

NCCN

Prostate Cancer, Version 2.2014

Clinical Practice Guidelines in Oncology

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Overview

Prostate cancer has surpassed lung cancer as the most common cancer in men. Experts generally accept that these changes resulted from prostate-specific antigen (PSA) screening that detected many early-stage prostate cancers. An estimated 233,000 new cases will be diagnosed in 2014, accounting for 27% of new cancer cases in men in 2014.¹ Fortunately, the age-adjusted death rates from prostate cancer have

Abstract

Prostate cancer has surpassed lung cancer as the most common cancer in men in the United States. The NCCN Guidelines for Prostate Cancer provide multidisciplinary recommendations on the clinical management of patients with prostate cancer based on clinical evidence and expert consensus. NCCN Panel guidance on treatment decisions for patients with localized disease is represented in this version. Significant updates for early disease include distinction between active surveillance and observation, a new section on principles of imaging, and revisions to radiation recommendations. The full version of these guidelines, including treatment of patients with advanced disease, can be found online at the NCCN website. (*J Natl Compr Canc Netw* 2014;12:686–718)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Prostate Cancer are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**

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Disclosures for the NCCN Prostate Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Prostate Cancer Panel members can be found on page 718. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

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declined (−4.1% annually from 1994 to 2001). Researchers have estimated prostate cancer to account for 29,480 deaths in 2014.¹ This comparatively low death rate suggests that, unless prostate cancer is becoming biologically less aggressive, increased public awareness with earlier detection and treatment has begun to affect mortality from this prevalent cancer. However, early detection and treatment of prostate cancers that do not threaten life expectancy result in unnecessary side effects, which impair quality of life and increase health care expenses, while decreasing the value of PSA and digital rectal exam (DRE) as early detection tests.

This guideline version includes NCCN Panel recommendations on treatment decisions for patients with localized disease. The full version of the guide-

line, including treatment of patients with advanced disease, can be found online at NCCN.org.

Estimates of Life Expectancy

Estimates of life expectancy have emerged as a key determinant of primary treatment, particularly when considering active surveillance or observation. Although estimating life expectancy for groups of men is possible, extrapolating these estimates to an individual patient is more difficult. Life expectancy can be estimated using the Minnesota Metropolitan Life Insurance Tables or the Social Security Administration Life Insurance Tables² and adjusted for individual patients by adding or subtracting 50% based on whether one believes the patient is in the healthiest

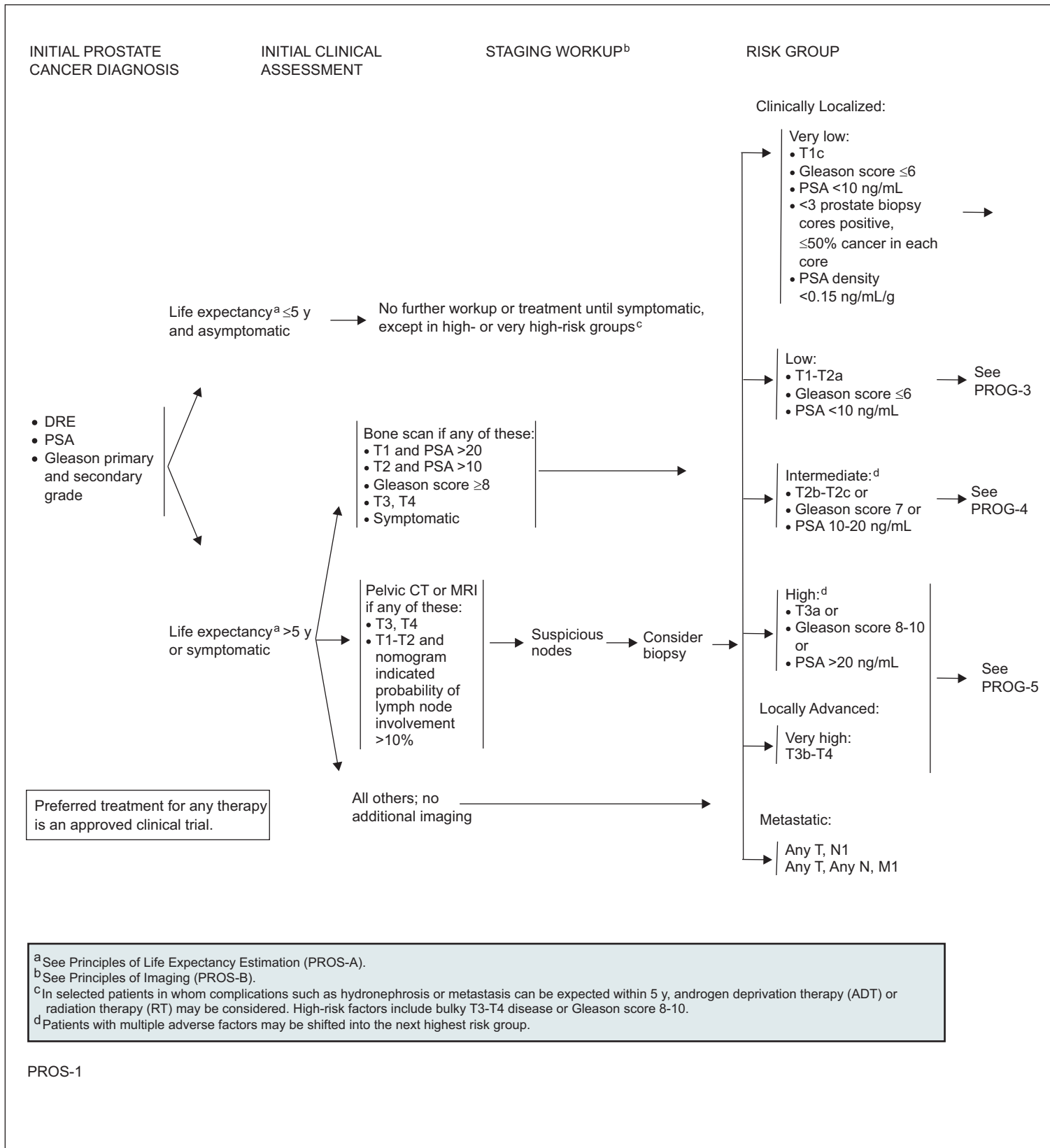
Text cont. on page 701.

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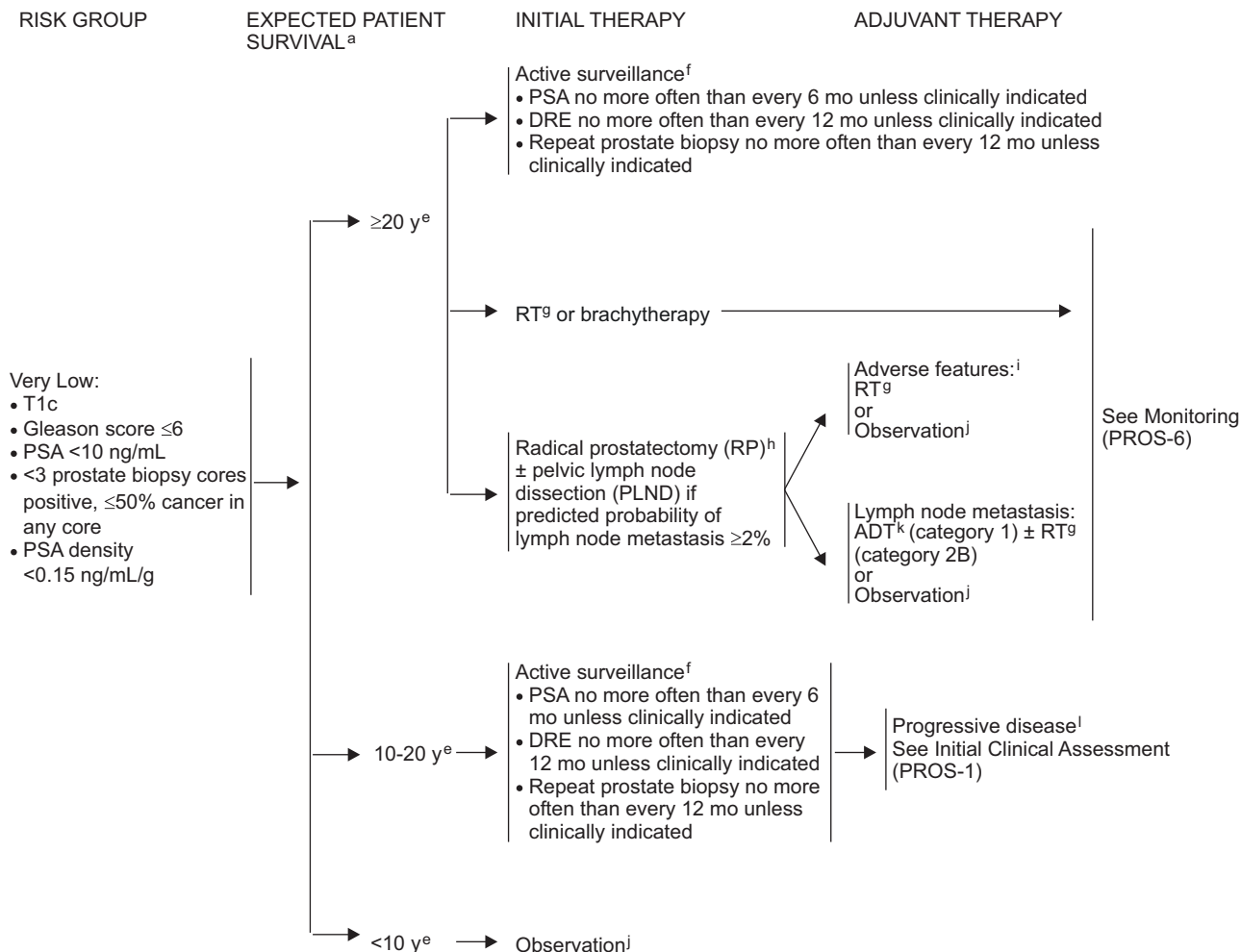
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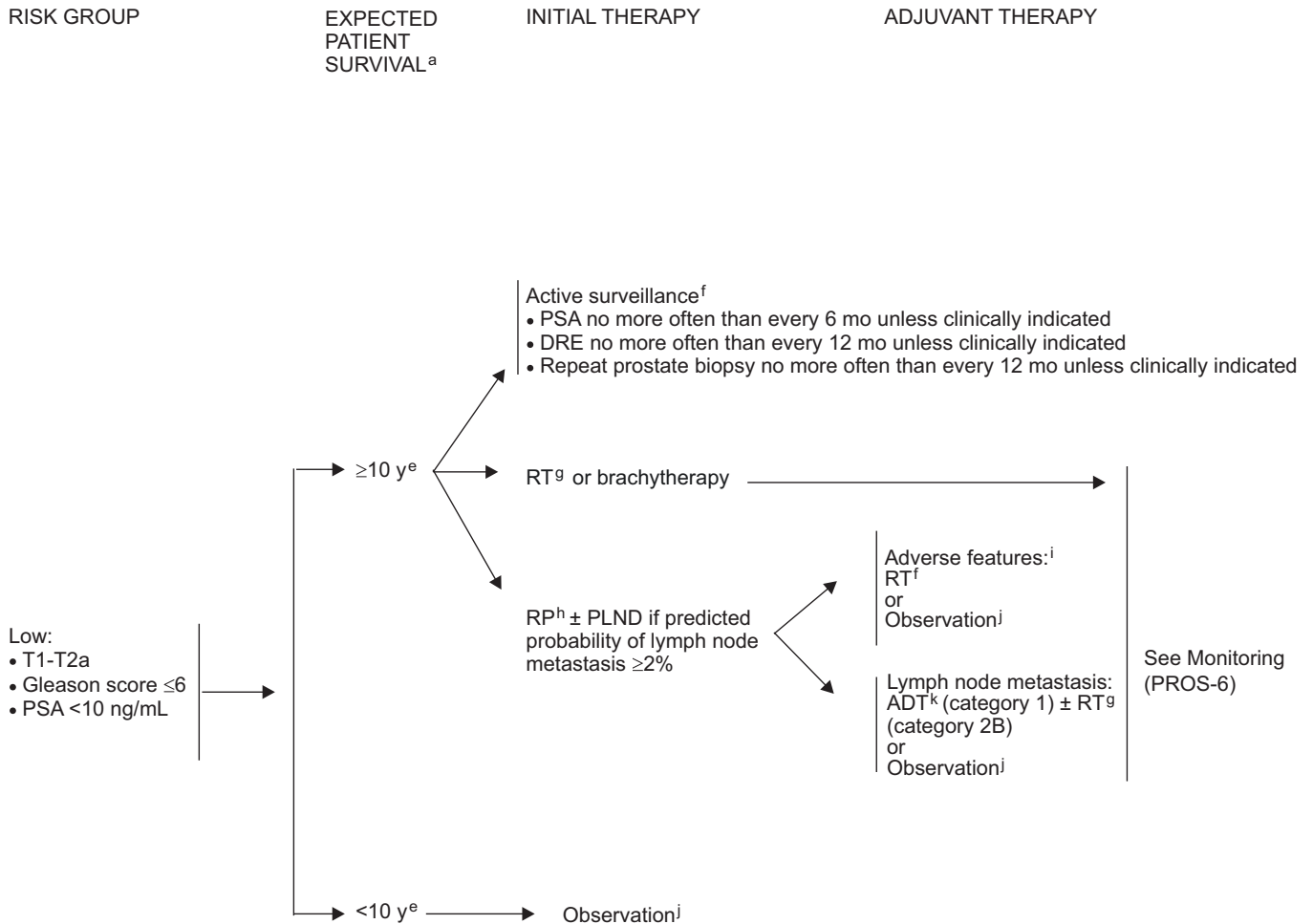
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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^aSee Principles of Life Expectancy Estimation (PROS-A).
^eThe Panel remains concerned about the problems of overtreatment related to the increased diagnosis of early prostate cancer from PSA testing. See the NCCN Guidelines for Prostate Cancer Early Detection (to view the most recent version of these guidelines, visit NCCN.org). Active surveillance is recommended for these subsets of patients.
^fActive surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See Principles of Active Surveillance and Observation (PROS-C).
^gSee Principles of Radiation Therapy (PROS-D).
^hSee Principles of Surgery (PROS-E).
ⁱAdverse laboratory/pathologic features include positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
^jObservation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in examination or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
^kSee Principles of Androgen Deprivation Therapy (PROS-F).
^lCriteria for progression are not well defined and require physician judgement; however, a change in risk group strongly implies disease progression.

