



National  
Comprehensive  
Cancer  
Network<sup>®</sup>

**NCCN Clinical Practice Guidelines in Oncology™**

# **Prostate Cancer**

V.1.2009

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¥ Patient advocacy

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[NCCN Guidelines Panel Disclosure](#)

## Table of Contents

[NCCN Prostate Cancer Panel Members](#)

[Summary of Guideline Updates](#)

[Initial Prostate Cancer Diagnosis, Staging Workup, Recurrence Risk \(PROS-1\)](#)

[Initial Therapy, Adjuvant Therapy \(PROS-2\)](#)

[Surveillance \(PROS-4\)](#)

[Salvage Workup: Post-Radical Prostatectomy \(PROS-5\)](#)

[Salvage Workup: Post-RT \(PROS-6\)](#)

[Disseminated Recurrence \(PROS-7\)](#)

[Systemic Therapy, Systemic Salvage Therapy \(PROS-7\)](#)

[Principles of Life Expectancy Estimation \(PROS-A\)](#)

[Principles of Active Surveillance \(PROS-B\)](#)

[Principles of Radiation Therapy \(PROS-C\)](#)

[Principles of Surgery \(PROS-D\)](#)

[Principles of Hormonal Therapy \(Androgen Deprivation Therapy\) \(PROS-E\)](#)

[Principles of Chemotherapy \(PROS-F\)](#)

**For help using these documents, please click here**

[Staging](#)

[Discussion](#)

[References](#)

[Guidelines Index](#)

[Print the Prostate Cancer Guideline](#)

The discussion is being updated to correspond with the newly updated algorithm.

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

To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical\\_trials/physician.html](http://nccn.org/clinical_trials/physician.html)

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

See [NCCN Categories of Evidence and Consensus](#)

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2008.

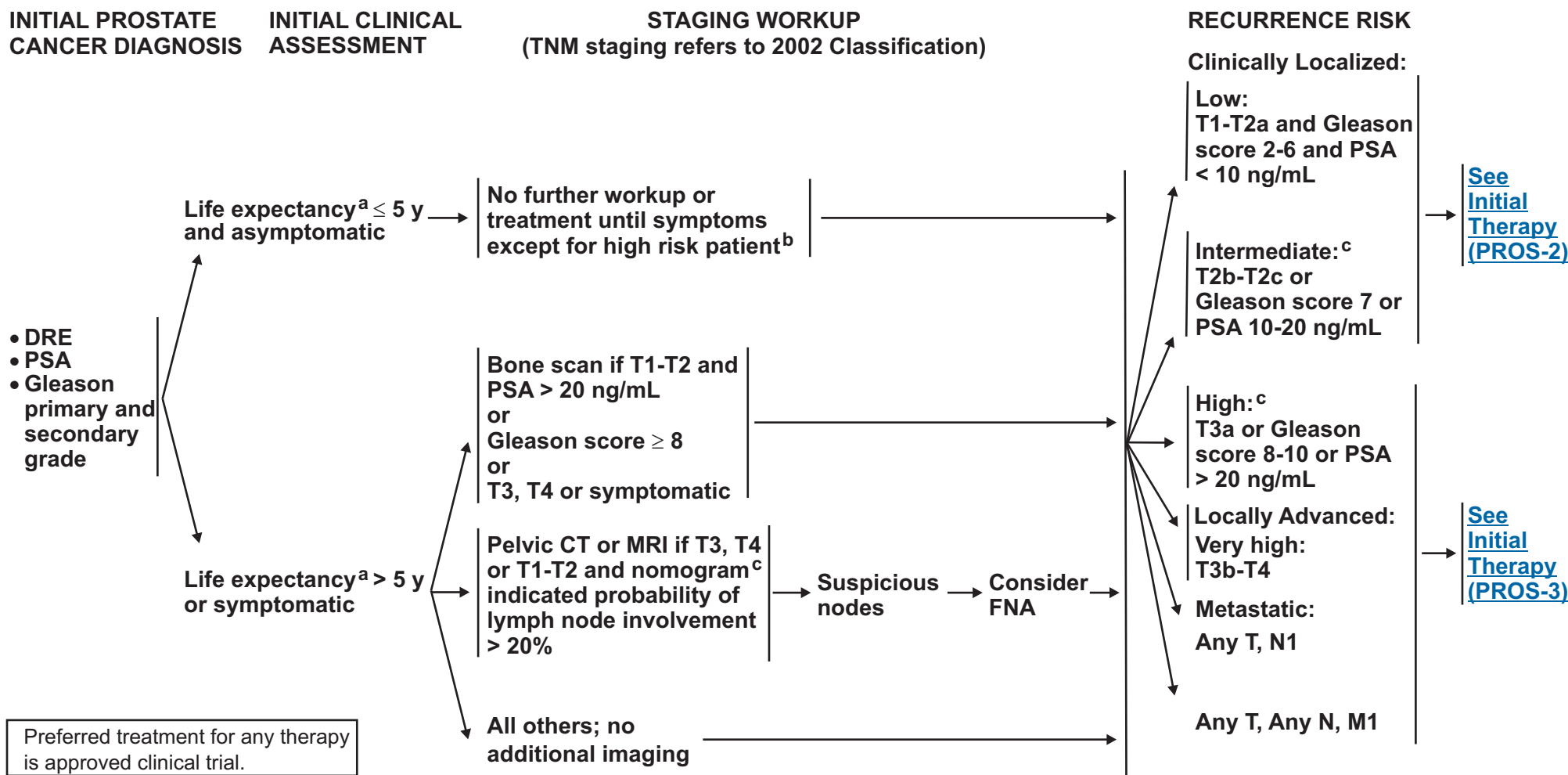
## Summary of the Guideline Updates

Summary of changes in the 2009 version of the Prostate Cancer Treatment guidelines from the 1.2008 version include:

- **Global Changes**
  - ▶ Expectant management was changed to active surveillance.
  - ▶ 3D-CRT was changed to 3D-CRT/IMRT with IGRT.
  - ▶ Androgen deprivation therapy (ADT) co-administered with 3D-CRT/IMRT with IGRT was changed to neoadjuvant/concomitant/adjuvant ADT.
- **[PROS-5](#) and [PROS-C](#): Post radical prostatectomy (RP) recurrence**
  - ▶ Indication for adjuvant or salvage radiation therapy (RT) have been simplified to reflect the demonstration that the survival benefit has been demonstrated for both salvage and adjuvant RT and that previously accepted clinical criteria for treatment did not predict response.
  - ▶ Post implant dosimetry is recommended to document quality.
- **[PROS-E](#)**
  - ▶ Frequency of adverse effects from ADT warrants a discussion among patient, oncologist and personal physicians, monitoring of osteoporosis, obesity, insulin resistance, alteration in lipids and appreciation for a greater risk of diabetes and cardiovascular disease.
  - ▶ Osteoporosis risk should be assessed using guidelines for the general population from the National Osteoporosis Foundation.
- **[PROS-F](#)**
  - ▶ Zoledronic acid is recommended to prevent skeletal-related events in men with castration recurrent prostate cancer who have documented bone metastases and creatinine clearance > 30 mL/min.

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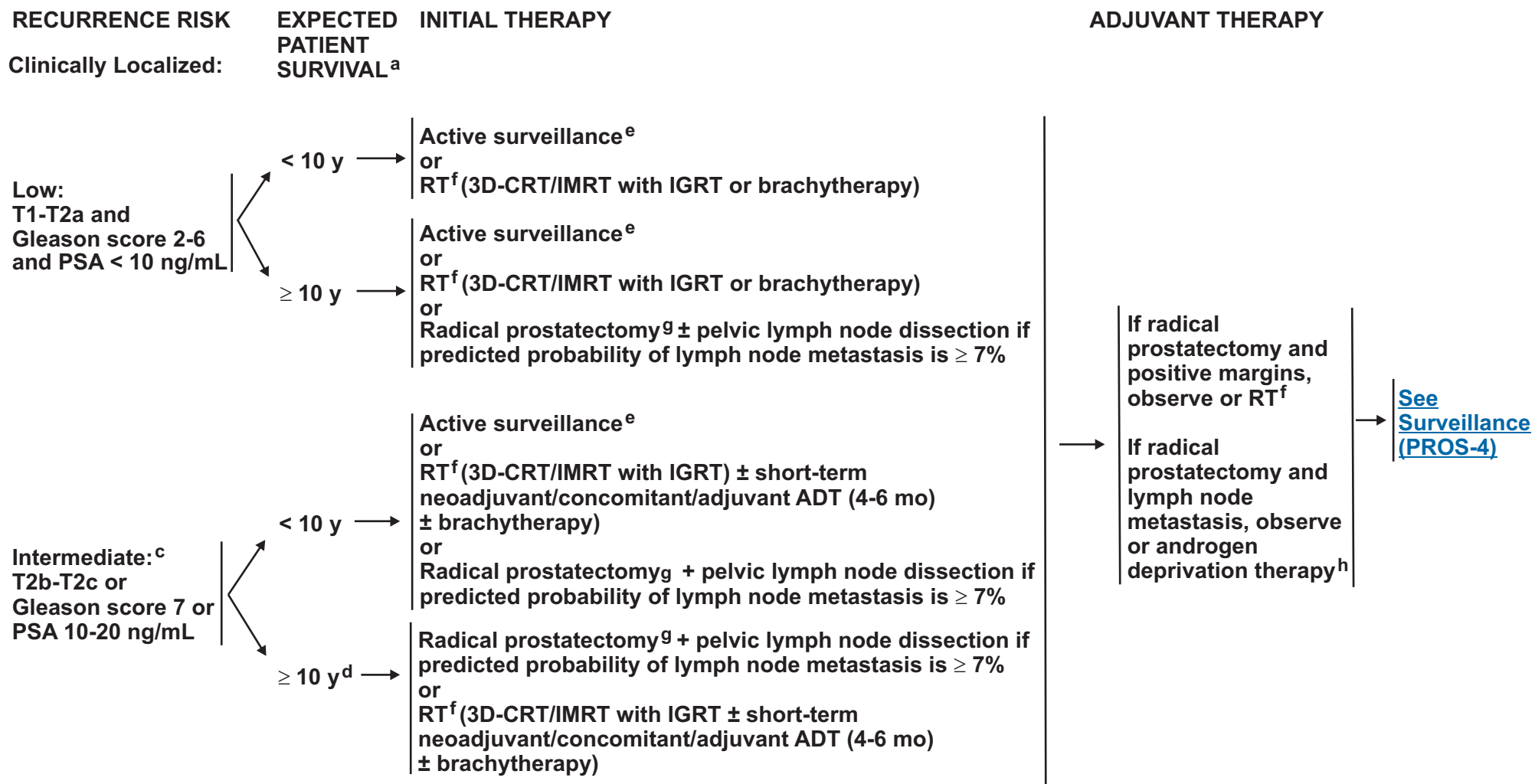


<sup>a</sup>See Principles of Life Expectancy (PROS-A).

<sup>b</sup>In selected patients where complications such as hydronephrosis or metastasis can be expected within 5 y, androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered. High risk factors include bulky T3-T4 disease or Gleason score 8-10.

