaches.
- Blood loss can be substantial with radical prostatectomy but can be reduced by careful control of 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 the degree of preservation of the cavernous nerves. Replacement of resected nerves with nerve grafts is investigational. Early restoration of erections may improve late recovery.
- Salvage radical prostatectomy is an option for highly selected patients with local recurrence after EBRT, brachytherapy, or cryotherapy in the absence of metastases, but the morbidity (incontinence, loss of erection, anastomotic stricture) is high.
PRINCIPLES OF HORMONAL THERAPY (ANDROGEN DEPRIVATION THERAPY - ADT) (page 1 of 2)

Neoadjuvant 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.
- 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 radiation therapy (See PROS-3). In the largest randomized trial to date using antiandrogen bicalutamide alone at high dose (150 mgs), there were indications of a delay in recurrence of disease but no improvement in survival. Longer follow-up is needed.
- In one randomized trial, immediate and continuous use of ADT in men with positive nodes following radical prostatectomy resulted in significantly improved overall survival than those with delayed ADT. Therefore, such patients should be considered for immediate ADT.

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

Optimal ADT
- LHRH agonist (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.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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 androgen deprivation therapy is a widely used approach to reduce side effects, but the long term efficacy remains unproven.
- Patients who do not achieve adequate suppression of serum testosterone (less than 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 androgen deprivation therapy (castration-recurrent prostate cancer); thus, ADT should be continued.
- A variety of strategies can be employed if initial ADT has failed which may afford clinical benefit, including antiandrogen withdrawal, and administration of antiandrogens, ketoconazole, or estrogens; however, none of these has yet been demonstrated to prolong survival in randomized clinical trials.

Monitor/Surveillance
- Patients being treated with either medical or surgical castration are at risk for having or developing osteoporosis. A baseline bone mineral density study should be considered in this group of patient, especially if longterm ADT is planned.
- Supplementation with calcium (500mg daily) and vitamin D (400 IU) is recommended for all men on long-term ADT.
- Men who are osteopenic/osteoporotic should be strongly considered for bisphosphonate therapy with zoledronic acid, pamidronate, alendronate, raloxifene or toremifene.
PRINCIPLES OF CHEMOTHERAPY

- Systemic chemotherapy should be reserved for patients with castration-recurrent metastatic prostate cancer except when studied in clinical trials.
- In this group of patients, docetaxel-based regimens have been shown to confer a survival benefit in two phase III studies:
  - SWOG 9916 compared docetaxel plus estramustine to mitoxantrone plus prednisone. Median survival for the docetaxel arm was 18 months vs. 15 months for the mitoxantrone arm (p=0.01).\(^1\)
  - TAX 327 compared two docetaxel schedules (weekly and every 3 weeks) to mitoxantrone and prednisone. Median survival for the every 3 week docetaxel arm was 18.9 months vs. 16.5 months for the mitoxantrone arm (p=0.009)\(^2\)
- Docetaxel-based regimens are now the standard of care for first-line treatment in this group of patients.
- Bisphosphonate therapy should be considered in patients with castration-recurrent metastatic prostate cancer since it may prevent skeletal-related events and improve bone mineral density. Bisphosphonate therapy can cause renal insufficiency and mandibular osteonecrosis in men with dental disease.
- Bisphosphonate therapy does not have a role in oncologic treatment of men with newly diagnosed, advanced prostate cancer although clinical trials are in progress.


## Staging

### Table 1

| 2002 American Joint Committee on Cancer (AJCC) TNM Staging System For Prostate Cancer |
|-----------|------------------|
| **Primary Tumor (T)** | **Pathologic (pT)** |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Clinically inapparent tumor neither palpable nor visible by imaging |
| T1a | Tumor incidental histologic finding in 5% or less of tissue resected |
| T1b | Tumor incidental histologic finding in more than 5% of tissue resected |
| T1c | Tumor identified by needle biopsy (e.g., because of elevated PSA) |
| T2 | Tumor confined within the prostate* |
| T2a | Tumor involves one-half of one lobe or less |
| T2b | Tumor involves more than one-half of one lobe but not both lobes |
| T2c | Tumor involves both lobes |
| T3 | Tumor extends through the prostatic capsule ** |
| T3a | Extracapsular extension (unilateral or bilateral) |
| T3b | Tumor invades the seminal vesicle(s) |
| T4 | Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall |

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c. 
**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2. 

### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th><strong>Clinical</strong></th>
<th><strong>Pathologic</strong></th>
</tr>
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<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes were not assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in regional lymph node(s)</td>
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### Distant Metastasis (M)*

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<th><strong>Clinical</strong></th>
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</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed (not evaluated by any modality)</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Non-regional lymph node(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone(s)</td>
</tr>
<tr>
<td>M1c</td>
<td>Other site(s) with or without bone disease</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>G</th>
</tr>
</thead>
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<td>M0</td>
<td>G1</td>
</tr>
<tr>
<td>II</td>
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<td>M0</td>
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<td>T1c</td>
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<td>N0</td>
<td>M0</td>
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### Histopathologic Type

This classification applies to adenocarcinomas and squamous carcinomas, but not to sarcoma or transitional cell carcinoma of the prostate. Adjectives used to describe adenocarcinomas can include mucinous, small cell, papillary, ductal, and neuroendocrine.

Transitional cell carcinoma of the prostate is classified as a urethral tumor. There should be histologic confirmation of the disease.

### Histopathologic Grade (G)

Gleason score is considered to be the optimal method of grading, because this method takes into account the inherent heterogeneity of prostate cancer, and because it has been clearly shown that this method is of great prognostic value. A primary and a secondary pattern (the range of each if 1 – 5) are assigned and then summed to yield a total score. Scores of 2 – 10 are thus possible. (If a single focus of disease is seen, it should be reported as both scores. For example, if a single focus of Gleason 3 disease is seen, it is reported as 3 + 3.)

