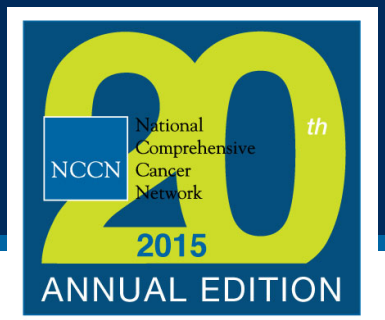

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer

Version 1.2015

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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Correction to Version 1.2015 of the NCCN Guidelines for Prostate Cancer:

PROS-11 and PROS-G (1 of 2)

- **Following CRPC, studies postive for metastases: Immunotherapy with sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0-1, added "category 1."**

Updates in Version 1.2015 of the NCCN Guidelines for Prostate Cancer from Version 2.2014 include:

PROS-1

- **Footnote "b" is new to the page. "Men with clinically localized disease could consider use of a tumor-based molecular assay to stratify better risk of adverse pathology at radical prostatectomy or chance of biochemical recurrence or disease-specific mortality after radical prostatectomy."**
- **Locally advanced, very-high-risk group added: "primary Gleason pattern 5 or >4 cores with Gleason score 8–10."**

PROS-6

- **Following post-EBRT recurrence, changed "rising PSA" to "biochemical failure."**
- **Modified footnote "q": "RTOG-ASTRO (Radiation Therapy Oncology Group-American Society for Therapeutic Radiology and Oncology) Phoenix Consensus-1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men."**

PROS-9

- **Divided the pathway into 2 branches: 1) M0 or low-volume M1 disease and 2) High-volume M1 disease.**
- **Added footnote "r": "High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis and vertebral column."**
- **Added "Continuous ADT and docetaxel 75 mg/m^2 without prednisone for 6 cycles" as a systemic therapy recommendation for patients who are castration sensitive and have high-volume M1 disease.**
- **Replaced "relapse" with "progression."**

PROS-11

- **Following CRPC, studies postive for metastases, added the following bullets:**
  - **Consider bone antiresorptive therapy with denosumab or zoledronic acid (both category 1) if bone metastases present**
  - **Immunotherapy with sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0-1**
  - **Palliative RT for painful bony metastases**
  - **Best supportive care**
- **Modifed footnote "v" by adding the following statement: "Sipuleucel-T has not been studied in patients with visceral metastases."**
- **Replaced "symptomatic" with "visceral metastases."**
- **First-line therapy, no visceral metastases:**
  - **Enzalutamide added "(category 1)"**
  - **Abiraterone acetate added "with prednisone (category 1)"**
  - **Docetaxel added "with prednisone (category 1)"**
  - **Added new bullet: "Radium-223 for symptomatic bone metastases (category 1)"**

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Continued on next page

Updates in Version 1.2015 version of the NCCN Guidelines for Prostate Cancer from Version 2.2014 include:

PROS-11 (continued)

- **First-line therapy, visceral metastases:**
  - **Enzalutamide added "(category 1)"**
  - **Changed mitoxantrone to "alternative chemotherapy (mitoxantrone)"**

PROS-12

- **This is a new page.**
- **Second-line therapy recommendations for patients without visceral metastases are stratified based on prior therapy:**
  - **Prior therapy enzalutamide/abiraterone:**
    - ◊ **Docetaxel with prednisone (category 1)**
    - ◊ **Abiraterone acetate or enzalutamide**
    - ◊ **Radium-223 (category 1) if bone-predominant disease**
    - ◊ **Clinical trial**
    - ◊ **Other secondary hormone therapy**
      - **– Antiandrogen**
      - **– Antiandrogen withdrawal**
      - **– Ketoconazole**
      - **– Corticosteroids**
      - **– DES or other estrogen**
    - ◊ **Best supportive care**
  - **Prior therapy docetaxel:**
    - ◊ **Enzalutamide (category 1)**
    - ◊ **Abiraterone acetate[l] with prednisone (category 1)**
    - ◊ **Radium-223 (category 1) if bone-predominant disease**
    - ◊ **Cabazitaxel with prednisone (category 1)**
    - ◊ **Clinical trial**
    - ◊ **Docetaxel rechallenge**
    - ◊ **Alternative chemotherapy**
    - ◊ **Other secondary hormone therapy**
      - **– Antiandrogen**
      - **– Antiandrogen withdrawal**
      - **– Ketoconazole**
      - **– Corticosteroids**
      - **– DES or other estrogen**
    - ◊ **Best supportive care**

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Updates in Version 1.2015 of the NCCN Guidelines for Prostate Cancer from Version 2.2014 include:

PROS-12 (continued)

- **Second-line therapy recommendations for patients with visceral metastases are stratified based on prior therapy:**
  - **Prior therapy enzalutamide/abiraterone:**
    - ◊ **Docetaxel with prednisone (category 1)**
    - ◊ **Clinical trial**
    - ◊ **Abiraterone acetate or enzalutamide**
    - ◊ **Other secondary hormone therapy**
      - – **Antiandrogen**
      - – **Antiandrogen withdrawal**
      - – **Ketoconazole**
      - – **Corticosteroids**
      - – **DES or other estrogen**
    - ◊ **Best supportive care**
  - **Prior therapy docetaxel:**
    - ◊ **Enzalutamide (category 1)**
    - ◊ **Abiraterone acetate[l] with prednisone (category 1)**
    - ◊ **Cabazitaxel with prednisone (category 1)[t]**
    - ◊ **Clinical trial**
    - ◊ **Docetaxel rechallenge[t]**
    - ◊ **Alternative chemotherapy (mitoxantrone)[t]**
    - ◊ **Other secondary hormone therapy**
      - – **Antiandrogen**
      - – **Antiandrogen withdrawal**
      - – **Ketoconazole**
      - – **Corticosteroids**
      - – **DES or other estrogen**
    - ◊ **Best supportive care**

PROS-B (1 of 3)

- **Under "Goals of Imaging," the first bullet was modifed: "Imaging is performed for the detection and characterization of disease to *select treatment or guide change in management*."**
- **Under "Efficacy of imaging," the third bullet was modified: "Conventional bone scans are rarely positive in asymptomatic men with PSA <10 ng/mL. The relative risk for bone metastasis or death increases as PSADT falls. Bone imaging should be performed more frequently when ≤8 mo, where there appears to be an inflection point."**

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Updates in Version 1.2015 of the NCCN Guidelines for Prostate Cancer from Version 2.2014 include:

PROS-B (1 of 3) (continued)

- **Under "Plain Radiography," the second bullet was added: "CT or MRI may be more useful to assess fracture risk as these modalities permit more accurate assessment of cortical involvement than plain films where osteoblastic lesions may obscure cortical involvement."**

PROS-B (2 of 3)

- **Under "Bone Scan," the first two bullets were replaced with the following:**
  - **The use of the term "bone scan" refers to the conventional 99-technetium bone scan in which 99-technetium is taken up by bone that is turning over and imaged with a gamma camera using planar imaging or 3-D imaging with single photon emission CT (SPECT).**
    - **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.**
  - **Newer technology using 18F-NaF as the tracer for a PET scan can be used as a diagnostic staging study. This test appears to have greater sensitivity than 99-technetium bone scan. However, there is controversy about how the results of 18F-NaF PET bone scan should be acted upon since all phase 3 clinical trials to date have based progression criteria on the 99-technetium bone scans.**
  - **PET and hybrid imaging bone scans appear more sensitive than conventional 99-technetium bone scans.**

PROS-B (3 of 3)

- **Under "Magnetic Resonance Imaging" added the following bullets:**
  - **Multi-parametric MRI (mpMRI) can be used in the staging and characterization of prostate cancer. mpMRI images are defined as images acquired with at least one more sequence in addition to the anatomical T2-weighted images, such as DWI or dynamic contrast-enhanced (DCE) images.**
  - **mpMRI may be used to risk stratify men better who are considering active surveillance. Additionally, mpMRI may detect large and poorly differentiatedprostate cancer (ie, Gleason score ≥7) and detect extracapsular extension (T staging). mpMRI has been shown to be equivalent to CT scan for pelvic lymph node evaluation.**

PROS-C (1 of 2)

- **The following bullets are new to the page:**
  - **Cancer progression may have occurred if:**
    - **Gleason grade 4 or 5 cancer is found upon repeat prostate biopsy**
    - **Prostate cancer is found in a greater number of prostate biopsies or occupies a greater extent of prostate biopsy.**

PROS-D (1 of 2)

- **Under "Primary/Salvage Brachytherapy," the first bullet was modified: "Low-dose rate (LDR) brachytherapy as monotherapy is indicated for patients with low-risk cancers and *selected patients with low-volume immediate-risk cancers*. Intermediate-risk cancers may be treated by combining LDR brachytherapy with EBRT (40–50 Gy) ± 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 LDR brachytherapy ± 2- to 3-y neoadjuvant/concomitant/adjuvant ADT."**

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Updates in Version 1.2015 of the NCCN Guidelines for Prostate Cancer from Version 2.2014 include:

PROS-D (2 of 2)

- **Under "Post-Prostatectomy Radiation Therapy," added the following bullet: "The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, and PSA doubling time to individualize treatment discussion. The panel also recommends consultation with the American Society for Therapeutic Radiology and Oncology (ASTRO) AUA Guidelines. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 2013;190:441-449."**
- **Changed the recommended prescribed doses for adjuvant/salvage post-prostatectomy RT from "64–70 Gy" to "64–72 Gy" in standard fractionation. Added the following statement: "Biopsy-proven gross recurrence may require higher doses."**
- **Under "Radiopharmaceutical Therapy," added the following statement to the first bullet: "Radium-223 alone has not been shown to extend survival in men with visceral metastases or bulky nodal disease greater than 3 to 4 cm."**

PROS-E

- **Under "Radical Prostatectomy": modified the last bullet: "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 and *the operation should be performed by surgeons who are experienced with salvage RP*."**

PROS-F (1 of 4)

- **Changed "ADT for Localized Disease" to "ADT for Clinically Localized Disease."**
  - **Added the following bullet: "ADT should not be used as monotherapy in clinically localized prostate cancer."**
- **Changed "ADT for Biochemical Failure" to "ADT for Biochemical Failure Without Metastases."**
  - **Modified the first bullet: "The timing of ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, the short- and long-term side effects of ADT, *and the underlying comorbidities of the patient*."**
  - **Added the following statement to the last bullet: "An unplanned subset analysis showed that men with Gleason sum 8–10 prostate cancer in the continuous arm had a median overall survival that was 14 mo longer (8 y) than those in the intermittent arm (6.8 y)."**

PROS-F (2 of 4)

- **"Optimal ADT," changed the following bullet from "should not be recommended" to "is not recommended": "Antiandrogen monotherapy appears to be less effective than medical or surgical castration and is not recommended. Removed the following statement: "The side effects are different but overall more tolerable."**
- **Modified the last bullet: "The optimal level of serum testosterone *to effect castration* has yet to be determined."**

PROS-F (3 of 4)

- **Modified the following bullet: "A phase 3 study of docetaxel-naive men showed that enzalutamide (160 mg daily) resulted in significant improvement in radiographic progression-free survival and overall survival. The use of enzalutamide in this setting is category 1. 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)."**
- **Changed the following statement to include enzalutamide: "Both abiraterone and enzalutamide are approved in this setting and have category 1 recommendations. Both drugs are suitable options for men who are not good candidates to receive docetaxel."**

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Updates in Version 1.2015 of the NCCN Guidelines for Prostate Cancer from Version 2.2014 include:

PROS-G (1 of 2)

- **Added a new bullet: "Men with high-volume, ADT-naïve, metastatic disease should be considered for ADT and docetaxel based on the results of the ECOG 3805 (CHAARTED) trial. In this study, 790 men were randomized to 6 cycles of docetaxel at 75 mg/m^2 every 3 weeks without prednisone with ADT vs. ADT alone. In the majority subset of patients with high-volume disease, defined as 4 or more bone metastases including one extra-axial bone lesion or visceral metastases, a 17-month improvement in overall survival was observed (HR 0.60; *P* = .0006). Improvements in PSA response, time to clinical progression, and time to recurrence were observed with use of docetaxel. Toxicities of 6 cycles of docetaxel without prednisone included fatigue, neuropathy, stomatitis, diarrhea, and neutropenia with or without fever. The use of white cell growth factors should follow NCCN Guidelines based on risk of neutropenic fever. Docetaxel should not be offered to men without metastatic prostate cancer or to men with low-volume metastatic prostate cancer, since this subgroup was not shown to have improved survival in either the ECOG study or a similar European (GETUG-AFU 15) trial."**
- **Modified the following bullet: "Every-3-week docetaxel with or without prednisone is the preferred first-line chemotherapy treatment based on phase 3 clinical trial data for men with symptomatic mCRPC. Radium-223 has been studied in symptomatic patients who are not candidates for docetaxel-based regimens and resulted in improved overall survival. "Abiraterone and enzalutamide have been shown to extend survival in patients who progressed on docetaxel. Mitoxantrone and prednisone may provide palliation but have not been shown to extend survival."**

PROS-G (2 of 2)

- **Modified the first bullet: "Mitoxantrone has not demonstrated a survival improvement in the post-docetaxel setting but remains a palliative therapeutic option, particularly in men who are not candidates for cabazitaxel *or radium-223 therapy*."**

