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Comprehensive
Cancer
Network[®]

NCCN Clinical Practice Guidelines in Oncology™

Prostate Cancer

V.3.2010

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

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

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

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

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Summary of the Guideline Updates

Summary of changes in the 3.2010 version of the Prostate Cancer Treatment guidelines from the 2.2010 version include:

PROS-9

- Added cabazitaxel + steroids (category 1) as an option under systemic salvage therapy of castration-recurrent prostate cancer
- Added mitoxantrone + steroids as an option under systemic salvage therapy of castration-recurrent prostate cancer

PROS-F

• Added two new bullets:

- Patients who have failed docetaxel-based chemotherapy should be encouraged to participate in clinical trials. However, cabazitaxel with prednisone has been shown in a randomized phase 3 study to prolong overall survival, progression-free survival, and improved PSA and radiologic responses when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second line setting. Selection of patients without severe neuropathy and adequate liver, kidney, and bone marrow function is necessary, given the high risk of neutropenia and other side effects in this population, with consideration of prophylactic granulocyte growth factor injections.
- Mitoxantrone has not demonstrated a survival improvement in this post-docetaxel setting but remains a palliative therapeutic option, particularly in men who are not candidates for cabazitaxel therapy. No chemotherapy regimen to date has demonstrated improved survival or quality of life following cabazitaxel, and trial participation should be strongly encouraged if appropriate. Outside of a trial, several systemic agents (for example, etoposide, estramustine, cyclophosphamide, navelbine, paclitaxel, others) have shown palliative benefits in single arm studies, but lack of controlled trials limits the ability to recommend one agent over another and treatment decisions should remain individualized in this setting based on comorbidities and functional status. Finally, for patients who have not demonstrated definitive evidence of progression on prior docetaxel therapy, retreatment with this agent can be attempted.

Summary of changes in the 2.2010 version of the Prostate Cancer Treatment guidelines from the 1.2010 version include:

PROS-9

- Added sipuleucel-T (category 1) as a bullet under systemic salvage therapy of castration-recurrent prostate cancer
- Also added a new footnote "Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. It is not recommended for patients with visceral disease and a life expectancy less than 6 months"

[2010 Updates continued on next page](#)

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

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Summary of the Guideline Updates

Summary of changes in the 1.2010 version of the Prostate Cancer Treatment guidelines from the 2.2009 version include:

PROS-1

- Changed Consider FNA to Consider biopsy
- Added a new risk category of Very Low Risk of Recurrence:
 - ◊ T1c
 - ◊ Gleason score ≤ 6
 - ◊ PSA < 10 ng/mL
 - ◊ Fewer than 3 biopsy cores positive, $\leq 50\%$ cancer in each core
 - ◊ PSA density < 0.15 ng/mL/g

PROS-2

- Added a new pathway for patients with Very Low Risk of Recurrence and expected survival < 20 y recommending active surveillance with PSA as often as every 6 mo and DRE as often as every 12 mo
- Added repeat biopsy as often as every 12 mo for men who choose active surveillance for Low Risk of Recurrence, when expected patient survival is ≥ 10 y
- Changed the recommendation for pelvic lymph node dissection if predicted probability of lymph node metastasis is $\geq 7\%$ to $\geq 2\%$
- Footnote "i" is new to the page: "Adverse pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension or detectable PSA."

PROS-3

- Added "daily" to recommendation for 3D-CRT with daily IGRT

PROS-4

- Locally Advanced, Very High Risk: changed recommendation for short term neoadjuvant/concomitant/adjuvant ADT (4-6 mo) to long-term ADT (2-3 y)

PROS-7

- Salvage workup, added option for endorectal MRI and PSADT
- Removed cryosurgery and brachytherapy from primary salvage therapy for biopsy negative, studies negative for metastases
- Removed ADT and observation from salvage therapy for studies positive for metastases
- Added recommendation for more aggressive workup for local recurrence (eg, repeat biopsy, MR spectroscopy, endorectal MRI)

PROS-8

- Removed the header "Disseminated disease"
- Changed blastic bone and/or other metastases and rising PSA to ADT naïve
- Changed visceral or lytic bone metastasis and low PSA or rapidly progressing soft tissue masses to castration-recurrent prostate cancer

PROS-9

- This page is new to the Guidelines: Systemic Salvage Therapy For Castration-Recurrent Prostate Cancer

PROS-B

- New bullet: "The guideline committee remains concerned about over-diagnosis and over-treatment of prostate cancer and recommends that patients and their physicians give careful consideration to active surveillance based on careful consideration of the risk file by the patient and his physicians (radiation oncologists, medical oncologists, primary care physicians)."
- Added the statement: "Follow up should be more rigorous in younger men than older men"
- Deleted "if PSA velocity > 0.75 " after cancer progression may have occurred

PROS-C

- External beam radiotherapy, added "Image guided radiation therapy (IGRT) is required if dose ≥ 78 Gy
- Palliative radiotherapy is a new section on this page

PROS-D

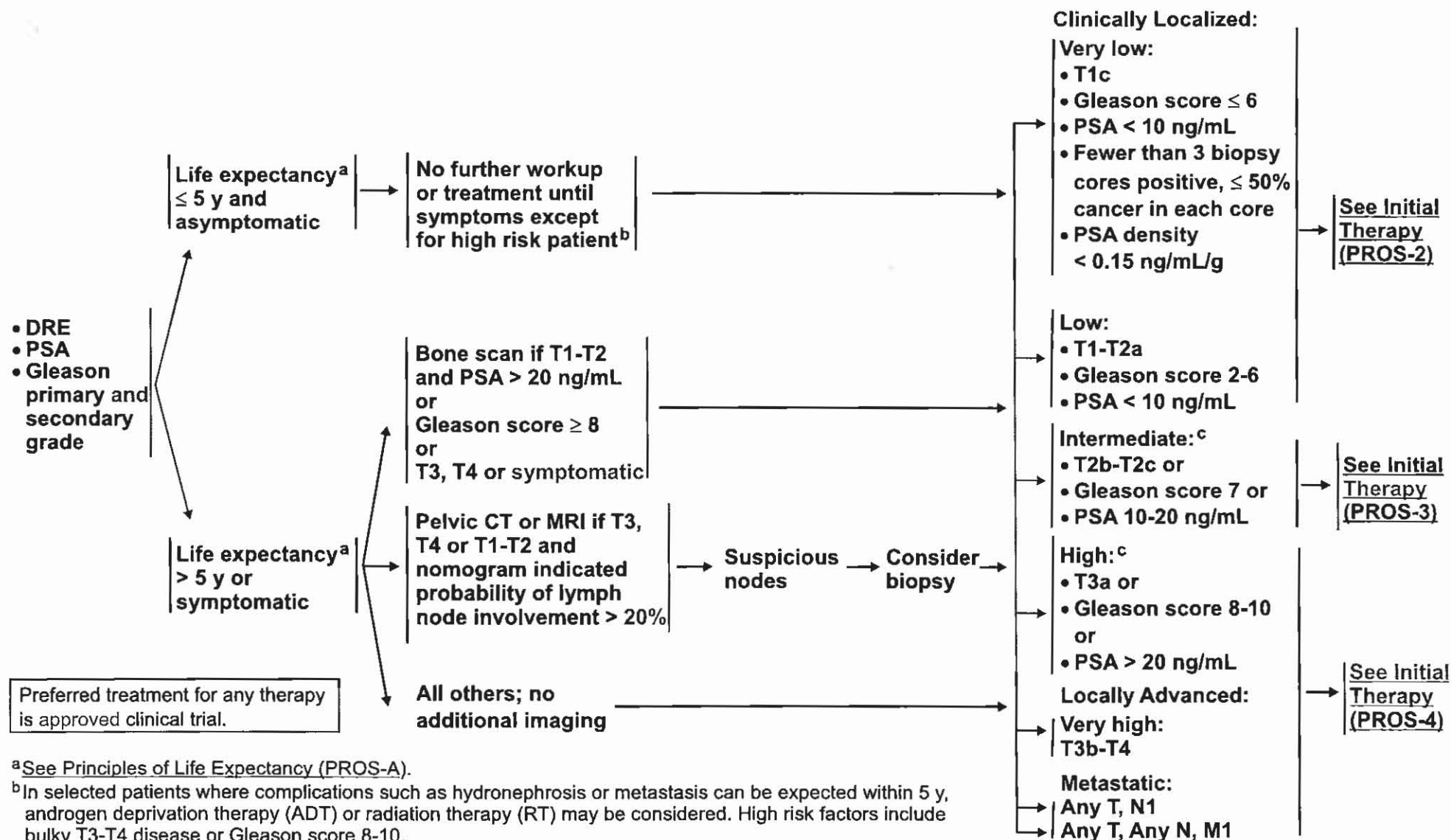
- The limited pelvic lymph node dissection has been eliminated in favor of extended pelvic lymph node dissection

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INITIAL PROSTATE
CANCER DIAGNOSISINITIAL CLINICAL
ASSESSMENTSTAGING WORKUP
(TNM staging refers to 2002 Classification)

RECURRENCE RISK



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RECURRENCE RISK

EXPECTED
PATIENT
SURVIVAL^a

INITIAL THERAPY

Clinically Localized:

Very low:^d

- T1c
- Gleason score ≤ 6
- PSA < 10 ng/mL
- Fewer than 3 biopsy cores positive, $\leq 50\%$ cancer in each core
- PSA density < 0.15 ng/mL/g

< 20 y

Active surveillance (category 2B)^e

- PSA as often as every 6 mo
- DRE as often as every 12 mo

< 10 y

Active surveillance^e

- PSA as often as every 6 mo
- DRE as often as every 12 mo

Low:

- T1-T2a
- Gleason score ≤ 6
- PSA < 10 ng/mL

 ≥ 10 yActive surveillance^e

- PSA as often as every 6 mo
- DRE as often as every 12 mo
- Repeat prostate biopsy as often as every 12 mo

RT^f (3D-CRT/IMRT with daily IGRT or brachytherapy)Radical prostatectomy^g

± pelvic lymph node dissection if predicted probability of lymph node metastasis $\geq 2\%$

Adverse pathologic features:ⁱ

Observe
or
RT^f

Lymph node metastasis:
Observe
or

Androgen deprivation therapy^j

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

See
Monitoring
(PROS-5)

^aSee Principles of Life Expectancy (PROS-A).

^dThe Panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing (see NCCN Prostate Early Detection Guidelines v1.2010). Active surveillance is preferred for this subset of patients.

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

^fSee Principles of Radiation Therapy (PROS-C).