- **GX** Grade cannot be assessed
- **G1** Well differentiated (slight anaplasia) (Gleason 2–4)
- **G2** Moderately differentiated (moderate anaplasia) (Gleason 5–6)
- **G3–4** Poorly differentiated or undifferentiated (marked anaplasia) (Gleason 7–10)

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Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit [www.cancerstaging.net](http://www.cancerstaging.net).) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.
In the late 1980s and early 1990s, the number of newly diagnosed prostate cancers in U.S. men increased dramatically, and prostate cancer greatly surpassed lung cancer as the most common cancer. This marked increase was followed by a decline in detection rates between 1992 and 1996. The trend of increasing prostate cancer cases has since resumed; an estimated 232,090 new cases will be diagnosed in 2005, and prostate cancer is expected to account for 33% of new cancer cases in 2005. It is generally accepted that these changes were probably a result of the widespread use of prostate-specific antigen (PSA) screening in previously unscreened populations and a concomitant increase in the detection of early-stage prostate cancers. As the population ages, the number of new cases is expected to grow substantially, because prostate cancer incidence increases with age faster than any other cancer. However, although the incidence of prostate cancer has been increasing (2.0% annually from 1995 to 2001), the age-adjusted death rates from prostate cancer have begun to decline (-4.1% annually from 1994 to 2001). Researchers expect prostate cancer to account for 30,350 deaths in 2005. This 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 this prevalent cancer. Of interest, the percentage of patients with low-risk disease has recently increased (45.3% in 1999-2001 compared with 29.8% in 1989-1992; P < .0001).

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

Manuscript

This manuscript is being updated to correspond with the newly updated algorithm.

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

In the late 1980s and early 1990s, the number of newly diagnosed prostate cancers in U.S. men increased dramatically, and prostate cancer greatly surpassed lung cancer as the most common cancer. This marked increase was followed by a decline in detection rates between 1992 and 1996. The trend of increasing prostate cancer cases has since resumed; an estimated 232,090 new cases will be diagnosed in 2005, and prostate cancer is expected to account for 33% of new cancer cases in 2005. It is generally accepted that these changes were probably a result of the widespread use of prostate-specific antigen (PSA) screening in previously unscreened populations and a concomitant increase in the detection of early-stage prostate cancers. As the population ages, the number of new cases is expected to grow substantially, because prostate cancer incidence increases with age faster than any other cancer. However, although the incidence of prostate cancer has been increasing (2.0% annually from 1995 to 2001), the age-adjusted death rates from prostate cancer have begun to decline (-4.1% annually from 1994 to 2001). Researchers expect prostate cancer to account for 30,350 deaths in 2005. This 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 this prevalent cancer. Of interest, the percentage of patients with low-risk disease has recently increased (45.3% in 1999-2001 compared with 29.8% in 1989-1992; P < .0001).

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Initial Prostate Cancer Diagnosis

Development of the NCCN prostate cancer treatment guidelines began with the assumption that the initial detection of most prostate cancers is made using either a digital rectal examination (DRE) or a PSA. A separate NCCN panel has written additional guidelines for prostate cancer early detection. The diagnosis requires a biopsy of the prostate, usually performed by 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 AJCC (American Joint Committee on Cancer). The goals of NCCN treatment guidelines are to optimize cancer survival while minimizing treatment-related morbidity.

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The NCCN Prostate Cancer Panel is in favor of 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 Management and Staging Evaluation

Patients are stratified at diagnosis for initial treatment recommendations based on anticipated life expectancy of the individual patient and on whether they are symptomatic from the cancer. For patients with a life expectancy of less than 5 years and without clinical symptoms, further workup or treatment may be delayed until symptoms develop. Evidence for a deferred therapy approach (ie, expectant management) is supported by data showing that the 5-year cancer-specific mortality is very low for most prostate cancers except those that are poorly differentiated. If high-risk factors (bulky T3-T4 cancers or Gleason score 8-10) for developing hydronephrosis or metastases are present, hormonal treatment or radiation therapy (RT) may be considered. The recommendation for prospective intervention was supported by results from the Medical Research Council (MRC) in which men with M0 disease showed less cancer-related morbidity after receiving earlier hormone deprivation therapy. The determination of which patients have rapidly growing cancer and are appropriate candidates for therapy is based on the clinician’s judgment.

For symptomatic patients and/or those with a life expectancy of greater than 5 years, a bone scan is appropriate for T1 to T2 disease in the presence of a PSA greater than 20 ng/mL, Gleason score of 8 or higher, clinical stage of T3 to T4, or symptomatic disease. Nomograms or risk tables may be used to identify patients with a higher likelihood of having metastatic disease. Patients at higher risk of metastatic disease may undergo pelvic computed tomography (CT) or magnetic resonance imaging (MRI) scanning with possible fine-needle aspiration of enlarged lymph nodes or staging lymph node dissection. If the nomogram indicates a probability of lymph node involvement greater than 20% or if the patient is stage T3 or T4, this is recommended as a threshold for doing a staging CT scan or MRI evaluation. For all other patients, no additional imaging is required for staging.

Treatment Considerations for Localized Prostate Cancer

As a result of widespread PSA testing, most patients are diagnosed...
with asymptomatic, clinically localized cancer. The combination of Gleason score, PSA level, and stage can effectively stratify patients into categories associated with different probabilities of achieving a cure. Further refinement of the patient's risk of recurrent cancer is currently being investigated using molecular markers and other radiologic evaluations of the prostate. However, these approaches remain investigational and are not currently available or validated for routine application. In addition to considering the probability of cure, the choice of initial treatment is highly influenced by estimated life expectancy, comorbidities, potential therapy side effects, and patient preference.