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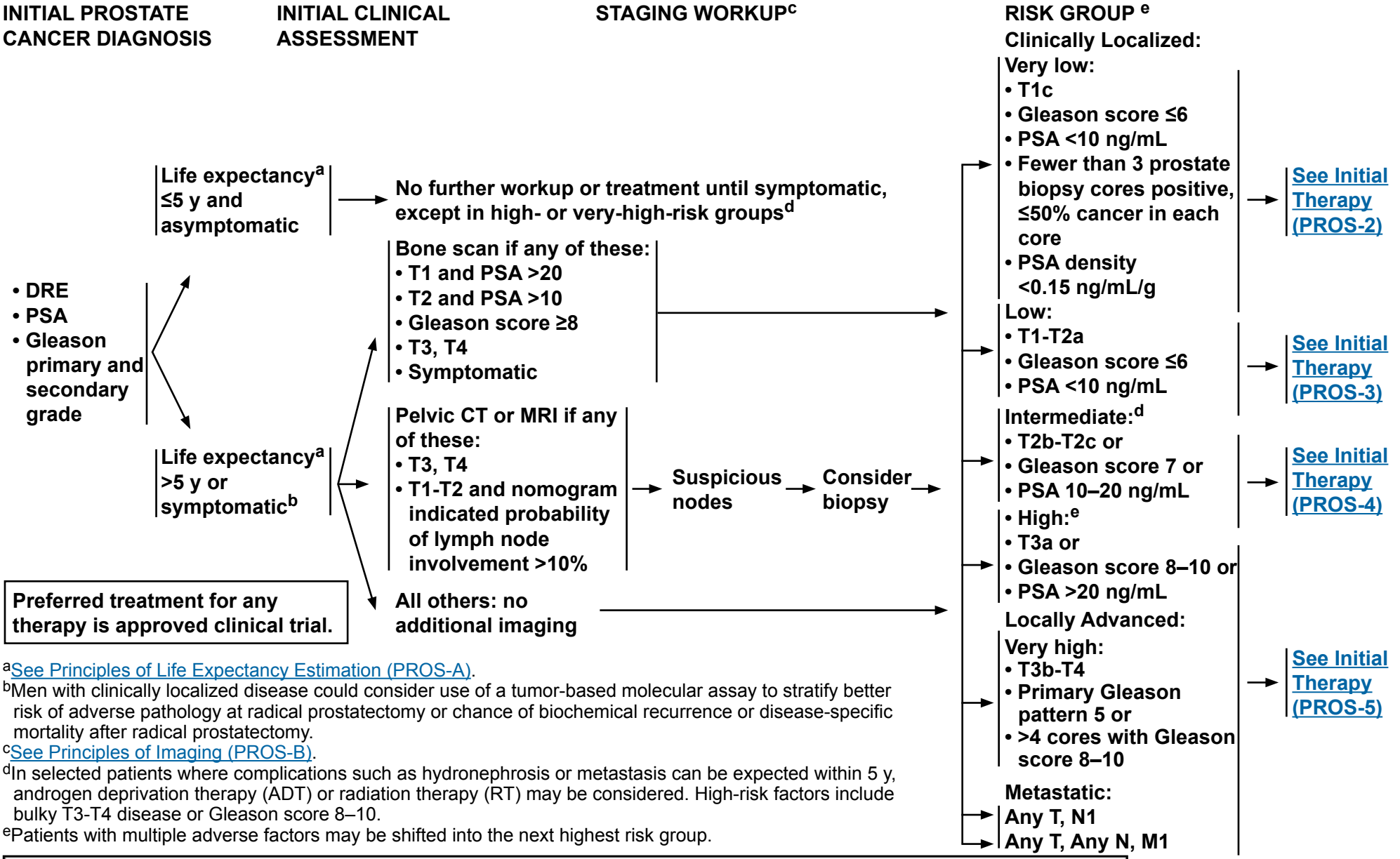

[a] See Principles of Life Expectancy Estimation (PROS-A).
[b] Men with clinically localized disease could consider use of a tumor-based molecular assay to stratify better risk of adverse pathology at radical prostatectomy or chance of biochemical recurrence or disease-specific mortality after radical prostatectomy.
[c] See Principles of Imaging (PROS-B).
[d] In selected patients where complications such as hydronephrosis or metastasis can be expected within 5 y, androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered. High-risk factors include bulky T3-T4 disease or Gleason score 8–10.
[e] Patients with multiple adverse factors may be shifted into the next highest risk group.

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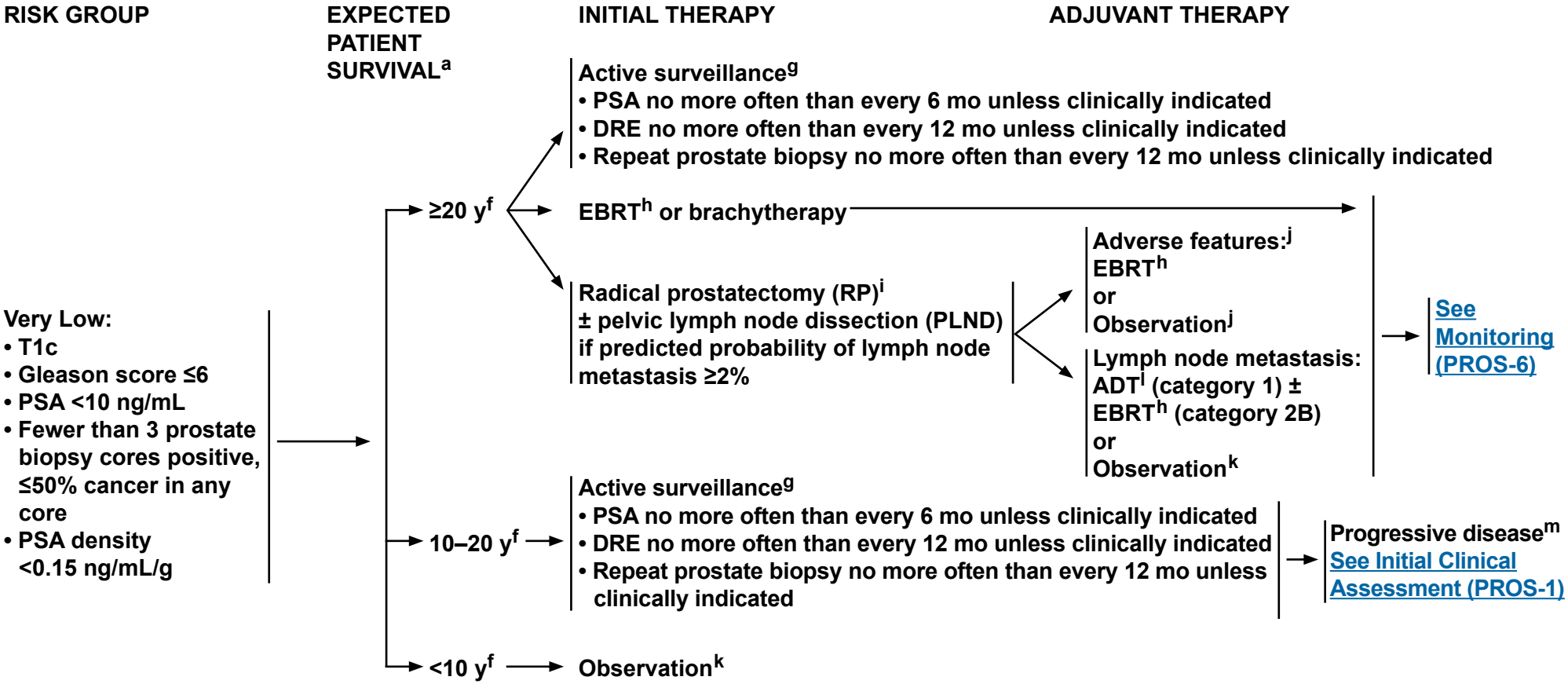

[a] See Principles of Life Expectancy Estimation (PROS-A).

[f] The panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. See NCCN Guidelines for Prostate Cancer Early Detection. Active surveillance is recommended for these subsets of patients.

[g] Active 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).

[h] See Principles of Radiation Therapy (PROS-D).

[i] See Principles of Surgery (PROS-E).

[j] Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.

[k] Observation 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).

[l] See Principles of Androgen Deprivation Therapy (PROS-F).

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

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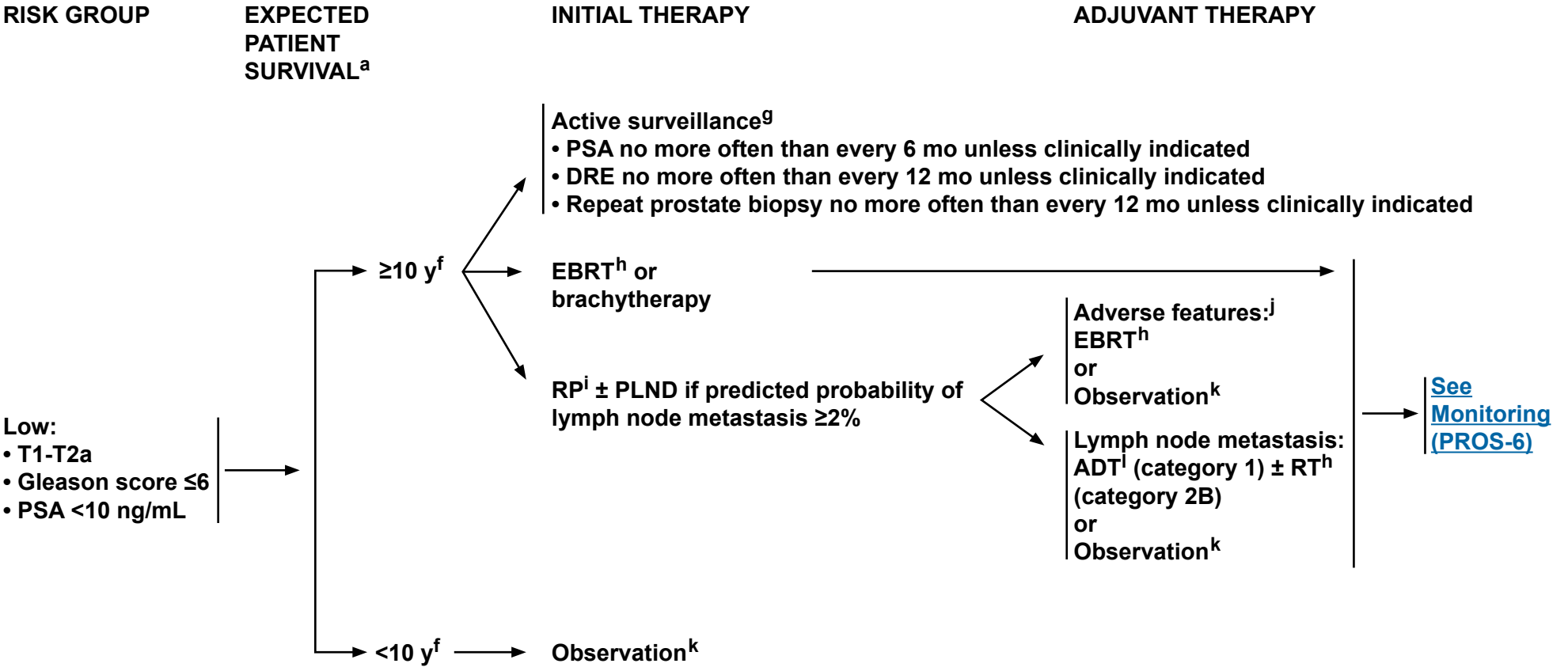

[a] See Principles of Life Expectancy Estimation (PROS-A).
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[g] Active surveillance involves actively monitoring the course of disease with the expectation to intervene with potentially curative therapy if the cancer progresses. See Principles of Active Surveillance and Observation (PROS-C).
[h] See Principles of Radiation Therapy (PROS-D).
[i] See Principles of Surgery (PROS-E).
[j] Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
[k] Observation 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).
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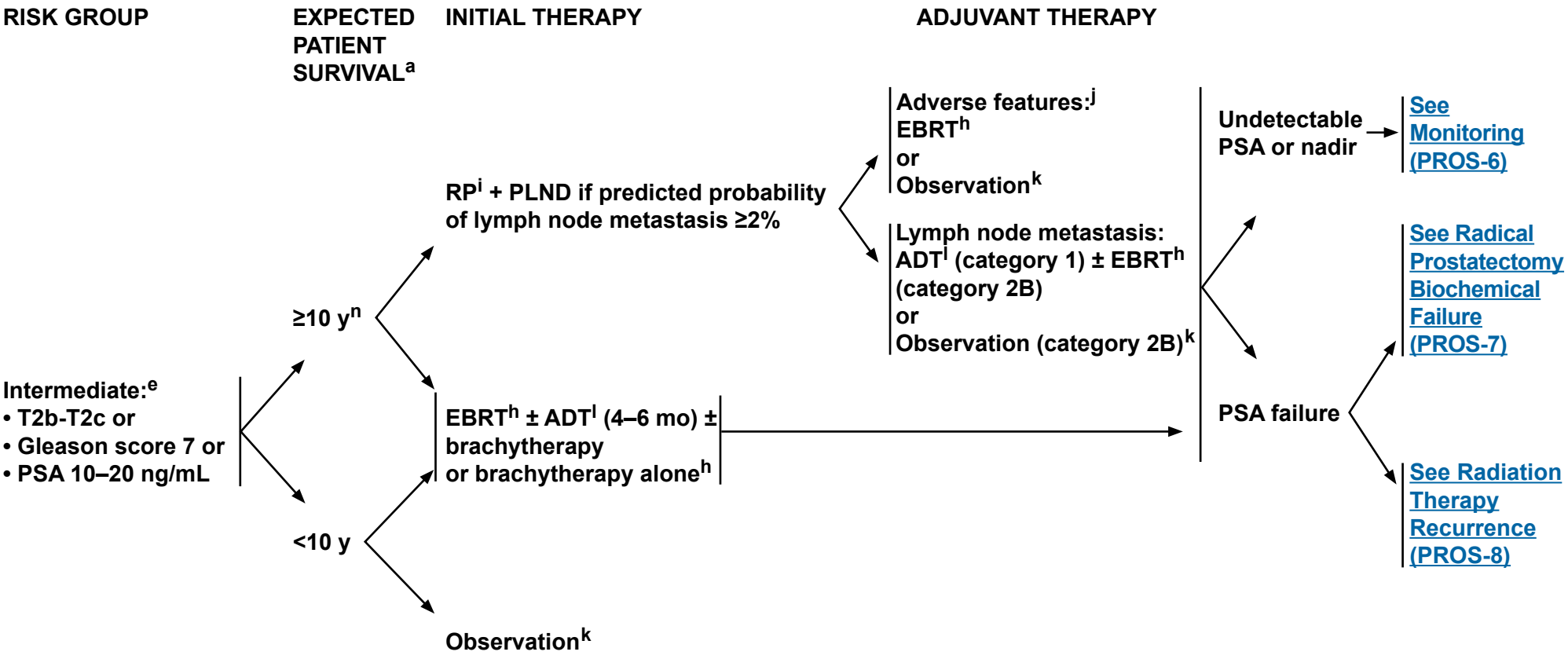

[a] See Principles of Life Expectancy Estimation (PROS-A).
[e] Patients with multiple adverse factors may be shifted into the next highest risk group.
[h] See Principles of Radiation Therapy (PROS-D).
[i] See Principles of Surgery (PROS-E).
[j] Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
[k] Observation 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).
[l] See Principles of Androgen Deprivation Therapy (PROS-F).
[n] Active surveillance of intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).