PROS-2



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

^eThe Panel remains concerned about the problems of overtreatment related to the increased diagnosis of early prostate cancer from PSA testing. See the NCCN Guidelines for Prostate Cancer Early Detection (to view the most recent version of these guidelines, visit NCCN.org). Active surveillance is recommended for these subsets of patients.

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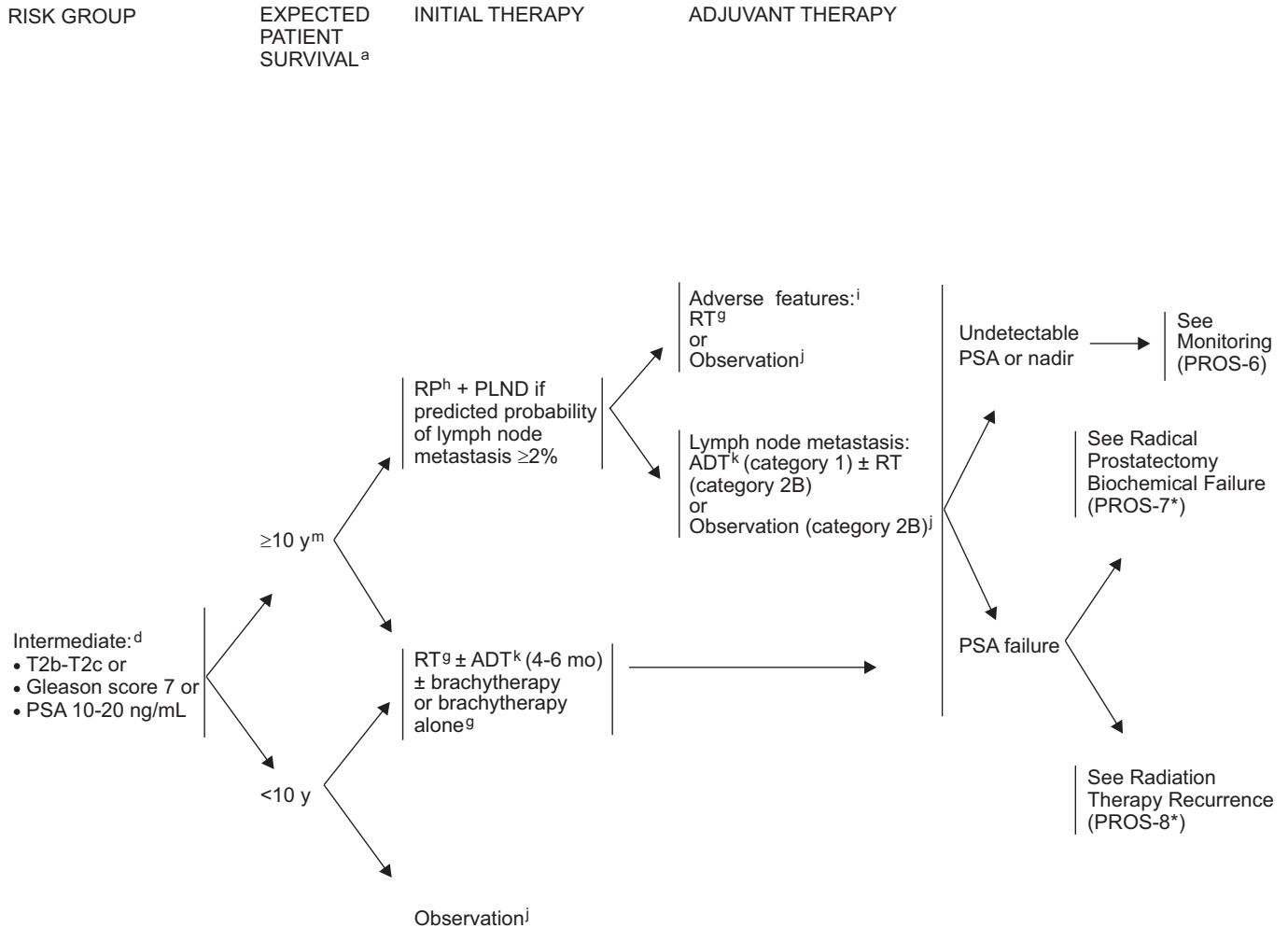
^jObservation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in examination or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).

^kSee Principles of Androgen Deprivation Therapy (PROS-F).

PROS-3

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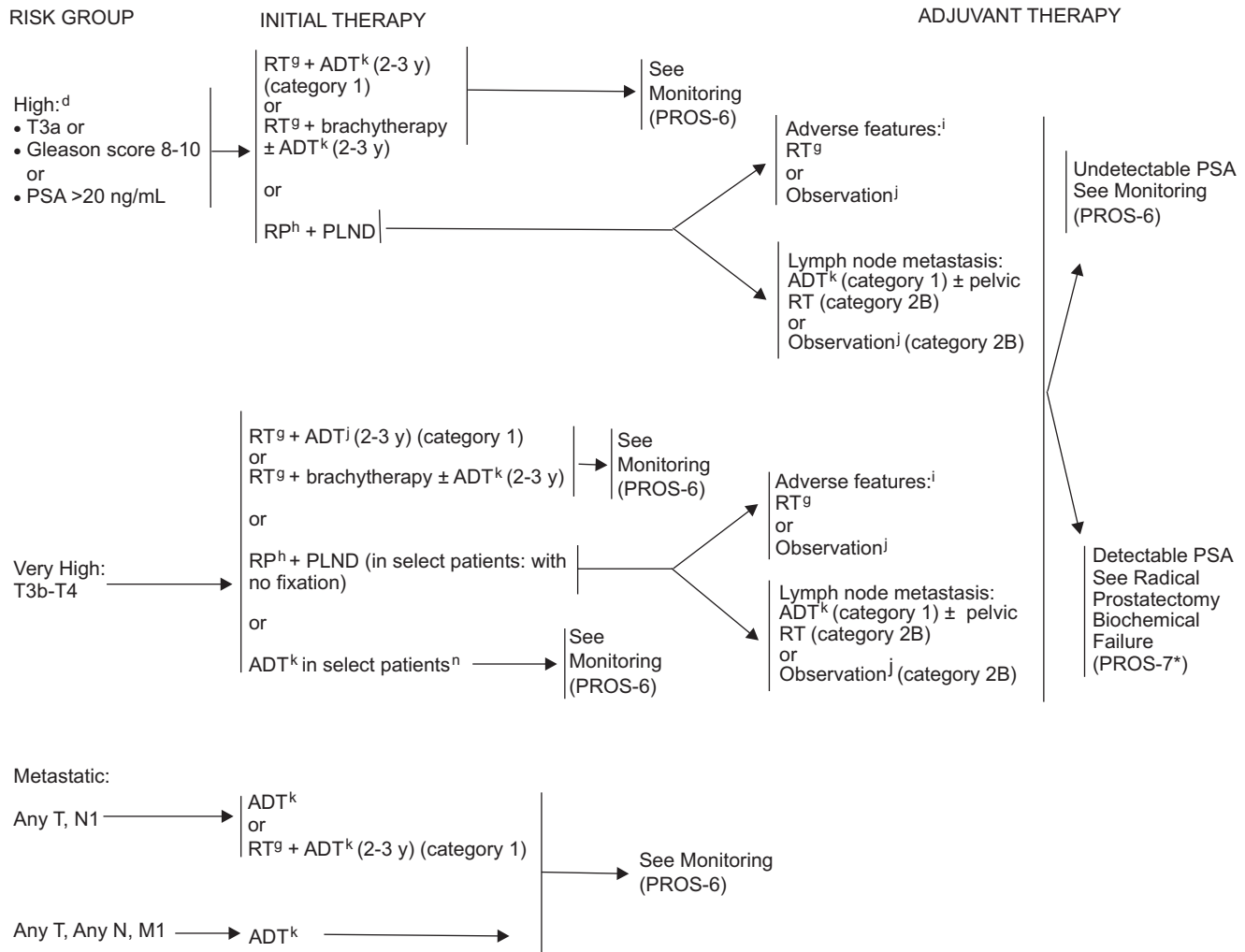
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*Available online, in these guidelines, at NCCN.org.