The primary treatment options for initial therapy for localized prostate cancer include radical prostatectomy or radiotherapy. Frequently, treatment is selected or recommended on the basis of patient considerations of the potential morbidity of the treatment, rather than on clear differences in rates of tumor control. Radiotherapy options for these guidelines include brachytherapy as monotherapy for patients with a low risk of recurrence. Brachytherapy as monotherapy is not recommended for disease control among patients with intermediate or advanced cancer, because evidence was believed to be insufficient in this subset of patients.

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? Prostate cancers are best characterized by clinical (TNM) stage determined by DRE, Gleason grade in the biopsy specimen, and serum PSA level. Imaging studies (ultrasound, MRI) have been intensively investigated but have yet to be accepted as essential adjuncts to staging. Each of the key characteristics predicts pathologic stage and prognosis, but more accurate prediction can be achieved by combining the individual factors into risk groups, which are easily remembered but contain a heterogeneous population of patients.

To quantify risk more accurately, one can devise a nomogram that incorporates the interactive effects of multiple prognostic factors to make accurate predictions about stage and prognosis for the individual patient. A nomogram is any predictive instrument that takes a set of input data (variables) and makes predictions about an outcome. However, the major disadvantage of nomograms is that they are awkward to use without a computer.

The most widely used nomogram in prostate cancer combines clinical stage, biopsy Gleason grade, and preoperative PSA level to predict pathologic stage, assigned as one of four mutually exclusive groups: (1) organ confined; (2) extracapsular (ie, extraprostatic) extension; (3) seminal vesicle invasion; or (4) lymph node metastasis.¹⁰ The tables give the probability (95% confidence intervals) that a patient with a certain clinical stage, Gleason score, and PSA will have a cancer of each pathologic stage. These staging tables are widely used in clinical practice and are an accurate way of predicting the probability of positive lymph nodes. In addition, estimates of pathologic stage are also important in treatment planning.

Predicting pathologic stage is important in clinical decision-making and may help determine the need for more intensive therapy (such as high-dose, 3-dimensional conformal external-beam irradiation therapy [3D-CRT] rather than lower dose radiotherapy) or for modifying surgical technique to resect a neurovascular bundle. However, pathologic stage is only a proxy for prognosis and does not predict success with a given form of treatment. Predicting prognosis is essential for patient decision-making, treatment
selection, and adjuvant therapy. These NCCN Guidelines incorporate a risk stratification scheme that uses stage, grade, and PSA to assign patients to risk groups that 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 widely published and validated, and it provides a better basis for treatment recommendations than clinical stage alone.

In addition, nomograms have also been developed to predict biochemical failure after radical prostatectomy, external-beam RT, and brachytherapy. Nomograms predict more accurately for the individual patient than risk groups, because they combine the relevant prognostic variables, regardless of value. With risk group assignment, a cancer could be considered intermediate risk or high risk based on a single adverse prognostic factor. With nomograms, discordant values (e.g., high PSA but low Gleason sum and clinical stage) can be incorporated into a more accurate prediction. With any model, the more clinically relevant information that is used in the calculation of time to PSA failure, the more accurate the result. Risk stratification schemas and validated nomograms are available for predicting 2-year freedom from biochemical recurrence after surgery or external-beam radiation and for predicting 5-year freedom from recurrence after surgery, external-beam radiation, or brachytherapy. After surgery, there are models that include pathologic stage to predict 7-year freedom from biochemical recurrence.

None of the current models predict with perfect accuracy, and only some of these models predict metastases and cancer-specific death. New independent prognostic factors are being developed. Given the competing causes of mortality, many men who sustain PSA failure will not live long enough either to develop clinical evidence of distant metastases or to die from prostate cancer. Those with a short PSA doubling time are at greatest risk of death. Not all PSA failures are clinically relevant; thus, PSA doubling time may be a more useful measure of risk of death. The next generation of nomograms will incorporate pretreatment and post-treatment variables to predict important clinical endpoints, making prognostic nomograms essential in the care of patients with prostate cancer. Until this time, the NCCN panel recommends incorporation of recurrent disease risk stratification using the available predictive features included in the guidelines, risk tables, and nomograms when discussing options for the treatment of clinically localized prostate cancer.

**Low Risk of Recurrence**

As defined by the NCCN guidelines, patients with low risk for biochemical recurrence include those with tumors stage T1 to T2a, a low Gleason score (2 to 6), and a PSA level below 10 ng/mL. Treatment options are based on anticipated life expectancies. In patients whose age or comorbidity leads to a life expectancy of less than 10 years, expectant management or RT (using either 3-D external-beam RT or brachytherapy) is an acceptable strategy. If the patient’s life expectancy is 10 years or more, the treatment recommendations are the same, with the addition of a third treatment option consisting of radical prostatectomy with or without a pelvic lymph node dissection. A recent study by Johansson and colleagues assessed the long-term natural history of untreated, early-stage prostate cancer in 223 patients during 21 years of follow-up. They found that most prostate cancers diagnosed at an early stage have an indolent course; however, local tumor progression and aggressive metastatic disease may develop in the long term. The mortality rate was significantly higher (approximately 6-fold) after 15 years of follow-up when compared with the first 5
Their findings support early radical treatment, notably among patients with an estimated life expectancy exceeding 15 years.

Expectant management (also referred to as deferred treatment) involves actively monitoring the course of the disease with the expectation to intervene if the cancer progresses or if symptoms become imminent.23 Watchful waiting refers to no treatment.22,24 Thus, expectant management requires a thorough staging evaluation as outlined previously, assessment of comorbidities, and active monitoring with close follow-up of the patients (ie, active surveillance). Patients on expectant management are likely to have progression of their tumors but with different velocity in different patients. Unfortunately, the currently established prognostic factors cannot accurately tell us which patients will have a slow or a rapid prostate cancer progression.