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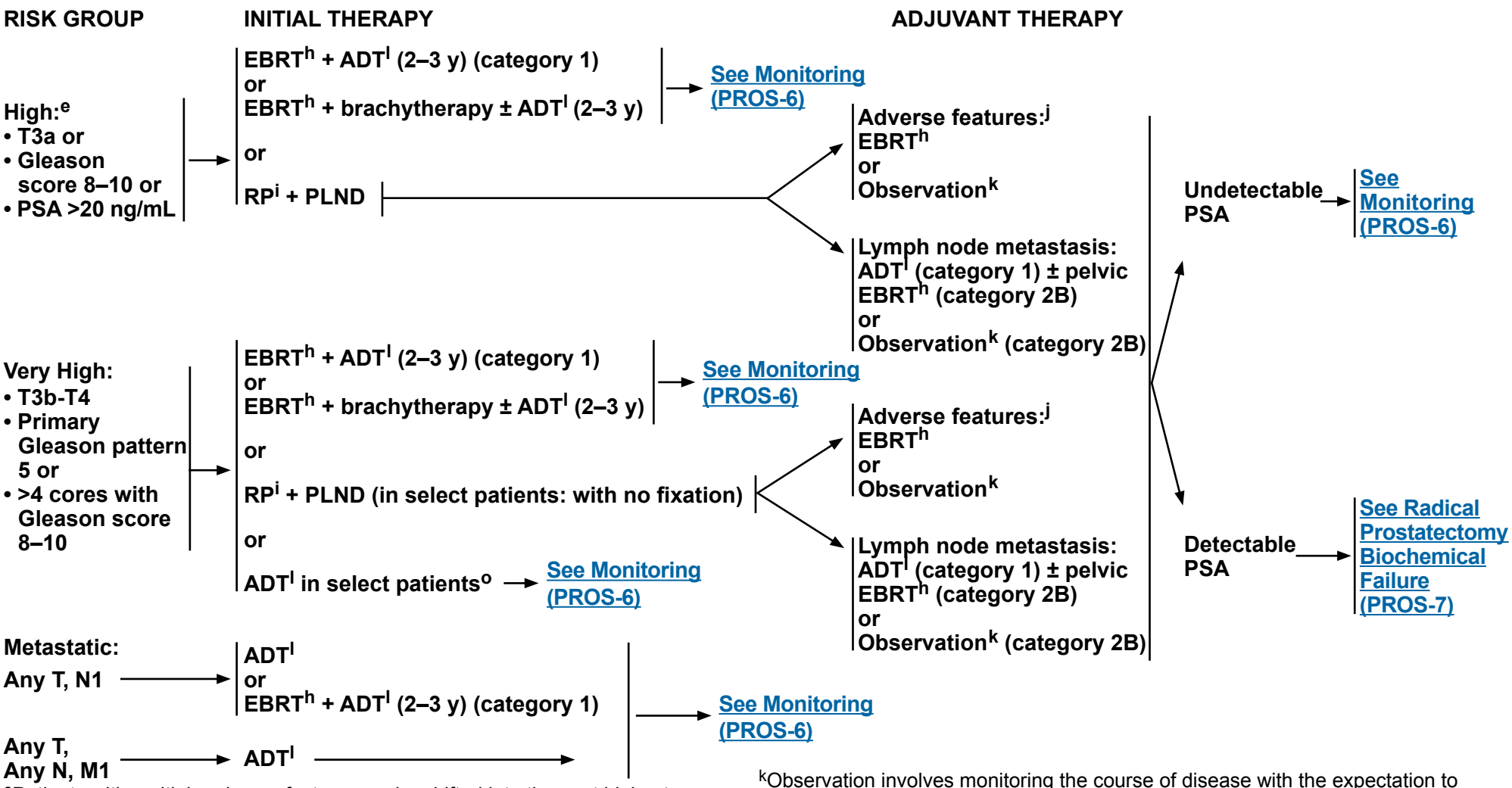

[e]Patients with multiple adverse factors may be shifted into the next highest risk group.
[h]See Principles of Radiation Therapy (PROS-D).
[i]See Principles of Surgery (PROS-E).
[j]Adverse laboratory/pathologic features include: positive margins, seminal vesicle invasion, extracapsular extension, or detectable PSA.
[k]Observation 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).
[l]See Principles of Androgen Deprivation Therapy (PROS-F).
[o]Primary therapy with ADT should be considered only for patients who are not candidates for definitive therapy.

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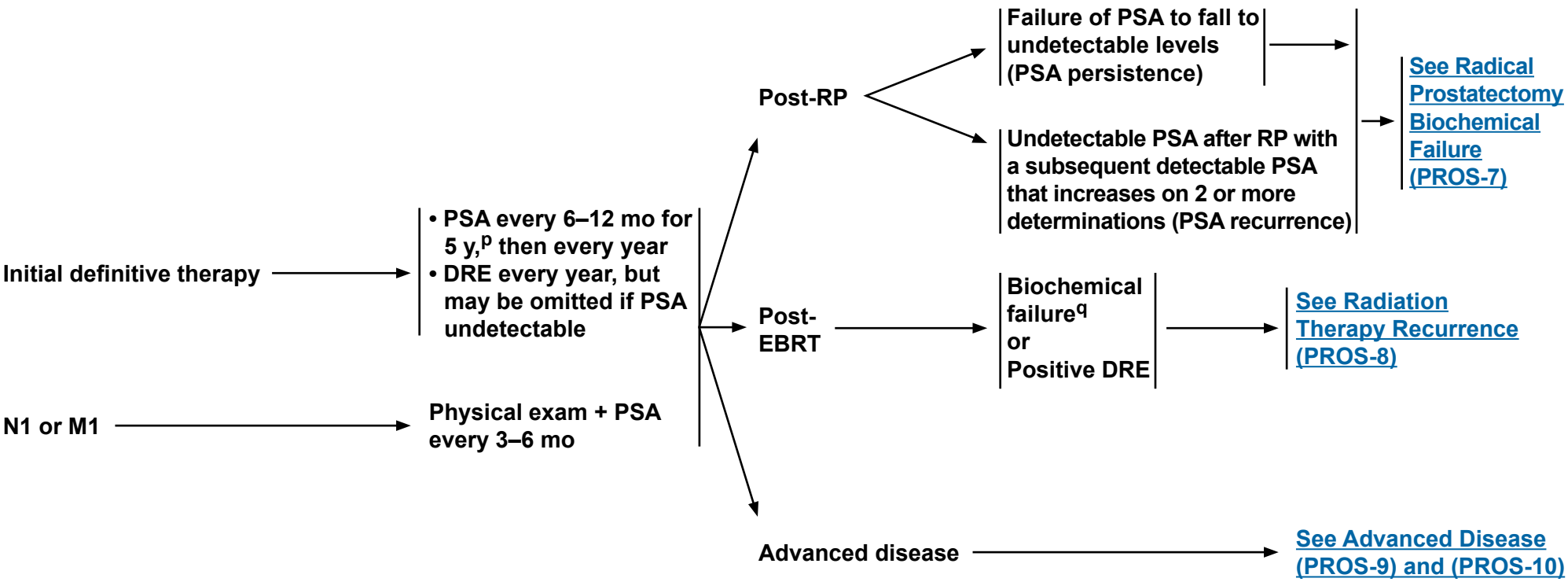

[p]PSA as frequently as every 3 mo may be necessary to clarify disease status, especially in high-risk men.

[q]RTOG-ASTRO (Radiation Therapy Oncology Group-American Society for Therapeutic Radiology and Oncology) Phoenix Consensus-1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

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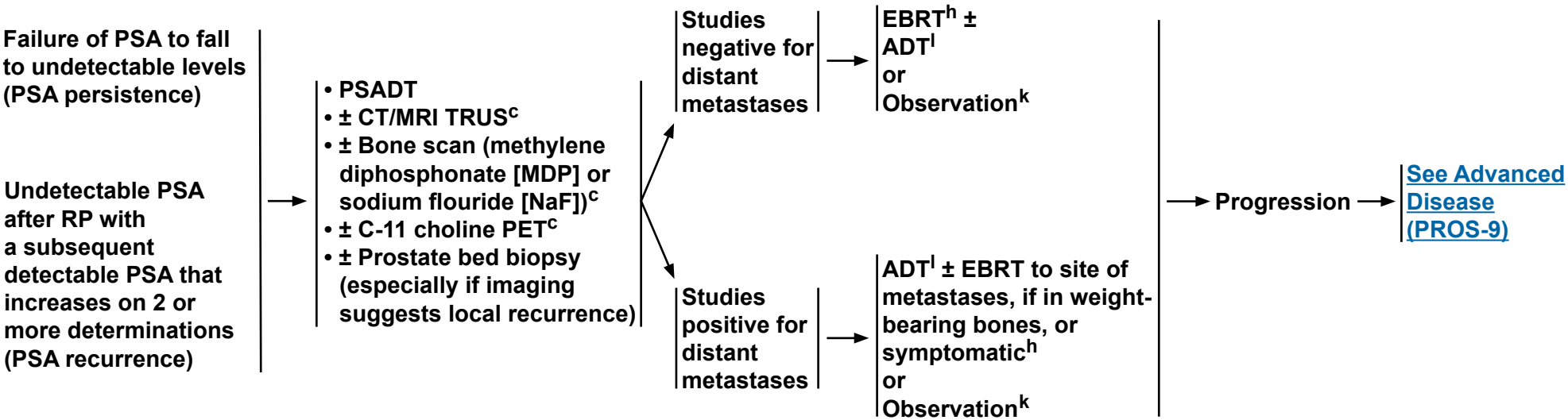
RADICAL PROSTATECTOMY BIOCHEMICAL FAILURE



[c] See Principles of Imaging (PROS-B).
[h] See Principles of Radiation Therapy (PROS-D).
[k] Observation 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).
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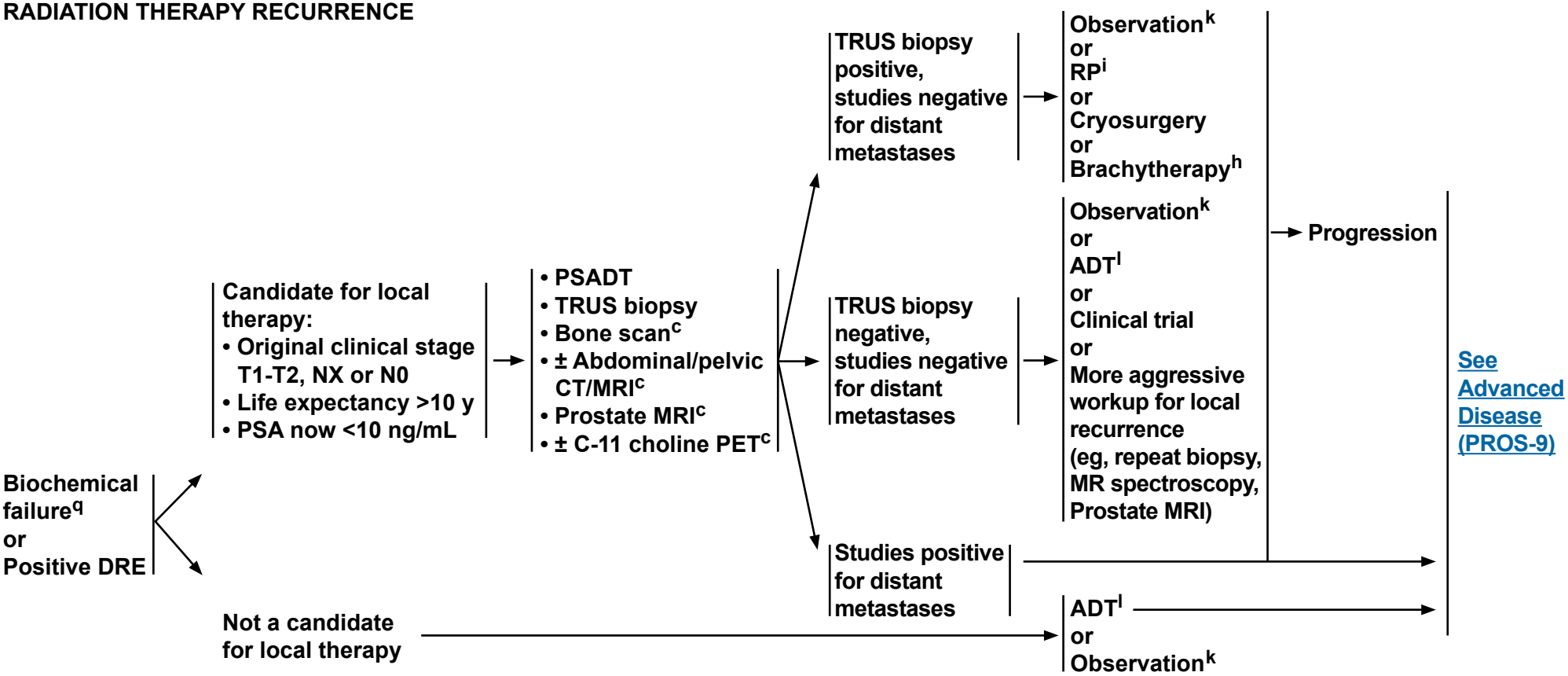
RADIATION THERAPY RECURRENCE



[c] See Principles of Imaging (PROS-B).
[h] See Principles of Radiation Therapy (PROS-D).
[i] See Principles of Surgery (PROS-E).
[k] Observation 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).
[l] See Principles of Androgen Deprivation Therapy (PROS-F).
[q] RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Therapeutic Radiology and Oncology) Phoenix Consensus - 1) PSA rise by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; 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.