^aSee Principles of Life Expectancy Estimation (PROS-A).
^dPatients with multiple adverse factors may be shifted into the next highest risk group.
^gSee Principles of Radiation Therapy (PROS-D).
ⁱAdverse laboratory/pathologic features include positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
^jObservation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
^kSee Principles of Androgen Deprivation Therapy (PROS-F).
^mActive surveillance of intermediate- and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).

PROS-4



*Available online, in these guidelines, at NCCN.org.

^dPatients with multiple adverse factors may be shifted into the next highest risk group.

^gSee Principles of Radiation Therapy (PROS-D).

^hSee Principles of Surgery (PROS-E).

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

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

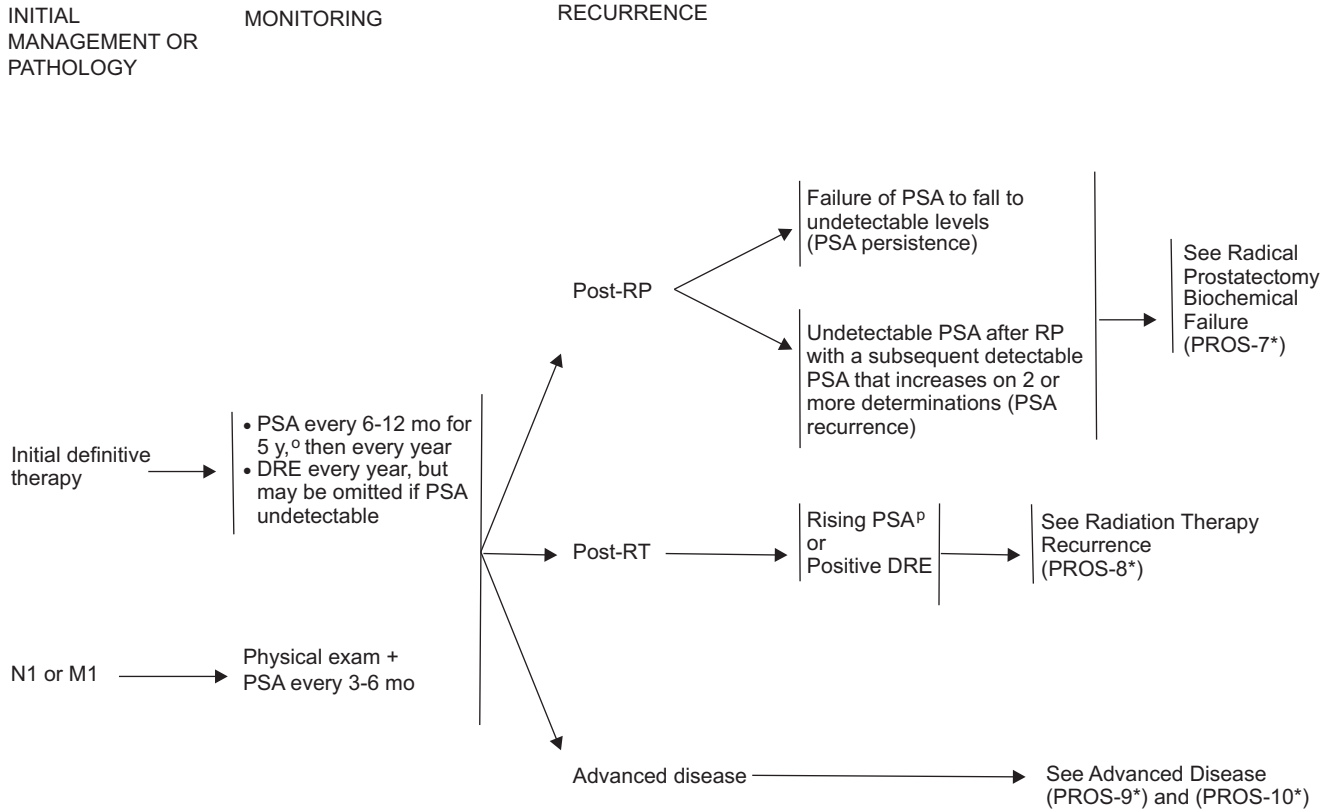
^kSee Principles of Androgen Deprivation Therapy (PROS-F).

ⁿPrimary therapy with ADT should be considered only for patients who are not candidates for definitive therapy.

PROS-5

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^oPSA as frequently as every 3 mo may be necessary to clarify disease status, especially in high-risk men.
^pRTOG-ASTRO (Radiation Therapy Oncology Group-American Society for Therapeutic Radiology and Oncology) Phoenix Consensus: 1) PSA rise by ≥ 2 ng/mL above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and 2) the date of failure is determined "at call" (not backdated). They recommended that investigators be allowed to use the ASTRO Consensus Definition after EBRT alone (with no hormonal therapy) with strict adherence to guidelines as to "adequate follow-up" to avoid the artifacts resulting from short follow-up. For example, if the median follow-up is 5 years, control rates at 3 years should be cited. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature.

PROS-6

PRINCIPLES OF LIFE EXPECTANCY ESTIMATION

- Life expectancy estimation is critical to informed decision-making in prostate cancer early detection and treatment.
- Estimation of life expectancy is possible for groups of men but challenging for individuals.
- Life expectancy can be estimated using the Social Security Administration tables (www.ssa.gov/OACT/STATS/table4c6.html).
- Life expectancy can then be adjusted using the clinician's assessment of overall health as follows:
 - Best quartile of health - add 50%
 - Worst quartile of health - subtract 50%
 - Middle 2 quartiles of health - no adjustment
- Example of 5-year increments of age are reproduced from the NCCN Guidelines for Senior Adult Oncology for life expectancy estimation (to view the most recent version of these guidelines, visit NCCN.org).¹

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

PRINCIPLES OF IMAGING

Goals of Imaging

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

Efficacy of Imaging

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

Plain Radiography

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

Ultrasound

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

Continued on next page

PROS-A
PROS-B
(1 of 3)

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PRINCIPLES OF IMAGING

Bone Scan

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

CT

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

MRI

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

PET/CT

- PET/CT using choline tracers may identify sites of metastatic disease in men with biochemical recurrence after primary treatment failure
 - Other choline radiotracers are under evaluation.
 - Further study is needed to determine the best use of choline PET/CT imaging in patients with prostate cancer.
- Oncologic PET/CT is performed typically using 18F-fluorodeoxyglucose (FDG), a radioactive analog of glucose.
 - In certain clinical settings, the use of FDG-PET/CT may provide useful information, but its routine use is not recommended at this time.
 - Data on the utility of FDG-PET/CT in patients with prostate cancer is limited.

PROS-B
(2 and 3)

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- The NCCN Prostate Cancer Panel and the NCCN Prostate Cancer Early Detection Panel (See NCCN Guidelines for Prostate Cancer Early Detection; available at NCCN.org) remain concerned about overdiagnosis and overtreatment of prostate cancer. The Panel recommends that patients and their physicians (eg, urologist, radiation oncologist, medical oncologist, primary care physician) consider active surveillance based on careful consideration of the patient's prostate cancer risk profile, age, and health.
- The 2014 NCCN Guidelines for Prostate Cancer distinguish between active surveillance and observation. Both involve at least every-6-month monitoring, but active surveillance may involve surveillance prostate biopsies. Evidence of progression will prompt conversion to potentially curative treatment in active surveillance patients, whereas monitoring continues until symptoms develop or are eminent (ie, PSA >100 ng/mL) in observation patients, who will then begin palliative ADT.
- Active surveillance is preferred for men with very low-risk prostate cancer and life expectancy ≤ 20 y. Observation is preferred for men with low-risk prostate cancer with a life expectancy <10 y. See Risk Group Criteria (PROS-2-PROS-5).
- Active surveillance involves actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses.
- Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or change in exam or PSA levels that suggest symptoms are imminent.
- Patients with clinically localized prostate cancers who are candidates for definitive treatment and choose active surveillance should have regular follow-up. Follow-up should be more rigorous in younger men than in older men. Follow-up should include:
 - PSA no more often than every 6 mo unless clinically indicated
 - DRE no more often than every 12 mo unless clinically indicated
 - Needle biopsy of the prostate should be repeated within 6 mo of diagnosis if initial biopsy was <10 cores or assessment discordant (eg, palpable tumor contralateral to side of positive biopsy)
 - A repeat prostate biopsy should be considered if prostate exam changes or PSA increases, but neither parameter is very reliable for detecting prostate cancer progression.
 - A repeat prostate biopsy should be considered as often as annually to assess for disease progression, because PSA kinetics may not be as reliable as monitoring parameters to determine progression of disease.
 - Repeat prostate biopsies are not indicated when life expectancy is <10 y or appropriate when men are undergoing observation.
 - PSADT seems to be unreliable for identifying progressive disease that remains curable. Although multiparametric MRI is not recommended for routine use, it may be considered if PSA increases and systematic prostate biopsy is negative to exclude the presence of an anterior cancer.
- Cancer progression may have occurred if:
 - Gleason grade 4 or 5 cancer is found on repeat prostate biopsy
 - Prostate cancer is found in a greater number of prostate biopsies or occupies a greater extent of prostate biopsies
- Advantages of active surveillance:
 - Avoidance of possible side effects of definitive therapy that may be unnecessary
 - Quality of life/normal activities potentially less affected
 - Risk of unnecessary treatment of small, indolent cancers reduced
- Advantages of observation:
 - Avoidance of possible side effects of unnecessary definitive therapy and early initiation and/or continuous ADT
- Disadvantages of active surveillance:
 - Chance of missed opportunity for cure
 - Risk of progression and/or metastases
 - Subsequent treatment may be more complex with increased side effects
 - Nerve sparing may be more difficult, which may reduce chance of potency preservation after surgery
 - Increased anxiety
 - Requires frequent medical exams and periodic biopsies, which are not without complications
 - Uncertain long-term natural history of prostate cancer
- Disadvantages of observation:
 - Risk of urinary retention or pathologic fracture without prior symptoms or concerning PSA level.

PROS-C

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PRINCIPLES OF RADIATION THERAPY*

Primary External-Beam Radiation Therapy (EBRT)

- Highly conformal RT techniques should be used to treat prostate cancer.
- Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate (\pm seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.
- Moderately hypofractionated image-guided IMRT regimens (2.4 to 4.0 Gy per fraction over 4-6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated.
- Extremely hypofractionated image-guided IMRT/SBRT regimens (≥ 6.5 Gy per fraction) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.
- Patients with high-risk cancers are candidates for pelvic lymph node irradiation and the addition of neoadjuvant/concomitant/adjuvant ADT for a total of 2-3 y (category 1).
- Patients with intermediate-risk cancer may be considered for pelvic lymph node irradiation and 4- to 6-mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with low-risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques of image-guided RT using CT, ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.