Patients and physicians involved in expectant management must be aware that the PSA is likely to rise and that the tumor will possibly grow with time. Patients should not be under the impression that the tumor will stay stable indefinitely and must be prepared to reevaluate the decision to defer treatment. Studies are in progress to develop trigger points for deciding when to start treatment with curative intent after initially choosing expectant management. Trigger points based on PSA, histologic progression, or clinical progression have been used.25-27 Also, in serial biopsies, a progression of ploidy and grade before clinical progression has been seen.28 In one series, 12 of 13 men undergoing deferred radical prostatectomy until biopsy grade progression had curable cancers.29 Whether these trigger points will ultimately be validated or not, however, still needs to be proven.

Because of potential perioperative morbidity, radical prostatectomy should be reserved for patients whose life expectancy is 10 years or more. This is consistent with data showing that fewer than 20% of low-risk patients with prostate cancer experience a cancer-specific death by 10 years.6 Furthermore, although 40% of men older than 50 years of age harbor prostate cancer, only 1 in 4 present clinically, and only 1 in 14 will die of a prostate cancer-specific death. Therefore, expectant management is an acceptable treatment option for men with low-risk prostate cancer and a life expectancy less than 10 years.

Although studies of surgical outcomes generally have the longest follow-up periods, with long-term cancer survival, the NCCN panel consensus was that modern radiotherapy and surgical series show similar progression-free survival in low-risk patients treated with radical prostatectomy or RT.12,29

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 biopsies.30

Intermediate Risk of Recurrence

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

For these patients with a life expectancy of less than 10 years, expectant management remains a reasonable option. Evidence supporting expectant management includes population-based cohort studies showing only a 24% mortality after 10 years.31 Similarly, Johansson and colleagues32 observed that only 13% of men developed metastases 15 years after diagnosis and only 11%
had died from prostate cancer. Other recommended treatment options include (1) external-beam RT (eg, 3D-CRT) with or without brachytherapy, or (2) radical prostatectomy with pelvic lymph node dissection (unless the predicted probability of lymph node metastasis is < 3%).

For patients with an expected survival of 10 years or more, expectant management should not be considered a reasonable alternative to active treatment in those with intermediate- or high-risk clinically localized cancers (category 1). Patients should be offered (1) radical prostatectomy with a pelvic lymph node dissection (unless the predicted probability of lymph node metastasis is < 3%), or (2) external-beam RT with or without brachytherapy. There is now category 1 evidence to support the recommendation of radical prostatectomy rather than expectant management. 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 (1) a component of Gleason pattern 4 or 5 cancer, or (2) a PSA value more than 10 ng/mL.

### High Risk of Recurrence

Men with prostate cancer that is clinically localized stage T3a, with Gleason score of 8 to 10, or PSA level greater than 20 ng/mL are categorized by the NCCN panel to be at high risk of recurrence after definitive therapy. Note that patients with multiple adverse factors may be shifted into the very high-risk category. Hormonal therapy (eg, androgen deprivation therapy) plus external-beam RT is recommended (category 1). This treatment option is supported by the EORTC (European Organisation for Research and Treatment of Cancer) trial results (as reported by Bolla and colleagues). A second treatment option involves external-beam RT with or without concurrent short-term androgen deprivation therapy for select patients with a single adverse high-risk factor. Finally, radical prostatectomy with pelvic lymph node dissection remains an option in select patients with low tumor volume and no fixation to adjacent organs. For patients with Gleason scores of 8 or greater, progression-free survival ranges from 28% to 36% after radical prostatectomy.

### Very High Risk of Recurrence

Patients at very high risk of recurrence are defined by the NCCN guidelines as those with either (1) clinical stage T3b to T4, or (2) nonlocalized cancer (any T, N1). Very high-risk patients are not considered candidates for radical prostatectomy. The options for this group include either (1) androgen deprivation therapy alone, or (2) a combination of RT and androgen deprivation therapy (category 1 for T3b-T4 cancer). Early hormonal deprivation therapy is supported by the MRC trial in which men receiving early androgen deprivation therapy showed improved survival and less local morbidity. RT may be administered to prevent or delay the onset of local symptoms. If the cancer has metastasized (any T, any N, M1), androgen deprivation therapy alone is recommended.

### Adjuvant Therapy

For patients undergoing radical prostatectomy, if the margins are positive, the follow-up options include RT or observation. No high-level evidence exists to recommend adjuvant RT at this time; however, if a patient undergoes a radical prostatectomy and microscopically positive margins are found, RT can reasonably be used after recuperation from surgery. Alternatively, close observation is acceptable until a detectable PSA develops. If adjuvant RT is considered, it should be administered before the PSA...
increases above 1.5 ng/mL.® Adjuvant antiandrogen therapy is not a standard treatment at this time. The largest randomized trial to date assessed the antiandrogen bicalutamide alone at high dose (150 mg).® Because 81% of the trial population were untreated before entry and would otherwise have undergone watchful waiting, the findings essentially reflect the results of immediate hormone therapy. At a median 5.3-year follow-up, patients with locally advanced disease had improved survival with bicalutamide, whereas those with localized disease had decreased survival with bicalutamide. In some randomized trials, immediate use of androgen deprivation therapy in men with positive nodes after radical prostatectomy resulted in significantly improved overall survival when compared with those receiving delayed androgen deprivation therapy; therefore, such patients should be considered for immediate androgen deprivation therapy. If positive lymph nodes are found after radical prostatectomy, either androgen deprivation therapy or expectant management is acceptable.