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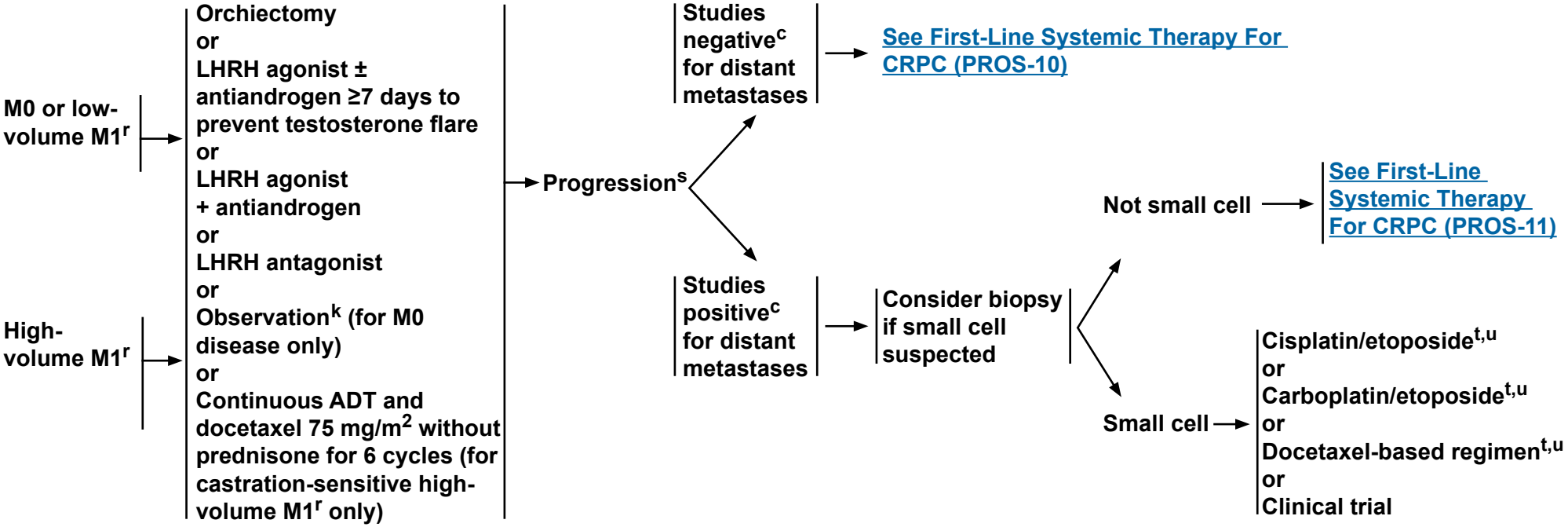
ADVANCED DISEASE: SYSTEMIC THERAPY



[c] See Principles of Imaging (PROS-B).

[k] Observation 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).

[r] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column.

[s] Assure castrate level of testosterone.

[t] See Principles of Immunotherapy and Chemotherapy (PROS-G).

[u] See NCCN Guidelines for Small Cell Lung Cancer.

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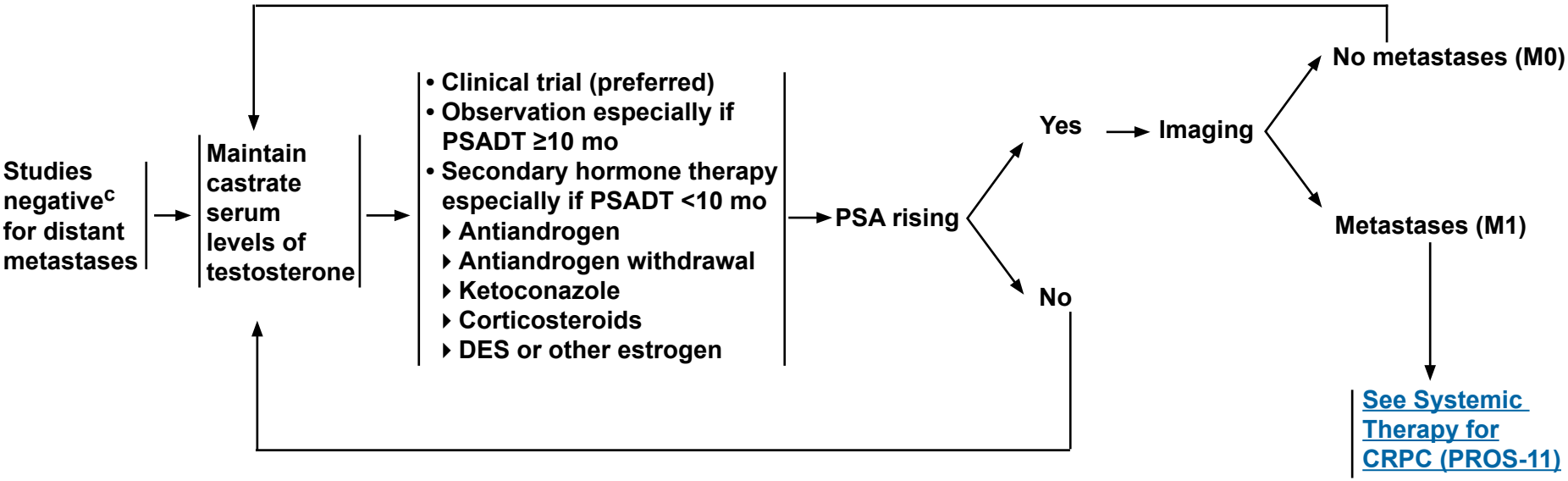
ADVANCED DISEASE: FIRST-LINE SYSTEMIC THERAPY FOR CRPC



[c] See Principles of Imaging (PROS-B).

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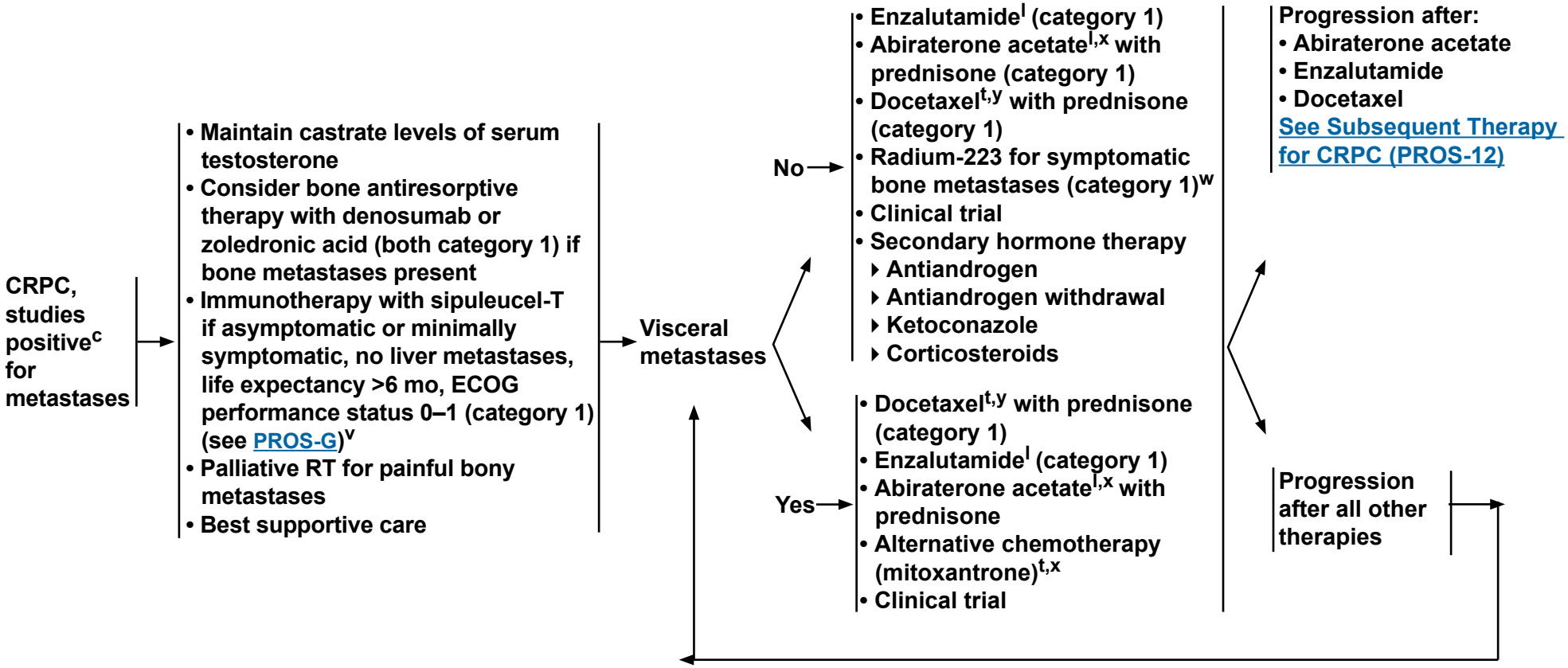
ADVANCED DISEASE: FIRST-LINE SYSTEMIC THERAPY FOR CRPC



[c] See Principles of Imaging (PROS-B).
[l] See Principles of Androgen Deprivation Therapy (PROS-F).
[t] See Principles of Immunotherapy and Chemotherapy (PROS-G).
[v] Sipuleucel-T has not been studied in patients with visceral metastases.
[w] Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 of 2).
[x] For patients who are not candidates for docetaxel-based regimens.
[y] Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or visceral metastases despite lack of symptoms.

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ADVANCED DISEASE: SUBSEQUENT SYSTEMIC THERAPY FOR CRPC

No visceral metastases →

Prior therapy enzalutamide/abiraterone:	Prior therapy docetaxel:
• Docetaxel with prednisone (category 1)[t] • Abiraterone acetate[l] or enzalutamide • Radium-223 (category 1) if bone-predominant disease • Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1 • Clinical trial • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care	• Enzalutamide (category 1) • Abiraterone acetate[l] with prednisone (category 1) • Radium-223 (category 1) if bone-predominant disease • Cabazitaxel with prednisone (category 1)[t] • Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1 • Clinical trial • Docetaxel rechallenge[t] • Alternative chemotherapy (mitoxantrone)[t] • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care

Visceral metastases →

Prior therapy enzalutamide/abiraterone:	Prior therapy docetaxel:
• Docetaxel with prednisone (category 1)[t] • Clinical trial • Abiraterone acetate[l] or enzalutamide • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care	• Enzalutamide (category 1) • Abiraterone acetate[l] with prednisone (category 1) • Cabazitaxel with prednisone (category 1)[t] • Clinical trial • Docetaxel rechallenge[t] • Alternative chemotherapy (mitoxantrone)[t] • Other secondary hormone therapy ▸ Antiandrogen ▸ Antiandrogen withdrawal ▸ Ketoconazole ▸ Corticosteroids ▸ DES or other estrogen • Best supportive care

[l]See Principles of Androgen Deprivation Therapy (PROS-F). [t]See Principles of Immunotherapy and Chemotherapy (PROS-G).

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PRINCIPLES OF LIFE EXPECTANCY ESTIMATION

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

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

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PRINCIPLES OF IMAGING

Goals of Imaging

- Imaging is performed for the detection and characterization of disease to select treatment or guide change in 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 prior to 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.
- Conventional bone scans are rarely positive in asymptomatic men with PSA <10 ng/mL. The relative risk for bone metastasis or death increases as PSADT falls. Bone imaging should be performed more frequently when ≤8 mo, where there appears to be an inflection point.

Plain Radiography

- Plain radiography can be used to evaluate symptomatic regions in the skeleton. 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.
- CT or MRI may be more useful to assess fracture risk as these modalities permit more accurate assessment of cortical involvement than plain films where osteoblastic lesions may obscure cortical involvement.

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.

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PRINCIPLES OF IMAGING

Bone Scan

- The use of the term "bone scan" refers to the conventional 99-technetium bone scan in which 99-technetium is taken up by bone that is turning over and imaged with a gamma camera using planar imaging or 3-D imaging with single photon emission CT (SPECT).
  - 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.
- Newer technology using 18F-NaF as the tracer for a PET scan can be used as a diagnostic staging study. This test appears to have greater sensitivity than bone scan. However, there is controversy about how the results of 18F-NaF PET bone scan should be acted upon since all phase 3 clinical trials to date have based progression criteria on bone scans.
  - PET and hybrid imaging bone scans appear more sensitive than conventional 99-technetium bone scans.
- 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 or more 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 or systemic therapy.

Computed Tomography

- CT provides a high level of anatomic detail, and may detect gross extracapsular disease, nodal metastatic disease, and/or visceral metastatic disease.
  - CT is generally not sufficient to evaluate the prostate gland.
- 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.
- 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 or more subsequent determinations, or after RT for rising PSA or positive DRE if the patient is a candidate for additional local therapy or systemic therapy.