^gSee Principles of Surgery (PROS-D).

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

ⁱAdverse pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension or detectable PSA.

^jSee Principles of Androgen Deprivation Therapy (PROS-E).

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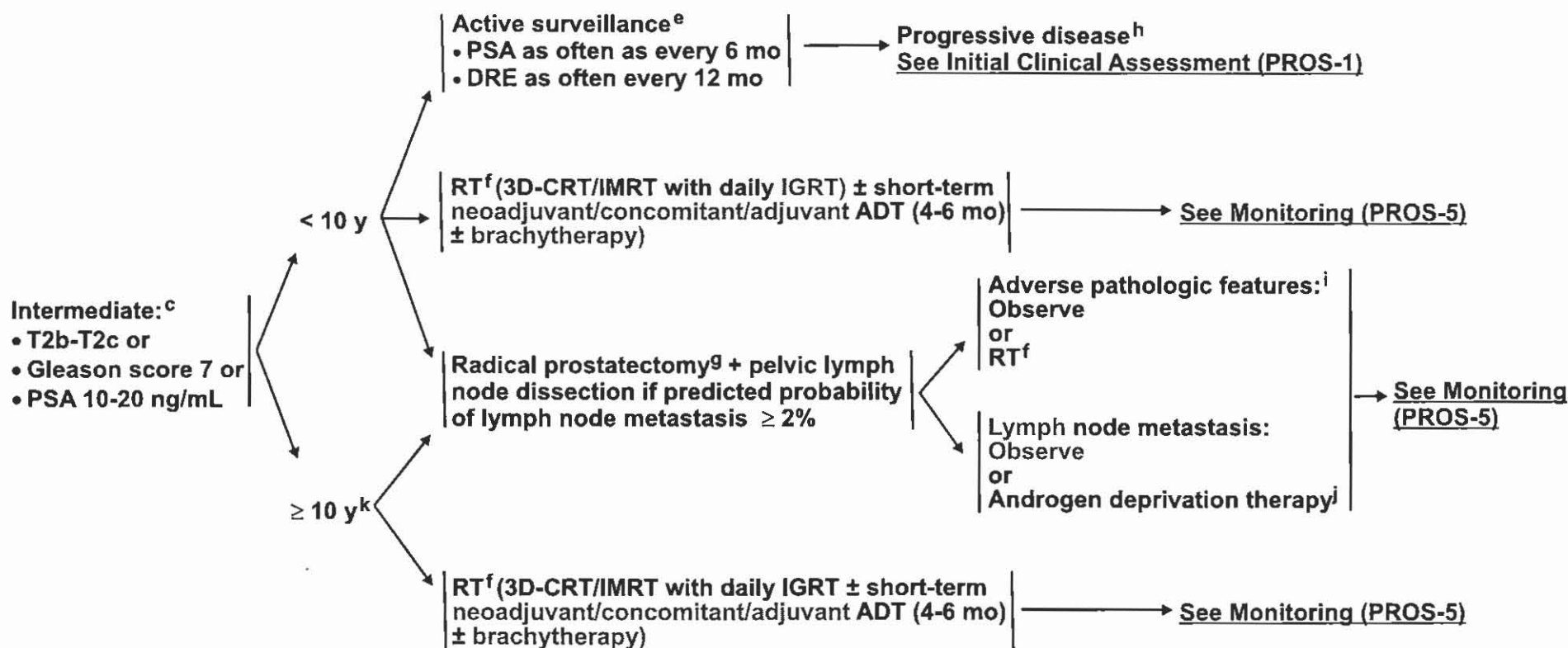
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RECURRENCE RISK

EXPECTED
PATIENT
SURVIVAL^a

INITIAL THERAPY

Clinically Localized:

^aSee Principles of Life Expectancy (PROS-A).^cPatients with multiple adverse factors may be shifted into the next higher risk group.^eActive surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses. See Principles of Active Surveillance (PROS-B).^fSee Principles of Radiation Therapy (PROS-C).^gSee Principles of Surgery (PROS-D).^hCriteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.ⁱAdverse pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension or detectable PSA.^jSee Principles of Androgen Deprivation Therapy (PROS-E).^kActive surveillance of intermediate and high risk clinically localized cancers is not recommended in patients with life expectancy > 10 years (category 1).**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.

RECURRENT
RISK

INITIAL THERAPY

ADJUVANT THERAPY

High:^c

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

RT^f (3D-CRT/IMRT with IGRT) (category 1) + long-term neoadjuvant/concomitant/adjuvant ADT (2-3 y)^j

or

Radical prostatectomy^g + pelvic lymph node dissection (selected patients with no fixation)

Adverse pathologic features:ⁱ

- Observation
- or
- RT^f

Lymph node metastasis:

- ADT^j
- or
- Observation

See Monitoring (PROS-5)

Undetectable
PSASee
Monitoring
(PROS-5)

Detectable PSA

See Salvage
Therapy
(PROS-6)Locally
Advanced
Very high:
T3b-T4

RT^f (3D-CRT/IMRT with IGRT) + long-term neoadjuvant/concomitant/adjuvant ADT (2-3y)^j (category 1)

or

Radical prostatectomy^g + pelvic lymph node dissection (selected patients: with no fixation)

or

ADT^j → See Monitoring (PROS-5)

Adverse pathologic features:ⁱ

- Observation
- or
- RT^f

Lymph node metastasis:

- ADT^j
- or
- Observation

See Monitoring (PROS-5)

Undetectable
PSASee
Monitoring
(PROS-5)

Detectable PSA

See Salvage
Therapy
(PROS-6)

Metastatic:

Any T, N1

ADT^j

or

RT^f (3D-CRT/IMRT with IGRT) + long-term neoadjuvant/concomitant/adjuvant ADT (2-3y)^j

See Monitoring (PROS-5)

Any T,
Any N, M1ADT^j^cPatients with multiple adverse factors may be shifted into the next higher risk group^fSee Principles of Radiation Therapy (PROS-C).^gSee Principles of Surgery (PROS-D).ⁱAdverse pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension or detectable PSA.^jSee Principles of Androgen Deprivation Therapy (PROS-E).

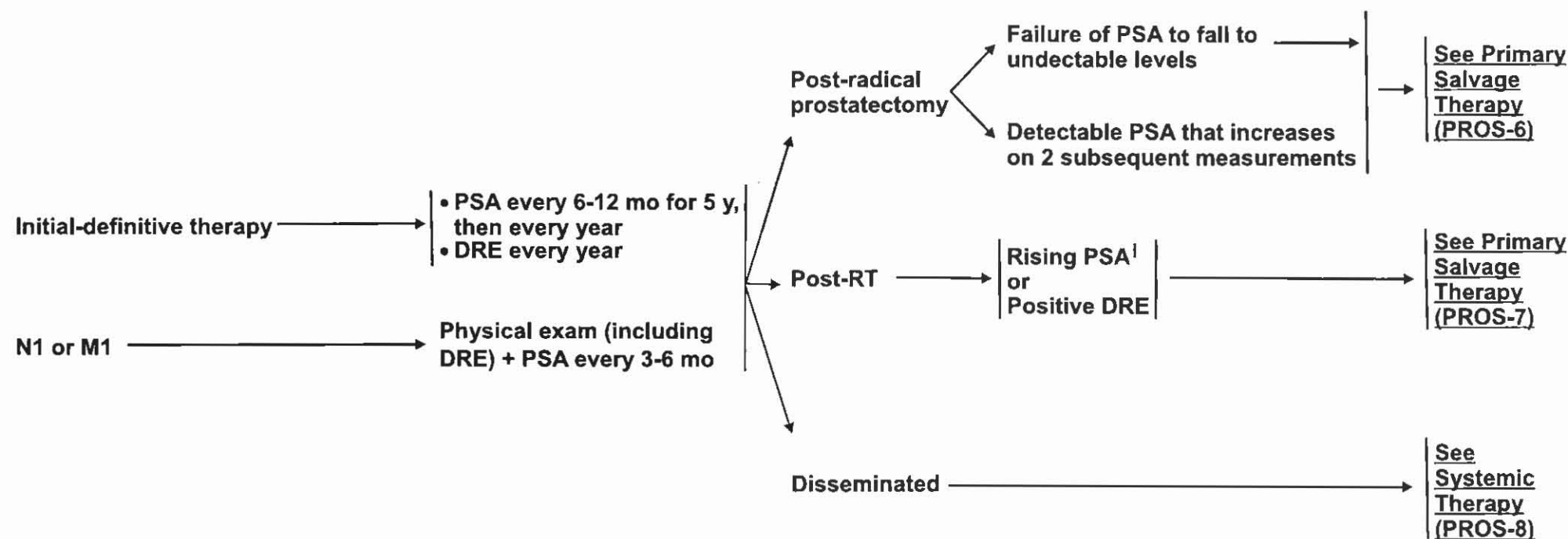
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INITIAL MANAGEMENT
OR PATHOLOGY

MONITORING

RECURRENCE



¹RTOG-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.

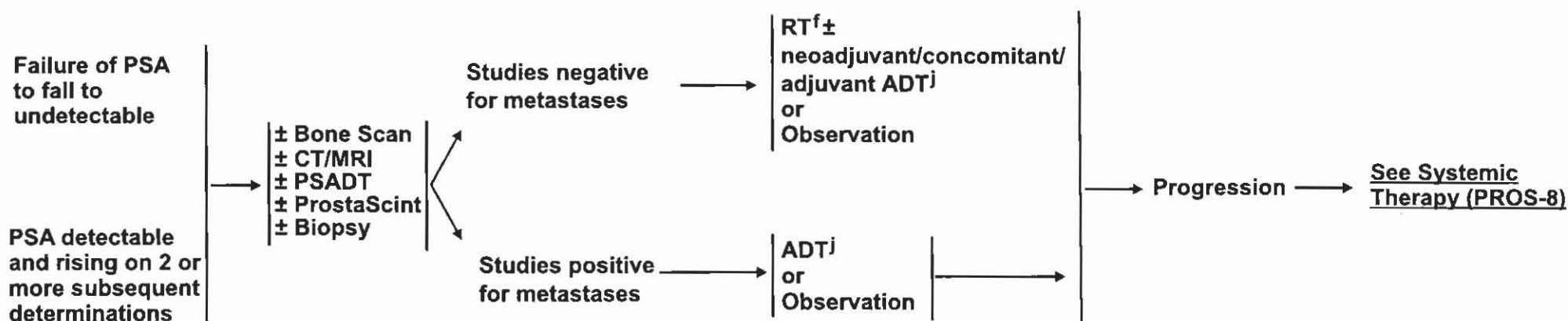
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POST-RADICAL PROSTATECTOMY RECURRENCE