Surveillance

In patients for whom the initial intervention is expectant management and who have a life expectancy of less than 10 years, a clinical evaluation is recommended every 6 to 12 months. Surveillance has been shown to offer 10-year survival rates and quality-adjusted life expectancy similar to radical prostatectomy or radiotherapy.® The decision to initiate treatment is driven primarily by the onset of symptoms. However, patients with high-risk disease may have a better 5-year overall and disease-specific survival with active intervention than with observation until symptomatic.®

For those with a life expectancy of 10 years or more and who therefore might benefit from definitive local therapy, appropriate surveillance includes a PSA determination and DRE every 6 months, along with a repeat prostate biopsy approximately 1 year after the original diagnosis unless the patient initially had a 10 to 12 core biopsy. Repeat biopsy is recommended to determine whether higher-grade elements are evolving, which may influence prognosis and, hence, the decision to continue observation or to proceed to definitive local therapy. After the initial recommended repeat biopsy, subsequent biopsies may be performed at the observing physician's discretion. As previously discussed, studies remain in progress to identify appropriate trigger points, after choosing deferred treatment, when interventions with curative intent may still be reliably successful. Note that criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression.

For patients initially treated with intent to cure, a serum PSA level should be measured every 6 months for the first 5 years and then rechecked annually. For recurrence after radical prostatectomy, Pound and colleagues® found that 45% of patients experienced recurrence within the first 2 years, 77% within the first 5 years, and 96% by 9 years. Because local recurrence may result in substantial morbidity and can, in rare cases, occur in the absence of a PSA elevation, an annual DRE is also appropriate to monitor for prostate cancer recurrence as well as for colorectal cancer. Similarly, after RT, the monitoring of serum PSA levels is recommended every 6 months for the first 5 years and then annually. 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 androgen deprivation therapy, radiotherapy, or both. Follow-up evaluation of these patients should include a history and physical
examination, DRE, and PSA determination every 3 to 6 months. Patients being treated with either medical or surgical castration are at risk for having or developing osteoporosis. A baseline bone mineral density study should be considered in this group of patients. Supplementation is recommended using calcium (500 mg) and vitamin D (400 IU). Men who are osteopenic/osteoporotic should be strongly considered for bisphosphonate therapy.

Bone scans are appropriate when patients develop symptoms or when the PSA level is increasing rapidly. In one study, the probability of a positive bone scan for a patient not on androgen deprivation therapy after radical prostatectomy was less than 5% unless the PSA increased to 40 to 45 ng/mL. Therefore, particularly in the androgen-dependent state, periodic bone scans as part of routine surveillance are not recommended, because they do not contribute significantly to the tests previously discussed.

**Salvage Workup and Primary Salvage Therapy**

**Postsurgery Patients**

Patients who have undergone a radical prostatectomy and experience a biochemical recurrence fall into two groups: (1) those whose PSA level fails to fall to undetectable levels after surgery, or (2) those with a persistently elevated (> 0.3 ng/mL) and rising PSA level (based on two or more laboratory determinations). For those whose PSA level does not fall to undetectable levels who have evidence of persistent local tumor, treatment options include either (1) RT (preferred) with or without androgen deprivation therapy; or (2) androgen deprivation therapy alone. Radiotherapy to attempt to eradicate local residual cancer is recommended and preferred for patients with no evidence of persistent local tumor and a lower risk of metastasis whose surgical margins are positive, seminal vesicles are negative, and PSA is less than 2 ng/mL or PSA doubling time is greater than 10 months. Less preferred options are androgen deprivation therapy alone or observation. Patients with detectable postoperative PSA levels, negative margins, and positive seminal vesicles or lymph nodes or with PSA doubling time less than 3 months are at higher risk of disseminated cancer. Therefore, observation or androgen deprivation therapy is recommended. Radiotherapy was not endorsed for this group.

Patients whose PSA is greater than 0.3 ng/mL and rising on two or more determinations (ie, biochemical recurrence after radical prostatectomy) may be candidates for further local therapy. A workup may include a bone scan, a transrectal anastomotic biopsy, and a CT or MRI scan. Currently available Prostascint scans (Cytogen Corporation, Princeton NJ) may be considered but are not generally recommended at this time. If the tests are negative for distant or nodal disease, salvage therapy options include RT with or without androgen deprivation therapy (preferred), observation, or androgen deprivation therapy alone. Patients are more likely to have local rather than distant disease if they have a rising PSA value more than 24 months after prostatectomy, PSA doubling time of more than 10 months, Gleason score of less than 8, and no involvement of the seminal vesicles; therefore, early RT is preferred in these patients. Androgen deprivation therapy (preferred) or observation remains an alternative for patients with metastatic disease or positive lymph nodes at surgery because of the lack of curative therapy, the unpredictable course of advanced prostate cancer in some patients, and the morbidity of some treatments.

**Postradiation Patients**

For patients treated with radiotherapy who later develop a rising PSA level or positive DRE, it is appropriate to define the extent of
recurrent cancer with a bone scan with or without abdomino/pelvic CT, MRI, or a ProstaScint scan. A rising PSA value after radiotherapy is defined as three consecutive rising PSA values at least 3 months apart; the NCCN panel accepts this definition, which was described by a consensus panel of the American Society for Therapeutic Radiology and Oncology (ASTRO). The date of biochemical failure is back dated to midway between the date of the postirradiation nadir PSA value and the first of the three consecutive increases. This definition was developed from observations of patients treated without androgen deprivation therapy and may not be applicable to patients receiving primary therapy consisting of combined external-beam radiation/androgen deprivation therapy or to those undergoing brachytherapy.

Options for salvage therapy include observation, androgen deprivation therapy alone, radical prostatectomy in selected cases, or local therapy (clinical trial preferred). Patients who may be appropriate candidates for salvage radical prostatectomy include those (1) whose original clinical stage was T1 or T2, NX or N0; (2) who have a Gleason score below 8, (3) with a current PSA less than 10 ng/mL; (4) with a positive biopsy specimen but no known metastatic disease; and (5) with a remaining life expectancy of greater than 10 years. The morbidity from salvage surgery (including incontinence, erectile dysfunction, and bladder neck contracture) remains significantly higher than when radical prostatectomy is used as initial therapy. Other localized interventions (such as cryotherapy) are used but are considered investigational with limited follow up; these should continue to be performed in the context of clinical trial, preferably. However, patients with metastatic diseases who are not candidates for local therapy should be observed or treated with androgen deprivation therapy.