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PRINCIPLES OF IMAGING

Magnetic Resonance Imaging

- 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 using 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.
- Multiparametric MRI (mpMRI) can be used in the staging and characterization of prostate cancer. mpMRI images are defined as images acquired with at least one more sequence in addition to the anatomical T2-weighted images, such as DWI or dynamic contrast-enhanced (DCE) images.
- mpMRI may be used to better risk stratify men who are considering active surveillance. Additionally, mpMRI may detect large and poorly differentiated prostate cancer (ie, Gleason score $\geq$7) and detect extracapsular extension (T staging). mpMRI has been shown to be equivalent to CT scan for pelvic lymph node evaluation.

Positron Emission Tomography/Computed Tomography

- 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 men with prostate cancer.
- Oncologic PET/CT is performed typically using 8F-fluorodeoxyglucose (FDG), a radioactive analog of glucose.
  - In certain clinical settings, the use of FDG-PET/CT may provide useful information, but FDG-PET/CT should not be used routinely since data on the utility of FDG-PET/CT in patients with prostate cancer is limited.

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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) remain concerned about over-diagnosis and over-treatment of prostate cancer. The panel recommends that patients and their physicians (ie, 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 no more often than 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 life expectancy <10 y. See Risk Group Criteria (PROS-2).
- Active surveillance involves actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses.
- Cancer progression may have occurred if:
  - Gleason grade 4 or 5 cancer is found upon repeat prostate biopsy
  - Prostate cancer is found in a greater number of prostate biopsies or occupies a greater extent of prostate biopsy.
- 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 less than 10 y or appropriate when men are on observation.
  - PSADT appears unreliable for identification of progressive disease that remains curable. Although multi-parametric MRI is not recommended for routine use, it may be considered if PSA rises and systematic prostate biopsy is negative to exclude the presence of an anterior cancer.

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PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **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**

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PRINCIPLES OF RADIATION THERAPY

Primary External Beam Radiation Therapy

- 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 (± 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 (2.4–4 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 or greater) 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 to 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 IGRT using CT, ultrasound, implanted fiducials, electromagnetic targeting/tracking, or an endorectal balloon to improve oncologic cure rates and reduce side effects.

Primary/Salvage Brachytherapy

- Low-dose rate (LDR) brachytherapy as monotherapy is indicated for patients with low-risk cancers and selected patients with low-volume immediate-risk cancers. Intermediate-risk cancers may be treated by combining LDR brachytherapy with EBRT (40–50 Gy) ± 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 LDR brachytherapy ± 2 to 3 y neoadjuvant/concomitant/adjuvant ADT.
- Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate 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 to 110 Gy for LDR and 9 to 12 Gy x 2 fractions for HDR.

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PRINCIPLES OF RADIATION THERAPY

Post-Prostatectomy Radiation Therapy

- The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, and PSADT to individualize treatment discussion. The panel also recommends consultation with the American Society for Therapeutic Radiology and Oncology (ASTRO) AUA Guidelines. Thompson IM, Valicenti RK, Albertsen P, et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 2013;190:441-449. Evidence supports offering adjuvant/salvage RT in most 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 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 pre-treatment PSA is <1 ng/mL and PSADT is slow.
- The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64–72 Gy in standard fractionation. Biopsy-proven gross recurrence may require higher doses.
- The defined target volumes include the prostate bed and may include the whole pelvis in selected patients.

Radiopharmaceutical Therapy

- Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in men who have CRPC with symptomatic bone metastases, but no visceral metastases. Radium-223 alone has not been shown to extend survival in men with visceral metastases or bulky nodal disease greater than 3 to 4 cm. Radium-223 differs from beta-emitting agents, such as samarium 153 and strontium 89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3–4 hematologic toxicity (2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency.
- Radium-223 is administered intravenously once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.
- Prior to the initial dose, patients must have absolute neutrophil count ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, and hemoglobin ≥10g/dL.
- Prior to subsequent doses, patients must have absolute neutrophil count ≥1 x 10^9/L and platelet count ≥50 x 10^9/L (per label, although this may be too low in practice). Radium-223 should be discontinued if a delay of 6 to 8 weeks does not result in the return of blood counts to these levels.
- Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms are likely related to the fact that radium-223 is predominantly eliminated by fecal excretion.
- At the present time, except on a clinical trial, radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression.
- Concomitant use of denosumab or zoledronic acid does not interfere with the beneficial effects of radium-223 on survival.

Palliative Radiotherapy

- 800 cGy as a single dose should be used instead of 3000 cGy in 10 fractions for non-vertebral metastases.
- Widespread bone metastases can be palliated using strontium 89 or samarium 153 with or without focal external beam radiation.

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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 appear comparable to 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 and the operation should be performed by surgeons who are experienced with salvage RP.

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Clinically Localized Disease

- Neoadjuvant ADT for RP is strongly discouraged outside of a clinical trial.
- ADT should not be used as monotherapy in clinically localized prostate cancer.
- 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 requires further study.
- In the largest randomized trial to date using the 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 following RP resulted in significantly improved overall survival compared to men who received delayed ADT. Therefore, such 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 Without Metastases

- The timing of ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, the short- and long-term side effects of ADT, and the underlying comorbidities of the patient.
- 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. Since the benefit of early ADT is not clear, treatment should be individualized until definitive studies are done. 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 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 3 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. An unplanned subset analysis showed that men with Gleason sum 8–10 prostate cancer in the continuous arm had a median overall survival that was 14 mo longer (8 y) than those in the intermittent arm (6.8 y).

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Metastatic Disease

- ADT is the gold standard for men with metastatic prostate cancer.
- A phase 3 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 to 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 is not recommended.
- No clinical data support the use of finasteride or dutasteride with combined androgen blockade.
- Patients who do not achieve adequate suppression of serum testosterone (less than 50 ng/dL) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, LHRH antagonists, or steroids), although the clinical benefit remains uncertain. The optimal level of serum testosterone to effect “castration” has yet to be determined.

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

Continued on next page

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

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, there are a variety of options that may afford clinical benefit. The available options are based on whether the patient has evidence of metastases by imaging, non-metastatic CRPC vs. metastatic CRPC (mCRPC), and whether or not the patient is symptomatic.
- In the setting in which patients are docetaxel-naive and have no or minimal symptoms, administration of secondary hormonal manipulations including addition of, or switching to, a different anti-androgen (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 prior to docetaxel chemotherapy, abiraterone (1000 mg daily on an empty stomach) and low-dose prednisone (5 mg BID) compared to 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, as well as the known side effects of ADT and long-term corticosteroid use.
- A phase 3 study of docetaxel-naive men showed that enzalutamide (160 mg daily) resulted in significant improvement in radiographic progression-free survival and overall survival. The use of enzalutamide in this setting is category 1. 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 pre-docetaxel setting were conducted in men who had no or minimal symptoms due to 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 post-docetaxel setting. Both abiraterone and enzalutamide are approved in this setting and have category 1 recommendations. Both drugs are suitable options for men who are not good candidates to receive docetaxel.
- In the post-docetaxel 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 pre- or post-docetaxel remains unavailable.

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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.

Continued on next page

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 daily) and vitamin D3 (800–1000 IU daily) for all men >50 y of age; and 2) additional treatment for men when the 10-y probability of hip fracture is ≥3% or the 10-y probability of a major osteoporosis-related fracture is ≥20%. Fracture risk can be assessed using 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 in men without metastases, include denosumab (60 mg SQ every 6 mo), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO 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 SQ every 6 mo), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly) increase bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either 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 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.

PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

- Men with advanced prostate cancer should be encouraged to participate in clinical trials and referred early to a medical oncologist.
- Men with high-volume, ADT-naïve, metastatic disease should be considered for ADT and docetaxel based on the results of the ECOG 3805 (CHAARTED) trial. In this study, 790 men were randomized to 6 cycles of docetaxel at 75 mg/m^2 every 3 weeks without prednisone with ADT vs. ADT alone. In the majority subset of patients with high-volume disease, defined as 4 or more bone metastases including one extra-axial bone lesion or visceral metastases, a 17-month improvement in overall survival was observed (HR 0.60; *P* = .0006). Improvements in PSA response, time to clinical progression, and time to recurrence were observed with use of docetaxel. Toxicities of 6 cycles of docetaxel without prednisone included fatigue, neuropathy, stomatitis, diarrhea, and neutropenia with or without fever. The use of white cell growth factors should follow NCCN Guidelines based on risk of neutropenic fever. Docetaxel should not be offered to men without metastatic prostate cancer or to men with low-volume metastatic prostate cancer, since this subgroup was not shown to have improved survival in either the ECOG study or a similar European (GETUG-AFU 15) trial.
- Men with asymptomatic or minimally symptomatic mCRPC may consider immunotherapy.
  - Sipuleucel-T has been shown in a phase 3 clinical trial to extend mean survival from 21.7 mo in the control arm to 25.8 mo in the treatment arm, which constitutes a 22% reduction in mortality risk.
  - Sipuleucel-T is well tolerated; common complications include chills, pyrexia, and headache.
  - Sipuleucel-T may be considered for men with CRPC who meet the following: (category 1)
    - ◊ Good performance status (ECOG 0-1)
    - ◊ Estimated life expectancy >6 mo
    - ◊ No hepatic metastases
    - ◊ No or minimal symptoms
- Systemic chemotherapy should be reserved for men with mCRPC, in particular those who are symptomatic except when studied in a clinical trial. Certain subsets of patients with mCRPC who have more anaplastic features may benefit from earlier chemotherapy, but this has not been studied adequately in prospective trials.
- Every-3-week docetaxel with or without prednisone is the preferred first-line chemotherapy treatment based on phase 3 clinical trial data for men with symptomatic mCRPC. Radium-223 has been studied in symptomatic patients who are not candidates for docetaxel-based regimens and resulted in improved overall survival. Abiraterone and enzalutamide have been shown to extend survival in patients who progressed on docetaxel. Mitoxantrone and prednisone may provide palliation but have not been shown to extend survival. (See PROS-F, 3 of 4).
- Only regimens utilizing docetaxel on an every-3-week schedule demonstrated beneficial impact on survival. The duration of therapy should be based on the assessment of benefit and toxicities. In the pivotal trials establishing survival advantage of docetaxel-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted.
- Rising PSA should not be used as the sole criteria for progression. Assessment of response should incorporate clinical and radiographic criteria.
- Men with mCRPC that has progressed following docetaxel-based chemotherapy should be encouraged to participate in clinical trials. However, cabazitaxel with prednisone has been shown in a randomized phase 3 study to prolong overall survival, progression-free survival, and PSA and radiologic responses when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second-line setting. Selection of patients without severe neuropathy and adequate liver, kidney, and bone marrow function is necessary, given the high risk of neutropenia and other side effects in this population, with consideration of prophylactic granulocyte growth factor injections.

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PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

- **Mitoxantrone has not demonstrated a survival improvement in the post-docetaxel setting but remains a palliative therapeutic option, particularly in men who are not candidates for cabazitaxel or radium-223 therapy. No chemotherapy regimen to date has demonstrated improved survival or quality of life after cabazitaxel, and trial participation should be strongly encouraged. Outside of a clinical trial, several systemic agents have shown palliative benefits in single-arm studies. Treatment decisions should be individualized based on comorbidities and functional status. Finally, for men who have not demonstrated definitive evidence of progression on prior docetaxel therapy, retreatment with this agent can be attempted.**
- **In men with CRPC who have bone metastases, denosumab and zoledronic acid have been shown to prevent disease-related skeletal complications, which include fracture, spinal cord compression, or the need for surgery or RT to bone.**
  - **When compared to zoledronic acid, denosumab was shown to be superior in prevention of skeletal-related events.**
  - **Choice of agent may depend on underlying comorbidities, whether the patient has been treated with zoledronic acid previously, logistics, and/or cost considerations.**
    - ◊ **Zoledronic acid is given intravenously every 3 to 4 weeks. The dose is based on the serum creatinine obtained just prior to each dose and must be adjusted for impaired renal function. Zoledronic acid is not recommended for creatinine clearance <30 mL/min.**
    - ◊ **Denosumab is given subcutaneously every 4 weeks. Although renal monitoring is not required, denosumab is not recommended in patients with creatinine clearance <30 mL/min. When creatinine clearance is <60 mL/min, the risk for severe hypocalcemia increases. Even in patients with normal renal function, hypocalcemia is seen twice as often with denosumab than zoledronic acid and all patients on denosumab should be treated with vitamin D and calcium with periodic monitoring of serum calcium levels.**
  - **Osteonecrosis of the jaw is seen with both agents; risk is increased in patients who have tooth extractions, poor dental hygiene, or a dental appliance. Patients should be referred for dental evaluation before starting either zoledronic acid or denosumab. If invasive dental procedures are required, bone-targeted therapy should be withheld until the dentist indicates that the patient has healed completely from all dental procedure(s).**
  - **The optimal duration of therapy for either denosumab or zoledronic acid remains uncertain.**
  - **The toxicity profile of denosumab when denosumab is used in patients who have been treated with zoledronic acid remains uncertain.**
  - **Clinical trials are in progress that assess a role for zoledronic acid or denosumab in men beginning ADT for bone metastases.**

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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.

Table 1.
TNM Staging System For Prostate Cancer

Primary Tumor (T)

Clinical

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

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

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

Pathologic(pT)*

pT2	Organ confined
pT2a	Unilateral, involving one-half of one side or less
pT2b	Unilateral, involving more than one-half of one side but not both sides
pT2c	Bilateral disease
pT3	Extraprostatic extension
pT3a	Extraprostatic extension or microscopic invasion of the bladder neck**
pT3b	Seminal vesicle invasion
pT4	Invasion of bladder, rectum

*Note: There is no pathologic T1 classification.