SALVAGE WORKUP

PRIMARY SALVAGE THERAPY

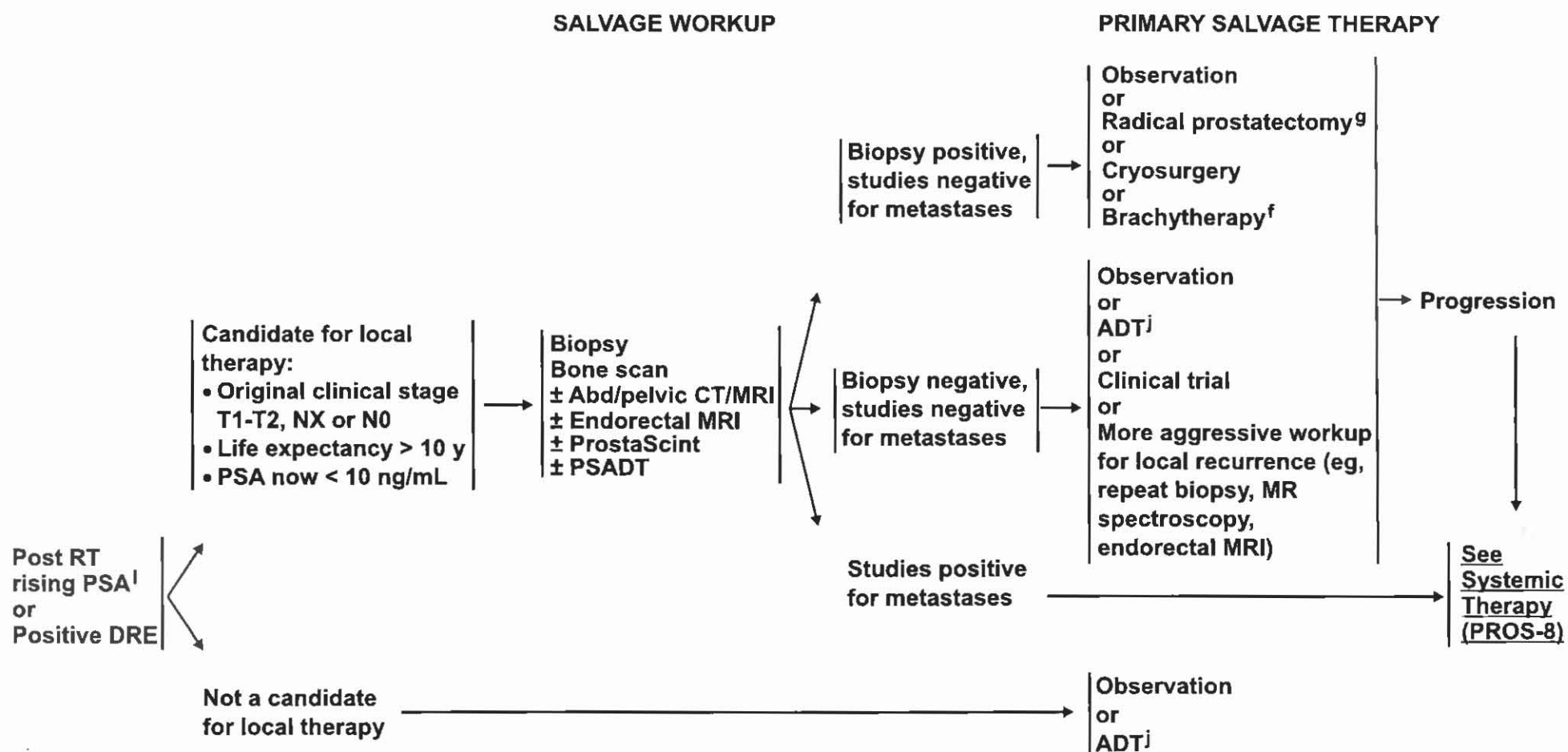


^fSee Principles of Radiation Therapy (PROS-C).

^jSee Principles of Androgen Deprivation Therapy (PROS-E).

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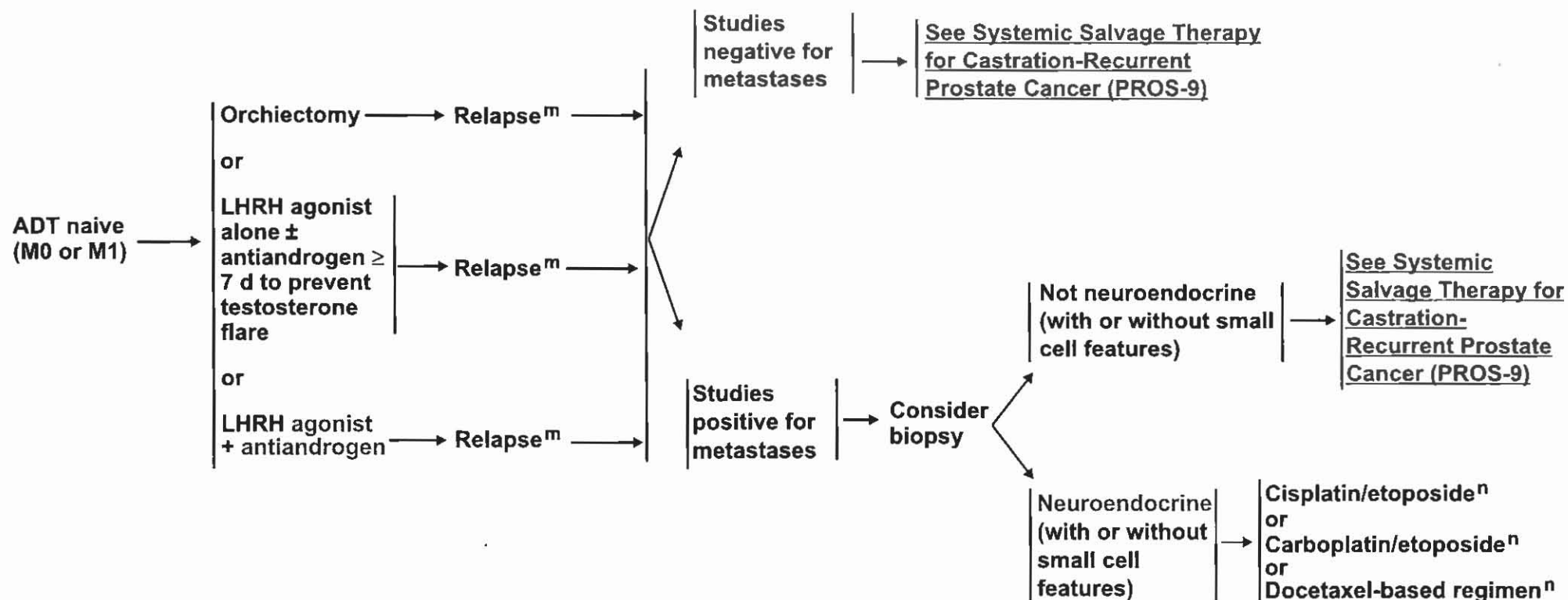
^fSee Principles of Radiation Therapy (PROS-C).⁹See Principles of Surgery (PROS-D).^jSee Principles of Androgen Deprivation Therapy (PROS-E).ⁱRTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus - (1) PSA rise by 2 ng/ml or more above 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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SYSTEMIC THERAPY

SYSTEMIC SALVAGE THERAPY



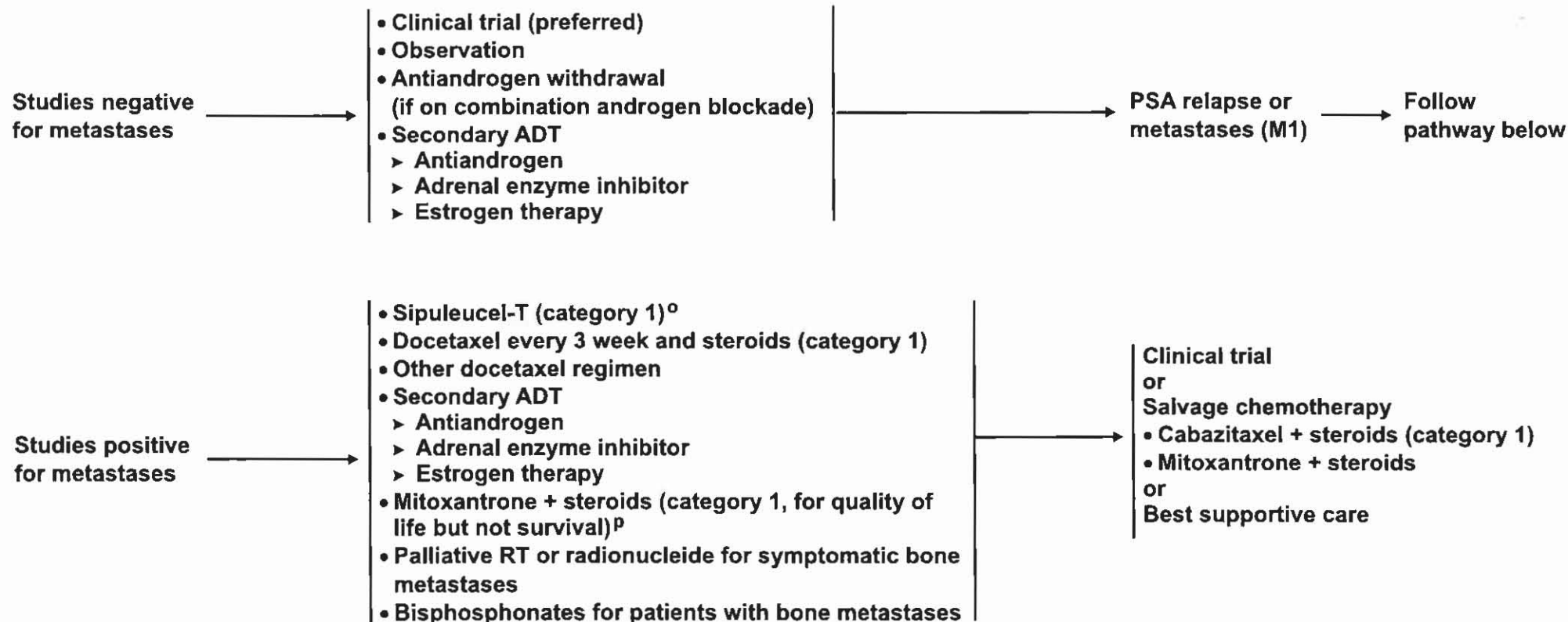
^mAssure castrate level of testosterone.