### Systemic Therapy

Systemic therapy is needed for initially disseminated cancer. For patients whose cancer progresses rapidly with blastic bone and/or other metastases and a rising PSA, androgen deprivation therapy is considered the most common form of systemic therapy (including orchiectomy, high-dose antiandrogen alone, LHRH [luteinizing hormone-releasing hormone] agonist with antiandrogen, or LHRH agonist alone). 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 2 to 4 weeks to block ligand binding to the androgen receptor.

For disease relapse, antiandrogen is recommended for patients with surgical castration (through orchiectomy) or with chemical castration (through LHRH agonist alone); second-line hormonal therapy is another option and includes either (1) ketoconazole with or without glucocorticoids, or (2) estrogens. For patients already undergoing antiandrogen treatment, discontinuation of antiandrogen is recommended; LHRH agonist or orchiectomy is considered if high-dose antiandrogen was the only systemic therapy.

In patients with rapidly progressing soft tissue masses or who develop visceral or lytic bone metastases in the presence of a low serum PSA level, neuroendocrine differentiation should be considered. 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. For most patients with no neuroendocrine differentiation features, systemic therapy follows the same pathway for blastic bone or other metastases, as explained previously. Patients should receive a clinical assessment to assure a castrate level of testosterone.

Systemic salvage therapy for patients with advanced prostate cancer includes bisphosphonates (which are recommended to prevent osteoporosis in patients with osteoblastic metastases undergoing androgen deprivation therapy [see below]) and any of the following: (1) systemic chemotherapy (docetaxel-based regimen with prednisone or estramustine is preferred); (2) systemic RT using samarium or strontium; or (3) supportive care. Systemic chemotherapy should be reserved for patients with hormone-refractory metastatic prostate cancer. In this group of patients, docetaxel-based regimens have been shown to confer a survival benefit in two phase III studies (Southwest Oncology Group [SWOG] 9916 and TAX 327). Thus, docetaxel-based regimens are now the standard of care for this group of patients; however, the value of adding estramustine to docetaxel remains to be determined. The Food and Drug Administration has approved docetaxel for injection in combination with prednisone for the treatment of metastatic, hormone-refractory (androgen-independent) prostate cancer.

Numerous systemic chemotherapeutic regimens offer significant palliative benefit in hormone-refractory metastatic prostate cancer including estramustine/paclitaxel, docetaxel/estramustine, mitoxantrone/prednisone, and several others; at this time, strongly recommending one over another is not possible. Mitoxantrone with prednisone has been shown to provide palliative benefit in patients with painful bony metastases from hormone-refractory prostate cancer. However, its efficacy as second-line therapy after docetaxel has not been determined. The traditional option of glucocorticoids and external-beam radiation for symptomatic bone metastases remains available for patients with focal pain or pending pathologic fractures. The use of systemic radiotherapy with either strontium-89 or samarium-153 may occasionally benefit 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 radiotherapy. The risk of bone marrow suppression, which might influence the ability to provide additional systemic chemotherapy, should be considered before this therapy is initiated.

**Bisphosphonates and Prostate Cancer**

Bisphosphonates are pyrophosphate analogs that inhibit bone resorption. Although the antiresorptive mechanism is not completely understood, bisphosphonates bind to bone and inhibit osteoclastic activity/proliferation. In this way, bisphosphonates can disrupt the cycle of abnormal bone remodeling that occurs in metastatic disease. Although prostate cancer is most frequently associated with osteoblastic lesions radiographically, osteolysis is a critical component in the cycle of abnormal bone metabolism that results when prostate cancer involves the skeleton. Thus, inhibition of bone resorption via inhibition of osteoclasts is a critical component in treating osteoblastic metastases.

Zoledronic acid (Zometa, Novartis Oncology) is a highly potent intravenous bisphosphonate that is approved for the treatment of patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Zoledronic acid was compared with placebo in prostate cancer patients with a history of metastatic bone disease who had a rising serum PSA level despite treatment with hormonal therapy in a randomized, double-blind, 15-
month clinical trial. The primary endpoint of this study was the proportion of patients experiencing at least one skeletal-related event, including pathological fracture, spinal cord compression, surgery or radiation therapy to bone, or a change in antineoplastic therapy to treat bone pain. Zoledronic acid demonstrated a 25% reduction in the proportion of patients with a skeletal-related event (P = .021). The time to the first skeletal-related event was at least 100 days later in patients receiving zoledronic acid compared with patients receiving placebo (P = .01). These improvements with zoledronic acid are certainly clinically significant and offer a new therapeutic strategy in prostate cancer patients with skeletal metastases.

Advanced prostate cancer can negatively affect normal bone physiology not only because of direct tumor involvement (bone metastases) but also, because androgen deprivation therapy is associated with osteoporotic effects. Cancer and/or treatment-related effects weaken bone and make the patient susceptible to fractures. Fracture risk is increased in men with prostate cancer who are treated with androgen deprivation therapy either by surgical castration or by the administration of a gonadotropin-releasing hormone (ie, LHRH) agonist. In a recent review of Medicare beneficiaries with nonmetastatic prostate cancer, use of a gonadotropin-releasing hormone agonist resulted in a 1.25 relative risk of sustaining a clinical fracture compared to men not receiving gonadotropin-releasing hormone therapy. This risk was magnified if men received treatment for 1 year or more. Preventing the adverse skeletal effects of long-term androgen deprivation therapy is increasingly important, because such treatment is often initiated in men with relatively long life expectancies.