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

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

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

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

<sup>e</sup> Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses. [See Principles of Active Surveillance \(PROS-B\)](#).

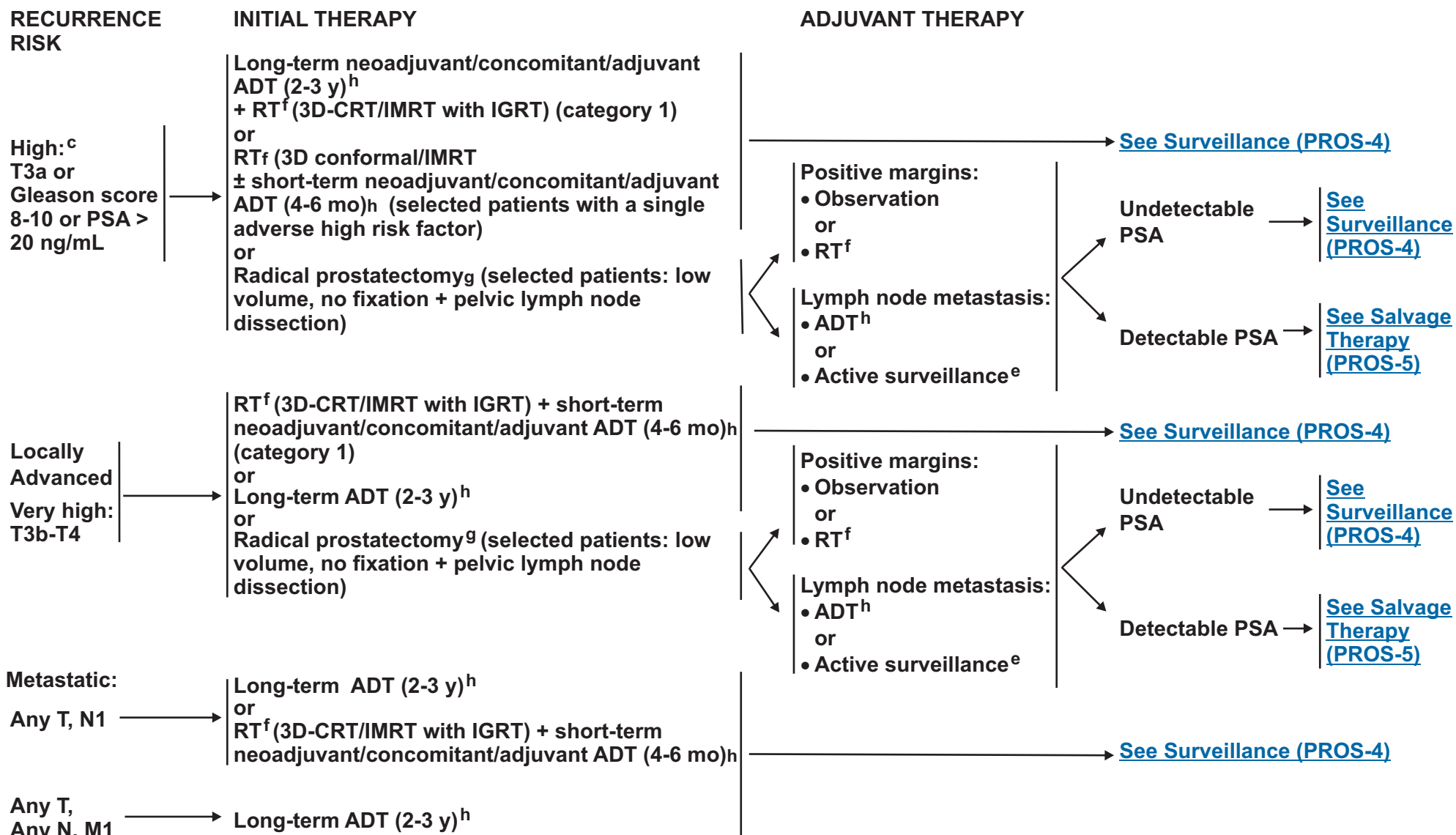
<sup>f</sup> [See Principles of Radiation Therapy \(PROS-C\)](#).

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

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

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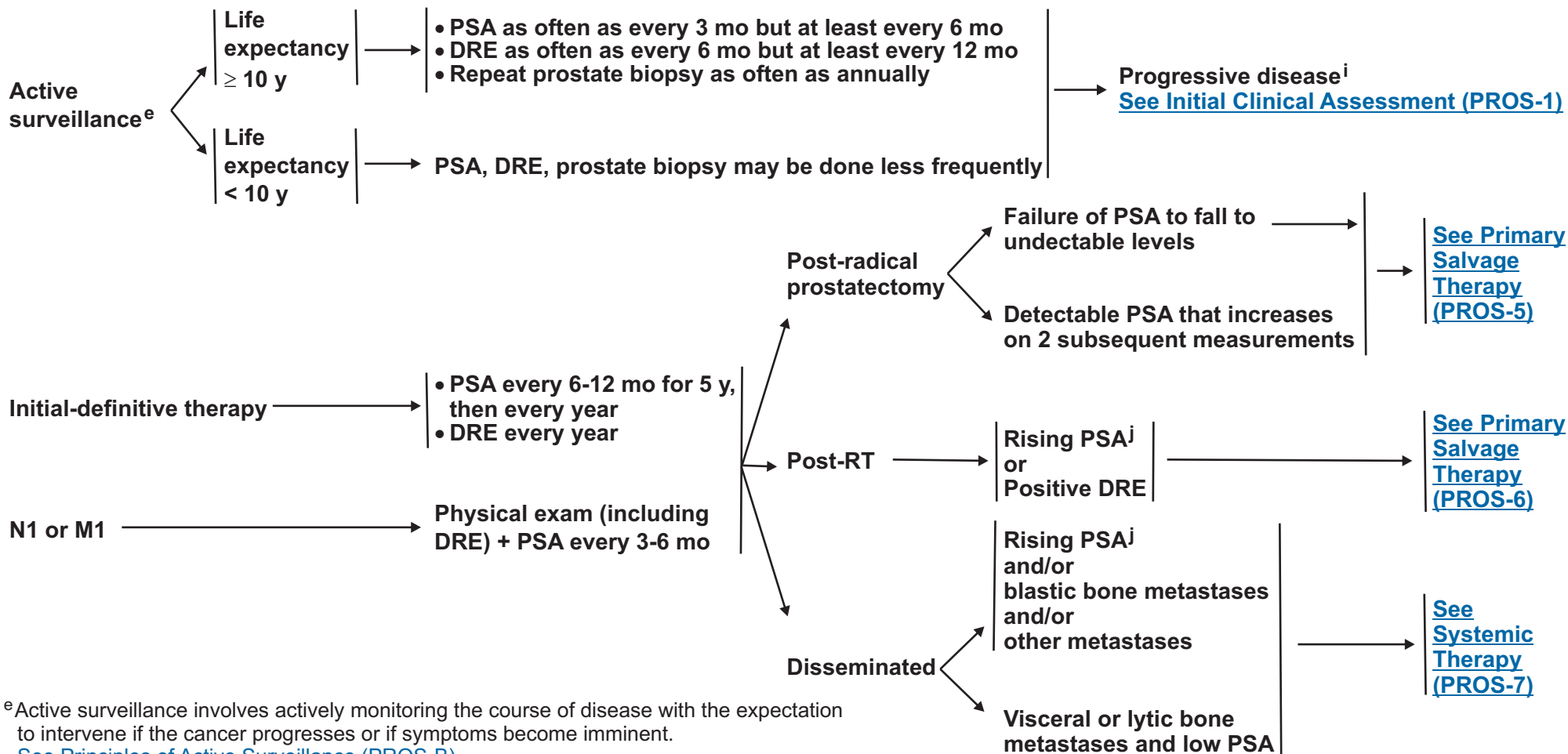
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INITIAL MANAGEMENT  
OR PATHOLOGY

SURVEILLANCE

RECURRENCE



<sup>e</sup>Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses or if symptoms become imminent. [See Principles of Active Surveillance \(PROS-B\)](#).

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

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

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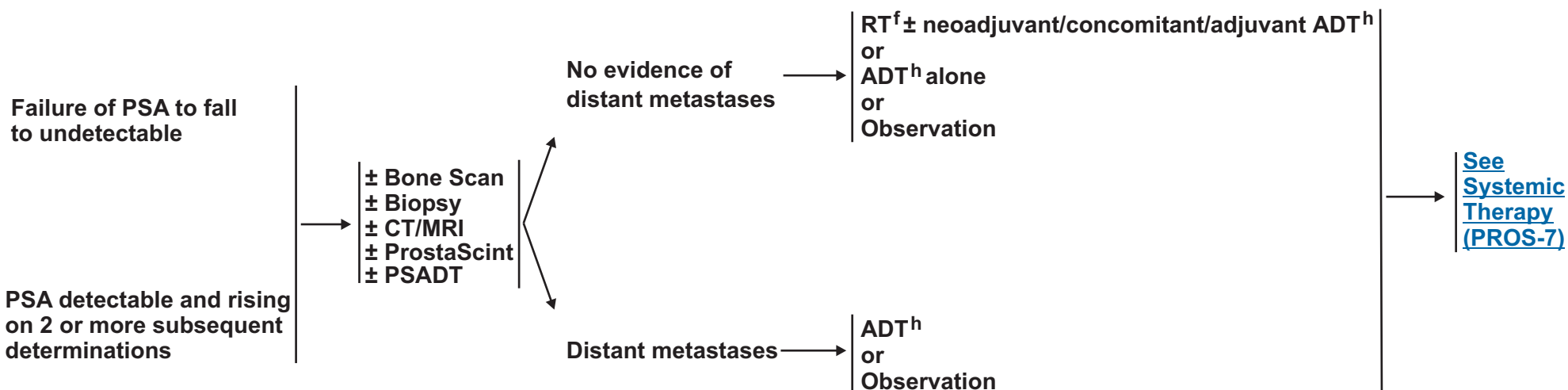
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POST-RADICAL PROSTATECTOMY RECURRENCE