ⁿSee Principles of Chemotherapy (PROS-F).

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SYSTEMIC SALVAGE THERAPY FOR CASTRATION-RECURRENT PROSTATE CANCER



°Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. It is not recommended for patients with visceral disease and a life expectancy less than 6 months.

PFor patients who cannot tolerate docetaxel-based regimens.

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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)
- 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

- The NCCN Prostate Cancer Guideline Panel and the NCCN Prostate Cancer Early Detection Panel (see NCCN Prostate Early Detection Guidelines v1.2010) remains concerned about over-diagnosis and over-treatment of prostate cancer. The Panel recommends that patients and their physicians consider active surveillance based on careful consideration of the patient's prostate cancer risk profile, age and health by the patient and all his physicians (urologist, radiation oncologist, medical oncologist, primary care physician).
- Active surveillance is usually appropriate for men with very low risk prostate cancer when life expectancy < 20 y or men with low risk prostate cancer when life expectancy < 10 y. See [Recurrence Risk Criteria \(PROS-2\)](#)
- Active surveillance involves actively monitoring the course of disease with the expectation to intervene if the cancer progresses
- Patients with clinically localized cancers who are candidates for definitive treatment and choose active surveillance should have regular follow up. Follow up should be more rigorous in younger men than older men. Follow up should include:
 - PSA as often as every 3 mo but at least every 6 mo
 - DRE as often as every 6 mo but at least every 12 mo
 - Needle biopsy of the prostate 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 initial biopsy ≥ 10 cores
- 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
- A repeat prostate biopsy is indicated for signs of disease progression by exam or PSA
- Advantages of active surveillance:
 - Avoid possible side effects of definitive therapy that may be unnecessary
 - Quality of life/normal activities retained
 - Risk of unnecessary treatment of small, indolent cancers reduced
- Disadvantages of active surveillance:
 - Chance of missed opportunity for cure
 - Risk of progression and/or metastases
 - Subsequent treatment may be more complex with increased side effects
 - Nerve sparing may be more difficult, which may reduce chance of potency preservation after surgery
 - Increased anxiety
 - Requires frequent medical exams and periodic biopsies
 - Uncertain long-term natural history of prostate cancer

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PRINCIPLES OF RADIATION THERAPY**External Beam Radiotherapy:**

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

Brachytherapy:

- Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers consider combining brachytherapy with EBRT (40-50 Gy) $\pm$ 4-6 mo neoadjuvant/comcomittant/adjuvant ADT. Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy; however, with the addition of EBRT and ADT, it may be effective in some patients.
- Patients with a very large 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. In addition, high dose rate (HDR) brachytherapy can be used in combination instead of lower dose.

Palliative Radiotherapy:

- 800 cGy as a single dose should be used instead of 3000 cGy in 10 fractions for non-vertebral metastases.
- Widespread bone metastases can be palliated using strontium 89 or samarium 153.

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PRINCIPLES OF SURGERY

Pelvic Lymph Node Dissection (PLND):

- An extended PLND will discover metastases approximately twice as often as a limited PLND. Extended PLND provides more complete staging and may cure some men with microscopic metastases, therefore, an extended PLND is preferred when PLND is performed.
- An extended PLND includes removal of all node-bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic sidewall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally.
- A PLND can be excluded in patients with < 2% predicated probability of nodal metastases by nomograms, although some patients with lymph node metastases will be missed.
- PLND can be performed using an open, laparoscopic or robotic technique.

Radical Prostatectomy:

- RP is 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 age at radical prostatectomy, preoperative erectile function and the degree of preservation of the cavernous nerves. Replacement of resected nerves with nerve grafts has not been shown beneficial. Early restoration of erections may improve late recovery.
- Salvage radical prostatectomy is an option for highly selected patients with local recurrence after EBRT, brachytherapy, or cryotherapy in the absence of metastases, but the morbidity (incontinence, loss of erection, anastomotic stricture) is high.

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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). Low volume, high grade prostate cancer may warrant adjuvant ADT for 4-6 mo but 2-3 y may be considered.
- In the largest randomized trial to date using antiandrogen bicalutamide alone at high dose (150 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

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

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

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

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

Secondary Hormonal Therapy

- 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). 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[®] by the World Health Organization (www.shef.ac.uk/FRAX/index.htm). ADT should be considered "secondary osteoporosis" using the FRAX[®] algorithm.
- Zoledronic acid (4 mg IV annually) and alendronate (70 mg PO weekly) increase bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either zoledronic acid or alendronate is recommended when the absolute fracture risk warrants drug therapy.
- Screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended in men receiving ADT. These medical conditions are common in older men and it remains uncertain whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in men receiving ADT should differ from the general population.

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

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

PRINCIPLES OF CHEMOTHERAPY

- Patients with advanced prostate cancer should be encouraged to participate in clinical trials and referred early to a medical oncologist.
- Systemic chemotherapy should be reserved for patients with castration-recurrent metastatic prostate cancer except when studied in clinical trials.
- Based 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, and every 3-week mitoxantrone and prednisone.
- 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 ($p=.01$).
 - 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 ($p=.009$).
- Only regimens utilizing docetaxel on an every 3 week schedule demonstrated beneficial impact on survival. The duration of therapy should be based on the assessment of benefit and toxicities. In the pivotal trials establishing survival advantage of docetaxel-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted.
- Rising PSA should not be used as the sole criteria for progression. Assessment of response should incorporate clinical and radiographic criteria.
- Patients who have failed docetaxel-based chemotherapy should be encouraged to participate in clinical trials. However, cabazitaxel with prednisone has been shown in a randomized phase 3 study to prolong overall survival, progression-free survival, and PSA and radiologic responses when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second line setting. Selection of patients without severe neuropathy and adequate liver, kidney, and bone marrow function is necessary, given the high risk of neutropenia and other side effects in this population, with consideration of prophylactic granulocyte growth factor injections.
- Mitoxantrone has not demonstrated a survival improvement in this post-docetaxel setting but remains a palliative therapeutic option, particularly in men who are not candidates for cabazitaxel therapy. No chemotherapy regimen to date has demonstrated improved survival or quality of life following cabazitaxel, and trial participation should be strongly encouraged if appropriate. Outside of a trial, several systemic agents (for example, etoposide, estramustine, cyclophosphamide, navelbine, paclitaxel, others) have shown palliative benefits in single arm studies, but lack of controlled trials limits the ability to recommend one agent over another and treatment decisions should remain individualized in this setting based on comorbidities and functional status. Finally, for patients who have not demonstrated definitive evidence of progression on prior docetaxel therapy, retreatment with this agent can be attempted.
- In men with 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 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.

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**

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

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

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

Pathologic(pT)

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

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

Pathologic

PNX	Regional nodes not sampled
pN0	No positive regional nodes
pN1	Metastases in regional nodes(s)

Distant Metastasis (M)*

MX	Distant metastasis cannot be assessed (not evaluated by any modality)
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	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

Stage I	T1a	N0	M0	G1
Stage II	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
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.

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 *muicous, 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 is 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 05/27/10

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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 in men.¹ It is generally accepted that these changes resulted from prostate-specific antigen (PSA) screening that detected many early-stage prostate cancers. For example, the percentage of patients with low-risk disease has increased (45.3% in 1999-2001 compared with 29.8% in 1989-1992; $P < .0001$).² The incidence of prostate cancer increased 2.0% annually from 1995 to 2001, and has since declined. An estimated 192,280 new cases will be diagnosed in 2009, and prostate cancer is expected to account for 25% of new cancer cases in men in 2009.¹ Fortunately, the age-adjusted death rates from prostate cancer have also declined (-4.1% annually from 1994 to 2001).¹ Researchers expect prostate cancer to account for 27,360 deaths in

2009.¹ This comparatively low death rate suggests that unless prostate cancer is becoming biologically less aggressive, increased public awareness with earlier detection and treatment of prostate cancer has begun to affect mortality from this prevalent cancer. However, early detection and treatment of prostate cancers that do not threaten life expectancy results in unnecessary side effects, which impair quality of life and health care expenses, while decreasing the value of PSA and digital rectal exam as early detection tests.^{3,4}

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

Estimates of Life Expectancy (PROS-A)

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

preference. The primary management options for initial therapy for clinically localized prostate cancer include active surveillance, radical prostatectomy or radiotherapy.

Estimates of life expectancy have emerged as a key determinant of treatment decision-making, particularly when considering active surveillance (see below). While it is possible to estimate life expectancy for groups of men, it is more difficult to extrapolate these estimates to an individual patient. Life expectancy can be estimated using the Minnesota Metropolitan Life Insurance Tables or the Social Security Administration Life Insurance Tables.⁵ The life expectancy can then be adjusted for individual patients by adding or subtracting 50% based upon whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively. As an example, the Social Security Administration Life Expectancy for a 65 year old American man is 16.05 years. If judged to be in the upper quartile of health, a life expectancy of 24 years is assigned. If judged to be in the lower quartile of health, life expectancy of 8 years is assigned. Thus, treatment recommendations could change dramatically using the NCCN guidelines if a 65 year old man was judged to be in either very poor or excellent health. 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.⁶ Twelve independent predictors of mortality were identified, including 2 demographic measures (i.e. age and sex), 6 comorbid conditions (including body mass index), and difficulty with 4 functional variables.

Nomograms and Predictive Models

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

Predicting prognosis is essential for patient decision-making, treatment selection, and adjuvant therapy. These NCCN Guidelines incorporate a risk stratification scheme that uses a minimum of stage, grade, and PSA to assign patients to risk groups. These risk groups are used to select the appropriate options that should be considered for treatment and to predict the probability of biochemical failure (i.e., probability of a rising PSA, which is also termed *biochemical recurrence* or *PSA failure*) after definitive local therapy.⁷ This risk group stratification has been published widely and validated, and it provides a better basis for treatment recommendations than clinical stage alone.^{8,9}

The Partin tables^{10,11} were the first prediction method to achieve widespread use for counseling men with clinically localized prostate cancer. The tables combine clinical stage, biopsy Gleason grade, and preoperative PSA level to predict pathologic stage, assigned as one of four mutually exclusive groups: (1) organ confined; (2) extracapsular (i.e., extraprostatic) extension; (3) seminal vesicle invasion; or (4) lymph node metastasis.¹¹ The tables give the probability (95% confidence intervals) that a patient with a certain clinical stage, Gleason score, and PSA will have a cancer of each pathologic stage.