Bisphosphonates have also proven useful in the management of osteoporosis. Their usefulness when orally administered is limited by low bioavailability, low potency, and gastrointestinal toxicity; however, intravenous treatment has overcome these limitations. In a study of postmenopausal women with low bone mineral density, zoledronic acid infusions at intervals of up to 1 year produced effects on bone turnover and bone density as large as those achieved by daily oral dosing. Zoledronic acid has also been examined in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. In a double-blind, placebo-controlled clinical trial, men with M0 (no distant metastases) prostate cancer beginning androgen deprivation therapy were randomly assigned to receive zoledronic acid (4 mg) or placebo intravenously every 3 months for 1 year. Mean bone mineral density at the spine and hip increased in the zoledronic acid group but decreased in the placebo group. These results suggest that intermittent administration of zoledronic acid prevents treatment-related bone loss and increases bone mineral density in men undergoing androgen deprivation therapy for prostate cancer.

Most men dying from metastatic prostate cancer have evidence of bone involvement. Many of these men will experience pain and/or skeletal complications, decreasing their quality of life. By inhibiting osteoclastic activity, bisphosphonates can interrupt these deleterious effects on normal bone, delaying or preventing patient morbidity. Osteoporosis and the resultant increase in fracture incidence occur in men treated with androgen deprivation therapy, even in the absence of bone metastases. Clinical studies have demonstrated that bisphosphonates prevent bone loss and increase bone mineral density in men treated with androgen deprivation therapy. Taken together, these findings suggest that early intervention with intravenous bisphosphonates may improve clinical outcomes and quality of life in men with prostate cancer who are treated with androgen deprivation therapy.
Principles of Expectant Management

Expectant management involves actively monitoring the course of the disease with the expectation to intervene if the cancer progresses or if symptoms become imminent. Expectant management is indicated for patients with low-risk cancers or for patients with a short life expectancy. Patients must be willing to accept the risk of local progression, which may reduce the chances of cure, or of metastases before active treatment is initiated. Contraindications include (1) a high-risk or very high-risk cancer in a patient with a long life expectancy, or (2) evidence of progression or metastases on expectant management.

The advantages of expectant management include (1) side effects of definitive therapy are avoided; (2) quality of life and normal activities are retained; (3) small indolent cancers do not receive unnecessary treatment; and (4) decreased initial costs. The disadvantages of expectant management are (1) the cancer may progress or metastasize before treatment; (2) treatment of a larger, more-aggressive cancer may be more intense with greater side effects; (3) the increased anxiety of living with an untreated cancer; (4) the requirement for frequent medical examinations and periodic biopsy; (5) the uncertain long-term natural history of untreated prostate cancer; and (6) the timing and value of periodic imaging studies have not been determined.

Patients with a clinically localized cancer (T1-3, NX or N0, MX or M0) who are candidates for definitive therapy but who select expectant management should be followed up regularly with DRE and serum PSA levels every 6 months. A systematic needle biopsy of the prostate should be repeated within 6 months of diagnosis if the initial biopsy was less than 10 cores, or if the assessment of the local extent of the cancer is discordant (eg, palpable tumor contralateral to side of positive biopsy). If 10 or more cores were obtained initially, a repeat biopsy should be performed within 18 months of diagnosis, then periodically. If medical history/physical examination or serum markers suggest progression, then a repeat biopsy is indicated to confirm the grade and extent of the cancer.

Patients with advanced cancer may be candidates for observation if the risks and complications of therapy are judged to be greater than the benefit in terms of prolonged life or improved quality of life.24

Principles of Surgical Therapy

Radical prostatectomy is appropriate therapy for any patient whose tumor is clinically confined to the prostate, has a life expectancy of 10 years or more, and has no serious comorbid conditions that would contraindicate elective surgery. Radical prostatectomy and pelvic lymph node dissection may be appropriate in selected patients with T3 or N+ cancer within the context of a multimodality treatment plan. A pelvic lymph node dissection can be excluded in patients with a low predicted probability of nodal metastases by nomograms, accepting that some patients with nodal metastases will be missed. A pelvic lymph node dissection may be performed using an open or laparoscopic technique. The standard template should include removal of all node-bearing tissue from the area bounded by the external iliac vein anteriorly, the pelvic side wall laterally, the bladder wall medially, Cooper’s ligament distally, and the hypogastric artery superiorly. An extended template dissection can be considered in patients with a high probability of nodal metastases unless external-beam RT is anticipated. Dissection of nodes anterior and lateral to the external iliac vessels is associated with an increased risk of lymphedema and is discouraged. An extraperitoneal approach is preferred if external-beam RT is anticipated.
Long-term cancer control has been achieved in most patients with both the retropubic and the perineal approaches. Laparoscopic radical prostatectomy is under development in selected centers; in highly experienced hands, the results may be comparable to open approaches. Blood loss can be substantial with radical prostatectomy but can be reduced through careful control of the dorsal vein complex and of the periprostatic vessels. 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. In contrast, bladder neck preservation may increase the risk of positive margins without improving continence. Anastomotic strictures that increase the risk of long-term incontinence are less frequent with modern surgical techniques. Recovery of erectile function is directly related to the degree of preservation of the cavernous nerves. For patients undergoing wide resection of the neurovascular bundles, replacement of resected nerves with nerve grafts is currently under investigation, with promising results. Early pharmacologic stimulation of erections 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 (eg, incontinence, loss of erections, anastomotic stricture) is high.

Principles of Radiation Therapy

RT for prostate cancer shows several distinct advantages over surgical therapy.\(^{57}\) RT avoids complications (such as bleeding and transfusion-related effects) as well as risks associated with anesthesia (such as myocardial infarction and pulmonary embolus). CT-based treatments are widely available in community practice and are possible for patients over a wide range of ages. This therapy includes a very low risk of urinary incontinence and stricture as well as a good chance of short-term preservation of erectile function when using CT. Combined with hormone therapy, radiation offers a chance for cure in advanced cancer, because treatments may eradicate extensions of tumor beyond the margins of the prostate. However, the addition of hormone therapy 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, there is a low but definite risk of protracted rectal symptoms from radiation proctitis, and the risk of erectile dysfunction increases over time. In addition, if the cancer recurs, salvage surgery is associated with a higher risk of complications than primary surgical therapy. Contraindications to RT include prior pelvic irradiation, active inflammatory disease of the rectum, permanent indwelling Foley catheter, and morbid obesity. Relative contraindications include very low capacity bladder, chronic moderate or severe diarrhea, bladder outlet obstruction requiring a suprapubic catheter, and inactive ulcerative colitis.