SALVAGE  
WORKUP

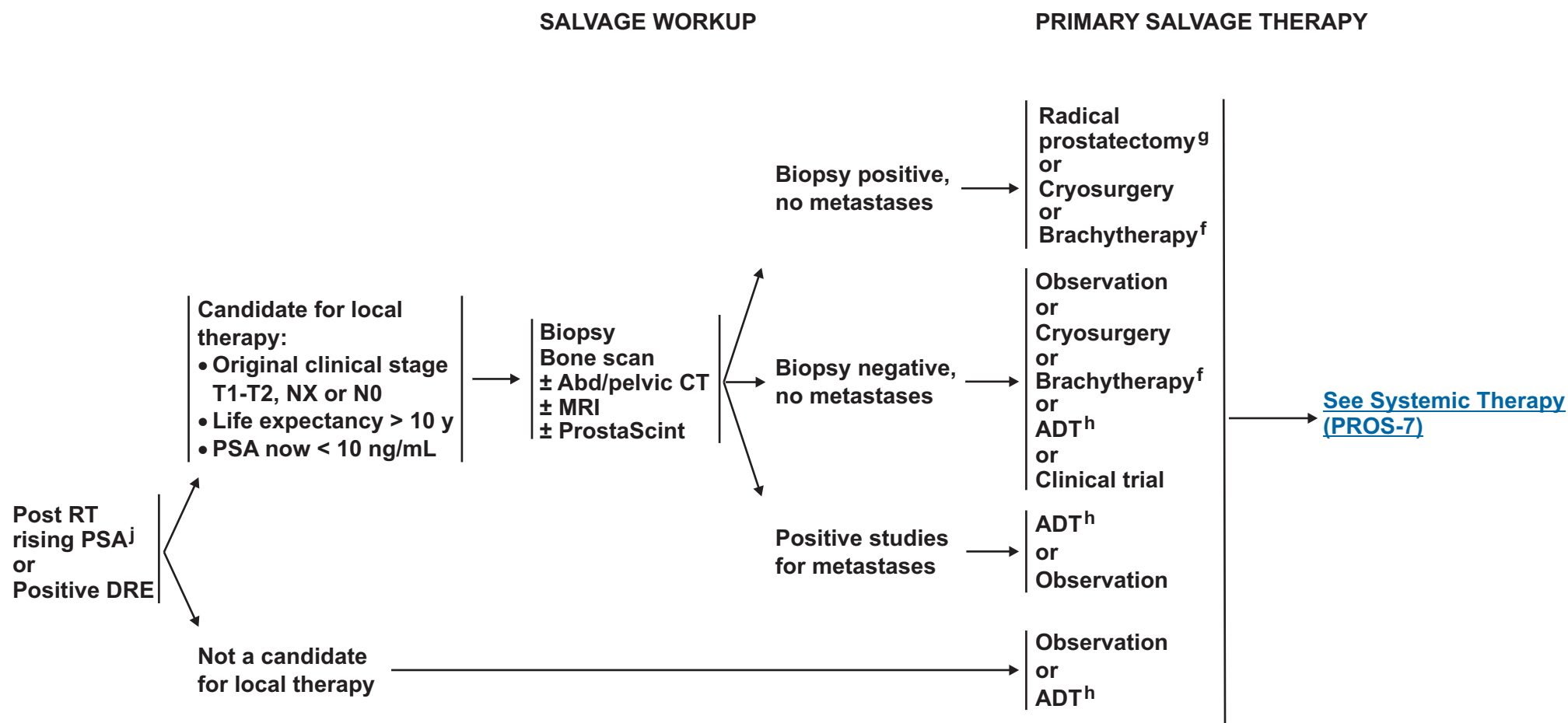
PRIMARY SALVAGE THERAPY



<sup>f</sup> See Principles of Radiation Therapy (PROS-C).

<sup>h</sup> See Principles of Androgen Deprivation Therapy (PROS-E).

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

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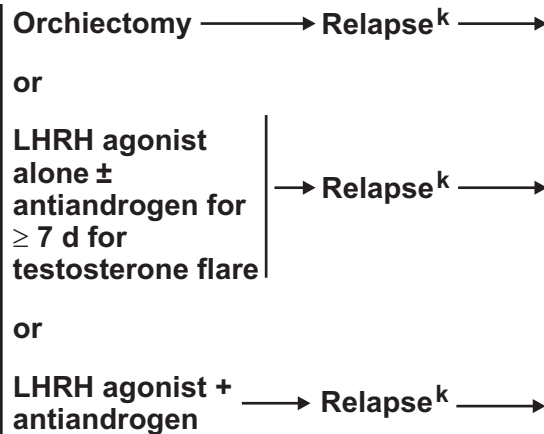
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SYSTEMIC THERAPY

SYSTEMIC SALVAGE THERAPY

Disseminated disease

Blastic bone  
and/or other  
metastases and  
rising PSA



Antiandrogen  
or  
Second-line hormonal therapy: ketoconazole ±  
glucocorticoids, or estrogens  
or  
Systemic chemotherapy<sup>l</sup> (docetaxel-based preferred)  
or  
Systemic RT:  
Samarium or strontium  
or  
Supportive care  
and  
Bisphosphonate treatment for prevention of skeletal-  
related events should be considered

Discontinue antiandrogen

[See Principles of Androgen Deprivation Therapy \(ADT\) \(PROS-E\)](#)

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  
or  
Docetaxel-based regimen

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

<sup>l</sup>[See Principles of Chemotherapy \(PROS-F\)](#).

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**PRINCIPLES OF LIFE EXPECTANCY ESTIMATION**

- Life expectancy estimation is critical to informed decision-making in prostate cancer early detection and treatment.
- Estimation of life expectancy is possible for groups of men but challenging for individuals.
- Life expectancy can be estimated using the Social Security Administration tables ([www.ssa.gov/OACT/STATS/table4c6.html](http://www.ssa.gov/OACT/STATS/table4c6.html))
- Life expectancy can then be adjusted using the 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.

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**PRINCIPLES OF ACTIVE SURVEILLANCE**

- Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses.
- Patients with clinically localized cancers who are candidates for definitive treatment and choose Active surveillance should have regular follow up:
  - ▶ DRE and PSA as often as every 6 mo but at least every 12 mo
  - ▶ 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 y or PSA velocity is > 0.75.
- A repeat prostate biopsy is indicated for signs of disease progression by exam or PSA.
- Advantages of active surveillance:
  - ▶ Avoid possible side effects of definitive therapy that may be unnecessary
  - ▶ Quality of life/normal activities retained
  - ▶ Risk of unnecessary treatment of small, indolent cancers is reduced.
- Disadvantages of active surveillance:
  - ▶ 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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**PRINCIPLES OF RADIATION THERAPY****External Beam Radiotherapy:**

- 3D conformal or IMRT (intensity modulated radiation therapy) techniques should be employed.
- Doses of 70-79 Gy in 35-41 fractions to the prostate ( $\pm$  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  $\pm$  adjuvant androgen deprivation therapy for a total of 2-3 y (category 1).
- Patients with intermediate risk cancer may be considered for pelvic lymph node irradiation and 4-6 mo neoadjuvant  $\pm$  adjuvant ADT
- Patients with low risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques such as IGRT using CT, ultrasound implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.
- New evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA.

**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)  $\pm$  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 very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate (TURP) are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant androgen deprivation therapy may be used to shrink the prostate to an acceptable size.
- Post-implant dosimetry should be performed to document the quality of the implant.
- The recommended prescribed doses for 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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### PRINCIPLES OF SURGERY

#### **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. An extended PLND is preferred when PLND is performed.
- 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.

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**PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY ADT (page 1 of 2)****ADT for Clinically Localized Disease**

- Neoadjuvant ADT for radical prostatectomy is strongly discouraged.
- Giving ADT before, during and/or after radiation prolongs survival in selected radiation managed patients.
- Studies of short-term (4-6 mo) and long-term (2-3 y) neoadjuvant ADT all have used complete androgen blockade. Whether the addition of an antiandrogen is necessary will require further studies.
- Adjuvant ADT given after completion of primary treatment is not a standard treatment at this time with the exception of selected high risk patients treated with 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 compared to men who received delayed ADT. Therefore, such patients should be considered for immediate ADT.
- The side effects of continuous ADT increase with the duration of treatment.

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

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

**Optimal ADT**

- LHRH agonist (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.

[Continued on next page](#)

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**PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY ADT (page 1 of 2)**

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

**Secondary Hormonal Therapy**

- The androgen receptor remains active in patients whose prostate cancer has recurred during ADT (castration-recurrent prostate cancer); thus, ADT should be continued.
- 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**

- ADT has a variety of adverse effects including osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease. Patients and their medical providers should be advised about these risks prior to treatment.
- Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation ([www.nof.org](http://www.nof.org)). The National Osteoporosis Foundation guidelines include recommendations for (1) supplemental calcium (1200 mg daily) and vitamin D3 (800-1000 IU daily) for all men over age 50 y and (2) additional treatment for men when the 10 y probability of hip fracture is  $\geq 3\%$  or the 10 y probability of a major osteoporosis-related fracture is  $\geq 20\%$ . Fracture risk can be assessed using the recently released algorithm called FRAX<sup>®</sup> by the World Health Organization ([www.shef.ac.uk/FRAX/index.htm](http://www.shef.ac.uk/FRAX/index.htm)). ADT should be considered “secondary osteoporosis” using the FRAX<sup>®</sup> algorithm.
- Zoledronic acid (4 mg IV annually) and alendronate (70 mg PO weekly) increase bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either zoledronic acid or alendronate is recommended when the absolute fracture risk warrants drug therapy.
- Screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended in men receiving ADT. These medical conditions are common in older men and it remains uncertain whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in men receiving ADT should differ from the general population.

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**PRINCIPLES OF CHEMOTHERAPY**

- Patients with advanced prostate cancer should be encouraged to participate in clinical trials and referred early to a medical oncologist.
- Based upon Phase III data, every 3-week docetaxel and prednisone is the preferred first-line chemotherapy treatment. Alternative regimens include every 3-week docetaxel and estramustine, weekly docetaxel and prednisone and every 3-week mitoxantrone and prednisone.
- 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 17 months vs. 15.6 months for the mitoxantrone arm (p=.01).<sup>1</sup>
  - 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 19.2 months vs. 16.3 months for the mitoxantrone arm (p=.009).<sup>2</sup>
- Docetaxel-based regimens are the standard of care for first-line treatment in this group of patients.
- In men with castration-recurrent prostate cancer and bone metastases, zoledronic acid every 3-4 weeks is recommended to prevent disease-related skeletal complications, which include pathological fractures, spinal cord compression, and the need for surgery or radiation therapy to bone. Treatment should be initiated at reduced dose in men with impaired renal function (estimated creatinine clearance 30-60 mL/min) and is not recommended for men with baseline creatinine clearance < 30 mL/min
- The optimal duration of zoledronic acid in men with castration-recurrent prostate cancer and bone metastases is undefined.
- Clinical trials are in progress to define the potential role of zoledronic acid in men with androgen stimulated prostate cancer and bone metastases.
- Zoledronic acid and other bisphosphonates have not been shown to prevent bone metastases.

<sup>1</sup>Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 351: 1513-1520.

<sup>2</sup>Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; vol. 351; 1502-1512.

**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.

## Staging

Table 1

**2002 American Joint Committee on Cancer (AJCC)  
TNM Staging System For Prostate Cancer****Primary Tumor (T)****Clinical**

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

**Pathologic(pT)**

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

\*Note: There is no pathologic T1 classification.