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

Regional Lymph Nodes (N)

Clinical

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

Pathologic

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

Distant Metastasis (M)*

M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

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

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ANATOMIC STAGE/PROGNOSTIC GROUPS *

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA <20	Gleason 7
	T1a-c	N0	M0	PSA ≥10 <20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥20	Any Gleason
	T1-2	N0	M0	Any PSA	Gleason ≥8
III	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

*Note: When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

Histopathologic Type

This classification applies to adenocarcinomas and squamous carcinomas, but not to sarcoma or transitional cell carcinoma of the prostate. Adjectives used to describe variants of prostate adenocarcinomas include mucinous, signet ring cell, ductal, adenosquamous and neuroendocrine small cell carcinoma. Transitional cell (urothelial) carcinoma of the prostate is classified as a urethral tumor. There should be histologic confirmation of the disease.

Histopathologic Grade (G)

Gleason score is recommended because as the grading system of choice, it takes into account the inherent morphologic heterogeneity of prostate cancer, and several studies have clearly established its prognostic value. A primary and a secondary pattern (the range of each is 1–5) are assigned and then summed to yield a total score. Scores of 2–10 are thus theoretically possible. The vast majority of newly diagnosed needle biopsy detected prostate cancers are graded Gleason score 6 or above. (If a single pattern of disease is seen, it should be reported as both grades. For example, if a single focus of Gleason pattern 3 disease is seen, it is reported as Gleason score 3 + 3 = 6.) In a radical prostatectomy, if a tertiary pattern is present, it is commented upon but not reflected in the Gleason score. It is recommended that radical prostatectomy specimens should be processed in an organized fashion where a determination can be made of a dominant nodule or separate tumor nodules. If a dominant nodule/s is present, the Gleason score of this nodule should be separately mentioned as this nodule is often the focus with highest grade and/or stage of disease.

Gleason X	**Gleason score** cannot be processed
Gleason ≤6	Well differentiated (slight anaplasia)
Gleason 7	Moderately differentiated (moderate anaplasia)
Gleason 8-10	Poorly differentiated/undifferentiated (marked anaplasia)

Discussion

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.

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Overview

Prostate cancer has surpassed lung cancer as the most common cancer in men. It is generally accepted 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 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 health care expenses, while decreasing the value of PSA and digital rectal exam (DRE) as early detection tests.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for prostate cancer, an electronic search of the PubMed database was performed to obtain key literature in prostate cancer published between 09/04/2013 and 09/04/2014, using the following search terms: prostate cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 260 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Estimates of Life Expectancy

Estimates of life expectancy have emerged as a key determinant of primary treatment, particularly when considering active surveillance or observation. While it is possible to estimate life expectancy for groups of men, it is more difficult to extrapolate these estimates to an individual patient. Life expectancy can be estimated using the Minnesota Metropolitan Life Insurance Tables or the Social Security Administration Life Insurance Tables[2] and adjusted for individual patients by adding or subtracting 50% based upon whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively.[3] As an example, the Social Security Administration Life Expectancy for a 65-year-old American man is 16 years. If judged to be in the upper quartile of health, a life expectancy of 24 years is assigned. If judged to be in the lower quartile of health, 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 going 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 Guidelines 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 observed in men placed in the high-risk group by clinical stage (T3a) compared to 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[8-10] 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,[11] radical prostatectomy,[12-14] neurovascular bundle preservation[15-17] or omission of pelvic lymph node dissection (PLND) during radical prostatectomy,[18] brachytherapy,[12,19-21] or external beam radiation therapy (EBRT).[12,22] Biochemical progression-free survival can be reassessed postoperatively using age, diagnostic serum PSA, and pathologic grade and stage.[23,24] Potential success of adjuvant or salvage radiation therapy (RT) after unsuccessful radical prostatectomy can be assessed using a nomogram.[12,25]

None of the current models predict with perfect accuracy, and only some of these models predict metastasis[12,24,26,27] and cancer-specific death.[14,28,29] 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.[30] The NCCN Guidelines Panel recommends that NCCN risk groups be used to begin the discussion of options for the treatment of clinically localized prostate cancer, and that nomograms be used to provide additional and more individualized information.

Molecular Testing

Personalized or precision medicine is a goal for many translational and clinical investigators. The Institute of Medicine has defined clearly lessons learned that should accelerate the development of useful biomarkers[31] to inform men and their physicians about more proper choices for treatment of localized prostate cancer. Dr. Hayes has warned us that a “bad tumor marker is as bad as a bad drug”.[32,33] The NCCN Prostate Cancer Guidelines Panel takes pride in its leadership regarding the need for life expectancy estimation, use of nomograms and recommendations for active surveillance as the only option for men with low risk prostate cancer and life expectancy less than 10 years or very low risk prostate cancer and life expectancy less than 20 years. American men continue to under select active surveillance for very low or low risk prostate cancer largely due to uncertainty about the risk of disease progression, an uncertainty that could be reduced by a molecular biomarker that can be measured accurately and reproducibly and provide prognostic or predictive information beyond NCCN risk group assignment and currently available tables and nomograms. Two tissue-based molecular assays appear further along in development and clinical use.

The Prolaris assay produces a cell cycle progression (CCP) score from RNA expression levels of 31 genes involved in CPP.[34] The Oncotype DX Prostate Cancer assay produces a Genomic Prostate Score (GPS) from RNA expression levels of 17 genes from 4 different molecular pathways (stromal response, cellular organization, androgen signaling and cell proliferation).[35,36] These tissue-based molecular assays can be performed on most formalin-fixed, paraffin-embedded prostate specimens. For example, Prolaris has been successful in 93% of radical prostatectomy specimens[37] and 79% of diagnostic prostate biopsy specimens[38]).

The Prolaris CCP score has been demonstrated predictive when applied in prospective-retrospective designs for biochemical recurrence or metastasis after radical prostatectomy,[34,39] for survival when men were observed after diagnosis on transurethral resection of prostate[34,39] or diagnostic needle biopsy,[38] and for biochemical recurrence and survival after external beam radiation therapy.[40] The Oncotype DX GPS was developed from evaluation of a diagnostic prostate biopsy and radical prostatectomy series from Cleveland Clinic and validated in a diagnostic prostate biopsy and radical prostatectomy series from University of California, San Francisco.[35] GPS performed in the diagnostic prostate biopsy has provided information beyond usual clinical information that predict the likelihood of Gleason sum 7 or extraprostatic disease on radical prostatectomy.[35] Prolaris has changed treatment recommendations in 32% to 65% of cases and may enhance adherence to the treatment recommended.[41,42] Oncotype DX GPS improved upon NCCN risk group assignment, which may enhance rates of compliance with recommended active surveillance or diminish the number of surveillance prostate biopsies.[35]

Both molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. Their clinical utility awaits evaluation by prospective, randomized clinical trials, which are unlikely to be done. The marketplace and comparative effectiveness research may be the only means for these tests and others like them to gain their proper place for better risk stratification for men with clinically localized prostate cancer.

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 (conventional Tc EDTMP scan), PET, and advanced MRI such as spectroscopy and diffusion-weighted imaging (DWI). More details on each technique are outlined under *Principles of Imaging* in the algorithm.

Transrectal ultrasonography (TRUS) is the most common technique for anatomic visualization of the prostate. TRUS is used to guide transrectal biopsies, and can be considered for patients with biochemical recurrence after surgery.

The utility of imaging for men with an early biochemical recurrence after radical prostatectomy depends on disease risk prior to operation, pathologic stage and grade and PSA and PSA doubling time after recurrence. Low- and intermediate-risk patients with low serum PSA levels postoperatively have a very low risk of positive bone scans or CT scans.[43,44] In a series of 414 bone scans performed in 230 men with a biochemical recurrence after RP, the rate of a positive bone scan for men with PSA less than 10 ng/mL was only 4%.[45] Serial PSA measurements can be helpful in stratifying men at highest risk of progression and metastases. Some men have detectable PSA after radical prostatectomy due to benign prostate tissue in the prostate fossa. They have low stable PSAs and a very low risk of prostate cancer progression.[46]

The use of multiparametric MRI (mpMRI) in the staging and characterization of prostate cancer has developed in the last few years. To be defined as “multi-parametric”, MRI images need to be acquired with at least one more sequence apart from the anatomical T2 weighted one, such as diffusion weighed images (DWI) or dynamic contrast enhanced images (DCE). Furthermore, a high quality mpMRI requires a 3.0 T magnet; the need for an endorectal coil remains controversial.

Evidence supports the implementation of mpMRI in several aspects of prostate cancer management. First, mpMRI helps detect large and poorly differentiated tumors (i.e. Gleason score ≥7).[47] MpMRI has been incorporated into MRI-TRUS fusion targeted biopsy protocols, which has led to an increase in the diagnosis of high grade tumors with fewer biopsy cores, while reducing detection of low-grade and insignificant tumors.[48,49] Second, mpMRI aids in the detection of extracapsular extension (T staging), with high negative predictive values in low-risk men.[50] MpMRI results may inform decision-making regarding nerve-sparing surgery.[51] Third, mpMRI has been shown equivalent to CT scan for N staging.[52,53] Finally, mpMRI out-performs bone scan and targeted X-rays for M staging, with sensitivity 98% to 100% and specificity 98% to 100% (vs. sensitivity 86% and specificity 98–100% for bone scan plus targeted X-rays).[54]

C-11 choline PET/CT has been used to detect and differentiate prostate cancer from benign tissue.[55] The sensitivity and specificity of the technique in restaging patients with biochemical failure are 85% and 88%, respectively.[56] C-11 choline PET/CT may be useful to detect distant metastases in these patients.

Risks of Imaging

As with any medical procedure, imaging is not without risk. Some of these risks are concrete and tangible, while others are less direct. Examples of risks associated with imaging include exposure to ionizing radiation, adverse reaction to contrast media, false positive scans, and over-detection.

Deterministic and stochastic are two types of effects from exposure to ionizing radiation by x-ray, CT, or PET/CT. Deterministic effects are those that occur at a certain dose level, and include events such as cataracts, radiation burns, etc. Below the dose threshold, no effect is

seen. Medical imaging is nearly always below the threshold for deterministic effects. Stochastic effects tend to occur late, and increase in likelihood as dose increases, but for which no lower “safe” limit is known.

The major stochastic effect of concern in medical imaging is radiation-induced malignancy. Unfortunately, no direct measurements are available to determine risk of cancer arising from one or more medical imaging events, so risks are calculated based on other models (such as atomic bomb survivors). The literature is conflicting with regards to the precise risk of secondary malignancies in patients undergoing medical imaging procedures. It is accepted that there is a small but finite risk of developing secondary malignancies as a result of medical imaging procedures, and that the risk is greatest in young patients. However, the absolute risk of fatal malignancy arising from a medical imaging procedure is very low, and is difficult to detect given the prevalence of cancer in the population and the multiple factors that contribute to oncogenesis.[57] Despite the low risk from medical imaging with ionizing radiation, efforts should be made to minimize dose from these procedures, which include judicious use of imaging only when justified by the clinical situation. One must also keep in mind that harm can arise from not imaging a patient, through disease non-detection or erroneous staging.

Many imaging studies make use of contrast material delivered by oral, intravenous, or rectal routes. The use of contrast material may improve study performance, but reactions to contrast material can occur and they should be used only when warranted. Some patients develop adverse reactions to iodinated intravenous contrast material. Most reactions are mild cutaneous reactions (e.g. hives, itching) but occasionally severe reactions can be life-threatening (e.g. bronchospasm, anaphylactoid). With current non-ionic contrast materials, the risk of severe reaction is low, on the order of 1:170,000 injections.[58] Both iodinated CT contrast material and gadolinium-based MR contrast materials can affect renal function, particularly in the setting of impaired renal function at baseline. MR contrast materials also have been associated with systemic nephrogenic sclerosis in patients with impaired renal function. Centers performing imaging studies with contrast materials should have policies in place to address the use of contrast in these patients.

Every imaging test has its limitations in sensitivity, specificity, and accuracy, which are modulated further by the expertise of the interpreting physician. While harm can arise from the failure to detect a tumor or tumor recurrence (i.e. false negative), harm to the patient and added expense to the medical system also can result from false positive scans. Improper interpretation of a benign finding as being potentially malignant can lead to significant patient anxiety, further unnecessary imaging, and invasive procedures that carry their own risk of adverse outcome.

Accurate and medically-relevant interpretation of imaging studies requires familiarity and expertise in the imaging modality, attention to detail in image review, knowledge of tumor biology, and familiarity with treatment options and algorithms. Challenging cases are best addressed through direct communication, either physician-to-physician or through a multidisciplinary tumor board setting.

Medical imaging is a critical tool in the evaluation and management of patients with malignancy. However, as with any medical procedure, imaging is not without risks to patients. Inappropriate use of imaging has also been identified as a significant contributor to healthcare costs in the United States and worldwide. Therefore, imaging should be performed only when medically appropriate, and in a manner which

reduces risk (eg, minimizing radiation dose). An algorithmic approach to the use of imaging, such as by NCCN and the Appropriateness Criteria developed by the American College of Radiology,[59] can help with medical decision-making.

Observation

Observation involves monitoring the course of prostate cancer with the expectation to deliver palliative therapy for development of symptoms or change in exam or PSA that suggests symptoms are imminent. Observation thus differs from active surveillance. The goal of observation is to maintain quality of life by avoiding non-curative treatment when prostate cancer is unlikely to cause mortality or significant morbidity. The main advantage of observation is avoidance of possible side effects of unnecessary definitive therapy or 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 and colleagues[60] observed that only 13% of men developed metastases 15 years after diagnosis of T0-T2 disease and only 11% had died from 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's discretion. Monitoring should include PSA and DRE no more often than every 6 months, but will not involve surveillance biopsies. 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 to defer treatment and its potential side effects. Because these patients have a longer life expectancy, they should be followed closely and treatment should start promptly should the cancer progress so as not to miss the chance for cure.