To quantify risk more accurately, one can devise a nomogram that incorporates the interactive effects of multiple prognostic factors to make accurate predictions about stage and prognosis for the individual patient. A nomogram is any predictive instrument that takes a set of input data (variables) and makes predictions about an outcome.

Nomograms predict more accurately for the individual patient than risk groups, because they combine the relevant prognostic variables, regardless of value. With risk group assignment, a cancer could be considered intermediate risk or high risk based on a single adverse prognostic factor. With nomograms, discordant values (e.g., high PSA but low Gleason sum and clinical stage) can be incorporated into a more accurate prediction. With any model, the more clinically relevant information that is used in the calculation of time to PSA failure, the more accurate the result.

Nomograms can be used to inform treatment decision-making for men contemplating active surveillance,¹² radical prostatectomy,¹³⁻¹⁵ neurovascular bundle preservation¹⁶⁻¹⁸ or omission of pelvic lymph node dissection during radical prostatectomy,¹⁹ brachytherapy^{13,20,21} or external beam radiation therapy.^{13,22} Biochemical progression-free survival can be reassessed post-operatively using age, diagnostic serum PSA, and pathologic grade and stage.^{6,23} Potential success of adjuvant or salvage radiation therapy after unsuccessful radical prostatectomy can be assessed using a nomogram.^{13,24}

None of the current models predict with perfect accuracy, and only some of these models predict metastasis^{6,13,25,26} and cancer-specific death.^{15,27} New independent prognostic factors are being developed.²⁸ Given the competing causes of mortality, many men who sustain PSA failure will not live long enough either to develop clinical evidence of distant metastases or to die from prostate cancer. Those with a short PSA doubling time are at greatest risk of death. Not all PSA failures are clinically relevant; thus, PSA doubling time may be a more useful

measure of risk of death.²⁹ Further refinement of the patient's risk of recurrent cancer is being investigated currently using molecular markers and other radiologic evaluations of the prostate. However, these approaches remain investigational and are not available currently or validated for routine application. The NCCN guideline panel recommends that NCCN risk categories are used to begin the discussion of options for the treatment of clinically localized prostate cancer and nomograms be used to provide additional and more individualized information.

Principles of Active Surveillance (PROS-B)

Active surveillance (also referred to as observation, watchful waiting, expectant management or deferred treatment) involves actively monitoring the course of the disease with the expectation to intervene if the cancer progresses. The high prevalence of prostate cancer upon autopsy of the prostate,³⁰ the high frequency of positive prostate biopsies in men with normal digital rectal exams and serum PSA values,³¹ the contrast between the incidence and mortality rates of the malignancy,¹ and the need to treat an estimated 48 men with screen-detected prostate cancer⁴ or 100 men with low-risk prostate cancer³² to prevent one death from the disease has fueled debate about the need to diagnose and treat every American man who has prostate cancer. The best models of prostate cancer detection and progression estimate that 23% - 42% of all U.S. screen-detected cancers are overtreated and that PSA detection was responsible for up to 6.9 years of lead-time bias.³³ The NCCN guideline panel has responded to these evolving data with careful consideration of which men should be recommended active surveillance – men with very low risk prostate cancer and life expectancy estimated < 20 years or men with low risk cancer and life expectancy estimated < 10 years.

However, the NCCN guideline panel recognizes the uncertainty associated with the estimation of chance of competing causes of death,

the definition of very low or low risk prostate cancer, the ability to detect disease progression without compromising chance of cure, and the chance and consequences of treatment side effects. Epstein et al. introduced clinical criteria to predict pathologically "insignificant" prostate cancer.³⁴ According to Epstein et al., insignificant prostate cancer is identified by: clinical stage T1c, biopsy Gleason score ≤ 6 , the presence of disease in fewer than 3 biopsy cores, and $\leq 50\%$ prostate cancer involvement in any core, and PSA density < 0.15 ng/mL/g. Despite the usefulness of these criteria, physicians are cautioned against using these as the sole decision maker. Studies have shown that as many as 8% of cancers that qualified as being insignificant using the Epstein criteria were not organ-confined based on postsurgical findings.^{23,35} A new nomogram may be better.³⁶ Although many variations upon this definition have been proposed (reviewed by Bastian et al.³⁷), a consensus of the NCCN guideline panel was reached that insignificant prostate cancer, especially when detected early using serum PSA, poses little threat to men with life expectancy < 20 years. The confidence that Americans with very low risk prostate cancer have a very small risk of prostate cancer death is enhanced by lead time bias introduced by PSA early detection that ranges from an estimated 12.3 years in a 55 year old man to 6 years in a 75 year old man.³⁸

Active surveillance is considered the best option for patients with low risk cancers or for patients with a short life expectancy. Recently, Lu-Yao and colleagues³⁹ reported that among patients who chose active surveillance, there was up to 74% reduction in disease-specific mortality for patients diagnosed between 1992 and 2002 compared to those diagnosed in earlier periods, when PSA testing was uncommon. The role for active surveillance should increase with the shift towards earlier-stage diagnosis attributed to PSA testing. However, results from randomized or cohort studies comparing this deferral strategy with immediate treatment are mixed, partly due to heterogeneity of the

patient populations (reviewed by Sanda and Kaplan⁴⁰). For example, a cohort of 3,331 participants showed no difference in the rate of metastases or disease-specific death at mean 7.7 years follow-up,⁴¹ while a randomized trial in 695 patients demonstrated a relative risk of 0.65 for both 12-year disease-specific mortality (95% CI, 0.45-0.94; $P = 0.03$) and distant metastases (CI, 0.47-0.88; $P = 0.006$) with active surveillance compared to radical prostatectomy.⁴² A recent clinical case presentation and poll with 3720 votes underscore the ongoing debate on the pros and cons of active surveillance and the difficulty to pin-point the optimal strategy for low risk disease.^{43,44} However, patients with high-risk disease have a better 5-year overall and disease-specific survival with active intervention than with observation until symptomatic⁴⁵ and these patients should not be observed unless aged and/or in poor health.

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

Patients and physicians involved in active surveillance must be aware that the PSA is likely to rise and that the tumor may grow with time. Patients should not be under the impression that the tumor will remain stable indefinitely and must be prepared to reevaluate the decision to defer treatment. Trigger points for intervention based on PSA, histologic progression, or clinical progression have been used.⁴⁶⁻⁴⁸ Whether these trigger points will ultimately be validated or not remains uncertain.

Patients must commit to a regular schedule of follow up, which includes DRE and PSA, and which may include repeat prostate needle biopsies, at frequencies outlined in PROS-B. 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, or if the PSA doubling time is less

than 3 years; in these situation, the NCCN guideline panel recommends treatment in most men.

The advantages of active surveillance include (1) avoiding the side effects of definitive therapy that may not be necessary; (2) quality of life and normal activities are retained; (3) small indolent cancers do not receive unnecessary treatment; and (4) decreased initial costs. The disadvantages of active surveillance are (1) chance of missed opportunity for cure; (2) the cancer may progress or metastasize before treatment; (3) treatment of a larger, more-aggressive cancer may be more complex with greater side effects; (4) nerve sparing at subsequent prostatectomy may be more difficult, which may reduce the chance of potency preservation after surgery; (5) the increased anxiety of living with an untreated cancer;⁴⁹ (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 active surveillance.

Principles of Radiation Therapy (PROS-C)

External Beam Radiation Therapy

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

Over the past several decades, RT techniques have evolved to allow higher doses of radiation to be administered safely. For example, standard 2-dimensional planning techniques used until the early 1990s

limited total doses to 67-70 Gy due to acute and chronic toxicities. In the 1990s, 3-dimensional planning techniques were developed that reduced the risk of acute toxicities and hence allowed treatment with higher doses. 3D-CRT uses computer software to integrate CT images of the patients' internal anatomy in the treatment position, which allows the volume receiving the high radiation dose to "conform" more exactly to the shape of the prostate. 3D-CRT allows higher cumulative doses to be delivered with lower risk of late effects.^{25,50-52} The second generation 3D technique, intensity-modulated radiation therapy (IMRT), is now state-of-the-art and required.

These techniques have permitted safer dose escalation, and results of randomized trials suggested that dose escalation is associated with improved biochemical outcomes.⁵³⁻⁵⁶ Kuban et al⁵⁶ recently published an updated analysis on their dose-escalation trial of 301 patients with stage T1b to T3 prostate cancer. With a median follow-up reaching 8.7 years, the authors reported superior freedom from biochemical or clinical failure in the group randomized to 78 Gy compared to 70 Gy (78% vs 59%, $P = 0.004$). The difference was even greater among patients with initial PSA > 10 ng/mL (78% vs 39%, $P = 0.001$). In light of these findings, the conventional 70 Gy is no longer considered adequate. A dose of 75.6-79 Gy in 36-41 conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Intermediate-risk and high-risk patients should receive doses between 75 and 80 Gy. For higher doses (above 75 Gy), daily prostate localization using daily image-guided radiation therapy (IGRT) is essential for target margin reduction and treatment accuracy. Imaging techniques, including ultrasound, implanted fiducials, electromagnetic targeting and tracking, or endorectal balloon, can be helpful in improving oncologic cure rates and minimizing complications.

One of the key aspects of RT planning includes identifying which patients will benefit from inclusion of pelvic lymph node irradiation and

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

External beam RT for prostate cancer shows several distinct advantages over surgical therapy. RT avoids complications associated with surgery, such as bleeding and transfusion-related effects as well as risks associated with anesthesia, such as myocardial infarction and pulmonary embolus. 3D-conformal and IMRT techniques are available widely in community practice and are possible for patients over a wide range of ages. This therapy includes a very low risk of urinary incontinence and stricture as well as a good chance of short-term preservation of erectile function.⁵⁷ Combined with ADT, radiation offers a survival benefit in locally advanced cancer, because treatments may eradicate extensions of tumor beyond the margins of the prostate.⁵⁸ However, the addition of ADT increases the risk for erectile dysfunction.⁵⁹

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.^{57,59} In addition, if the cancer recurs, salvage surgery is associated with a higher risk of complications

than primary surgical therapy.⁶⁰ Contraindications to RT include prior pelvic irradiation, active inflammatory disease of the rectum or a permanent indwelling Foley catheter. Relative contraindications include very low capacity bladder, chronic moderate or severe diarrhea, bladder outlet obstruction requiring a suprapubic catheter, and inactive ulcerative colitis.

Brachytherapy

Brachytherapy involves placing radioactive sources into the prostate tissue. Most 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 (over 90%) for low-risk tumors with medium-term follow up.⁶¹ 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.⁵⁹ Disadvantages of brachytherapy include the requirement for general anesthesia and the risk of acute urinary retention. Frequently, irritative voiding symptoms may persist for as long as 1 year after implantation. The risk of incontinence is greater

after TURP because of acute retention and bladder neck contractures, and many patients develop progressive erectile dysfunction over several years.

Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers, brachytherapy may be combined with external-beam RT (40-50 Gy) with or without neoadjuvant ADT, but the complication rate increases. Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy; however, with the addition of external-beam RT and ADT, brachytherapy may be effective in selected patients. D'Amico and colleagues studied a cohort of 1,342 patients with PSA over 20 ng/mL and clinical T3/T4 and/or Gleason score 8-10 disease.⁶² Addition of either external beam RT or ADT to brachytherapy did not confer an advantage over brachytherapy alone. But the use of all three reduced prostate cancer-specific mortality compared to brachytherapy alone (adjusted HR = 0.32; 95% CI, 0.14-0.73).

Patients with very large or very small prostates, symptoms of bladder outlet obstruction (high International Prostate Symptom Score), or a previous TURP are not ideal candidates for brachytherapy. For these patients, implantation may be more difficult and there is an increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size. Post-implant dosimetry should be performed to document the quality of the implant.⁶³ The recommended prescribed doses for monotherapy are 145 Gy for ¹²⁵Iodine and 125 Gy for ¹⁰³Palladium. After 40 to 50 Gy external-beam RT, the corresponding boost doses are 110 and 100 Gy, respectively.

Proton Therapy

Proton beams can be used as an alternative radiation source. Theoretically, protons may reach deeply-located tumors with less damage to surrounding tissues. However, proton therapy is not

recommended for routine use at this time, since clinical trials have not yet yielded data that demonstrates superiority or equivalence of proton beam compared to conventional external beam for treatment of prostate cancer.

Palliative Radiation

Radiation is an effective means of palliating bone metastases from prostate cancer. Recent studies have confirmed the common practice in Canada and Europe of managing prostate cancer with bone metastases with a short course of radiation.⁶⁴ A short course of 800 cGy x 1 is as effective and less costly than 3000 cGy in 10 fractions.⁶⁵ Most patients should be managed with a single fraction of 800 cGy for non-vertebral metastases based on therapeutic guidelines from the American College of Radiology.⁶⁶

Radiopharmaceuticals are an effective and appropriate option for patients with wide-spread metastatic disease, particularly if they are no longer candidates for effective chemotherapy.⁶⁶ Since many patients have multi-focal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Radiopharmaceuticals developed for the treatment of painful bone metastases most commonly used for prostate cancer include Strontium 89 (⁸⁹Sr) and Samarium 153 (¹⁵³Sm).⁶⁷

Principles of Surgical Therapy (PROS-D)

Radical Prostatectomy

Radical prostatectomy is appropriate therapy for any patient whose tumor is clinically confined to the prostate. However, because of potential perioperative morbidity, radical prostatectomy should be reserved for patients whose life expectancy is 10 years or more. This recommendation is consistent with data showing that fewer than 10% of low-grade patients with prostate cancer experience a cancer-specific death after 20 years of follow up.^{68,69} Stephenson and colleagues¹⁵

reported a low 15-year prostate cancer-specific mortality of 12% in patients who underwent radical prostatectomy (5% for low risk patients), although it is unclear whether the favorable prognosis is due to the effectiveness of the procedure or the low lethality of cancers detected in the PSA era.

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

Laparoscopic and robot-assisted radical prostatectomy are used commonly and are considered comparable to conventional approaches in experienced hands.^{70,71} In a recent cohort study using US Surveillance, Epidemiology, and End Results (SEER) Medicare-linked data on 8837 patients, minimally invasive surgery compared to open surgery was associated with shorter length of hospital stay, less need of blood transfusions, and fewer surgical complications, but rates of incontinence and erectile dysfunction were higher.⁷² Oncologic outcome assessed by use of additional therapies was similar.

Return of urinary continence after surgery may be improved by preserving the urethra beyond the prostatic apex and by avoiding damage to the distal sphincter mechanism. Anastomotic strictures that increase the risk of long-term incontinence are less frequent with modern surgical techniques. Recovery of erectile function is related directly to the degree of preservation of the cavernous nerves, age at surgery, and preoperative erectile function. Improvement in urinary function was also seen with nerve-sparing techniques.⁷³ For patients undergoing wide resection of the neurovascular bundles, replacement of resected nerves with nerve grafts does not appear effective.⁷⁴ Early pharmacologic stimulation of erection may improve late recovery of sexual function. Salvage radical prostatectomy may be considered an option for highly selected patients with local recurrence after external-beam RT, brachytherapy, or cryotherapy in the absence of

metastases; however, the morbidity (e.g., incontinence, loss of erections, anastomotic stricture) is high.

Pelvic Lymph Node Dissection (PLND)

The decision to perform PLND should be guided by the probability of nodal metastases. The NCCN guideline panel chose 2% as the cutoff for PLND since this avoids 47.7% of PLNDs at a cost of missing 12.1% of positive lymph nodes.⁷⁵

PLND should be performed using an extended technique. An extended PLND includes removal of all node bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic side wall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally. Removal of more lymph nodes has been associated with an increased likelihood of finding lymph node metastases, thereby providing more complete staging.⁷⁶⁻⁷⁸ A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to the elimination of microscopic metastases.^{77,79-81} PLND can be performed safely laparoscopically, robotically, or open, and complication rates should be similar for the three approaches.

Principles of Androgen Deprivation Therapy (PROS-E)

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.^{82,83}

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

Several alternative treatment regimens to continuous ADT have undergone limited study. Intermittent ADT is a widely used approach to reduce side effects and does not alter survival compared to continuous ADT, but its long-term efficacy remains unproven as large intergroup studies comparing intermittent and continuous ADT (SWOG 9346 and NCI Canada PR7) are still ongoing. 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 active surveillance patients with localized disease.⁸⁴ 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.⁸⁵⁻⁸⁹ ADT is also used routinely for metastatic disease. Earlier ADT will delay the appearance of symptoms and metastases, but whether earlier ADT will prolong survival is not clear. The complications of long-term ADT have not been documented adequately.

Patients with a rising PSA level and with no symptomatic or clinical evidence of cancer following definitive treatment present a therapeutic dilemma regarding the role of ADT. Some of these patients will ultimately die of their cancer. 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 unclear,⁹⁰ treatment should be individualized until definitive studies are completed. Patients with an elevated PSA and/or a shorter PSA doubling time (rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.

Studies on the benefit of adjuvant ADT in patients with positive pelvic lymph nodes reveal mixed findings. Messing and colleagues randomly assigned patients to immediate ADT (n=47) or observation (n=51) who were found to have positive lymph nodes at the time of radical prostatectomy.⁹¹ At a median follow-up of 11.9 years, those receiving immediate ADT had a significant improvement in overall survival (HR = 1.84; 95% CI, 1.01-3.35). The results of this trial have been called into question. A meta-analysis resulted in a recommendation against ADT for lymph node metastatic prostate cancer in the ASCO guidelines.⁹⁰ A recent cohort analysis of 731 men failed to demonstrate a survival benefit of ADT initiated within 4 months of radical prostatectomy compared to observation.⁹²

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 2006.⁹³ Patients with either localized (T1-2, N0) or locally advanced prostate cancer (T3-4, any N, or any 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 improved progression-free survival in patients with locally advanced prostate cancer, irrespective of primary therapy.

The results of the North American component of this trial have been reported separately.⁹⁴ 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.

Finally, ADT has been used commonly as primary therapy for early stage, low risk disease especially in the elderly. In a cohort study of 19,271 elderly men with localized prostate cancer (T1-T2), Lu-Yao and colleagues report no survival benefit in patients receiving ADT compared to observation alone;⁹⁵ placing elderly patients with prostate cancer on ADT should not be routine practice.

Adverse Effects of ADT

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. In general, the side effects of continuous ADT increase with the duration of treatment. Patients and their medical providers should be advised about these risks prior to treatment.

Osteoporosis is an important but under-appreciated problem in men worldwide.⁹⁶ In the United States, 2 million men have osteoporosis and another 12 million are at risk for the disease. Hypogonadism, chronic glucocorticoid therapy, and alcohol abuse are the major causes of acquired osteoporosis in men.

ADT is associated with greater risk for clinical fractures. In large population-based studies, for example, ADT was associated with a 21-54% relative increase in fracture risk.⁹⁷⁻⁹⁹ Longer treatment duration conferred greater fracture risk. Age and comorbidity were also associated with higher fracture incidence. ADT increases bone turnover and decrease bone mineral density,¹⁰⁰⁻¹⁰³ a surrogate for fracture risk. Bone mineral density of the hip and spine decreases by approximately 2-3% per year during initial therapy. Most studies have reported that bone mineral density continues to decline steadily during long-term therapy. ADT significantly decreases muscle mass.¹⁰⁴ and treatment-related sarcopenia appears to contribute to frailty and increased risk of falls in older men.

Screening and treatment for osteoporosis are recommended according to guidelines for the general population from the National Osteoporosis Foundation (www.nof.org). The National Osteoporosis Foundation guidelines include recommendations for (1) supplemental calcium (1,200 mg daily) and vitamin D3 (800-1,000 IU daily) for all men over age 50 years, and (2) additional treatment for men when the 10-year

probability of hip fracture is $\geq 3\%$ or the 10-year probability of a major osteoporosis-related fracture is $\geq 20\%$. Fracture risk can be assessed using the algorithm FRAX[®], recently released by the World Health Organization (<http://www.shef.ac.uk/FRAX/>). ADT should be considered "secondary osteoporosis" using the FRAX[®] algorithm.

Limited evidence exists about fracture prevention during ADT. Several small randomized controlled trials have demonstrated that bisphosphonates increase bone mineral density, a surrogate for fracture risk, during ADT. Intravenous pamidronate significantly decreased biochemical markers of bone turnover and increased bone mineral density of the hip and spine in men receiving GnRH agonist therapy.^{103,105} In a 12-month multicenter placebo-controlled study of 106 men with prostate cancer, intravenous zoledronic acid every 3 months increased bone mineral density of the hip and spine by a difference of 3.9% and 7.8%, respectively.¹⁰⁶ Similar results have been reported with annual zoledronic acid.¹⁰⁷ In a randomized, controlled trial of 112 men with prostate cancer, alendronate increased bone mineral density of the hip and spine by 2.3% and 5.1% after 12 months.¹⁰⁸ Currently, treatment with either zoledronic acid (4 mg IV annually) or alendronate (70 mg po weekly) is recommended when the absolute fracture risk warrants drug therapy.