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

**Regional Lymph Nodes (N)****Clinical**

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

**Pathologic**

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

**Distant Metastasis (M)\***

|            |   |
|------------|---|
| <b>MX</b>  | Distant metastasis cannot be assessed (not evaluated by any modality) |
| <b>M0</b>  | No distant metastasis   |
| <b>M1</b>  | Distant metastasis  |
| <b>M1a</b> | Non-regional lymph node(s)  |
| <b>M1b</b> | Bone(s)   |
| <b>M1c</b> | Other site(s) with or without bone disease                            |

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

[Continue](#)

**Stage Grouping**

|                  |       |       |    |         |
|------------------|-------|-------|----|---------|
| <b>Stage I</b>   | T1a   | N0    | M0 | G1      |
| <b>Stage II</b>  | T1a   | N0    | M0 | G2, 3-4 |
|                  | T1b   | N0    | M0 | Any G   |
|                  | T1c   | N0    | M0 | Any G   |
|                  | T1    | N0    | M0 | Any G   |
|                  | T2    | N0    | M0 | Any G   |
| <b>Stage III</b> | T3    | N0    | M0 | Any G   |
| <b>Stage IV</b>  | T4    | N0    | M0 | Any G   |
|                  | Any T | N1    | M0 | Any G   |
|                  | Any T | Any N | M1 | Any G   |

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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)

## Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 02/21/08

### NCCN Categories of Evidence and Consensus

**Category 1:** The recommendation is based on high-level evidence, and there is uniform NCCN consensus.

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

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

**Category 3:** Based on any level of evidence but reflects major disagreement.

**All recommendations are category 2A unless otherwise noted.**

## Introduction

In the late 1980s and early 1990s, the number of newly diagnosed prostate cancers in U.S. men increased dramatically, and prostate cancer surpassed lung cancer as the most common cancer.<sup>1</sup> It is generally accepted that these changes resulted from prostate-specific antigen (PSA) screening that detected many early-stage prostate cancers. For example, the percentage of patients with low-risk disease has recently increased (45.3% in 1999-2001 compared with 29.8% in 1989-1992;  $P < .0001$ ).<sup>2</sup> The incidence of prostate cancer increased 2.0% annually from 1995 to 2001, and has since declined. An estimated 218,890 new cases will be diagnosed in 2007, and prostate cancer is expected to account for 29% of new cancer cases in men in 2007.<sup>1</sup> Fortunately, the age-adjusted death rates from prostate cancer have also declined (-4.1% annually from 1994 to 2001).<sup>1</sup> Researchers expect prostate cancer to account for another new low of 27,050 deaths in 2007. 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 mortality from this prevalent cancer.<sup>3</sup>

To properly identify and to manage patients with prostate cancer or any other malignancy, physicians must have an in-depth understanding of the natural history and the diagnostic, staging and treatment options. To this end, an NCCN panel of leading experts from the fields of urology, radiation oncology, and medical oncology at member institutions developed guidelines for the treatment of prostate cancer. The panel representing NCCN member institutions reviews and updates the prostate guidelines every year, which are available on the NCCN web site ([www.nccn.org](http://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.

### Estimates of Life Expectancy

As a result of widespread PSA testing, most patients are diagnosed with asymptomatic, clinically localized cancer. The combination of Gleason score, PSA level, and stage can effectively stratify patients into categories associated with different probabilities of achieving a cure. 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 management options for initial therapy for clinically localized prostate cancer include expectant management, radical prostatectomy or radiotherapy.

Estimates of life expectancy have emerged as a key determinant of treatment decision-making, particularly when considering expectant

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

### Nomograms and Predictive Models

Optimal treatment of prostate cancer requires assessment of risk: how likely is a given cancer to be confined to the prostate or to spread to the regional lymph nodes? How likely is the cancer to progress or metastasize after treatment? Prostate cancers are best characterized by clinical (TNM) stage determined by digital rectal examination (DRE), Gleason score in the biopsy specimen, and serum PSA level. Imaging

studies (ultrasound, MRI) have been 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.

Predicting pathologic stage is important in clinical decision-making and may help determine the need for more intensive therapy (such as escalated dose, 3-dimensional conformal external-beam irradiation therapy [3D-CRT] rather than lower dose radiotherapy) or for modifying surgical technique, such as resecting 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.<sup>7</sup> This risk group stratification has been published widely and validated, and it provides a better basis for treatment recommendations than clinical stage alone.<sup>8</sup>

To quantify risk more accurately, one can devise a nomogram that incorporates the interactive effects of multiple prognostic factors to make accurate predictions about stage and prognosis for the individual patient. A nomogram is any predictive instrument that takes a set of input data (variables) and makes predictions about an outcome. Nomograms predict more accurately for the individual patient than risk groups, because they combine the relevant prognostic variables, regardless of value.<sup>9-11</sup> 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.

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 (i.e., extraprostatic) extension; (3) seminal vesicle invasion; or (4) lymph node metastasis.<sup>12</sup> The tables give the probability (95% confidence intervals) that a patient with a certain clinical stage, Gleason score, and PSA will have a cancer of each pathologic stage. 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.

Nomograms have also been developed to predict biochemical failure after radical prostatectomy,<sup>10</sup> external-beam RT<sup>9</sup> and brachytherapy.<sup>11</sup> Risk stratification schemas and validated nomograms are available for predicting 2-year freedom from biochemical recurrence after surgery or external-beam radiation<sup>7</sup> and for predicting 5-year freedom from recurrence after surgery<sup>13</sup>, external-beam radiation<sup>9</sup>, or brachytherapy.<sup>11</sup> After surgery, there are models that include pathologic stage to predict 7-year freedom from biochemical recurrence.<sup>14</sup> Also, recently Stephenson et al. have developed a nomogram that predicts the 6 year progression-free probability after salvage radiation therapy for men with PSA recurrence after radical prostatectomy.<sup>15</sup>

None of the current models predict with perfect accuracy, and only some of these models predict metastases<sup>16</sup> and cancer-specific death.<sup>17</sup> New independent prognostic factors are being developed.<sup>18</sup> Given the competing causes of mortality, many men who sustain PSA failure will not live long enough either to develop clinical evidence of

distant metastases or to die from prostate cancer. Those with a short PSA doubling time are at greatest risk of death.<sup>19</sup> 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. Further refinement of the patient's risk of recurrent cancer is being investigated currently using molecular markers and other radiologic evaluations of the prostate. However, these approaches remain investigational and are not available currently or validated for routine application. The NCCN 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.

### Principles of Expectant Management

*Expectant management* (also referred to as observation, watchful waiting, active surveillance or deferred treatment) involves actively monitoring the course of the disease with the expectation to intervene if the cancer progresses or if symptoms become imminent.<sup>20-22</sup> Thus, expectant management requires thorough staging, life expectancy estimation, assessment of comorbidities, and active monitoring with close follow-up of patients (i.e., active surveillance).

There is a growing literature that attempts to distinguish “clinically significant” from “clinically insignificant” prostate cancer. There seems to be a consensus developing that insignificant prostate cancer has a Gleason score <8, less than 50% of prostate biopsies show cancer and the serum PSA level is below 10-15 ng/dL. For example, using similar guidelines, Choo and colleagues assessed an expectant management protocol in 206 patients with favorable clinical parameters.<sup>23</sup> Patients were followed every 3 months for the first 2 years and every 6 months

thereafter. Serum PSA was measured and digital rectal examination was performed at each visit and repeat prostate biopsy was performed 18 months after study enrollment. Active treatment was deferred until disease progression was detected, defined by the following 3 parameters: 1. rate of PSA increase; 2. clinical progression; or 3. histological upgrade on repeat prostate biopsy. Most patients remained on watchful waiting for two years and approximately one half remained on observation after 4 years. In addition, of those who converted from expectant management to active treatment, the majority did so for reasons other than prostate cancer progression.

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 which patients will have a slow or a rapid prostate cancer progression.

Expectant management has been shown to offer 10-year survival rates and quality-adjusted life expectancy similar to radical prostatectomy or radiotherapy,<sup>24,25</sup> and is considered an option for patients with low-risk cancers or for patients with a short life expectancy. 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.<sup>26</sup>

Patients and physicians involved in expectant management must be aware that the PSA is likely to rise and that the tumor may grow with time. Patients should not be under the impression that the tumor will remain stable indefinitely and must be prepared to reevaluate the decision to defer treatment. Trigger points for intervention based on PSA, histologic progression, or clinical progression have been used.<sup>23,27,28</sup> Also, in serial biopsies, a progression of ploidy and grade before clinical progression has been seen.<sup>29</sup> In one series, 12 of 13

men undergoing deferred radical prostatectomy until biopsy grade progression had curable cancers.<sup>27</sup> Whether these trigger points will ultimately be validated or not, however, still needs to be proven.

Patients must commit to a regular schedule of follow up including repeat DRE, PSA and needle biopsy. Cancer progression is suggested if a Gleason grade of 4 or 5 is found on repeat biopsy, if the prostate cancer is found in a greater number of prostate biopsies or occupies a greater extent of prostate biopsies, if the PSA doubling time is less than 3 years, or if the PSA velocity is  $> 0.75$ . Contraindications to expectant management include (1) a high-risk or very high-risk cancer in a patient with a long life expectancy, or (2) evidence of progression on expectant management.

The advantages of expectant management include (1) avoiding the side effects of definitive therapy that may not be necessary; (2) quality of life and normal activities are retained; (3) small indolent cancers do not receive unnecessary treatment; and (4) decreased initial costs. The disadvantages of expectant management are (1) chance of missed opportunity for cure; (2) the cancer may progress or metastasize before treatment; (3) treatment of a larger, more-aggressive cancer may be more intense with greater side effects; (4) nerve sparing at subsequent prostatectomy may be more difficult, which may reduce the chance of potency preservation after surgery; (5) the increased anxiety of living with an untreated cancer; (6) the requirement for frequent medical examinations and periodic prostate biopsies; (7) the uncertain long-term natural history of untreated prostate cancer; and (8) the timing and value of periodic imaging studies have not been determined. Studies are in progress to develop trigger points for deciding when to start treatment with curative intent after initially choosing expectant management.



### Principles of Radiation Therapy

External beam radiation therapy is one of the principle treatment options for clinically localized prostate cancer. 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,<sup>8,30</sup> although studies of surgical outcomes generally have longer follow-up.

Over the past several decades, interest in exploring dose escalation as a technique to reduce the incidence of local recurrence has continued, based on an anticipated favorable dose response curve. For example, with standard 2D planning techniques used until the early 1990s, doses were limited to 67-70 Gy due to acute and chronic toxicities. In the 1990s, 3D planning techniques (3D-CRT) were developed that reduced the risk of acute toxicities.<sup>31,32</sup> 3D-CRT uses computer software to integrate CT images of the patients' internal anatomy in the treatment position, which allows the volume receiving the high radiation dose to "conform" more exactly to the shape of the prostate. 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 lower risk of late effects.<sup>33-36</sup> These techniques have permitted further dose escalation studies, and results of three randomized controlled trials suggested that dose escalation is associated with improved biochemical outcomes.<sup>37-39</sup> Intensity modulated radiation therapy (IMRT) is a further evolution of 3D-CRT that is designed to allow even more precise treatment planning.

The standard dose of 70-79 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. Extra attention to daily prostate localization (e.g., ultrasound, implanted fiducials, or endorectal

balloon) is indicated if target margins are reduced for doses above 75 Gy.