Primary/Salvage Brachytherapy

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

Post-Prostatectomy Radiation Therapy

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

*Principles of Rational Therapy on Radiopharmaceutical Therapy and Palliative Radiotherapy are available online, in these Guidelines, at NCCN.org.

PROS-D

PRINCIPLES OF SURGERY

Pelvic Lymph Node Dissection

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

Radical Prostatectomy

- RP is an appropriate therapy for any patient with clinically localized prostate cancer that can be completely excised surgically, who has a life expectancy of ≥ 10 years, and has no serious comorbid conditions that would contraindicate an elective operation.
- High-volume surgeons in high-volume centers generally provide better outcomes.
- Laparoscopic and robot-assisted RP are used commonly. In experienced hands, the results of these approaches seem comparable to those of open surgical approaches.
- Blood loss can be substantial with RP, but can be reduced by careful control of the dorsal vein complex and periprostatic vessels.
- Urinary incontinence can be reduced by preservation of urethral length beyond the apex of the prostate and avoiding damage to the distal sphincter mechanism. Bladder neck preservation may decrease the risk of incontinence. Anastomotic strictures increase the risk of long-term incontinence.
- Recovery of erectile function is directly related to age at RP, preoperative erectile function, and the degree of preservation of the cavernous nerves. Replacement of resected nerves with nerve grafts has not been shown to be beneficial. Early restoration of erections may improve late recovery.
- Salvage RP is an option for highly selected patients with local recurrence after EBRT, brachytherapy, or cryotherapy in the absence of metastases, but the morbidity (ie, incontinence, loss of erection, anastomotic stricture) is high.

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Localized Disease

- Neoadjuvant ADT for RP is strongly discouraged outside of a clinical trial.
- Giving ADT before, during, and/or after radiation prolongs survival in selected radiation managed patients.
- Studies of short-term (4-6 mo) and long-term (2-3 y) neoadjuvant ADT all have used complete androgen blockade. Whether the addition of an antiandrogen is necessary will require further studies.
- In the largest randomized trial to date using antiandrogen bicalutamide alone at high dose (150 mg), there were indications of a delay in recurrence of disease but no improvement in survival. Longer follow-up is needed.
- In one randomized trial, immediate and continuous use of ADT in men with positive nodes after RP resulted in significantly improved overall survival compared to men who received delayed ADT. Therefore, these patients should be considered for immediate ADT.
- Many of the side effects of continuous ADT are cumulative over time on ADT.

ADT for Biochemical Failure

- The timing of ADT for patients whose only evidence of cancer is an increasing PSA is influenced by PSA velocity, patient anxiety, and the short- and long-term side effects of ADT.
- Most patients will have a good 15-year prognosis, but their prognosis is best approximated by the absolute level of PSA, the rate of change in the PSA level (PSADT), and the initial stage, grade, and PSA level at the time of definitive therapy.
- Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Because the benefit of early ADT is not clear, treatment should be individualized until definitive studies are performed. Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.
- Some patients are candidates for salvage therapy after biochemical failure, which may include radiation after failed operation or RP, or cryosurgery after failed radiation.
- Men with prolonged PSADTs (>12 mo) and who are older are candidates for observation.
- Men who choose ADT should consider intermittent ADT. A phase III trial that compared intermittent to continuous ADT showed that intermittent ADT was not inferior to continuous ADT with respect to survival, and quality of life was better for the intermittent ADT arm. The 7% increase in prostate cancer deaths in the intermittent ADT arm was balanced by more non-prostate cancer deaths in the continuous ADT arm.

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Prostate Cancer, Version 2.2014

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Metastatic Disease

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

Optimal ADT

- LHRH agonist or antagonist (medical castration) and bilateral orchiectomy (surgical castration) are equally effective.
- Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides modest to no benefit over castration alone in patients with metastatic disease.
- Antiandrogen therapy should precede or be coadministered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.
- Antiandrogen monotherapy appears to be less effective than medical or surgical castration and should not be recommended. The side effects are different but overall more tolerable.
- No clinical data support the use of triple androgen blockade (finasteride or dutasteride with combined androgen blockade).
- Patients who do not achieve adequate suppression of serum testosterone (<50 ng/dL) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, or steroids), although the clinical benefit remains uncertain. The optimal level of serum testosterone decline has yet to be defined.

Secondary Hormonal Manipulation

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

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Monitor/Surveillance

- ADT has a variety of adverse effects including hot flashes, loss of libido and erectile dysfunction, shrinkage of penis and testicles, loss of muscle mass and strength, fatigue, depression, hair loss, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease. Patients and their medical providers should be advised about these risks prior to treatment.
- Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation (www.nof.org). The National Osteoporosis Foundation guidelines include recommendations for: 1) supplemental calcium (1200 mg/d) and vitamin D3 (800-1000 IU/d) for all men >50 y of age; and 2) additional treatment for men when the 10-y probability of hip fracture is $\geq 3\%$ or the 10-y probability of a major osteoporosis-related fracture is $\geq 20\%$. Fracture risk can be assessed using FRAX, the algorithm recently released by WHO. ADT should be considered “secondary osteoporosis” when using the FRAX algorithm. Treatment options to increase bone density, a surrogate for fracture risk, include denosumab (60 mg subcutaneously every 6 mo), zoledronic acid (5 mg intravenously annually), and alendronate (70 mg orally weekly).
- A baseline DEXA scan should be obtained before starting therapy in men at increased risk for fracture based on FRAX screening. A follow-up DEXA scan after 1 year of therapy is recommended by the International Society for Clinical Densitometry, although there is no consensus on the optimal approach to monitoring the effectiveness of drug therapy. Use of biochemical markers of bone turnover to monitor response to therapy is not recommended.
- The serum level of 25-hydroxy vitamin D and average daily dietary intake of vitamin D will assist the nutritionist in making a patient-specific recommendation for vitamin D supplementation. There are currently no guidelines on how often to monitor vitamin D levels. However, for those who require monitoring with DEXA scans, it makes sense to check the serum vitamin D level at the same time.
- Denosumab (60 mg subcutaneously every 6 mo), zoledronic acid (5 mg intravenously annually), and alendronate (70 mg orally weekly) increase bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either denosumab, zoledronic acid, or alendronate sodium is recommended when the absolute fracture risk warrants drug therapy.
- Screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended in men receiving ADT. These medical conditions are common in older men and it remains uncertain whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in men receiving ADT should differ from those for the general population.

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

Text cont. from page 687.

or unhealthiest quartile, respectively.³ As an example, the Social Security Administration Life Expectancy for a 65-year-old American man is 16 years. If he is judged to be in the upper quartile of health, a life expectancy of 24 years is assigned. If he is judged to be in the lower quartile of health, a life expectancy of 8 years is assigned. Thus, treatment recommendations could change dramatically using the NCCN Guidelines if a 65-year-old man was judged to be in either very poor or excellent health.

Risk Stratification

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 adjuvant or salvage radiation to control cancer after an unsuccessful radical prostatectomy? Prostate cancers are best characterized by clinical (TNM) stage determined by DRE, Gleason score in the biopsy specimen, and serum PSA level. Imaging studies (ultrasound, MRI) have been investigated intensively but have yet to be accepted as essential adjuncts to staging.

The 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 after definitive local therapy.⁴ Risk group stratification has been published widely and validated, and provides a better basis for treatment recommendations than clinical stage alone.^{5,6} The NCCN Prostate Cancer Panel recognized that heterogeneity exists within each risk group. For example, an analysis of 12,821 patients reported that men assigned to the intermediate-risk group by clinical stage (T2b–T2c) had a lower risk of recurrence than men categorized according to Gleason score (7) or PSA level (10–20 ng/mL).⁷ A similar trend of superior recurrence-free survival was seen in men placed in the high-risk group by clinical stage (T3a) compared with those assigned by Gleason score (8–10) or PSA level (>20 ng/mL), although it did not reach statistical significance.

The more clinically relevant information that is used in the calculation of time to PSA failure, the

more accurate the result. The Partin tables^{8,9} were the first to achieve widespread use for counseling men with clinically localized prostate cancer. 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. A nomogram is a 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. Nomograms can be used to inform treatment decision-making for men contemplating active surveillance,¹⁰ radical prostatectomy,^{11–13} neurovascular bundle preservation,^{14–16} or omission of pelvic lymph node dissection (PLND) during radical prostatectomy,¹⁷ brachytherapy,^{11,18,19} or external beam radiation therapy (EBRT).^{11,20} Biochemical progression-free survival can be reassessed postoperatively using age, diagnostic serum PSA, and pathologic grade and stage.^{21,22} Potential success of adjuvant or salvage radiation therapy (RT) after unsuccessful radical prostatectomy can be assessed using a nomogram.^{11,23}

None of the current models predict with perfect accuracy, and only some of these models predict metastasis^{11,22,24,25} and cancer-specific death.^{13,26} 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.²⁷ The NCCN Prostate Cancer Panel recommends that NCCN risk groups be used to begin discussing options for treatment of clinically localized prostate cancer and that nomograms be used to provide additional and more individualized information.

Imaging

Imaging techniques are useful for detecting metastases and tumor recurrence. Anatomic imaging techniques include radiographs, ultrasound, CT, and MRI. Functional techniques include radionuclide bone scan, PET, and advanced MRI such as spectroscopy and diffusion-weighted imaging.

Observation

Observation involves monitoring the course of prostate cancer with the expectation of providing palliative therapy when symptoms develop or a change in exam or PSA results suggest symptoms are imminent. Observation thus differs from active surveillance. The goal of observation is to maintain quality of life by avoiding noncurative treatment when prostate cancer is unlikely to cause mortality or significant morbidity. The main advantage of observation is avoiding possible side effects of unnecessary definitive therapy or androgen-deprivation therapy (ADT). But patients may be at risk for urinary retention or pathologic fracture without prior symptoms or increasing PSA level.

Observation is applicable to elderly men or frail patients with comorbidity that will likely out-compete prostate cancer. Johansson et al²⁸ noted that only 13% of men developed metastases 15 years after diagnosis of T0 to T2 disease and only 11% had died of prostate cancer. Since prostate cancer will not be treated for cure for patients with shorter life expectancies, observation for as long as possible is a reasonable option based on physician discretion. Monitoring should include PSA and DRE. When symptoms develop or are imminent, patients can begin palliative ADT.

Active Surveillance

Active surveillance (also referred to as *watchful waiting*, *expectant management*, or *deferred treatment*) involves actively monitoring the course of the disease with the expectation to intervene if the cancer progresses. Unlike observation, active surveillance is mainly applicable to younger men with seemingly indolent cancer with the goal of deferring treatment and potential side effects. Because these patients have a longer life expectancy, they should be followed closely and treatment should start promptly if the cancer progressed, to avoid missing the chance for cure.