Three-dimensional CRT or intensity-modulated radiation therapy (IMRT) techniques should be employed over conventional techniques. These techniques use 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 tumor. Three-dimensional CRT has reduced both acute and late normal tissue toxicity in patients with prostate cancer and allows higher cumulative doses to be delivered with a lower risk of late effects.\(^{58,59}\)
standard dose of 70-75 Gy in 35 to 41 fractions to the prostate (with or without seminal vesicles) remains appropriate for patients with low-risk cancers. However, intermediate-risk and high-risk patients should receive doses between 75 and 80 Gy. Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant with or without adjuvant androgen deprivation therapy therapy. If target margins are reduced for doses above 75 Gy, extra attention to daily prostate localization (eg, ultrasound, implanted fiducials, or endorectal balloon) is indicated.

Brachytherapy involves placing radioactive sources into the prostate tissue itself. Most centers use permanent implants, where the sources are implanted into the prostate and gradually lose their radioactivity. Because of the short range of the irradiation emitted from these low-energy sources, adequate dose levels can be delivered to the cancer within the prostate, whereas excessive irradiation of the bladder and rectum can be avoided. Very high doses are not possible with brachytherapy, because the radiation is delivered at a much slower dose rate than with external-beam RT, resulting in the reduced biological effectiveness. Current brachytherapy techniques attempt to improve the radioactive seed placement and radiation dose distribution. Prostate brachytherapy as monotherapy has become a popular treatment option for early, clinically organ-confined prostate cancer (cT1cT2a, 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 generally comparable to surgery for low-risk tumors with medium-term follow up. In addition, the risk of incontinence is minimal in patients without a previous transurethral resection of the prostate (TURP), and erectile function is preserved in the short term. Disadvantages of brachytherapy include the requirement for general anesthesia and the risk of acute urinary retention.

The treatment should be appropriately limited to selected patients with small-volume prostate glands (< 60 gm) confined to the prostate. Frequently, irritative voiding symptoms may persist for as long as 1 year after implantation. The risk of incontinence is great after TURP because of acute retention, and many patients develop progressive erectile dysfunction over several years; therefore, the long-term rate of potency is lower with TURP than with external-beam RT.

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) and with or without neoadjuvant androgen deprivation therapy, 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 androgen deprivation therapy, brachytherapy may be effective in select patients. Patients with large prostates (> 60 g), symptoms of bladder outlet obstruction (International Prostate Symptom Score > 15), or a previous TURP are not ideal candidates for brachytherapy because of increased risk of urinary morbidity. Neoadjuvant androgen deprivation therapy 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.

**Principles of Hormonal (Androgen deprivation therapy) Therapy**

The principal therapy for the treatment of metastatic prostate carcinoma is androgen deprivation therapy. Early androgen
deprivation therapy will delay the appearance of symptoms and metastases, but whether earlier androgen deprivation therapy will prolong survival is not clear. Treatment should begin immediately in the presence of tumor-related symptoms or overt metastases (category 1). The complications of long-term androgen deprivation therapy have not been adequately documented.

**Rising PSA**

Patients with a rising PSA level and with no symptomatic or clinical evidence of cancer present a therapeutic dilemma. Some of these patients 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 androgen deprivation therapy for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient and physician anxiety, and the short-term and long-term side effects of hormonal therapy. Although early, sustained androgen deprivation therapy is acceptable, an alternative is close observation until progression of cancer, at which time appropriate therapeutic options may be considered. Earlier androgen deprivation therapy may be better than delayed therapy, although the definitions of early and late (ie, what level of PSA) remain controversial. Because the benefit of androgen deprivation therapy is not clear, treatment should be individualized until definitive studies are completed. Patients with a short PSA doubling time (rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider androgen deprivation therapy earlier, unless they regard the side effects as unacceptable.

When androgen deprivation therapy is initiated, it can be accomplished with an LHRH agonist (medical castration) or with bilateral orchiectomy (surgical castration), which are equally effective. Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides limited benefit over castration alone. Antiandrogen therapy should precede LHRH agonist and be continued in combination for 1 month for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH analogue alone. 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 androgen blockade have undergone limited study. Intermittent androgen deprivation therapy is a widely used approach to reduce side effects, but the long-term efficacy remains unproven. Antiandrogen monotherapy appears 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 expectant management patients with localized disease. In such patients, smaller studies suggest that high-dose bicalutamide may be equivalent to castration. The side effects are different but considered less tolerable overall. No clinical data support the use of triple androgen blockade (finasteride, LHRH agonist, and antiandrogen).

**Secondary Hormonal Therapy**

Additional sequential androgen deprivation therapy depends on the type of initial salvage therapy. For patients responsive to orchiectomy or LHRH agonists alone, the addition of an antiandrogen may be considered. The androgen receptor remains active in patients with “hormone refractory prostate cancer;” thus,
testosterone suppression should be continued. For patients whose treatment consisted of an LHRH agonist plus an antiandrogen, the antiandrogen should be discontinued. Additional hormonal strategies, including administration of ketoconazole or estrogens, may afford clinical benefit after failure of initial androgen deprivation therapy; however, none has yet been shown to prolong survival in randomized clinical trials.

Summary

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


17. Graefen M, Karakiewicz PI, Cagiannos I, et al. A validation of two preoperative nomograms predicting recurrence following radical pros-
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52. Lipton A, Demers L, Daniloff Y, et al. Increased urinary excretion of