One of the key aspects of RT planning includes identifying which patients will benefit from pelvic lymph node irradiation and adjuvant androgen deprivation therapy (ADT). Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant with or without subsequent ADT for a total of 2-3 years or 4-6 months 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 months of neoadjuvant ADT with or without subsequent adjuvant ADT. Patients with low risk cancers should not receive either pelvic lymph node radiation or ADT.

External beam RT for prostate cancer shows several distinct advantages over surgical therapy.<sup>40</sup> RT avoids complications associated with radical prostatectomy, such as bleeding and transfusion-related effects as well as risks associated with anesthesia, such as myocardial infarction and pulmonary embolus. 3D-CRT and IMRT techniques are available widely in community practice and are possible for patients over a wide range of ages. This therapy includes a very low risk of urinary incontinence and stricture as well as a good chance of short-term preservation of erectile function. Combined with ADT, 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 ADT increases the risk for erectile dysfunction.

The disadvantages of external-beam RT include a treatment course of 8 to 9 weeks. Up to 50% of patients have some temporary bladder or bowel symptoms during treatment, 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 or a permanent indwelling Foley catheter. Relative contraindications include very low capacity bladder, chronic moderate or severe diarrhea, bladder outlet obstruction requiring a suprapubic catheter, and inactive ulcerative colitis.

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

The advantage of brachytherapy is that the treatment is completed in 1 day with little time lost from normal activities. In appropriate patients, the cancer-control rates appear comparable to surgery 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). 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 bladder neck contractures, and many patients develop progressive erectile dysfunction over several years.

Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers, brachytherapy may be combined with external-beam RT (40-50 Gy) with or without neoadjuvant ADT, but the complication rate increases. Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy; however, with the addition of external-beam RT and neoadjuvant ADT, brachytherapy may be effective in select patients. Patients with large prostates (> 60 g), small prostates (15-20 gr), 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 ADT may be used to shrink the prostate to an acceptable size. Post-implant dosimetry should be performed to document the quality of the implant. The recommended prescribed doses for monotherapy are 145 Gy for <sup>125</sup>Iodine and 125 Gy for <sup>103</sup>Palladium. After 40 to 50 Gy external-beam RT, the corresponding boost doses are 110 and 100 Gy, respectively.

### Principles of Surgical Therapy

Radical prostatectomy is appropriate therapy for any patient whose tumor is clinically confined to the prostate. However, because of potential perioperative morbidity, radical prostatectomy should be reserved for patients whose life expectancy is 10 years or more. This is consistent with data showing that fewer than 20% of low-risk patients with prostate cancer experience a cancer-specific death by 10 years.<sup>41</sup>

Long-term cancer control has been achieved in most patients with both the retropubic and the perineal approaches; high volume surgeons in high volume centers generally provide superior outcomes.

Laparoscopic and robot-assisted radical prostatectomy are used commonly, with similar results compared to conventional approaches in experienced hands.<sup>42-44</sup> Blood loss can be substantial with open radical prostatectomy, but can be reduced through careful control of the dorsal vein complex and of the periprostatic vessels. Blood loss is usually reduced using laparoscopic or robot-assisted approaches. Return of urinary continence after surgery may be improved by preserving the urethra beyond the prostatic apex and by avoiding damage to the distal sphincter mechanism. Anastomotic strictures that increase the risk of long-term incontinence are less frequent with modern surgical techniques. Recovery of erectile function is related directly to the degree of preservation of the cavernous nerves. For patients undergoing wide resection of the neurovascular bundles, replacement of resected nerves with nerve grafts remains under investigation. 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 (e.g., incontinence, loss of erections, anastomotic stricture) is high.

Two key components of surgical planning include 1) whether a pelvic lymph node dissection is warranted and 2) extent of the lymph node dissection. The decision to perform a pelvic lymph node dissection should be guided by the probability of nodal metastases.<sup>45,46</sup> For example, a lymph node dissection may be omitted in patients with < 7% predicted probability of nodal metastasis although some patients with nodal metastasis may be missed. The chance of pelvic lymph node metastases differs between the Partin tables<sup>47</sup> and the Memorial Sloan Kettering nomograms;<sup>48</sup> the chance of lymph node metastases is usually higher using the Memorial Sloan Kettering nomograms, which may reflect the preference for limited pelvic lymph node dissection at Johns Hopkins and extended pelvic lymph node dissection at Memorial

Sloan Kettering. A pelvic lymph node dissection may be performed in a limited or extended fashion. An extended pelvic lymph node dissection includes removal of all node bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic side wall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.<sup>46</sup> A limited pelvic lymph node dissection excludes removal of node bearing tissue posterior to the obturator nerve. Pelvic lymph node dissection can be performed safely laparoscopically, robotically, or open and complication rates should be similar for all three approaches and whether an extended or limited pelvic lymph node dissection is performed.<sup>49</sup> An extended pelvic lymph node dissection will discover metastasis as much as twice as often compared to a limited pelvic lymph node dissection.<sup>49</sup> An extended pelvic lymph node dissection provides more complete staging<sup>46,50</sup> and may cure some men with microscopic metastasis.<sup>51</sup> An extended pelvic lymph node dissection should be considered for patients with high probability of nodal metastasis unless external beam radiation therapy is anticipated. Dissection of nodes anterior and lateral to the external iliac vessels is associated with an increased risk of lymphedema and is discouraged.

### Principles of Androgen Deprivation Therapy – ADT

Androgen deprivation therapy (ADT) is commonly used in the treatment of prostate cancer. ADT can be accomplished using an LHRH agonist (medical castration) or bilateral orchiectomy (surgical castration), which are equally effective. Combined androgen blockade (medical or surgical castration combined with an antiandrogen) or triple androgen blockade (finasteride or dutasteride, antiandrogen, plus medical or surgical castration) provides no proven benefit over castration alone. In patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone, antiandrogen therapy should precede or be co-administered with LHRH agonist and be continued in combination for at least 7 days.<sup>52,53</sup>

Patients who do not show adequate suppression of serum testosterone (< 50 ng/mL) with medical or surgical castration can be considered for additional hormonal manipulation (with estrogens, antiandrogens, or steroids), although the clinical benefit is not clear.

Several alternative treatment regimens to continuous ADT have undergone limited study. Intermittent ADT is a widely used approach to reduce side effects, 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.<sup>54</sup> The side effects are different than ADT but antiandrogen monotherapy is considered less tolerable overall.

ADT is used routinely in conjunction with definitive radiation therapy in patients with high risk clinically localized disease or locally advanced disease. In this setting, ADT before, during and after radiation therapy prolongs survival in selected patients. ADT is also used routinely for metastatic disease.<sup>41,55</sup> Earlier ADT will delay the appearance of symptoms and metastases, but whether earlier ADT 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 ADT have not been documented adequately.

Patients with a rising PSA level and with no symptomatic or clinical evidence of cancer present a therapeutic dilemma regarding the role of ADT. 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 ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient and physician anxiety, and

the short-term and long-term side effects of ADT. Although early, sustained ADT is acceptable, an alternative is close observation until progression of cancer, at which time appropriate therapeutic options may be considered. Earlier ADT may be better than delayed therapy, although the definitions of early and late (i.e., what level of PSA) remain controversial. Because the benefit of ADT is not clear,<sup>56</sup> 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 ADT earlier, unless they regard the side effects as unacceptable.

Other studies have reported a positive benefit for adjuvant ADT in patients with positive pelvic lymph nodes. For example, Messing and colleagues examined the role of immediate ADT in patients with positive pelvic nodes found at initial surgery.<sup>57</sup> During the period of 1988 to 1993, patients were randomly assigned to immediate ADT (n=47) or observation (n=51). The primary endpoint was progression free survival. At a median follow-up of 11.9 years, those receiving immediate ADT had a significant improvement in overall survival compared to the observation group. Therefore if positive lymph nodes are found after radical prostatectomy, either ADT or expectant management is acceptable.

Antiandrogen monotherapy after completion of primary treatment has also been investigated as an adjuvant therapy in patients with early prostate cancer as a strategy to reduce progression or recurrence. The Early Prostate Cancer (EPC) was the largest prostate cancer trial ever undertaken and evaluated 150 mg daily bicalutamide as adjuvant therapy in 8113 patients with prostate cancer who were managed with watchful waiting, radiotherapy or radical prostatectomy. The original study was published in 2001, with additional analyses in 2004 and the 7.4 year follow up was published in 2006.<sup>58</sup> Patients with either localized (T1-2, N0) or locally advanced prostate cancer (T3-4, any N,

or T, N+) were enrolled. The primary endpoints were progression-free survival (PFS) and overall survival. The authors reported that patients with localized disease did not appear to derive clinical benefit from added bicalutamide. However, adding bicalutamide 150 mg to standard care provided significant clinical benefits in patients with locally advanced prostate cancer, irrespective of primary therapy. However, there was no improvement in overall survival.

The results of the North American component of this trial have been reported separately.<sup>59</sup> In this subset, all patients had undergone either prostatectomy or radiotherapy; patients with positive pelvic nodes were not included. Patients were randomized to receive either adjuvant 150 mg daily bicalutamide or placebo for 2 years. With a median follow up of 7.7 years, there were few clinical events in either group, and no differences in the primary endpoints of progression free or overall survival were seen. However, bicalutamide significantly increased the time to PSA progression. The authors concluded that the data does not support a benefit of adjuvant bicalutamide in patients with early prostate cancer. The authors also note that these results were not consistent with the results reported for the trial as a whole.

#### *The Metabolic Syndrome*

The metabolic syndrome, as a possible complication of prostate cancer therapy, is an issue of growing concern. Prostate cancer patients on medical or surgical androgen deprivation therapy, ADT are at risk for developing complications related to the metabolic syndrome.<sup>60,61</sup> Low serum testosterone levels have been associated with each aspect of this syndrome.<sup>60,62-67</sup> The diagnosis of the metabolic syndrome,<sup>68</sup> requires the presence of at least 3 of the following risk factors: 1) Abdominal obesity with waist measurement > 40 inches, 2) hypertriglyceridemia  $\geq$  150 mg/dl, 3) HDL (High-Density Lipoprotein cholesterol) < 40 mg/dl, 4) blood pressure  $\geq$  130/85 mm Hg, or 5) High fasting blood sugar > 110 mg/dl. Patients on anti-hypertensive,

lipid-lowering or hypoglycemic medications are considered to meet the respective criterion. In a contemporary study, the metabolic syndrome was present in 55% of men receiving ADT vs. 20% in disease or age matched controls.<sup>69</sup> The presence of the metabolic syndrome in the prostate cancer patient on ADT has been shown to increase the risk of insulin resistance and subsequent diabetes mellitus,<sup>70</sup> cardiovascular disease (CDV),<sup>71</sup> and mortality.<sup>72</sup> A recent article demonstrated a higher cumulative incidence of death from CVD in 65 year old or older prostate cancer patients on ADT after external beam radiation therapy, brachytherapy, cryotherapy or radical prostatectomy, (but statistical significance was reached in the latter group only).<sup>73</sup> The relationship between the metabolic syndrome and ADT needs to be evaluated further and should be considered when counseling prostate cancer patients on long-term ADT.