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) decreased initial costs. The disadvantages of active surveillance include: 1) chance of missed opportunity for cure; 2) the cancer may progress or metastasize before treatment; 3) treatment of a larger, more aggressive cancer may be more complex with greater side effects; 4) nerve sparing at subsequent radical prostatectomy may be more difficult, which may reduce the chance of potency preservation after operation; 5) the increased anxiety of living with an untreated cancer;[61] 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 NCCN Guidelines Panel remains concerned about the problems of over-treatment related to the increased frequency of diagnosis of prostate cancer from widespread use of PSA for early detection or screening (see NCCN Guidelines for Prostate Cancer Early Detection).

The debate about the need to diagnose and treat every man who has prostate cancer is fueled by: the high prevalence of prostate cancer

upon autopsy of the prostate[62]; the high frequency of positive prostate biopsies in men with normal DREs and serum PSA values[63]; 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 [64,65] or 100 men with low-risk prostate cancer[66] to prevent one death from the disease. The controversy regarding over-treatment of prostate cancer and the value of prostate cancer early detection[64-70] has been informed further by publication of the Goteborg study, a subset of the European Randomized Study for Screening of Prostate Cancer (ERSPC).[71] Many believe that this study best approximates proper use of PSA for early detection since 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 >3 and >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 to 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 to 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 as a whole where 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.[72]

The best models of prostate cancer detection and progression estimate that 23% to 42% of all U.S. screen-detected cancers are overtreated[73] and that PSA detection was responsible for up to 12.3 years of lead-time bias.[74] The NCCN Guidelines Panel responded to these evolving data with careful consideration of which men should be recommended active surveillance. However, the NCCN Guidelines 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 and colleagues[75] introduced clinical criteria to predict pathologically “insignificant” prostate cancer. Insignificant prostate cancer is identified by: clinical stage T1c, biopsy Gleason score ≤6, the presence of disease in fewer than 3 biopsy cores, ≤50% prostate cancer involvement in any core, and PSA density <0.15 ng/mL/g. Despite the usefulness of these criteria, physicians are cautioned against using these as the sole decision maker. Studies have shown that as many as 8% of cancers that qualified as being insignificant using the Epstein criteria were not organ-confined based on postoperative findings.[23,76] A new nomogram may be better.[77] Although many variations upon this definition have been proposed (reviewed by Bastian, and colleagues[78]), a consensus of the NCCN Guidelines Panel was reached 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.[74]

The role for active surveillance should increase with the shift towards earlier-stage diagnosis attributed to PSA testing. However, results from randomized or cohort studies comparing this deferral strategy with immediate treatment are mixed, partly due to heterogeneity of the patient populations (reviewed by Sanda and Kaplan[79]).

Ultimately, a recommendation for active surveillance must be based on careful individualized weighing of a number of factors: 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 to men of other races.[80]

Surveillance Program and Reclassification Criteria

Each of the major active surveillance series has used different criteria for reclassification.[81-85] Reclassification criteria have been met by 23% of men with a median follow-up of 7 years in the Toronto experience,[83] 33% of men with a median follow-up of 3 years in the Johns Hopkins experience,[85] and 16% of men with a median follow-up of 3.5 years in the UCSF experience[82] (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 PSA doubling time <3 years could not be improved upon by using a PSA threshold of 10 or 20, PSA doubling time calculated in various ways, or PSA velocity >2 ng/mL/yr.[86] 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.[87] Unfortunately, neither PSA doubling time (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 treatment of most men who demonstrate reclassification on prostate biopsy prevents evaluation of biopsy reclassification as a criterion for treatment or reduction of survival. Early experience supports the utilization of mpMRI in biopsy protocols to better risk-stratify men under active surveillance.[88,89]

Repeat biopsy is useful to determine whether higher-grade elements are evolving although the risks appear small,[90] which 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.[85] However, whether treatment of all who progress to Gleason pattern 4 was necessary remains uncertain. Studies remain in progress to identify the best trigger points when 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.[83] 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%.[83] Of the 30% (n=145) of men who progressed, 8% were from an increase in Gleason score, 14% were for PSA doubling time <3 years, 1% were for development of a prostate nodule, and 3% were for anxiety. One hundred and thirty-five of these 145 men were treated: 35 by radical prostatectomy, 90 by RT with or without androgen deprivation therapy (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,[85] 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 where 74 men who progressed on active surveillance and underwent radical prostatectomy were compared with 148 men who were matched by clinical parameters. The two groups were similar by pathologic Gleason grade, pathologic stage, and margin positivity. All men treated by radical prostatectomy after progression on active surveillance had freedom from biochemical progression at median follow-up 37.5 months, compared to 97% of men in the primary radical prostatectomy group at median follow-up 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,[68] those with urinary tract infection are often fluoroquinolone-resistant,[91] and radical prostatectomy may become technically challenging after multiple sets of biopsies, especially as it pertains to potency preservation.[92]

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 and colleagues[14] 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 to watchful waiting in a randomized trial of 695 patients with early-stage prostate cancer (mostly T2).[93,94] 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.[93] The reduction in mortality was confirmed at 23 years of followup, with an absolute difference of 11%.[94] Overall, 8 men needed to be treated to avert one death; that number fell to 4 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.[95] Patients without these characteristics showed higher 10-year biochemical-free and disease-specific survival after radical prostatectomy compared to 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.[96,97] Overall and cancer-specific 10-year survival ranged from 54% to 89% and 70% to 83%, respectively.[96] Patient selection is important and salvage prostatectomy should only be performed by highly experienced surgeons.

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.[98,99] Laparoscopic and robot-assisted radical prostatectomy are used commonly and are considered comparable to conventional approaches in experienced hands.[100,101] In a cohort study using U.S. 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.[102] A second large study has reported similar findings.[103] Oncologic outcome of a robotic versus open approach was similar when assessed by use of additional therapies[102] or rate of positive surgical margins,[104] although longer follow-up is necessary. A meta-analysis on 19 observational studies (n=3893) reported less blood loss and lower transfusion rates with minimally invasive techniques than with open operation.[104] Risk of positive surgical margins was the same. Two recent meta-analyses showed a statistically significant advantage in favor of a robotic approach compared to an open approach in 12-month urinary continence [105] and potency recovery.[106]

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.[107] 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 urological procedures than those who underwent radical prostatectomy, but higher incidence for hospital admissions, rectal or anal procedures, open surgical procedures, and secondary malignancies.[108]

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.[109] 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.[110] Replacement of resected nerves with nerve grafts does not appear to be effective for patients undergoing wide resection of the neurovascular bundles.[111] The ability of mpMRI to detect extracapsular extension can aid in decision-making in nerve-sparing surgery.[51]

Pelvic Lymph Node Dissection

The decision to perform PLND should be guided by the probability of nodal metastases. The NCCN Guidelines Panel chose 2% as the cutoff for PLND since this avoids 47.7% of PLNDs at a cost of missing 12.1% of positive pelvic lymph nodes.[112]

PLND should be performed using an extended technique.[113,114] An extended PLND includes removal of all node-baring 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.[115-117] A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to elimination of microscopic metastases.[116,118-120] PLND can be performed safely laparoscopically, robotically, or open, and complication rates should be similar for the three approaches.

Radiation Therapy

External Beam Radiation Therapy

Over the past several decades, RT techniques have evolved to allow higher doses of radiation to be administered safely. 3D 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 lower risk of late effects.[26,121-123] The second-generation 3D technique, intensity-modulated radiation therapy (IMRT), is used increasingly in practice[124] because compared to 3D-CRT, it significantly reduces the risk of gastrointestinal toxicities and rates of salvage therapy in some, but not all studies, although treatment cost is increased.[125-128]

Daily prostate localization using image-guided radiation therapy (IGRT) 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, or 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.[129-133] Kuban and colleagues[132] published an analysis on 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 Gy compared to 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 >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. Intermediate-risk and high-risk patients should receive doses up to 81.0 Gy.[125,134,135] 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.[136,137] 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 operation, such as bleeding and transfusion-related effects, and risks associated with anesthesia, such as myocardial infarction and pulmonary embolus. 3D-CRT and IMRT techniques are available widely and are possible for patients over 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.[138]

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.[138,139] In addition, if the cancer recurs, salvage radical prostatectomy is associated with a higher risk of complications than primary radical prostatectomy.[140] 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 Guidelines Panel consensus 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.[141]

EBRT for High-Risk or Very High-Risk Patients

EBRT has demonstrated efficacy in patients at high risk and very high risk. One study randomized 415 patients to EBRT alone or EBRT plus 3-year ADT.[142] In another study (RTOG 8531), 977 patients with T3 disease treated with RT were randomized to adjuvant ADT or ADT at relapse.[143] Two other randomized phase III trials evaluated long-term ADT with or without radiation in mostly T3 patients.[144,145] In all four studies, the combination group showed improved disease-specific and overall survival compared to single-modality treatment.

EBRT for Node-positive Disease

See section *Adjuvant or Salvage Therapy after Radical Prostatectomy* under *NCCN Recommendations*.

Stereotactic Body Radiotherapy

The relatively slow proliferation rate of prostate cancer is reflected in a low α/β ratio,[146] 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.[147] 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 to standard radiation techniques.[146-152] According to a pooled analysis of phase II trials, the 5-year biochemical relapse free survival is 95%, 84%, and 81% for low-, intermediate-, and high-risk patients, respectively.[153] 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 to conventional fractionation (1.8-2.0 Gy per fraction). One retrospective study of 4005 patients reported higher genitourinary toxicity at 24 months after SBRT than IMRT (44% vs. 36%; P = .001).[154]

Brachytherapy

Brachytherapy is used traditionally for low-risk cases since earlier studies found it less effective than EBRT for high-risk disease.[6,155] 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.[156] Brachytherapy involves placing radioactive sources into the prostate tissue. There are currently two 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.[157] 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.[139] 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.[158,159]

Permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers (cT1c–T2a, Gleason grade 2-6, PSA <10 ng/mL) and selected patients with low volume intermediate-risk cancers. Brachytherapy may be combined with EBRT (45 Gy) with or without neoadjuvant ADT for intermediate-risk cancers, but the complication rate increases.[160,161] Patients with high-risk cancers are generally considered poor candidates for permanent brachytherapy alone.

Patients with very large or very small prostates, symptoms of bladder outlet obstruction (high International Prostate Symptom Score), or a previous TURP are not ideal candidates for brachytherapy. For these patients, implantation may be more difficult and there is an increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size, however, increased toxicity would be expected from ADT and prostate size may not decline. Post-implant dosimetry should be performed to document the quality of the implant.[162] 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.[163-166] Studies have demonstrated reduced risk of recurrence with the addition of brachytherapy to EBRT.[167-169] An analysis of a cohort of 12,745 high-risk patients found that treatment with brachytherapy (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 to EBRT alone.[170] Common boost doses include 9.5 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, or 4.0 to 6.0 Gy x 4 fractions. A commonly used regimen for HDR treatment alone includes 13.5 Gy x 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.[171,172] However, it remains unclear whether the ADT component contributes to outcome improvement. D'Amico and colleagues studied a cohort of 1342 patients with PSA over 20 ng/mL and clinical T3/T4 and/or Gleason score 8 to 10 disease.[173] Addition of either EBRT or ADT to brachytherapy did not confer an advantage over brachytherapy alone. The use of all three modalities reduced prostate cancer-specific mortality compared to 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.[174,175]

Two groups have observed a lower risk of urinary frequency, urgency, and rectal pain with HDR brachytherapy compared with LDR brachytherapy (permanent seed implant).[176,177] Vargas and colleagues[178] reported that HDR brachytherapy results in a lower risk of erectile dysfunction than LDR brachytherapy.

Proton Therapy

Proton beam radiation therapy has been used to treat cancer patients since the 1950's. Proponents of proton therapy argue that this form of radiation therapy could have advantages over X-ray (photon) based radiations in certain clinical circumstances. X-ray-based therapies like IMRT and proton therapy can deliver highly conformal doses to the prostate. Proton-based therapies will deliver less radiation dose to some of the surrounding normal tissues like muscle, bone, vessels and fat not immediately adjacent to the prostate. These tissues do not routinely contribute to the morbidity of prostate radiation, are relatively resilient to radiation injury, and so the benefit of decreased dose to these types of normal, non-critical tissues has not been apparent. The critical normal structures adjacent to the prostate that can create prostate cancer treatment morbidity include the bladder, rectum, neurovascular bundles, and occasionally small bowel.

The weight of the current evidence about prostate cancer treatment morbidity supports the notion that the volume of the rectum and bladder that receives radiobiologically high doses of radiation near the prescription radiation dose is what accounts for the likelihood of long-term treatment morbidity, as opposed to higher volume lower dose exposures. Numerous dosimetric studies have been performed trying to compare X-ray based IMRT plans to proton therapy plans to illustrate how one or the other type of treatment can be used to spare the bladder or rectum from the higher dose parts of the exposure. These studies may suffer from the biases and talents of the investigators in planning and creating computer models of dose deposition for one therapy over the other.[179] Although dosimetric studies in-silico can suggest that the right treatment planning can make an IMRT plan beat a proton therapy plan and vice-versa, they do not predict accurately clinically meaningful endpoints.

Some clinically meaningful toxicity comparative effectiveness studies have been published recently. Several comparisons between men treated with proton therapy or EBRT show similar early toxicity rates.[180,181] A single-center report of prospectively collected quality-of-life data for proton therapy at 3 months, 12 months, and >2 years after treatment revealed significant problems with incontinence, bowel

dysfunction, and impotence. [180] In that report, only 28% of men with normal erectile function maintained normal erectile function after therapy. A prospective quality of life comparison of patient-reported outcomes using the EPIC instrument between IMRT (204 patients) and proton therapy (1234 patients) concluded that "No differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts" after up to 2 years of followup.[182] The largest retrospective comparative effectiveness analysis to date comparing IMRT to proton therapy has been performed using SEER-Medicare claims data for the following long-term endpoints: gastrointestinal morbidity, urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, and hip fractures.[183] With followup as mature as 80 months and using both propensity scoring and instrumental variable analysis, the authors concluded that men receiving IMRT therapy had statistically significantly lower gastrointestinal morbidity than patients receiving proton therapy, whereas rates of urinary incontinence, non-incontinence urinary morbidity, sexual dysfunction, hip fractures, and additional cancer therapies were statistically indistinguishable between the cohorts.