Two large randomized controlled trials of novel agents to prevent bone loss and fractures during ADT were completed recently. One study demonstrated increased bone mineral density and reduced incidence of fractures with biannual denosumab, a novel human monoclonal antibody targeted receptor activator of NF- κ B ligand (RANKL).¹⁰⁹ The other study evaluated toremifene, a selective estrogen receptor modulator.^{110,111} Interim reports of the ongoing trial revealed improvements in bone density as well as lipid profiles in the toremifene arm compared to placebo.^{110,111}

In a landmark population-based study, ADT was associated with higher incidence of diabetes and cardiovascular disease.¹¹² After controlling for other variables, including age and comorbidity, ADT with a GnRH agonist was associated with a greater risk for new diabetes (HR 1.44; $P < 0.001$), coronary artery disease (HR 1.16; $P < 0.001$), and myocardial infarction (HR 1.11; $P = 0.03$). A subsequent large population-based study also reported a significant association between ADT and greater incidence of cardiovascular morbidity.¹¹³ Studies that have evaluated the potential relationship between ADT and cardiovascular mortality produced mixed results.^{112,114-118}

Several mechanisms may contribute to a greater risk for diabetes and cardiovascular disease during ADT. ADT increases fat mass and decreases lean body mass.^{104,119,120} ADT with a GnRH agonist increases fasting plasma insulin levels^{121,122} and decreases insulin sensitivity.¹²³ ADT also increases serum levels of cholesterol and triglycerides.^{121,124}

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

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.³¹ A separate NCCN guideline panel has written additional guidelines for prostate cancer early detection (see [NCCN Prostate Cancer Early Detection Guidelines](#)). Definitive diagnosis requires biopsies of the prostate, usually performed by the urologist using a needle under transrectal ultrasound guidance. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Clinical staging is based on the TNM 2002 classification from the AJCC (American Joint Committee on Cancer) (see [ST-1](#)).¹²⁵ The goals of NCCN treatment guidelines are to optimize cancer survival while minimizing treatment-related morbidity.

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The NCCN guideline panel is in favor of pathology synoptic reports from the College of American Pathologists (CAP).¹²⁶

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 ([PROS-1](#))

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, although staging studies may not be cost effective until the chance of lymph node positivity reaches 45%.¹²⁷ Biopsy should be considered for further evaluation of suspicious nodal findings. For all other patients, no additional imaging is required for staging.

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

Low Risk of Recurrence ([PROS-2](#))

As defined by the NCCN guidelines, patients with low risk for biochemical recurrence include those with tumors stage T1 to T2a, low Gleason score (≤ 6), and serum PSA level below 10 ng/mL. Although 40% of men older than 50 years of age harbor prostate cancer, only 1 in 4 present clinically, and only 1 in 14 will die of a prostate

cancer-specific death. Therefore, active surveillance is recommended for men with low-risk prostate cancer and life expectancy less than 10 years. Evidence for this approach is supported by data showing that the 5 to 10-year cancer-specific mortality is very low for most prostate cancers except those that are poorly differentiated.^{68,69,128}

If the patient's life expectancy is 10 years or more, the treatment recommendations also include radical prostatectomy with or without a pelvic lymph node dissection if the predicted probability of pelvic lymph node involvement is 2% or greater. A study by Johansson and colleagues assessed the long-term natural history of untreated, early-stage prostate cancer in 223 patients during 21 years of follow-up.¹²⁹ They found that most prostate cancers diagnosed at an early stage have an indolent course; however, local tumor progression and aggressive metastatic disease may develop in the long term. The mortality rate was significantly higher after 15 years of follow-up when compared with the first 5 years. Their findings support early radical prostatectomy, especially among patients with an estimated life expectancy exceeding 15 years. Radiation therapy using either 3D-CRT/IMRT with daily IGRT or brachytherapy is another option. Surgery, external beam RT and brachytherapy carry different side effects profile that will likely influence decision-making. An analysis of 475 men treated for localized disease revealed higher rates of incontinence and lower likelihood of regaining baseline sexual function, but lower rates of bowel dysfunction, after prostatectomy than after radiation.¹³⁰

ADT as a primary treatment for localized prostate cancer does not improve survival and is not recommended by the NCCN guideline panel.⁹⁵

Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that achieves damage to tumor tissue through local freezing. Based on different definitions of biochemical failure, the reported 5-year biochemical disease-free rate following

cryotherapy ranged from 65% to 92% in low-risk patients.¹³¹ However, this technique is not recommended as primary therapy due to lack of data from long-term studies for comparison with radiation and radical prostatectomy.

Very low risk of recurrence (PROS-2)

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

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

Intermediate Risk of Recurrence (PROS-3)

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

For these patients with a life expectancy of less than 10 years, active surveillance remains a reasonable option. Johansson and colleagues¹³² observed that only 13% of men developed metastases 15 years after diagnosis of T0-T2 disease and only 11% had died from prostate cancer. Treatment options include RT and radical prostatectomy. External-beam RT (3D-CRT/IMRT with daily IGRT with or without brachytherapy) may include neoadjuvant/concomitant/adjuvant ADT. ADT should be given as short term therapy for 4 to 6 months. Another option is radical prostatectomy with pelvic lymph node dissection unless the predicted probability of lymph node metastasis is < 2%.

Treatment options for patients with an expected survival of 10 years or more include RT and radical prostatectomy. Radical prostatectomy should include a pelvic lymph node dissection if the predicted probability of lymph node metastasis is 2% or greater. Radical prostatectomy was compared to watchful waiting in a randomized trial of 695 patients with early stage prostate cancer (mostly T2).⁴² With a median follow up of 11 years, those assigned to the radical prostatectomy group had significant improvements in disease specific mortality, overall mortality and risk of metastasis and local progressions. The results of this trial offer high quality evidence to support radical prostatectomy as a treatment option.

External-beam RT (3D-CRT/IMRT with daily IGRT with or without brachytherapy) with or without 4 to 6 months of neoadjuvant/concomitant/adjuvant ADT is another treatment option. Three randomized trials^{89,115,133} have evaluated whether 4 to 6 months

of ADT prolongs survival when added to external beam RT. Radiation Therapy Oncology Group (RTOG) 8610¹¹⁵ contained nearly all high-risk patients whereas Tran-Tasman Radiation Oncology Group (TROG) 9601⁸⁹ and Dana Farber Cancer Institute (DFCI) 95096¹³³ contained approximately 20% and 60% of men with intermediate-risk prostate cancer. Both an overall and cancer-specific survival benefit was noted in DFCI 95096¹³³, which had the highest proportion of men with intermediate-risk prostate cancer whereas a cancer-specific survival benefit only was noted in TROG 9601⁸⁹ and RTOG 8610¹¹⁵. Since none of these studies examined men with intermediate-risk disease only, the addition of short course ADT to RT in men with intermediate-risk disease is a viable option.

Brachytherapy as monotherapy is not recommended for this group of men. Risk stratification analysis has shown that brachytherapy alone is inferior to external-beam RT or radical surgery as measured by biochemical-free survival for patients who showed (1) a component of Gleason pattern 4 or 5 cancer, or (2) a serum PSA value greater than 10 ng/mL.⁹

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

High Risk of Recurrence (PROS-4)

Men with prostate cancer that is clinically localized stage T3a, Gleason score 8 to 10, or PSA level greater than 20 ng/mL are categorized by the NCCN guideline panel to be at high risk of recurrence after definitive therapy. Patients with multiple adverse factors may be shifted into the very high-risk category. The preferred treatment for this group is 3D-CRT/IMRT with daily IGRT in conjunction with long-term ADT; ADT alone is insufficient (category 1).¹³⁴ In particular, patients with low volume, high grade tumor warrant aggressive local radiation combined with typically 2-3 years of ADT.

Increasing evidence favors long-term over short-term neoadjuvant/concurrent/adjuvant ADT in high-risk patients. The RTOG 92-02 trial included 1,521 patients with T2c-T4 prostate cancer who received 4 months of ADT before and during RT.¹³⁵ They were randomized to no further treatment or an additional 2 years of ADT. At 10 years, the long-term group is superior for all end points except overall survival. A subgroup analysis of patients with Gleason score 8-10 found an advantage in overall survival for long-term ADT (32% vs 45%, $P = 0.0061$). The EORTC 22961 trial also showed superior survival when 2.5 years of ADT was added to RT given with 6 months of ADT in 970 patients, mostly with T2c-T3, N0 disease.¹³⁶

Radical prostatectomy with pelvic lymph node dissection remains an option in selected patients with no fixation to adjacent organs. For patients with Gleason scores of 8 or greater, a 36% progression-free survival rate has been reported after radical prostatectomy.¹³⁷

Very High Risk of Recurrence (PROS-4)

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

Metastatic Disease (PROS-4)

ADT or radiation plus neoadjuvant/concomitant/adjuvant ADT (2-3 years) are available options for patients with N1 disease, but only ADT is recommended for patients with M1 cancer.

Active Surveillance

Those electing active surveillance with life expectancy of 10 years or more might benefit from definitive local therapy if the cancer

progresses. Therefore, appropriate surveillance includes a PSA determination as often as every 3 months but at least every 6 months, a DRE as often as every 6 months but at least every 12 months, and a repeat prostate biopsy as often as annually. If the patient initially had a 10 to 12 core biopsy, repeat needle biopsy is not necessary for at least 18 months. (PROS-B) Surveillance may be less intense for those with a life expectancy < 10 years; PSA and DRE may be done less frequently (as often as every 6-12 months) and follow-up prostate biopsies are rarely necessary.

Repeat biopsy is recommended to determine whether higher-grade elements are evolving although the risks appear small¹³⁸, which may influence prognosis and, hence, the decision to continue active surveillance or to proceed to definitive local therapy. After an initial repeat biopsy, subsequent biopsies may be performed at the observing physician's discretion. 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. The criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression. If progressive disease is detected, the patient may require RT or radical prostatectomy.

Monitoring After Treatment (PROS-5)

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 10 years.¹³⁹ 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 6-12 months.