## Algorithms

### Initial Prostate Cancer Diagnosis

Initial suspicion of prostate cancer is based on an abnormal digital rectal examination (DRE) or an elevated PSA level. A PSA value of 4.0 ng/mL or less is considered normal; however, 15% of men with this “normal” PSA will have prostate cancer and 2% will have high-grade cancer. In fact, there is no PSA level below which cancer has not been detected; a few men with PSA values of 0.5 ng/mL or less have had high-grade prostate cancer on diagnostic biopsies.<sup>74</sup> A separate NCCN panel has written additional guidelines for prostate cancer early detection (see [NCCN Prostate Cancer Early Detection Guidelines](#)).

Definitive diagnosis requires biopsies of the prostate, usually performed by the urologist using a needle under transrectal ultrasound guidance. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Clinical staging is based on the TNM 2002 classification from the AJCC (American Joint Committee on Cancer).<sup>75</sup> 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).<sup>76</sup>

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

### Initial Clinical Assessment and Staging Evaluation

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

For patients with a life expectancy of less than 5 years and without clinical symptoms, further workup or treatment may be delayed until symptoms develop. If high-risk factors (bulky T3-T4 cancers or Gleason score 8-10) for developing hydronephrosis or metastases are present, ADT or radiation therapy (RT) may be considered. Patients with advanced cancer may be candidates for observation if the risks and complications of therapy are judged to be greater than the benefit in terms of prolonged life or improved quality of life.

For symptomatic patients and/or those with a life expectancy of greater than 5 years, a bone scan is appropriate for patients with T1 to T2 disease who also have a PSA greater than 20 ng/mL or a Gleason score of 8 or higher. Patients with T3 to T4 disease or symptomatic disease should also receive a bone scan. Pelvic computed tomography (CT) or magnetic resonance imaging (MRI) scanning is recommended if there is T3 or T4 disease, or T1 or T2 disease and a nomogram

indicates that there is greater than 20% chance of lymph node involvement. For all other patients, no additional imaging is required for staging.

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

### Low Risk of Recurrence

As defined by the NCCN guidelines, patients with low risk for biochemical recurrence include those with tumors stage T1 to T2a, low Gleason score (2 to 6), and serum PSA level below 10 ng/mL. Although 40% of men older than 50 years of age harbor prostate cancer, only 1 in 4 present clinically, and only 1 in 14 will die of a prostate cancer-specific death. Therefore, expectant management is an acceptable treatment option for men with low-risk prostate cancer and a life expectancy less than 10 years. Evidence for this approach 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.<sup>22,41,77</sup> Additionally, results from the Medical Research Council (MRC) reported that men with M0 disease showed less cancer-related morbidity after receiving earlier ADT.<sup>26</sup> The determination of which patients have rapidly growing cancer and are appropriate candidates for therapy is based on the clinician's judgment. Radiation therapy using either 3-D conformal RT or brachytherapy is another option.

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 if the predicted probability of pelvic lymph node involvement is 7% or greater. A study by Johansson and colleagues

assessed the long-term natural history of untreated, early-stage prostate cancer in 223 patients during 21 years of follow-up.<sup>20</sup> They found that most prostate cancers diagnosed at an early stage have an indolent course; however, local tumor progression and aggressive metastatic disease may develop in the long term. The mortality rate was significantly higher (approximately 6-fold) after 15 years of follow-up when compared with the first 5 years. Their findings support early radical prostatectomy, especially among patients with an estimated life expectancy exceeding 15 years.

### Intermediate Risk of Recurrence

As defined by the NCCN guidelines, the intermediate-risk category includes patients with any T2b to T2c cancer, Gleason score of 7, or PSA value of 10 to 20 ng/mL. 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.<sup>78</sup> Similarly, Johansson and colleagues<sup>79</sup> 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/IMRT) with or without brachytherapy, or (2) radical prostatectomy with pelvic lymph node dissection (unless the predicted probability of lymph node metastasis is < 7%).

Treatment options for patients with an expected survival of 10 years or more include radical prostatectomy with a pelvic lymph node dissection if the predicted probability of lymph node metastasis is 7% or greater. Radical prostatectomy was compared to watchful waiting in a randomized trial of 695 patients with early stage prostate cancer.<sup>22</sup> With a median follow up of 8.2 years, those assigned to the radical

prostatectomy group had significant improvements in disease specific mortality, overall mortality and risk of metastasis and local progressions. The results of this trial offer high quality evidence to support radical prostatectomy as a treatment option. Expectant management is not recommended for those with a life expectancy of greater than 10 years (category 1).

External-beam RT with or without brachytherapy and pelvic node dissection is another treatment option. ADT during and after RT is recommended for patients with high risk disease, as noted below. However, none of the trials explicitly focused on patients with intermediate disease and this recommendation for patients with intermediate disease is the subject of ongoing controversy.

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 serum PSA value greater than 10 ng/mL.<sup>8</sup>

### High Risk of Recurrence

Men with prostate cancer that is clinically localized stage T3a, Gleason score 8 to 10, or PSA level greater than 20 ng/mL are categorized by the NCCN 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. Patients may be treated with 3D-CRT/IMRT in conjunction with ADT for at least 2-3 years (category 1). This treatment option is supported by the EORTC (European Organization for Research and Treatment of Cancer) trial.<sup>55</sup> More recent trials have focused on different durations of ADT. For example, one option involves external-beam RT with or without neoadjuvant and concurrent short-term ADT (for 4 to 6 months).<sup>80-83</sup> 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.<sup>84,85</sup>

### 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). The options for this group include either (1) ADT alone, or (2) a combination of 3D-CRT/IMRT and ADT (category 1 for T3b-T4 cancer), or (3) Radical Prostatectomy in selected patients with low tumor volume and no fixation to adjacent organs. Early ADT is supported by the MRC trial in which men receiving early ADT showed improved survival and less local morbidity.<sup>26</sup> 3D-CRT/IMRT may be administered to prevent or delay the onset of local symptoms. If the cancer has metastasized (any T, any N, M1), ADT alone is recommended.

### Adjuvant Therapy

If a patient undergoes a radical prostatectomy and microscopically positive margins are found, RT can reasonably be used after recuperation from surgery. No high-level evidence exists to recommend adjuvant RT at this time.<sup>86,87</sup> For example, Thompson and colleagues reported the results of a trial enrolling 425 men with extraprostatic cancer treated with radical prostatectomy. Patients were randomized to receive either adjuvant radiation therapy or usual care.<sup>86</sup> Patients were followed for a median of 10.6 years. The study results revealed that adjuvant radiation therapy reduced the risk of PSA relapse and disease recurrence without statistically significant impact on metastasis-free or overall survival. In another recent prospective randomized trial Swanson and colleagues randomized 374 patients, with extraprostatic disease after radical prostatectomy, to adjuvant radiation therapy or observation alone.<sup>87</sup> The patients were followed for a median of 10.2

years. The study results revealed that patients with high-risk features at prostatectomy experience a high rate of biochemical and clinical treatment failure and that adjuvant radiation reduces both biochemical and clinical treatment failure.

Collectively, these trial results suggest that continued follow-up of this series of patients may show a survival advantage and that; young healthy men with biochemical progression after prostatectomy should be offered adjuvant radiation as standard treatment

If adjuvant RT is considered, it should be administered before the PSA increases above 1.5 ng/mL.<sup>88</sup> Alternatively, close observation is acceptable until a detectable PSA develops. Adjuvant ADT is recommended for patients with positive lymph nodes found during surgery. As discussed earlier, adjuvant antiandrogen therapy is not a standard treatment at this time.

### Surveillance

Those electing expectant management with a life expectancy of 10 years or more might benefit from definitive local therapy if the cancer progresses. Therefore, appropriate surveillance includes a PSA determination as often as every 3 months, a DRE as often as every 6 months, and a repeat prostate biopsy as often as annually. If the patient initially had a 10 to 12 core biopsy, repeat needle biopsy may not be necessary for 18 months. Surveillance may be less intense for those with a life expectancy of less than 10 years; PSA, DRE and prostate biopsy may be done less frequently.

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. If progressive disease is detected, the patient is managed with RT or radical prostatectomy, as outlined on PROS-2 and PROS-3.

For patients initially treated with intent to cure, a serum PSA level should be measured every 6-12 months for the first 5 years and then rechecked annually. When prostate cancer recurred after radical prostatectomy, Pound and colleagues found that 45% of patients experienced recurrence within the first 2 years, 77% within the first 5 years, and 96% by 9 years.<sup>89</sup> Because local recurrence may result in substantial morbidity and can, in rare cases, occur in the absence of a PSA elevation, an annual DRE is also appropriate to monitor for prostate cancer recurrence as well as for colorectal cancer. Similarly, after RT, the monitoring of serum PSA levels is recommended every 6 months for the first 5 years and then annually and a DRE is recommended at least annually.

For patients presenting with locally advanced or metastatic disease, the intensity of clinical monitoring is determined by the response to initial ADT, 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.

## 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 who achieve an undetectable PSA after surgery with a subsequent detectable PSA level that increases on two or more laboratory determinations. The work up for both of these groups focuses on the identification of distant metastases. The specific tests depend on the clinical history, but potentially include a bone scan, prostate biopsy, CT/MRI or radioimmunologic scintigraphy (i.e. ProstaScint scan). Bone scans are appropriate when patients develop symptoms or when the PSA level is increasing rapidly. In one study, the probability of a positive bone scan for a patient not on ADT after radical prostatectomy was less than 5% unless the PSA increased to 40 to 45 ng/mL.<sup>90</sup> Therefore, particularly in the androgen-stimulated setting, periodic bone scans as part of routine surveillance are not recommended, because they do not contribute significantly to the tests previously discussed.

Biochemical failure may indicate local failure, distant failure or both. Since PSA failure often precedes clinically detectable failure by several years, it is important to identify those patients without identifiable distant metastases who are likely to have local disease alone, and thus would be candidates for salvage RT. Several retrospective studies have assessed the prognostic value of various combinations of pretreatment PSA levels, Gleason scores, PSA doubling time and the presence or absence of positive surgical margins.<sup>91-95</sup> The largest of these studies included a retrospective review of 501 patients who received salvage radiotherapy for detectable and increasing PSA after prostatectomy.<sup>95</sup> By multivariate analysis, the predictors of progression were a Gleason score between 8-10, pre-RT PSA level greater than 2 ng/mL, negative surgical margins and a PSA doubling time of greater 10 months. Caution is suggested regarding salvage radiotherapy given the lack of a

survival benefit reported in the randomized trial, discussed above, which reported that there was no survival benefit association with adjuvant radiation therapy in patients with extraprostatic disease.<sup>86</sup>

### Postradiation Recurrence

Originally postradiation recurrence was defined by a consensus panel of the American Society for Therapeutic Radiology and Oncology (ASTRO) as three consecutive rising PSA values at least 3 months apart, with the date of biochemical failure back dated to midway between the date of the postirradiation nadir PSA value and the first of the three consecutive increases.<sup>96</sup> However, there were several limitations to this definition. For example, the definition was not linked to clinical progression or survival and it performed poorly in patients receiving ADT. Finally backdating the time of failure biased the Kaplan-Meier estimates of event-free survival. A second Consensus Conference was sponsored by ASTRO and the Radiation Therapy Oncology Group in Phoenix, Arizona in 2005, and a revised definition, referred to as the Phoenix definition, was published in 2006.<sup>88</sup> The panel recommended 1) a rise by 2 ng/mL or more above the nadir PSA (defined as the lowest PSA achieved) be considered as the current standard definition for biochemical failure after external beam radiotherapy with or without neoadjuvant ADT therapy. Also the panel recommended that the date of failure be determined “at call” and not backdated.