The advantages of active surveillance include 1) avoiding the side effects of definitive therapy that may not be necessary; 2) retaining quality of life and normal activities; 3) ensuring that small indolent cancers do not receive unnecessary treatment; and 4) decreasing initial costs. The disadvantages of active surveillance include 1) chance of missed oppor-

tunity for cure; 2) chance 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 radical prostatectomy may be more difficult, which may reduce the chance of potency preservation after surgery; 5) increased patient anxiety of living with an untreated cancer;²⁹ 6) the requirement for frequent medical examinations and periodic prostate biopsies; 7) the uncertain long-term natural history of untreated prostate cancer; and 8) the timing and value of periodic imaging studies have not been determined.

Rationale

The panel remains concerned about the problems of overtreatment related to the increased frequency of diagnosis of prostate cancer from widespread use of PSA for early detection or screening (see NCCN Guidelines for Prostate Cancer Early Detection; available online at NCCN.org).

The debate about the need to diagnose and treat every man who has prostate cancer is fueled by the high prevalence of prostate cancer on autopsy of the prostate³⁰; the high frequency of positive prostate biopsies in men with normal DREs and serum PSA values³¹; the contrast between the incidence and mortality rates of prostate cancer; and the need to treat an estimated 37 men with screen-detected prostate cancer^{32,33} or 100 men with low-risk prostate cancer³⁴ to prevent one death from the disease. The controversy regarding overtreatment of prostate cancer and the value of prostate cancer early detection³²⁻³⁸ has been informed further by publication of the Göteborg study, a subset of the European Randomized Study for Screening of Prostate Cancer (ERSPC).³⁹ Many believe that this study best approximates proper use of PSA for early detection because it was population based and involved a 1:1 randomization of 20,000 men who received PSA every 2 years and used thresholds for prostate biopsy of PSA greater than 3 and greater than 2.5 since 2005. The follow-up of 14 years is longer than the European study as a whole (9 years) and Prostate, Lung, Colorectal, and Ovarian (PLCO) (11.5 years).

Prostate cancer was diagnosed in 12.7% of the screened group compared with 8.2% of the control group. Prostate cancer mortality was 0.5% in the screened group and 0.9% in the control group, which gave a 40% absolute cumulative risk reduction of

prostate cancer death (compared with ERSPC [20%] and PLCO [0%]). Most impressively, 40% of the patients were initially managed by active monitoring and 28% were still on active surveillance at the time these results were analyzed. To prevent a prostate cancer death, 12 men would need to be diagnosed and treated as opposed to the ERSPC in which 37 needed to be treated. Thus, early detection when applied properly should reduce prostate cancer mortality. However, that reduction comes at the expense of over-treatment that may occur in as many as 50% of men treated for PSA-detected prostate cancer.⁴⁰

The best models of prostate cancer detection and progression estimate that 23% to 42% of all screen-detected cancers in the United States are overtreated⁴¹ and that PSA detection was responsible for up to 12.3 years of lead-time bias.⁴² The NCCN Prostate Cancer Panel responded to these evolving data with careful consideration of which men should be recommended for active surveillance. However, the panel recognizes the uncertainty associated with the estimation of chance of competing causes of death, the definition of very low- or low-risk prostate cancer, the ability to detect disease progression without compromising chance of cure, and the chance and consequences of treatment side effects.

Application

Epstein et al⁴³ introduced clinical criteria to predict pathologically “insignificant” prostate cancer. Insignificant prostate cancer is identified by clinical stage T1c, biopsy Gleason score of 6 or lower, the presence of disease in fewer than 3 biopsy cores, 50% or less prostate cancer involvement in any core, and PSA density less than 0.15 ng/mL/g. Despite the usefulness of these criteria, physicians are cautioned against using these criteria as the sole decision point. Studies have shown that as many as 8% of cancers that qualified as *insignificant* using the Epstein criteria were not organ-confined based on postoperative findings.^{21,44}

A new nomogram may be better.⁴⁵ Although many variations on this definition have been proposed (reviewed by Bastian et al⁴⁶), the panel reached a consensus that insignificant prostate cancer, especially when detected early using serum PSA, poses little threat to men with life expectancy less than 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.⁴²

The role for active surveillance should increase with the shift toward earlier-stage diagnosis attributed to PSA testing. However, results from randomized or cohort studies comparing this deferral strategy with immediate treatment are mixed, partly due to heterogeneity of the patient populations (reviewed by Sanda and Kaplan⁴⁷).

Ultimately, a recommendation for active surveillance must be based on careful individualized weighing of a number of factors, including life expectancy, general health condition, disease characteristics, potential side effects of treatment, and patient preference. Race is emerging as another important factor to consider, since African-American men who meet the criteria of very low-risk have been reported to show higher rates of upgrading and adverse pathology compared with men of other races.⁴⁸

Surveillance Program and Reclassification Criteria

Each of the major active surveillance series has used different criteria for reclassification.^{49–53} Reclassification criteria were met by 23% of men with a median follow-up of 7 years in the Toronto experience,⁵¹ 33% of men with a median follow-up of 3 years in the Johns Hopkins experience,⁵³ and 16% of men with a median follow-up of 3.5 years in the UCSF experience⁵⁰ (Table 1). Uncertainty regarding reclassification criteria and the desire to avoid missing an opportunity for cure have driven several reports in the past year that have dealt with the validity of commonly used reclassification criteria. The Toronto group demonstrated that a PSA trigger point of a PSA doubling time less than 3 years could not be improved on using a PSA threshold of 10 or 20, PSA doubling time calculated in various ways, or PSA velocity greater than 2 ng/mL/yr.⁵⁴

The Johns Hopkins group used biopsy-demonstrated reclassification to Gleason pattern 4 or 5 or increased tumor volume on biopsy as their only criteria for reclassification. Of 290 men on an annual prostate biopsy program, 35% demonstrated reclassification at a median follow-up of 2.9 years.⁵⁵ Unfortunately, neither PSA doubling time (area under the curve [AUC], 0.59) nor PSA velocity (AUC, 0.61) was associated with prostate biopsy reclassification. Both groups have concluded that PSA kinetics cannot replace regular prostate biopsy, although

Table 1 Active Surveillance Experience in North America

Center	Toronto ⁵¹	Johns Hopkins ^{49,52,53}	UCSF ⁵⁰
Patients, n	450	769	531
Age, y	70	66	63
Median follow-up, mo	82	36	43
Overall survival	68%	98%	98%
Cancer-specific survival	97%	100%	100%
Conversion to treatment	30%	33%	24%
Reason for treatment			
Gleason grade change	8%	14%	38%
PSA increase	14%*	—	26%†
Positive lymph node	1%	—	—
Anxiety	3%	9%	8%

* PSA doubling time <3 years

† PSA velocity >0.75 ng/mL/year

Abbreviations: PSA, prostate-specific antigen; UCSF, University of California, San Francisco.

treatment of most men who show reclassification on prostate biopsy prevents evaluation of biopsy reclassification as a criterion for treatment or reduction of survival.

Repeat biopsy is useful to determine whether higher-grade elements are evolving although the risks appear small.⁵⁶ This may influence prognosis and, hence, the decision to continue active surveillance or to proceed to definitive local therapy. Treatment of all men who developed Gleason pattern 4 on annual prostate biopsies has thus far avoided a prostate cancer death among 769 men in the Johns Hopkins study.⁵³ However, whether treatment of all men who progressed to Gleason pattern 4 was necessary remains uncertain. Studies are in progress to identify the best trigger points at which interventions with curative intent may still be successful.

The Toronto group published on 3 patients who died of prostate cancer in their experience with 450 men.⁵¹ These 3 deaths led to them to revise their criteria for offering men active surveillance, since each of these 3 men probably had metastatic disease at the time of entry onto active surveillance. In 450 men followed for a median of 6.8 years, overall survival was 78.6% and prostate cancer-specific survival was 97.2%.⁵¹ Of the 30% (n=145) of men who progressed, 8% showed an increase in Gleason score, 14% showed PSA doubling time less than 3 years, 1% showed development of a prostate nodule, and 3% expressed anxiety. One hundred and thirty-five of these 145

men were treated; 35 by radical prostatectomy, 90 by RT with or without ADT, and 10 with ADT alone. Follow-up is available for 110 of these men, and 5-year biochemical progression-free survival is only 62% for those undergoing radical prostatectomy and 43% for those undergoing radiation.

By comparison, among 192 men on active surveillance who underwent delayed treatment at a median of 2 years after diagnosis in the Johns Hopkins experience,⁵³ 5-year biochemical progression-free survival was 96% for those undergoing radical prostatectomy and 75% for those undergoing radiation. These experiences contrast with the UCSF experience, in which 74 men who progressed on active surveillance and underwent radical prostatectomy were compared with 148 men who were matched by pathologic Gleason grade, pathologic stage, and margin positivity. All men treated using radical prostatectomy after progression on active surveillance had freedom from biochemical progression at a median follow-up of 37.5 months, compared with 97% of men in the primary radical prostatectomy group at a median follow-up of 35.5 months.

The panel believes there is an urgent need for further clinical research regarding the criteria for recommending active surveillance, the criteria for reclassification on active surveillance, and the schedule for active surveillance especially as it pertains to prostate biopsies, which unfortunately come within an increasing burden. Literature suggests that as many as 7% of men undergoing prostate biopsy will suffer an adverse event,³⁶ those with urinary tract infection are often fluoroquinolone-resistant,⁵⁷ and radical prostatectomy may become technically challenging after multiple sets of biopsies, especially as it pertains to potency preservation.⁵⁸

Radical Prostatectomy

Radical prostatectomy is appropriate 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. Stephenson et al¹³ 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.

Radical prostatectomy was compared with watchful waiting in a randomized trial of 695 patients with early-stage prostate cancer (mostly T2).⁵⁹ With a median follow-up of 12.8 years, those assigned to the radical prostatectomy group had significant improvements in disease-specific survival, overall survival, and risk of metastasis and local progression. Overall, 15 men needed to be treated to avert 1 death; that number fell to 7 for men younger than 65 years of age. The results of this trial offer high-quality evidence to support radical prostatectomy as a treatment option.

Some patients at high or very high risk may still benefit from radical prostatectomy. In an analysis of 842 men with Gleason scores 8 to 10 at biopsy who underwent radical prostatectomy, predictors of unfavorable outcome included PSA level over 10 ng/mL, clinical stage T2b or higher, Gleason score 9 or 10, higher number of biopsy cores with high-grade cancer, and over 50% core involvement.⁶⁰ Patients without these characteristics showed higher 10-year biochemical-free and disease-specific survival after radical prostatectomy compared with those with unfavorable findings (31% vs 4% and 75% vs 52%, respectively).