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

Adjuvant or Salvage Therapy after Radical Prostatectomy

Most patients who have undergone a radical prostatectomy are cured of prostate cancer. However, some men will suffer pathologic or biochemical failure. Selecting men appropriately for adjuvant or salvage radiation is difficult. However, recently published trials provide high level evidence that can be used to counsel patients more appropriately. Thompson and colleagues reported the results of the SWOG 8794 trial enrolling 425 men with extraprostatic cancer treated with radical prostatectomy. Patients were randomized to receive either adjuvant RT or usual care and follow-up has reached a median of 12.6 years.¹⁴⁰ The initial study report revealed that adjuvant RT reduced the risk of PSA relapse and disease recurrence.¹⁴¹ An update reported improved 10-year biochemical failure-free survival for high risk patients (seminal vesicle positive) receiving post-prostatectomy adjuvant radiation compared to observation (36% vs. 12%, $p = 0.001$).¹⁴² Most recently, SWOG 8794 has demonstrated improved overall and metastasis-free

survival.¹⁴⁰ Another randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC)¹⁴³ compared post-prostatectomy observation and adjuvant RT in 1,005 patients. All patients had extraprostatic extension and/or positive surgical margins. The 5-year biochemical progression-free survival significantly improved with RT compared to observation for patients with positive surgical margins (78% vs. 49%), but benefit was not seen for patients with negative surgical margins. Recently, a German study by Wiegel et al reported results on 268 patients.¹⁴⁴ All participants had pT3 disease and undetectable PSA levels after radical prostatectomy. Post-operative radiation improved 5-year biochemical progression-free survival compared to observation alone (72% vs. 54%; HR = 0.53; 95% CI, 0.37 – 0.79). Collectively, these trial results suggest that continued follow-up of these series of patients may show a survival advantage.

Based on these results, adjuvant RT after recuperation from surgery is likely beneficial in men with adverse pathologic features including positive margin, seminal vesicle invasion, and/or extracapsular extension. Positive surgical margins are especially unfavorable if diffuse (>10 mm margin involvement or ≥ 3 sites of positivity) or associated with persistent serum levels of PSA. If adjuvant RT is considered, it should be administered before the PSA exceeds 1.5 ng/mL. Adjuvant ADT should be considered for patients with positive lymph nodes found during surgery. However, the survival advantage reported for early and continuous ADT⁹¹ has been refuted by more recent reports.^{90,92} Therefore, observation is recommended until a detectable PSA develops, at which time clinical trials or ADT should be considered.

Several retrospective studies have assessed the prognostic value of various combinations of pretreatment PSA levels, Gleason scores, PSA doubling time and the presence or absence of positive surgical margins.¹⁴⁵⁻¹⁴⁹ A large retrospective review of 501 patients who

received salvage radiotherapy for detectable and increasing PSA after prostatectomy¹⁴⁸ showed that the predictors of progression were Gleason score 8-10, pre-RT PSA level greater than 2 ng/mL, seminal vesicle invasion, negative surgical margins and a PSA doubling time of 10 months or less. However, separation of men into those likely to have local recurrence versus systemic disease and hence response to postoperative radiation has proven not possible for individual patients using clinical and pathologic criteria.¹⁵⁰ Unfortunately, delivery of adjuvant or salvage RT becomes both therapeutic and diagnostic – PSA response indicates local persistence/recurrence. Delayed biochemical recurrence requires restaging and a new nomogram^{13,24} may prove useful to predict response but it has not yet been validated.

Men who suffer a biochemical recurrence following prostatectomy 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. Since PSA elevation alone does not necessarily lead to clinical failure,¹⁵¹ the workup for both of these groups focuses on the assessment of distant metastases (PROS-6). The specific tests depend on the clinical history, but potentially include a bone scan, biopsy, PSA doubling time assessment, CT/MRI or radioimmunologic scintigraphy (i.e. ProstaScint scan). Bone scans are appropriate when patients develop symptoms or 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.¹⁵²

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

acceptable for select patients. In all cases, the form of primary or secondary systemic therapy should be based on the hormonal status of the patient (PROS-7).

Post-irradiation Recurrence (PROS-7)

According to the 2006 Phoenix definition revised by ASTRO and the Radiation Therapy Oncology Group in Phoenix,¹⁵³ a rise in PSA by 2 ng/mL or more above the nadir PSA (defined as the lowest PSA achieved) is the current standard definition for biochemical failure after external beam RT with or without neoadjuvant ADT therapy. The date of failure should be determined "at call" and not backdated.

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

Further work up is indicated in patients who are considered candidates for local therapy. These patients include those with original clinical stage T1-2, a life expectancy of greater than 10 years, and a current PSA of less than 10 ng/mL.¹⁵⁴ Work up includes a prostate biopsy, bone scan, and additional tests as clinically indicated, such as an abdominal/pelvic CT, MRI, or a radioimmunologic scintigraphy (i.e. ProstaScint scan).

Options for primary salvage therapy for those with positive biopsy but low suspicion of metastases include observation or salvage prostatectomy in selected cases. Morbidity (including incontinence, erectile dysfunction, and bladder neck contracture) remains significantly higher than when radical prostatectomy is used as initial therapy.¹⁵⁵ Other options for localized interventions include cryotherapy¹⁵⁶ and brachytherapy (reviewed by Allen et al¹⁵⁷). Treatment, however, needs

to be individualized based upon the patient's risk of progression, the likelihood of success, and the risks involved with the therapy.

A negative biopsy following post-radiation biochemical recurrence poses clinical uncertainties. Observation, ADT, or enrolling in clinical trials are viable options. Alternatively, the patients may undergo more aggressive workup, such as repeat biopsy, MR spectroscopy, and/or endorectal MRI.^{158,159}

Patients with positive study results indicating metastatic disease or patients who are not initial candidates for local therapy should be observed or treated with ADT (PROS-7).

Systemic Therapy (PROS-8)

ADT using medical or surgical castration is the most common form of systemic therapy. In patients with radiographic evidence of metastases who are treated with LHRH agonist alone, "flare" in serum LH (luteinizing hormone) and testosterone levels may occur within the first several weeks after therapy is initiated, which may worsen the existing disease. Thus, LHRH agonist is often used in conjunction with antiandrogen for at least 7 days to diminish ligand binding to the androgen receptor.

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

Neuroendocrine differentiation should be considered in patients who do not respond to ADT. Those with an initial Gleason score of 9 or 10 are especially at risk. Thus, a biopsy of accessible lesions should be considered to identify patients with neuroendocrine differentiation who are managed with subsequent cytotoxic chemotherapy, such as cisplatin/etoposide or carboplatin/etoposide.¹⁶⁰

Systemic therapy after failure of primary androgen deprivation therapy (PROS-9)

Patients relapsing after primary ADT with castration-recurrent prostate cancer should receive a laboratory assessment to assure a castrate level of testosterone. A number of options for systemic therapy should be considered based on metastasis status. For patients without signs of metastasis (M0), clinical trial is the preferred choice and observation is the second option. For patients who have undergone CAB, the antiandrogen should be discontinued to exclude an "antiandrogen withdrawal response".^{161,162} Secondary hormonal therapy is also feasible in M0 patients since the androgen receptor may remain active. This can be achieved using an antiandrogen (for patients who initially received medical or surgical castration), ketoconazole (adrenal enzyme inhibitor) with or without glucocorticoids, or estrogens/progesterone.¹⁶³ However, none of these strategies has yet been shown to prolong survival in randomized clinical trials. Supportive care should be provided to all patients.

Systemic therapy for patients with metastatic prostate cancer (M1) includes bisphosphonates, systemic chemotherapy, immunotherapy, secondary hormonal therapy, or systemic RT using samarium or strontium (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),¹⁶⁴⁻¹⁶⁶ and every 3-week docetaxel and steroids is the preferred first-line chemotherapy treatment. PSA rise alone does not define docetaxel failure. If clinical progression is not apparent, the patient may benefit from continued chemotherapy. The addition of estramustine to docetaxel has been shown to increase side effects without enhancing efficiency and is not recommended.¹⁶⁷

Mitoxantrone with prednisone has been shown to provide palliative benefit in patients with painful bony metastases from castration-recurrent prostate cancer. However, its impact on survival as

second-line therapy after docetaxel has not been determined. The traditional option of glucocorticoids and external-beam 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.⁶⁷ The risk of bone marrow suppression, which might influence the ability to provide additional systemic chemotherapy, should be considered before this therapy is initiated.

Currently, no consensus exists for the best additional therapy following docetaxel failure in metastatic patients. Clinical trial enrollment is encouraged. Chemotherapy and best supportive care are both reasonable options.

Bisphosphonates and Prostate Cancer

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

In a pivotal multicenter study, 643 men with castration-recurrent prostate cancer and asymptomatic or minimally symptomatic bone metastases were assigned randomly to intravenous zoledronic acid (4 or 8 mg every 3 weeks) or placebo.¹⁶⁸ All men continued ADT (bilateral orchiectomies or treatment with a GnRH agonist) throughout the study and received additional antineoplastic therapy at the discretion of the investigator. The primary study endpoint was the proportion of men who experienced one or more skeletal-related events (pathological fracture,

spinal cord compression, surgery or radiation therapy to bone, or change in antineoplastic treatment to treat bone pain) by 15 months. Adverse renal events prompted 2 study amendments. In the first amendment, the infusion time for zoledronic acid was increased from 5 to 15 minutes. In the second amendment, the zoledronic dose in the 8 mg treatment group was reduced to 4 mg, serum creatinine monitoring was implemented prior to each dose, and the primary efficacy assessment became the comparison of the 4 mg group versus placebo.

At 15 months, fewer men in the zoledronic acid 4 mg group had skeletal-related events than men in the placebo group (33% versus 44%; $P=0.02$). An update at 24 months also revealed an increase in the median time to first skeletal-related event (488 days versus 321 days; $P=0.01$).¹⁶⁹ No significant differences were found in overall survival. Based on the results of this study, zoledronic acid (4 mg IV every 3–4 weeks) was approved to treat men with prostate cancer metastatic to bone and disease progression despite first line ADT.

Zoledronic acid should be initiated at reduced dose in men with impaired renal function (estimated creatinine clearance 30–60 ml/min). Treatment is not recommended for men with baseline creatinine clearance <30 ml/min. The optimal duration of zoledronic acid in men with castration-recurrent prostate cancer and bone metastases is undefined. Zoledronic acid and other bisphosphonates are associated with increased risk of osteonecrosis of the jaw (ONJ). Most but not all patients who develop ONJ have preexisting dental problems.^{170,171} Oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce risk of ONJ.¹⁷²

Clinical trials are in progress to define the potential role of zoledronic acid in men with newly diagnosed prostate cancer and bone metastases. Zoledronic acid or other bisphosphonates have not been shown to prevent bone metastases. Large randomized controlled trials

to evaluate the role of denosumab, a novel human monoclonal antibody targeted receptor activator of NF- κ B ligand (RANKL), for prevention and treatment of bone metastases in men with prostate cancer are ongoing.

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.

Discussion
update in
progress

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Discussion
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