To avoid the artifacts resulting from short follow-up, the reported date of control should be listed as 2 years short of the median follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition would allow comparisons with a large existing body of literature.

Further work up is indicated in patients who are considered candidates for local therapy. These patients include those with original clinical

stage T1-2, NX, N), a life expectancy of greater than 10 years, and a current PSA of less than 10 ng/mL.<sup>97</sup> Work up includes a prostate biopsy, bone scan, and additional tests as clinically indicated, such as an abdomino/pelvic CT, MRI, or a radioimmunologic scintigraphy (i.e. ProstaScint scan).

Options for primary salvage therapy for those without metastases include salvage prostatectomy in selected cases. The morbidity (including incontinence, erectile dysfunction, and bladder neck contracture) remains significantly higher than when radical prostatectomy is used as initial therapy.<sup>98</sup> Other options for localized interventions include cryotherapy<sup>99-101</sup> and brachytherapy.<sup>102</sup> Treatment, however, needs to be individualized based upon the patient's risk of progression, the likelihood of success, and the risks involved with the therapy. However, patients with metastatic disease should be observed or treated with ADT.

### Systemic Therapy

ADT using medical or surgical castration is the most common form of systemic therapy for disseminated disease for patients whose cancer progresses rapidly with blastic bone and/or other metastases and a rising PSA (PROS-7). In patients with radiographic evidence of metastases who are treated with LHRH agonist alone, “flare” in serum LH (luteinizing hormone) and testosterone levels may occur within the first several weeks after therapy is initiated, which may worsen the existing disease. Thus, LHRH agonist is often used in conjunction with antiandrogen for at least 7 days to block ligand binding to the androgen receptor.

Even in patients relapsing after initial ADT with castration recurrent prostate cancer, the androgen receptor remains active and testosterone suppression should be continued. Additional sequential hormonal therapy depends on the type of initial salvage therapy. For patients

whose treatment consisted of an LHRH agonist plus an antiandrogen, the antiandrogen should be discontinued.<sup>103</sup> In patients relapsing after orchiectomy or LHRH alone, an antiandrogen or second line hormonal therapy may be considered. Additional hormonal strategies include ketoconazole with or without glucocorticoids or estrogens.<sup>104</sup> None of these strategies has yet been shown to prolong survival in randomized clinical trials.

Systemic salvage therapy for patients with castration-recurrent, metastatic prostate cancer includes bisphosphonates and any of the following: (1) systemic chemotherapy (docetaxel-based regimen is preferred); (2) systemic RT using samarium or strontium; or (3) supportive care. Systemic chemotherapy should be reserved for patients with castration recurrent metastatic prostate cancer (see PROS-F). 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).<sup>105,106</sup> 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 castration recurrent metastatic (hormone-refractory; androgen-independent) prostate cancer. Based on the phase III trials<sup>106</sup>, every 3-week docetaxel and prednisone is the preferred first-line chemotherapy treatment. Alternative regimens include every 3-week docetaxel and estramustine<sup>105</sup>, weekly docetaxel and prednisone and every 3-week mitoxantrone and prednisone.

Mitoxantrone with prednisone has been shown to provide palliative benefit in patients with painful bony metastases from castration recurrent 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 impending pathologic fractures. The use of systemic radiotherapy with either strontium-89 or samarium-153 occasionally benefits patients with widely metastatic, painful, skeletal involvement that is not responding to palliative chemotherapy or systemic analgesia and who are not candidates for localized, 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.<sup>107</sup>

Neuroendocrine differentiation should be considered 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. 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.<sup>108,109</sup> 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.

### **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.<sup>110,111</sup> Thus, inhibition of bone resorption

via inhibition of osteoclasts is a critical component in treating osteoblastic metastases.

Zoledronic acid 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 ADT in a randomized, double-blind, 15-month clinical trial.<sup>112</sup> 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 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 ADT 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 ADT 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 LHRH.<sup>113</sup> This risk was magnified if men received treatment for 1 year or more. Preventing the

adverse skeletal effects of long-term ADT 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.<sup>114</sup> Zoledronic acid has also been examined in men receiving ADT for nonmetastatic prostate cancer. In a double-blind, placebo-controlled clinical trial, men with M0 (no distant metastases) prostate cancer beginning ADT were randomly assigned to receive zoledronic acid (4 mg) or placebo intravenously every 3 months for 1 year.<sup>115</sup> 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 ADT for prostate cancer.

## 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 patient.

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

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Discussion  
update in  
progress

## References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2007. *CA Cancer J Clin* 2007;57:43-66.
2. Cooperberg MR, Lubeck DP, Meng MV, et al. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol* 2004;22:2141-2149.
3. Brenner H, Arndt V. Long-term survival rates of patients with prostate cancer in the prostate-specific antigen screening era: population-based estimates for the year 2000 by period analysis. *J Clin Oncol* 2005;23:441-447.
4. Social Security Administration. In <http://www.ssa.gov/OACT/STATS/table4c6.html>, editor. *Period Life Table* 2001.
5. Howard DH. Life expectancy and the value of early detection. *J Health Econ*. 2005;24:891-906.
6. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA* 2006;295:801-808.
7. D'Amico AV, Whittington R, Malkowicz SB, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. *J Clin Oncol* 1999;17:168-172.
8. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-974.
9. Kattan MW, Zelefsky MJ, Kupelian PA, et al. Pretreatment nomogram for predicting the outcome of three-dimensional conformal radiotherapy in prostate cancer. *J Clin Oncol* 2000;18:3352-3359.
10. Kattan MW, Eastham JA, Stapleton AM, et al. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst* 1998;90:766-771.
11. Kattan MW, Potters L, Blasko JC, et al. Pretreatment nomogram for predicting freedom from recurrence after permanent prostate brachytherapy in prostate cancer. *Urology* 2001;58:393-399.
12. Partin AW, Mangold LA, Lamm DM, et al. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology* 2001;58:843-848.
13. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol* 1999;17:1499-1507.
14. Graefen M, Karakiewicz PI, Cagiannos I, et al. A validation of two preoperative nomograms predicting recurrence following radical prostatectomy in a cohort of European men. *Urol Oncol* 2002;7:141-146.
15. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol*. 2007;25: 2035-2041.
16. Kattan MW, Zelefsky MJ, Kupelian PA, et al. Pretreatment nomogram that predicts 5-year probability of metastasis following three-dimensional conformal radiation therapy for localized prostate cancer. *J Clin Oncol* 2003;21:4568-4571.
17. D'Amico AV, Cote K, Loffredo M, et al. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. *J Clin Oncol* 2002;20:4567-4573.
18. D'Amico AV, Chen MH, Roehl KA, et al. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med* 2004;351:125-135.
19. D'Amico AV, Moul JW, Carroll PR, et al. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Natl Cancer Inst* 2003;95:1376-1383.

20. Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. *JAMA* 2004;291:2713-2719.
21. Patel MI, DeConcini DT, Lopez-Corona E, et al. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. *J Urol* 2004;171:1520-1524.
22. Bill-Axelsson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005;352:1977-1984.
23. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. *J Urol* 2002;167:1664-1669.
24. Fleming C, Wasson JH, Albertsen PC, et al. A decision analysis of alternative treatment strategies for clinically localized prostate cancer. Prostate Patient Outcomes Research Team. *JAMA* 1993;269:2650-2658.
25. Johansson JE. Expectant management of early stage prostatic cancer: Swedish experience. *J Urol* 1994;152:1753-1756.
26. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. *Br J Urol* 1997;79:235-246.
27. Carter HB, Walsh PC, Landis P, et al. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. *J Urol* 2002;167:1231-1234.
28. Stephenson AJ, Aprikian AG, Souhami L, et al. Utility of PSA doubling time in follow-up of untreated patients with localized prostate cancer. *Urology* 2002;59:652-656.
29. Adolfsson J, Tribukait B. Evaluation of tumor progression by repeated fine needle biopsies in prostate adenocarcinoma: modal deoxyribonucleic acid value and cytological differentiation. *J Urol* 1990;144:1408-1410.
30. Potters L, Klein EA, Kattan MW, et al. Monotherapy for stage T1-T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation. *Radiother Oncol* 2004;71:29-33.
31. Hanks GE, Hanlon AL, Epstein B, Horwitz. Does response in prostate cancer with 8-12 years' follow up. *Int J Radiation Oncol Biol Phys* 2002;54:427-435.
32. Khoo VS. Radiotherapeutic techniques for prostate cancer, dose escalation and brachytherapy. *Clin Oncol (R Coll Radiol)*. 2005;17:560-571.
33. Hanlon AL, Watkins Bruner D, Peter R, et al. Quality of life study in prostate cancer patients treated with three-dimensional conformal radiation therapy: comparing late bowel and bladder quality of life symptoms to that of the normal population. *Int J Radiat Oncol Biol Phys* 2001;49:51-59.
34. Michalski JM, Purdy JA, Winter K, et al. Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. *Int J Radiat Oncol Biol Phys* 2000;46:391-402.
35. Dearnaley DP, Khoo VS, Norman AR et al. Comparison of radiation side effects of conformal and conventional radiation therapy in prostate cancer. A randomized trial. *Lancet* 1999;353:267-272.
36. Koper PC, Stroom JC, van Putten WL et al. Acute morbidity reduction using 3DCRT for prostate cancer: A randomized study. *Int J Radiat Oncol Biol Phys* 1999;43:727-734.
37. Peeters STH, Heemsbergen WD, Koper PCM et al. Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24:1990-1996.
38. Pollack A, Zagars GK, Starkschall G et al. Prostate cancer radiation dose response: Results of the MD Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097-1105.
39. Zeitman AL, DeSilvio ML, Slater JD et al. Comparison of conventional dose vs. high dose conformal radiation therapy in clinically