Radical prostatectomy is a salvage option for patients experiencing biochemical recurrence after primary RT, but morbidity (incontinence, erectile dysfunction, and bladder neck contracture) remains significantly higher than when radical prostatectomy is used as initial therapy.^{61,62} Overall and cancer-specific 10-year survival ranged from 54% to 89% and 70% to 83%, respectively.⁶¹

Operative Techniques and Adverse Effects

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.^{63,64} Laparoscopic and robot-assisted radical prostatectomy are used commonly and are considered comparable to conventional approaches in experienced hands.^{65,66} In a cohort study using US Surveillance, Epidemiology, and End Results (SEER) Medicare-linked data on 8837 patients, minimally invasive compared to open radical prostatectomy was associated with shorter length of hospital stay, less need for blood transfusions, and fewer surgical complications,

but rates of incontinence and erectile dysfunction were higher.⁶⁷ Oncologic outcome of a robotic versus open approach was similar when assessed by use of additional therapies⁶⁷ or rate of positive surgical margins,⁶⁸ although longer follow-up is necessary. A meta-analysis of 19 observational studies (n=3893) reported less blood loss and lower transfusion rates with minimally invasive techniques than with open surgery.⁶⁸ Risk of positive surgical margins was the same. Two recent meta-analyses showed a statistically significant advantage in favor of a robotic approach compared with an open approach in 12-month urinary continence⁶⁹ and potency recovery.⁷⁰

An analysis of the Prostate Cancer Outcomes Study on 1655 men with localized prostate cancer compared long-term functional outcomes after radical prostatectomy or RT.⁷¹ At 2 and 5 years, patients who underwent radical prostatectomy reported higher rates of urinary continence and erectile function but lower rates of bowel urgency. However, no significant difference was observed at 15 years. In a large retrospective cohort study involving 32,465 patients, patients who received RT had a lower 5-year incidence of urologic procedures than those who underwent radical prostatectomy but a higher incidence of hospital admissions, rectal or anal procedures, open surgical procedures, and secondary malignancies.⁷²

Return of urinary continence after radical prostatectomy may be improved by preserving the urethra beyond the prostatic apex and by avoiding damage to the distal sphincter mechanism. Bladder neck preservation may allow more rapid recovery of urinary control.⁷³ 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 also was seen with nerve-sparing techniques.⁷⁴ Replacement of resected nerves with nerve grafts does not appear to be effective for patients undergoing wide resection of the neurovascular bundles.⁷⁵

PLND

The decision to perform PLND should be guided by the probability of nodal metastases. The NCCN Prostate Cancer Panel chose 2% as the cutoff for

PLND because this avoids 47.7% of PLNDs at a cost of missing 12.1% of positive pelvic lymph nodes.⁷⁶

PLND should be performed using an extended technique.^{77,78} 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 using the extended technique has been associated with an increased likelihood of finding lymph node metastases, thereby providing more complete staging.^{79–81} A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to elimination of microscopic metastases.^{80,82–84} PLND can be performed safely laparoscopically, robotically, or open, and complication rates should be similar for the three approaches.

RT

EBRT

Over the past several decades, RT techniques have evolved to allow higher doses of radiation to be administered safely. Three-dimensional conformal radiation therapy (3D-CRT) uses computer software to integrate CT images of the patients' internal anatomy in the treatment position, which allows higher cumulative doses to be delivered with a lower risk of late effects.^{24,85–87} The second-generation 3D technique, intensity-modulated radiation therapy (IMRT), is used increasingly in practice⁸⁸ because compared with 3D-CRT it significantly reduces the risk of gastrointestinal toxicities and rates of salvage therapy without increasing side effects, although treatment cost is increased.^{89–91}

Daily prostate localization using image-guided RT is essential with either 3D-CRT or IMRT for target margin reduction and treatment accuracy. Imaging techniques such as ultrasound, implanted fiducials, electromagnetic targeting and tracking, and endorectal balloon, can improve cure rates and decrease complications.

These techniques have permitted safer dose escalation, and results of randomized trials have suggested that dose escalation is associated with improved biochemical outcomes.^{92–95} Kuban et al⁹⁵ published an analysis of their dose-escalation trial of 301 patients with stage T1b to T3 prostate cancer. Freedom

from biochemical or clinical failure was higher in the group randomized to 78 compared with 70 Gy (78% vs 59%; $P=.004$) at a median follow-up of 8.7 years. The difference was even greater among patients with diagnostic PSA greater than 10 ng/mL (78% vs 39%; $P=.001$). In light of these findings, the conventional 70 Gy dose is no longer considered adequate. A dose of 75.6 to 79.2 Gy in conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Patients at intermediate and high risk should receive doses up to 81.0 Gy.^{89,96,97} Moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) have been tested in randomized trials, and efficacy and toxicity have been similar to conventionally fractionated IMRT.^{98,99} These RT techniques can be considered as an alternative to conventionally fractionated regimens when clinically indicated.

EBRT of the primary prostate tumor shows several distinct advantages over radical prostatectomy. RT avoids complications associated with surgery, such as bleeding and transfusion-related effects, and risks associated with anesthesia, such as myocardial infarction and pulmonary embolus. IMRT and 3D-CRT techniques are available widely and are possible for patients at a wide range of ages. EBRT includes a low risk of urinary incontinence and stricture as well as a good chance of short-term preservation of erectile function.¹⁰⁰

The disadvantages of EBRT include a treatment course of 8 to 9 weeks. Up to 50% of patients have some temporary bladder or bowel symptoms during treatment. There is a low but definite risk of protracted rectal symptoms from radiation proctitis, and the risk of erectile dysfunction increases over time.^{100,101} In addition, if the cancer recurs, salvage radical prostatectomy is associated with a higher risk of complications than primary radical prostatectomy.¹⁰² Contraindications to RT include prior pelvic irradiation, active inflammatory disease of the rectum, or a permanent indwelling Foley catheter. Relative contraindications include very low bladder capacity, chronic moderate or severe diarrhea, bladder outlet obstruction requiring a suprapubic catheter, and inactive ulcerative colitis.

EBRT for Early Disease: EBRT is one of the principle treatment options for clinically localized prostate cancer. The NCCN Prostate Cancer panel con-

sensus was that modern RT and surgical series show similar progression-free survival in low-risk patients treated with radical prostatectomy or RT. In a study of 3546 patients treated with brachytherapy plus EBRT, disease-free survival remained steady at 73% between 15 and 25 years of follow up.¹⁰³

EBRT for High-Risk or Very High-Risk Patients:

EBRT has shown efficacy in patients at high risk and very high risk. One study randomized 415 patients to EBRT alone or EBRT plus 3-year ADT.¹⁰⁴ In another study (RTOG 8531), 977 patients with T3 disease treated with RT were randomized to adjuvant ADT or ADT at relapse.¹⁰⁵ Two other randomized phase III trials evaluated long-term ADT with or without radiation in mostly T3 patients.^{106,107} In all 4 studies, the combination group showed improved disease-specific and overall survival compared with single-modality treatment.

Stereotactic Body Radiotherapy

The relatively slow proliferation rate of prostate cancer is reflected in a low α/β ratio,¹⁰⁸ most commonly reported between 1 and 4. These values are similar to that for the rectal mucosa. Since the α/β ratio for prostate cancer is similar to or lower than the surrounding tissues responsible for most of the toxicity reported with RT, appropriately designed radiation treatment fields and schedules using extremely hypofractionated regimens should result in similar cancer control rates without an increased risk of late toxicity.

Stereotactic body radiotherapy (SBRT) is an emerging treatment technique that delivers highly conformal, high-dose radiation in 5 or fewer treatment fractions, which are safe to administer only with precise, image-guided delivery.¹⁰⁹ Single institution series with median follow-up as long as 6 years report excellent biochemical progression-free survival and similar early toxicity (bladder, rectal, and quality of life) compared with standard radiation techniques.^{108–114} According to a pooled analysis of phase II trials, the 5-year biochemical relapse-free survival rates are 95%, 84%, and 81% for low-, intermediate-, and high-risk patients, respectively.¹¹⁵ SBRT can be considered cautiously as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise. Longer follow-up and prospective multi-institutional data are required to evaluate longer-

term results, especially since late toxicity theoretically could be worse in hypofractionated regimens compared with conventional fractionation (1.8–2.0 Gy per fraction).

Brachytherapy

Brachytherapy is used traditionally for low-risk cases since earlier studies found it less effective than EBRT for high-risk disease.^{6,116} However, increasing evidence suggests that technical advancements in brachytherapy may provide a role for contemporary brachytherapy in high-risk localized and locally advanced prostate cancer.¹¹⁷ Brachytherapy involves placing radioactive sources into the prostate tissue. There are currently 2 methods for prostate brachytherapy: low dose-rate (LDR) and high dose-rate (HDR).

LDR Brachytherapy: LDR brachytherapy consists of placement of permanent seed implants in the prostate. The short range of the radiation emitted from these low-energy sources allows delivery of adequate dose levels to the cancer within the prostate, whereas excessive irradiation of the bladder and rectum can be avoided. Current brachytherapy techniques attempt to improve the radioactive seed placement and radiation dose distribution.

The advantage of brachytherapy is that the treatment is completed in 1 day with little time lost from normal activities. In appropriate patients, the cancer-control rates appear comparable to radical prostatectomy (over 90%) for low-risk tumors with medium-term follow-up.¹¹⁸ 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.¹⁰¹ Disadvantages of brachytherapy include the requirement for general anesthesia and the risk of acute urinary retention. Irritative voiding symptoms may persist for as long as 1 year after implantation. The risk of incontinence is greater after TURP because of acute retention and bladder neck contractures, and many patients develop progressive erectile dysfunction over several years. IMRT causes less acute and late genitourinary toxicity and similar freedom from biochemical failure compared with iodine-125 or palladium-103 permanent seed implants.^{119,120}

Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers (cT1c–T2a; Gleason grade, 2–6; PSA, <10 ng/mL). For intermediate-risk cancers, brachytherapy may be combined

with EBRT (45 Gy) with or without neoadjuvant ADT, but the complication rate increases.^{121,122} Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy.

Patients with very large or very small prostates, symptoms of bladder outlet obstruction (high International Prostate Symptom Score), or a previous TURP are not ideal candidates for brachytherapy. These patients have an increased risk of side effects, and implantation may be more difficult with them. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size, however, increased toxicity would be expected from ADT and prostate size may not decline. Postimplant dosimetry should be performed to document the quality of the implant.¹²³ The recommended prescribed doses for monotherapy are 145 Gy for iodine-125 and 125 Gy for palladium-103.

HDR Brachytherapy: HDR brachytherapy, which involves temporary insertion of a radiation source, is a newer approach that provides a “boost” dose in addition to EBRT for patients at high risk of recurrence. Combining EBRT (40–50 Gy) and HDR brachytherapy allows dose escalation while minimizing acute or late toxicity in patients with high-risk localized or locally advanced cancer.^{124–127} Studies have demonstrated reduced risk of recurrence with the addition of brachytherapy to EBRT.^{128–130} Analysis of a cohort of 12,745 patients at high risk found that treatment with brachytherapy (hazard ratio [HR], 0.66; 95% CI, 0.49–0.86) or brachytherapy plus EBRT (HR, 0.77; 95% CI, 0.66–0.90) lowered disease-specific mortality compared with EBRT alone.¹³¹ Common boost doses include 9.5 to 11.5 Gy times 2 fractions, 5.5 to 7.5 Gy times 3 fractions, or 4.0 to 6.0 Gy times 4 fractions. A commonly used regimen for HDR treatment alone includes 13.5 Gy times 2 fractions.