- localized adenocarcinoma of the prostate. A randomized controlled trial. JAMA 2005;294:1233-1239.
40. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst 2004;96:1358-1367.
41. Albertsen PC, Hanley JA, Gleason DF, et al. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 1998;280:975-980.
42. Smith JA, Herrell SD. Robotic assisted laparoscopic prostatectomy: Do minimally invasive approaches offer significant advantages? J Clin Oncol 2005;23:8170-8175.
43. Herrell SD, Smith JA. Robotic-assisted laparoscopic prostatectomy: What is the learning curve? Urology 2005;66:105-107.
44. Patel VR, Tully AS, Holmes R, Lindsay J. Robotic radical prostatectomy in the community setting – the learning curve and beyond: Initial 200 cases. J Urol 2005;174:269-272.
45. Burkhard FC, Schumacher M, Thalmann GN, Studer UE. Is pelvic lymphadenectomy really necessary in patients with a serum prostate-specific antigen level of <10 ng/ml undergoing radical prostatectomy for prostate cancer? BJU Int 2005;95:275-278.
46. Heidenreich A, Varga Z, Von Knobloch R. Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph node metastasis. J Urol 2002;167:1681-1686.
47. <http://urology.jhu.edu/prostate/partintables.php>.
48. <http://www.mskcc.org/mskcc/html/10088.cfm>.
49. Stone NN, Stock RG, Unger P. Laparoscopic pelvic lymph node dissection for prostate cancer: comparison of the extended and modified techniques. J Urol 1997;158:1891-1894.
50. Burkhard FC, Studer UE. The role of lymphadenectomy in prostate cancer. Urol Oncol 2004;22(3):198-202; discussion -4.
51. Bader P, Burkhard FC, Markwalder R, Studer UE. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? J Urol 2003;169:849-854.
52. Schulze H, Senge T. Influence of different types of antiandrogens on luteinizing hormone-releasing hormone analogue-induced testosterone surge in patients with metastatic carcinoma of the prostate. J Urol 1990;144:934-941.
53. Labrie F, Dupont A, Belanger A, Lachance R. Flutamine eliminates the risk of disease flare in prostatic cancer patients treated with a luteinizing hormone-releasing hormone agonist. J Urol 1987;138:804-806.
54. Iversen P, Johansson JE, Lodding P, et al. Bicalutamide (150 mg) versus placebo as immediate therapy alone or as adjuvant to therapy with curative intent for early nonmetastatic prostate cancer: 5.3-year median followup from the Scandinavian Prostate Cancer Group Study Number 6. J Urol 2004;172:1871-1876.
55. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295-300.
56. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol. 2007;25:1596-1605.
57. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol. 2006;7:472-479.



58. McLeod DG, Iversen P, See WA et al. Bicalutamide 150 mg plus standard care vs. standard care alone for early prostate cancer. *BJU Int.* 2006;97:247-254.
59. McLeod DG, See WA, Klimberg et al. The bicalutamide 150 mg early prostate cancer program: findings of the North American trial at 7.7-year median follow-up. *J Urol.* 2006;176:75-80.
60. Muller M, Grobbee DE, den Tonkeiaar I, et al. Endogenous sex hormones and metabolic syndrome in aging men. *J Clin Endocrinol Metab.* 2005;90: 2618-2623.
61. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care.* 2004;27:1036-1041.
62. Basaria S, Lieb J 2nd, Tang AM, et al: Long-term effects of androgen deprivation therapy in prostate cancer patients. *Clin Endocrinol (Oxf).* 2002; 56: 779-786.
63. Stellato RK, Feldman HA, Hamdy O, et al. Testosterone, sex hormone binding globulin, and the development of type 2 diabetes in middle-aged men: Prospective results from the Massachusetts male aging study. *Diabetes Care.* 2000; 23:490-494.
64. Simon D, Charles MA, Nahoul K, et al. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. *J Clin Endocrinol Metab.* 1997; 82:682-685.
65. Haffner SM, Mykkanen L, Valdez RA, et al. Relationship of sex hormones to lipids and lipoproteins in nondiabetic men. *J Clin Endocrinol Metab.* 1993; 77:1610-1615.
66. Basaria S, and Dobs AS. Risks versus benefits of testosterone therapy in elderly men. *Drugs Aging.* 1999;15:131-142.
67. Khaw KT, Barrett-Conner E. Blood pressure and endogenous testosterone in men: An inverse relationship. *J Hypertens* 1988; 6:329-332.
68. National Institutes of Health. Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda, Md: National Institutes of Health; 2001. NIH Publication 01-3670.
69. Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic Syndrome in Men With Prostate Cancer Undergoing Long-Term Androgen-Deprivation Therapy. *J Clin Oncol.* 2006; 24:3979-3983.
70. Basaria S, Muller DC, Carducci MA, et al. Hyperglycemia and insulin resistant in men with prostate carcinoma who receive androgen deprivation therapy. *Cancer.* 2006; 106:581-588.
71. Keating NL, O'Malley AJ, and Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24:4448-4456.
72. Phillips GB, Pinkernell BH, Jing TY et al. The association of hypotestosteronemia with coronary artery disease in men. *Arterioscler Thromb.* 1994;14:701-706.
73. Tsai HK, D'Amico AV, Sadetsky N, Chen M, Carroll PR. Androgen Deprivation Therapy for Localized Prostate Cancer and the Risk of Cardiovascular Mortality. *J Natl Cancer Inst* 2007;99:1516-1524
74. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng per milliliter. *N Engl J Med* 2004;350:2239-2246.
75. Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*, 6th ed. New York: Springer-Verlag, 2002.
76. [http://www.cap.org/apps/docs/cancer\\_protocols/2006/prostate06\\_ckw.pdf](http://www.cap.org/apps/docs/cancer_protocols/2006/prostate06_ckw.pdf)
77. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med* 1994;330:242-248.

78. Albertsen PC, Fryback DG, Storer BE, et al. Long-term survival among men with conservatively treated localized prostate cancer. *JAMA* 1995;274:626-631.
79. Johansson J, Holmberg L, Johansson S, et al. Fifteen-year survival in prostate cancer. *JAMA* 1997;277:467-471.
80. Pilepich MV, Krall JM, Al-Sarraf M, et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the radiation therapy oncology group. *Urology* 1995;45:616-623.
81. D'Amico AV, Manola J, Loffredo M et al. 6-month androgen suppression plus radiation therapy vs. radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. *JAMA* 2004;292:821-827.
82. Denham JW, Steigler A, Lamb DS et al. Short term androgen deprivation and radiotherapy for locally advanced prostate cancer: Results from Trans-Tasman Radiation Oncology Group. *Lancet Oncol* 2005;6:841-850.
83. Laverdiere J, Nabid A, De Bedoya LD et al. The efficacy and sequencing of a short course of androgen suppression on freedom from biochemical failure when administered with radiation therapy for T2-T3 prostate cancer. *J Urol* 2004;171:1137-1140.
84. Lau WK, Bergstralh EJ, Blute ML, et al. Radical prostatectomy for pathological Gleason 8 or greater prostate cancer: influence of concomitant pathological variables. *J Urol* 2002;167:117-122.
85. Ohori M, Goad J, Wheeler J, et al. Can radical prostatectomy alter the progressing of poorly differentiated prostate cancer? *J.Urol* 1994;152:1843-1849.
86. Thompson IM Jr, Tangen CM, Paradelo J et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA*. 2006;296:2329-2335.
87. Swanson GP, Hussey MA, Tangen CM, et al; SWOG 8794. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol*. 2007;25:2225-2229.
88. Roach M 3rd, Hanks G, Thames H Jr et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65:965-974.
89. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591-1597.
90. Cher ML, Bianco FJ Jr., Lam JS, et al. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. *J Urol* 1998;160:1387-1391.
91. Lee AK, D'Amico AV. Utility of prostate-specific antigen kinetics in addition to clinical factors in the selection of patients for salvage local therapy. *J Clin Oncol* 2005;23:8192-8197.
92. Cheung R, Kamet AM, de Reviser R et al. Outcome of salvage radiotherapy for biochemical failure after radical prostatectomy with or without hormonal therapy. *Int j Radiat Oncol Biol Phys* 2005;63:134-140.
93. Patel R, Leper H, Thiele RP, Tania SS. Prostate specific antigen velocity accurately predicts response to salvage radiotherapy in men with biochemical relapse after radical prostatectomy. *Urol* 2005;65:942-946.
94. Ward JF, Zincked H, Bergstralh EJ et al. Prostate specific antigen doubling time subsequent to radical prostatectomy as a prognosticator of outcome following salvage radiotherapy. *J Urol* 2004;172:2244-2248.
95. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004;291:1325-1332.
96. Cox JD, Gallagher MJ, Hammond EH, et al. Consensus statements on radiation therapy of prostate cancer: guidelines for prostate

re-biopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *J Clin Oncol* 1999;17:1155-1163.

97. Rogers E, Ohori M, Kassabian VS, et al. Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. *J Urol* 1995;153:104-110.

98. Shekarriz B, Upadhyay J, Pontes JE. Salvage radical prostatectomy. *Urol Clin North Am* 2001;28:545-553.

99. Han KR, Cohen JK, Miller RJ, et al. Treatment of organ confined prostate cancer with third generation cryosurgery: Preliminary multicenter experience. *J Urol*.2003;170:1126-1130.

100. Anastasiadis AG, Sachdev R, Salomon L, et al: Comparison of health-related quality of life and prostate-associated symptoms after primary and salvage cryotherapy for prostate cancer. *J Cancer Res Clin Oncol*. 2003;129:676-682.

101. Ismail M, Ahmed S, Kastner C, et al: Salvage cryotherapy for recurrent prostate cancer after radiation failure: A prospective case series of the first 100 patients. *BJU Int*. 2007;100:760-764.

102. Allen GW, Howard AR, Jarrard DF, Ritter MA. Management of prostate cancer recurrences after radiation therapy-brachytherapy as a salvage option. *Cancer*. 2007;110:1405-1416. Review.

103. Kelly WK, Scher HI. Prostate specific antigen decline after antiandrogen withdrawal: the flutamide withdrawal syndrome. *J Urol* 1993;149:607-609.

104. Small EJ, Halabi S, Dawson NA, et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: A phase III trial (CALGB 9583). *J Clin Oncol* 2004;22:1025-1033.

105. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for

advanced refractory prostate cancer. *N Engl J Med* 2004;351:1513-1520.

106. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004;351:1502-1512.

107. Ben-Josef E, Porter AT. Radioisotopes in the treatment of bone metastases. *Ann Med* 1997;29:31-35.

108. van der Gaast A, Verwij J, Planting AS, et al. The value of immunohistochemistry in patients with poorly differentiated adenocarcinomas and undifferentiated carcinomas of unknown primary. *J Cancer Res Clin Oncol* 1996;122:181-185.

109. Sella A, Konichezky M, Flex D, et al. Low PSA metastatic androgen- independent prostate cancer. *Eur Urol* 2000;38:250-254.

110. Clarke NW, McClure J, George NJ. Morphometric evidence for bone resorption and replacement in prostate cancer. *Br J Urol* 1991;68:74-80.

111. Lipton A, Demers L, Daniloff Y, et al. Increased urinary excretion of pyridinium cross-links in cancer patients. *Clin Chem* 1993;39:614-618.

112. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid with patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458-1468.

113. Smith MR, Lee WC, Krupsi T, et al. Association between androgen deprivation therapy and fracture risk: A population-based cohort study in men with non-metastatic prostate cancer (abstract). *ASCO Annual Meeting Proceedings (post-meeting edition)*. *J Clin Oncol* 2004; 22:4507.

114. Reid IR, Brown JP, Burckhardt P, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. *N Engl J Med* 2002;346:653-661.

115. Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol* 2003;169:2008-2012.



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