Addition of ADT (2 or 3 years) to brachytherapy and EBRT is common for patients at high risk of recurrence. The outcome of trimodality treatment is excellent, with 9-year progression-free survival and disease-specific survival reaching 87% and 91%, respectively.^{132,133} However, it remains unclear whether the ADT component contributes to outcome improvement. D’Amico et al¹³⁴ studied a cohort of 1342 patients with PSA over 20 ng/mL and clinical T3/T4 and/or Gleason score 8 to 10 disease. Addition of either EBRT or ADT to brachytherapy did not confer

an advantage over brachytherapy alone. The use of all 3 modalities reduced prostate cancer-specific mortality compared with brachytherapy alone (adjusted HR, 0.32; 95% CI, 0.14–0.73). Other analyses did not find an improvement in failure rate when ADT was added to brachytherapy and EBRT.^{135,136}

Two groups have observed a lower risk of urinary frequency, urgency, and rectal pain with HDR brachytherapy compared with LDR brachytherapy (permanent seed implant).^{137,138} Vargas et al¹³⁹ reported that HDR brachytherapy results in a lower risk of erectile dysfunction than LDR brachytherapy.

Proton Therapy

Proton beams can be used as an alternative radiation source.¹⁴⁰ The costs associated with proton beam facility construction and proton beam treatment are high.¹⁴¹ Two comparisons between proton beam therapy and EBRT show similar early toxicity rates.^{141,142} A single-center report of prospectively collected quality-of-life data 3 months, 12 months, and more than 2 years after treatment revealed significant problems with incontinence, bowel dysfunction, and impotence.¹⁴² Perhaps most concerning is that only 28% of men with normal erectile function maintained normal erectile function after therapy.

The NCCN panel echoed the following statement by ASTRO in its review of proton beam therapy:

“Prostate cancer has the most patients treated with conformal proton therapy of any other disease site. The outcome is similar to IMRT therapy, however, with no clear advantage from clinical data for either technique in disease control or prevention of late toxicity. This is a site where further head-to-head clinical trials may be needed to determine the role of proton beam therapy. In addition, careful attention must be paid to the role of dosimetric issues including correction for organ motion in this disease. Based on current data, proton therapy is an option for prostate cancer, but no clear benefit over the existing therapy of IMRT photons has been demonstrated.”¹⁴³

Other Local Therapies

Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that achieves damage to tumor tissue through local freezing. The reported 5-year biochemical disease-free rate after cryotherapy ranged from 65% to 92% in low-risk patients using different definitions of biochemical failure.¹⁴⁴ A report suggests that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer.¹⁴⁵ A study by Donnelly et al¹⁴⁶ randomly assigned 244 men with T2 or T3 disease to either cryotherapy or RT. All patients received neoadjuvant ADT. No difference was seen in 3-year overall or disease-free survival. Patients who received cryotherapy reported poorer sexual function.¹⁴⁷ For patients with locally advanced cancer, cryoablation was associated with lower 8-year biochemical progression-free rate compared with EBRT in a small trial of 62 patients, although disease-specific and overall survival were similar.¹⁴⁸

Other emerging local therapies, such as high intensity focused ultrasound and vascular-targeted photodynamic therapy, also warrant further study.¹⁴⁹

Androgen Deprivation Therapy

ADT for Low-Risk Patients

In the community, ADT has commonly been used as primary therapy for early-stage, low-risk disease, especially in the elderly. This practice was challenged in a study with a large cohort of 19,271 elderly men with T1 or T2 tumors.¹⁵⁰ No survival benefit was found in patients receiving ADT compared with observation alone. Placing elderly patients with early prostate cancer on ADT should not be routine practice.

ADT for Intermediate-Risk Patients

The addition of short-term ADT to radiation improved overall and cancer-specific survival in 3 randomized trials including 20% to 60% of men with intermediate-risk prostate cancer (Tran Tasman Radiation Oncology Group [TROG] 9601, Dana Farber Cancer Institute [DFCI] 95096, and Radiation Therapy Oncology Group [RTOG] 9408).^{151–153} Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly high-risk men (RTOG 8610).¹⁵⁴ The addition of short-course ADT to RT in men with intermediate-risk disease is an option.

ADT for High-Risk or Very High-Risk Patients

As discussed previously, ADT combined with RT is an effective primary treatment for patients at high risk or very high risk. Combination therapy was associated consistently with improved disease-specific and overall survival compared with single-modality treatment in randomized phase III studies.^{104–107}

Increasing evidence favors long-term over short-term neoadjuvant, concurrent, or adjuvant ADT for high-risk patients. The RTOG 9202 trial included 1521 patients with T2c to T4 prostate cancer who received 4 months of ADT before and during RT.¹⁵⁵ They were randomized to no further treatment or an additional 2 years of ADT. At 10 years, the long-term group was superior for all endpoints except overall survival. A subgroup analysis of patients with Gleason score 8 to 10 found an advantage in overall survival for long-term ADT (32% vs 45%; $P=.0061$). The EORTC 22961 trial also showed superior survival when 2.5 years of ADT were added to RT given with 6 months of ADT in 970 patients, most of whom had T2c to T3, N0 disease.¹⁵⁶ In a secondary analysis of RTOG 8531 that mandated lifelong ADT, those who adhered to the protocol had better survival than those who discontinued ADT within 5 years.¹⁵⁷

Adjuvant ADT after Radical Prostatectomy

Neoadjuvant or adjuvant ADT generally confers no added benefit in men who have undergone radical prostatectomy.¹⁵⁸ The role of adjuvant ADT after radical prostatectomy is restricted to cases in which positive pelvic lymph nodes are found, although reports in this area reveal mixed findings. Messing et al¹⁵⁹ randomly assigned patients to immediate ADT or observation who were found to have positive lymph nodes at the time of radical prostatectomy. 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). However, a meta-analysis resulted in a recommendation against ADT for pathologic lymph node metastatic prostate cancer in the ASCO guidelines.¹⁶⁰ A cohort analysis of 731 men with positive nodes failed to demonstrate a survival benefit of ADT initiated within 4 months of radical prostatectomy compared with observation.¹⁶¹

Anti-androgen monotherapy (bicalutamide) after completion of primary treatment was investigated as an adjuvant therapy in patients with localized

or locally advanced prostate cancer, but results did not support its use in this setting.^{162,163}

NCCN Recommendations

Initial Clinical Assessment and Staging Evaluation

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

For symptomatic patients or those with a life expectancy of more than 5 years, a bone scan is appropriate for patients with any of the following: 1) T1 disease with PSA over 20 ng/mL or T2 disease with PSA over 10 ng/mL;¹⁶⁴ 2) a Gleason score of 8 or higher; 3) T3 to T4 tumors; or 4) symptomatic disease. Pelvic CT or MRI scanning is recommended in T3 or T4 disease, or if T1 or T2 disease and a nomogram indicate that a greater than 10% chance of lymph node involvement, although staging studies may not be cost effective until the chance of lymph node positivity reaches 45%.¹⁶⁵ Biopsy should be considered for further evaluation of suspicious nodal findings. For all other patients, no additional imaging is required for staging. NCCN panelists voiced concern about inappropriate use of PET imaging in the community setting. FDG or fluoride PET is not recommended for initial assessment.

The staging workup is used to categorize patients according to their risk of recurrence or disease progression or recurrence into those with clinically localized disease at very low, low, intermediate, or high risk, or those with locally advanced disease at very high risk, or those with metastatic disease.

Very Low Risk

Men with all of the following tumor characteristics are categorized in the very low-risk group: clinical stage T1c, biopsy Gleason score 6 or lower, PSA lower than 10 ng/mL, presence of disease in fewer than 3 biopsy cores, 50% or less prostate cancer involve-

ment in any core, and PSA density less than 0.15 ng/mL/g. Given the potential side effects of definitive therapy, men in this group who have an estimated life expectancy less than 10 years should undergo observation. Unlike active surveillance, observation schedules do not involve biopsies. Men with very low risk and a life expectancy of 10 to 20 years should undergo active surveillance. For patients who meet the very low-risk criteria but who have a life expectancy of 20 years or above, the NCCN Panel agreed that active surveillance, RT or brachytherapy, or radical prostatectomy are all viable options.

Low Risk

The NCCN Guidelines define the low-risk group as patients with tumors stage T1 to T2a, low Gleason score (≤ 6), and serum PSA level below 10 ng/mL. Observation is recommended for men with low-risk prostate cancer and life expectancy less than 10 years. If the patient's life expectancy is 10 years or more, initial treatment options include 1) active surveillance; 2) RT or brachytherapy; or 3) radical prostatectomy with or without a PLND if the predicted probability of pelvic lymph node involvement is 2% or greater. ADT as a primary treatment for localized prostate cancer does not improve survival and is not recommended by the NCCN panel.

At this time, cryotherapy or other local therapies are not recommended as routine primary therapy for localized prostate cancer due to lack of long-term data comparing these treatments to radiation or radical prostatectomy.

Intermediate Risk

The NCCN Guidelines define the intermediate-risk group as 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.

Options for patients with life expectancy less than 10 years include 1) observation; 2) RT with or without ADT (4 to 6 months), and with or without brachytherapy; or 3) brachytherapy alone. Initial treatment options for patients with an expected survival of 10 years or more include 1) radical prostatectomy, including a PLND if the predicted probability of lymph node metastasis is 2% or greater; 2) RT with or without 4 to 6 months of ADT and with or without brachytherapy; or 3) brachytherapy alone for patients with favorable factors (cT1c, Gleason

score 7, low volume). Active surveillance is not recommended for patients with a life expectancy more than 10 years (category 1).

High Risk

Men with prostate cancer that is clinically localized stage T3a, Gleason score 8 to 10, or PSA level greater than 20 ng/mL are categorized by the NCCN Guidelines panel as high risk. Patients with multiple adverse factors may be shifted into the very high-risk category. The preferred treatment is RT in conjunction with 2 to 3 years of ADT (category 1); ADT alone is insufficient. In particular, patients with low-volume, high-grade tumor warrant aggressive local radiation combined with typically 2 or 3 years of ADT. The combination of EBRT and brachytherapy, with or without ADT (typically 2 or 3 years), is another primary treatment option. However, the optimal duration of ADT in this setting remains unclear.

Radical prostatectomy with PLND remains an option as a subset of men in the high-risk group may benefit from surgery.

Very High Risk

Patients at very high risk are defined by the NCCN Guidelines as those with clinical stage T3b to T4 (locally advanced). The options for this group include 1) RT and long-term ADT (category 1); 2) EBRT plus brachytherapy with or without long-term ADT; 3) radical prostatectomy plus PLND in selected patients with no fixation to adjacent organs; or 4) ADT for patients not eligible for definitive therapy.

Disease Monitoring

For patients who choose active surveillance, an appropriate active surveillance schedule includes a PSA determination no more often than every 6 months unless clinically indicated, a DRE no more often than every 12 months unless clinically indicated, and repeat prostate biopsy no more often than every 12 months unless clinically indicated. A repeat prostate biopsy within 6 months of diagnosis is indicated if the initial biopsy was less than 10 cores or if assessment results show discordance.

Reliable parameters of prostate cancer progression await the results of ongoing clinical trials. A change in prostate exam results or increase in PSA level may prompt consideration of a repeat biopsy at the discretion of the physician. A repeat biopsy can be considered as often as annually to assess for disease progression. Repeat biopsies are not indicated

when life expectancy is less than 10 years or when men are on observation. Multiparametric MRI may be considered to exclude the presence of anterior cancer if the PSA level rises and systematic prostate biopsy remains negative.¹⁶⁶ However, multiparametric MRI is not recommended for routine use. PSA doubling time is not considered reliable enough to be used alone to detect disease progression.¹⁶⁷

If the repeat biopsy shows Gleason 4 or 5 disease or if tumor is found in a greater number of cores or in a higher percentage of a given core, cancer progression may have occurred.

For patients initially treated with intent to cure, a serum PSA level should be measured every 6 to 12 months for the first 5 years and then annually. PSA testing every 3 months may be required for men at high risk of recurrence. When prostate cancer recurred after radical prostatectomy, Pound et al¹⁶⁸ found that 45% of patients experienced recurrence within the first 2 years, 77% within the first 5 years, and 96% by 10 years. Because local recurrence may result in substantial morbidity and can, in rare cases, occur in the absence of a PSA elevation, an annual DRE also is appropriate to monitor for prostate cancer recurrence as well as to detect colorectal cancer. Similarly, after RT, the monitoring of serum PSA levels is recommended every 6 months for the first 5 years and then annually and a DRE is recommended annually. The clinician may opt to omit the DRE if PSA levels remain undetectable.

The intensity of clinical monitoring for patients presenting with nodal positive or metastatic disease is determined by the response to initial ADT, radiotherapy, or both. Follow-up evaluation of these patients should include a history and physical examination, DRE, and PSA determination every 3 to 6 months based on clinical judgment.

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 for these patients. Supplementation is recommended using calcium (500 mg) and vitamin D (400 IU). Men who are osteopenic or osteoporotic should be considered for bisphosphonate therapy.

Patients under observation should be monitored for symptom development at 6 to 12 month intervals. PSA, renal function, and red cell mass may be assessed.

Adjuvant Therapy after Radical Prostatectomy

Most patients who have undergone a radical prostatectomy are cured of prostate cancer. However, some men will experience pathologic or biochemical failure. Selecting men appropriately for adjuvant or salvage radiation is difficult. However, recently published trials provide high-level evidence that can be used to counsel patients more appropriately. Thompson et al¹⁶⁹ reported the results of the SWOG 8794 trial enrolling 425 men with extraprostatic cancer treated with radical prostatectomy. Patients were randomized to receive either adjuvant RT or usual care, and follow-up has reached a median of 12.6 years. The initial study report revealed that adjuvant RT reduced the risk of PSA relapse and disease recurrence.¹⁷⁰ An update reported improved 10-year biochemical failure-free survival for high-risk patients (seminal vesicle positive) receiving postprostatectomy adjuvant radiation compared with observation (36% vs 12%; $P=.001$).¹⁷¹

Another randomized trial conducted by the EORTC¹⁷² compared postprostatectomy observation and adjuvant RT in 1005 patients. All patients had extraprostatic extension or positive surgical margins. The 5-year biochemical progression-free survival significantly improved with RT compared with observation for patients with positive surgical margins (78% vs 49%), but benefit was not seen for patients with negative surgical margins.

A German study by Wiegel et al¹⁷³ reported results for 268 patients. All participants had pT3 disease and undetectable PSA levels after radical prostatectomy. Postoperative radiation improved 5-year biochemical progression-free survival compared with observation alone (72% vs 54%; HR, 0.53; 95% CI, 0.37–0.79). Collectively, these trial results suggest that continued follow-up of these series of patients may show a survival advantage.

Although observation after radical prostatectomy is appropriate, adjuvant RT after recuperation from surgery (usually within 1 year) is likely beneficial in men with shorter PSA doubling times (<9 months) or adverse laboratory or pathologic features, which include positive surgical margin, seminal vesicle invasion, and extracapsular extension. Positive surgical margins are unfavorable especially if diffuse (>10 mm margin involvement or ≥ 3 sites of positivity) or associated with persistent serum levels of PSA. The defined target volumes include the prostate bed.

The pelvic lymph nodes may be irradiated, but pelvic radiation is not necessary.

Several management options should be considered if positive lymph nodes are found during or after radical prostatectomy. ADT is a category 1 option. Another option is observation, which is a category 2A recommendation for very low-risk or low-risk patients but category 2B for patients at intermediate, high, or very high risk. A third option is addition of pelvic RT to ADT (category 2B). This is based on retrospective data demonstrating improved biochemical recurrence-free survival and cancer-specific survival with postprostatectomy RT and ADT compared with adjuvant ADT alone in 250 patients with lymph node metastases.¹⁷⁴

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Individual Disclosures for the NCCN Prostate Cancer Panel					
Panel Member	Clinical Research Support/Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Andrew J. Armstrong, MD, ScM	Active Biotech AB; Bristol-Myers Squibb Company; Dendreon Corporation; ImClone Systems Incorporated; Johnson & Johnson; Novartis Pharmaceuticals Corporation; KangLaiTe USA; Medivation, Inc.; Pfizer Inc.; and sanofi-aventis U.S.	Amgen Inc.; Bayer HealthCare; Bristol-Myers Squibb Company; Dendreon Corporation; Johnson & Johnson; Ipsen; and sanofi-aventis U.S.	None	None	5/15/13
Robert R. Bahnson, MD	AVEO Pharmaceuticals, Inc.	AVEO Pharmaceuticals, Inc.	None	None	11/22/13
Michael Cohen, MD	None	Myriad Genetic Laboratories, Inc.; LivingstonBarger; Otorowski, et al.; and Simmons Ferrine et al.	None	None	6/26/13
Anthony Victor D'Amico, MD, PhD	None	None	None	None	4/9/14
James A. Eastham, MD	None	None	None	None	10/8/12
Charles A. Enke, MD	None	Myriad Genetic Laboratories, Inc.	None	None	5/23/13
Thomas A. Farrington, BSEE	None	None	None	None	8/6/12
Celestia S. Higano, MD	Bayer HealthCare; Exelixis Inc.; Genentech, Inc.; Millennium Pharmaceuticals, Inc.; Aragon Pharmaceuticals Inc.; Medivation, Inc.; and Teva Pharmaceutical Industries Ltd.	Abbott Laboratories; Bayer HealthCare; Genentech, Inc.; Johnson & Johnson; Millennium Pharmaceuticals, Inc.; Ferring Pharmaceuticals Inc.; Medivation, Inc.; and Pfizer Inc.	None	Dendreon Corporation; and Veridex, LLC	11/11/13
Eric Mark Horwitz, MD	None	None	None	None	6/5/13
Christopher J. Kane, MD	Genentech, Inc.	Dendreon Corporation; Genomic Health, Inc.; Janssen Pharmaceutica Products, LP; Myriad Genetic Laboratories, Inc.; and sanofi-aventis U.S.	None	None	4/21/14
Philip W. Kantoff, MD	Bavarian Nordic Immunotherapy (BN-IT); OncoGenex Pharmaceuticals Inc.; and Takeda Pharmaceuticals North America, Inc.	Amgen Inc.; Bayer HealthCare; Celgene Corporation; Dendreon Corporation; Exelixis Inc.; Genomic Health, Inc.; Janssen Pharmaceutica Products, LP; Millennium Pharmaceuticals, Inc.; Aragon Pharmaceuticals; Archimedes Pharma US, Inc.; Astellas US LLC; Auvon Therapeutics; Bellicum Pharmaceuticals, Inc.; BIND Biosciences, Inc.; Blend Therapeutics, Inc.; BN ImmunoTherapeutics, Inc.; Endocyte/TRM Oncology; GTX, Inc.; Medivation, Inc.; Metamark Genetics, Inc.; MorphoSys AG; OncoCellMDX; OncoGenex Pharmaceuticals Inc.; Progenics Pharmaceuticals, Inc.; SOTIO, LLC; Teva Oncogenix; Tokai Pharmaceuticals, Inc.; Pfizer Inc.; and sanofi-aventis U.S.	None	None	4/15/14
Mark H. Kawachi, MD	None	None	None	None	6/20/13
Michael Kuettel, MD, MBA, PhD	None	None	None	None	10/9/12
Timothy M. Kuzel, MD	Bayer HealthCare; Bristol-Myers Squibb Company; CureTech Ltd.; Eli Lilly and Company; GlaxoSmithKline; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; Alton Pharmaceuticals, Inc.; Argos Therapeutics, Inc.; AVEO Pharmaceuticals, Inc.; and Biovex, Inc./Amgen	Boehringer Ingelheim GmbH; Celgene Corporation; Genentech, Inc.; Janssen Pharmaceutical Products, LP; Elorac, Inc.; Prometheus Laboratories; and Pfizer Inc.	None	None	7/3/13
Richard J. Lee, MD, PhD	None	None	None	None	8/7/12
Arnold W. Malcolm, MD	None	None	None	None	4/24/13
James L. Mohler, MD	Roswell Park Cancer Institute	Genomic Health, Inc.	None	Androbiosys, Inc.	2/25/14
David Miller, MD, MPH	Blue Cross Blue Shield of Michigan	UnitedHealthcare	None	None	10/10/12
Elizabeth R. Plimack, MD, MS	Bristol-Myers Squibb Company; Dendreon Corporation; GlaxoSmithKline; Merck & Co., Inc.; and Acceleron Pharma, Inc.	Dendreon Corporation; GlaxoSmithKline; and Astellas US LLC	None	None	8/3/13
Julio M. Pow-Sang, MD	None	Myriad Genetic Laboratories, Inc.	None	None	3/29/13
David Raben, MD	None	None	None	None	Pending
Sylvia Richey, MD	None	Astellas / Medivation Speaker	None	None	5/20/13
Mack Roach III, MD	None	AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Aristopharma Ltd.; Astellas US LLC; and Ferring Pharmaceuticals Inc.	None	None	5/23/13
Eric Rohren, MD, PhD	None	None	None	None	5/17/13
Stan Rosenfeld	None	None	None	None	10/22/12
Edward Schaeffer, MD, PhD	Genome Dx	MetaMark Diagnostics	None	None	1/15/14
Eric J. Small, MD	None	None	None	None	1/9/14
Guru Sonpavde, MD	Bristol-Myers Squibb Company; Novartis Pharmaceuticals Corporation; and sanofi-aventis U.S.	GlaxoSmithKline; Millennium Pharmaceuticals, Inc.; and sanofi-aventis U.S.	None	None	12/19/13
Sandy Srinivas, MD	Medivation, Inc.	Johnson & Johnson; Medivation, Inc.; and sanofi-aventis U.S.	None	None	12/9/13
Cy Stein, MD, PhD	None	None	None	Amgen Inc.; Janssen Pharmaceutica Products, LP; and sanofi-aventis U.S.	3/28/14
Seth A. Strobe, MD, MPH	None	None	None	None	10/9/12
Jonathan Tward, MD, PhD	None	Myriad Genetic Laboratories, Inc.	None	None	8/3/12

The NCCN guidelines staff have no conflicts to disclose.