The costs associated with proton beam facility construction and proton beam treatment are high compared to the expense of building and using the more common photon linear accelerator based practice.[181] The American Society of Radiation Oncology (ASTRO) has evaluated proton therapy and created a model policy to support the society's position on payment coverage for proton therapy. ASTRO's current policy states that "Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry."[184,185]

An ongoing prospective randomized trial is accruing patients and comparing prostate proton therapy to prostate IMRT. The NCCN panel believes there is no clear evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to X-ray based regimens at clinics with appropriate technology, physics, and clinical expertise.

Radiation for Distant Metastases

Radiation is an effective means of palliating bone metastases from prostate cancer. In May 2013, the Food and Drug Administration (FDA) approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This first-in-class radiopharmaceutical was approved for treatment of metastatic castration-recurrent prostate cancer (CRPC) in patients with symptomatic bone metastases and no known visceral metastatic disease. Approval was based on clinical data from a multicenter, phase III, randomized trial (ALSYMPCA) including 921 men with symptomatic CRPC, 2 or more bone metastases, and no known visceral disease.[186] Fifty-seven percent of the patients received prior docetaxel and all patients received best supportive care. Patients were randomized in a 2:1 ratio to 6 monthly radium-223 intravenous injections or placebo. Compared to placebo, radium-223 significantly improved overall survival (median 14.9 months vs. 11.3 months; HR, 0.70; 95% CI, 0.058–0.83; $P < .001$) and prolonged time to first skeletal-related event (SRE) (median 15.6 months vs. 9.8 months). Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, 13% anemia), likely due to the short range of radioactivity.[186] Fecal elimination of the agent led to generally mild non-hematological side effects, which included nausea, diarrhea, and vomiting.

Beta-emitting radiopharmaceuticals are an effective and appropriate option for patients with wide-spread metastatic disease, particularly if they are no longer candidates for effective chemotherapy.[187] Since

many patients have multifocal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Unlike the alpha-emitting agent radium-223, beta-emitters confer no survival advantage and are palliative. Radiopharmaceuticals developed for the treatment of painful bone metastases most commonly used for prostate cancer include strontium-89 (89Sr) and samarium-153 (153Sm).[188]

Isolated symptomatic bone metastases can be managed with EBRT. Recent studies have confirmed the common practice in Canada and Europe of managing prostate cancer with bone metastases with a short course of radiation. A short course of 8 Gy x 1 is as effective as and less costly than 30 Gy in 10 fractions.[189] In a randomized trial of 898 patients with bone metastases, grade 2-4 acute toxicity was observed less often in the 8-Gy arm (10%) than the 30-Gy arm (17%) (P = .002); however, the retreatment rate was higher in the 8-Gy group (18%) than in the 30-Gy group (9%) (P < .001).[190] In another study of 425 patients with painful bone metastases, a single dose of 8 Gy was non-inferior to 20 Gy in multiple fractions in terms of overall pain response to treatment.[191] Most patients should be managed with a single fraction of 8 Gy for non-vertebral metastases based on therapeutic guidelines from the American College of Radiology.[187]

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 following cryotherapy ranged from 65% to 92% in low-risk patients using different definitions of biochemical failure.[192] A report suggests that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer.[193] A study by Donnelly and colleagues[194] randomly assigned 244 men with T2 or T3 disease to either cryotherapy or RT. All patients received neoadjuvant ADT. There was no difference in 3-year overall or disease-free survival. Patients who received cryotherapy reported poorer sexual function.[195] For patients with locally advanced cancer, cryoablation was associated with lower 8-year biochemical progression-free rate compared to EBRT in a small trial of 62 patients, although disease-specific and overall survival were similar.[196]

Other emerging local therapies, such as high intensity focused ultrasound (HIFU) and vascular-targeted photodynamic (VTP), also warrant further study.[197]

Androgen Deprivation Therapy

ADT is administered as primary systemic therapy in advanced disease or as neoadjuvant/concomitant/adjuvant therapy in combination with radiation in localized or locally advanced prostate cancers.

Types of ADT

ADT can be accomplished using bilateral orchiectomy (surgical castration) or a luteinizing hormone-releasing hormone (LHRH, also known as gonadotropin-releasing hormone or GnRH) agonist or antagonist (medical castration), which are equally effective. In patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone, anti-androgen therapy should precede or be coadministered with LHRH agonist for at least 7 days to diminish ligand binding to the androgen receptor.[198,199] LHRH antagonists rapidly and directly inhibit the release of androgens, unlike LHRH agonists that initially stimulate LHRH receptors before leading to hypogonadism. Therefore, no initial flare is associated with these agents and no coadministration of anti-androgen

is necessary. Medical or surgical castration combined with an anti-androgen is known as combined androgen blockade (CAB). No prospective randomized studies have demonstrated a survival advantage with CAB over the serial use of an LHRH agonist and an anti-androgen.[200] Meta-analysis data suggest that bicalutamide may provide an incremental relative improvement in overall survival by 5% to 20% over LHRH agonist monotherapy, but a clinical trial is necessary to test this hypothesis.[201,202] More complete disruption of the androgen axis (finasteride or dutasteride, anti-androgen, plus medical or surgical castration) provides little if any benefit over castration alone.[203] Anti-androgen monotherapy appears to be less effective than medical or surgical castration and is not recommended as primary ADT.

ADT for Low-Risk Patients

In the community, ADT has been used commonly as primary therapy for early-stage, low-risk disease, especially in the elderly. This practice has been challenged by a large cohort study of 66,717 elderly men with T1-T2 tumors.[204] No 15-year survival benefit was found in patients receiving ADT compared to observation alone. Similarly, another cohort study of 15,170 men diagnosed with clinically localized prostate cancer who were not treated with curative intent therapy reported no survival benefit from primary ADT after adjusting for demographic and clinical variables.[205] Placing 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 three randomized trials containing 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).[206-208] Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly high-risk men (RTOG 8610).[209] 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 in the *Radiation Therapy* section, 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 to single-modality treatment in randomized phase III studies.[142-145]

Increasing evidence favors long-term over short-term neoadjuvant/concurrent/adjuvant ADT for high-risk patients. The RTOG 9202 trial included 1521 patients with T2c-T4 prostate cancer who received 4 months of ADT before and during RT.[210] 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 European Organization for Research and Treatment of Cancer (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-T3, N0 disease.[211] 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.[212]

Adjuvant ADT after Radical Prostatectomy

Neoadjuvant or adjuvant ADT generally confers no added benefit in men who have undergone radical prostatectomy.[213] The role of adjuvant

ADT after radical prostatectomy is restricted to cases where positive pelvic lymph nodes are found, although reports in this area reveal mixed findings. Messing and colleagues randomly assigned patients to immediate ADT or observation who were found to have positive lymph nodes at the time of radical prostatectomy.[214] 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.[200] 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 to observation.[215]

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.[216,217]

ADT for Biochemical Recurrence

Patients with a rising PSA level and with no symptomatic or clinical evidence of cancer after definitive treatment present a therapeutic dilemma regarding the role of ADT. Some of these patients will ultimately die of their cancer. Timing of ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient and physician anxiety, the short-term and long-term side effects of ADT, and underlying co-morbidities of the patient. Although early, sustained ADT is acceptable, an alternative is close observation until progression of cancer, at which time appropriate therapeutic options may be considered. Earlier ADT may be better than delayed therapy, although the definitions of early and late (ie, what level of PSA) remain controversial. Because the benefit of ADT is unclear,[200] treatment should be individualized until definitive studies are completed. Patients with an elevated PSA and/or a shorter PSA doubling time (rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.

Intermittent Versus Continuous ADT (Non-metastatic)

ADT is associated with substantial side effects, which generally increase with the duration of treatment. Intermittent ADT is an approach based on the premise that cycles of androgen deprivation followed by re-exposure may delay “androgen independence,” reduce treatment morbidity, and improve quality of life.[218,219]

The Canadian-led PR.7 trial provided the best phase III data to date comparing intermittent and continuous ADT in non-metastatic patients experiencing biochemical failure. Crook and colleagues[220] randomly assigned 1386 patients with PSA >3 ng/mL after radiation therapy to intermittent ADT or continuous ADT. At a median follow-up of 6.9 years, the intermittent approach was non-inferior to continuous ADT with respect to overall survival (8.8 vs. 9.1 years, respectively; HR, 1.02; 95% CI, 0.86–1.21). More patients died from prostate cancer in the intermittent ADT arm (120 of 690 patients) than the continuous ADT arm (94 of 696 patients), but this was balanced by more non-prostate cancer deaths in the continuous ADT arm. Physical function, fatigue, urinary problems, hot flashes, libido, and erectile dysfunction showed modest improvement in the intermittent ADT group.

The test population was heterogenous, so it remains unclear which of these asymptomatic patients benefitted from treatment. It is possible that many of these patients could have delayed ADT without harm. The test population had a low disease burden and 59% of deaths in the trial were not related to prostate cancer. Follow-up longer than 6.9 years

may be required for disease-specific deaths to out-balance deaths by other causes.

An unplanned Cox regression analysis of the trial showed that men with Gleason sum >7 in the continuous ADT arm had a median survival (8 years) that was 14 months longer than those with the same Gleason sum in the intermittent ADT arm (6.8 years).[220] The caveats to this analysis are that pathology was not centrally reviewed and the study was not powered to detect a small difference based on Gleason sum.

Consideration for Choosing Intermittent or Continuous ADT

If ADT is going to be administered at all, intermittent ADT is a reasonable option based on non-inferiority in the NCIC PR-7 trial. However, those with a Gleason score of 8 or more should consider continuous over intermittent ADT because of the 14 month difference in median survival favoring the CAD arm.[221] In this situation, patients should be given the option to weigh the effects of ADT on quality of life against the possible impact on survival.

ADT for Nodal or Metastatic Disease

The EORTC 30846 trial randomized 234 treatment-naïve, node-positive patients to immediate versus delayed ADT.[222] At 13 years, the authors report similar survival between the two arms, although the study was not powered to show non-inferiority.

ADT is the gold standard of initial treatment for patients with metastatic disease at presentation.[200] A PSA value of 4 ng/mL or less after 7 months of ADT is associated with improved survival of patients newly diagnosed with metastatic prostate cancer.[223]

Intermittent versus Continuous ADT (Metastatic)

Hussain and colleagues[224] conducted the SWOG (Southwest Oncology Group) 9346 trial to compare intermittent and continuous ADT in metastatic patients. After 7 months of induction ADT, 1535 patients whose PSA dropped to 4 ng/mL or below (thereby demonstrating androgen-sensitivity) were randomized to intermittent or continuous ADT. At a median follow-up of 9.8 years, median survival was 5.1 years for the intermittent ADT arm and 5.8 years for the continuous ADT arm. The hazard ratio for death with intermittent ADT was 1.10 with a 90% confidence interval between 0.99 and 1.23, which exceeded the pre-specified upper boundary of 1.20 for non-inferiority. The authors stated that the survival results were inconclusive, and that a 20% greater mortality risk with the intermittent approach cannot be ruled out. The study demonstrated better erectile function and mental health in patients receiving intermittent ADT at 3 months, but the difference became insignificant thereafter, most likely due to contamination of assessments of those on the intermittent arm who were actually back on ADT at the pre-specified time points.

In a post hoc stratification analysis of the trial, patients with minimal disease had a median survival of 5.4 years when receiving intermittent ADT versus 6.9 years when receiving continuous ADT (HR, 1.19; 95% CI, 0.98–1.43).[224] The median survival was 4.9 years in the intermittent ADT arm compared to 4.4 years in the continuous ADT arm for patients with extensive disease (HR, 1.02; 95% CI, 0.85–1.22). These subgroup analyses are hypothesis-generating.

Two meta-analyses on randomized controlled trials reported no difference in survival between the intermittent ADT and continuous ADT.[225,226]

Considerations for choosing intermittent or continuous ADT

All patients with metastatic disease should be treated initially with ADT. After 7 months of ADT, patients can be assigned a risk category based on the PSA value at that time point[223]: low risk is defined by a PSA less than 0.2 ng/mL (median survival of 75 months); intermediate risk is defined by PSA between 0.2 and 4.0 ng/mL (median survival 44 months), and high risk is defined by PSA higher than 4.0 ng/mL (median survival 13 months). Those patients who have few or no symptoms related to ADT after 7 months of therapy will not benefit from intermittent ADT in terms of quality of life, and therefore continuous therapy makes sense as it is easier to administer.[221] However, for those patients with significant side effects impacting quality of life, intermittent ADT should be considered for those with low or intermediate risk after a discussion about the impact on survival. Those with high risk disease probably have early castration resistant disease and should stay on ADT. A final consideration is based on a subgroup analysis of S9346 that suggested that those who present initially with pain have better survival on continuous than intermittent therapy.

Adverse Effects of Traditional ADT

ADT has a variety of adverse effects including hot flashes, hot flushes, vasomotor instability, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes, acute kidney injury, and cardiovascular disease.[227-229] In general, the side effects of continuous ADT increase with the duration of treatment. Patients and their medical providers should be advised about these risks prior to treatment.

Bone Health During ADT

ADT is associated with greater risk for clinical fractures. In large population-based studies, for example, ADT was associated with a 21% to 54% relative increase in fracture risk.[230-232] Longer treatment duration conferred greater fracture risk. Age and comorbidity also were associated with higher fracture incidence. ADT increases bone turnover and decreases bone mineral density,[233-236] a surrogate for fracture risk in patients with non-metastatic disease. Bone mineral density of the hip and spine decreases by approximately 2% to 3% per year during initial therapy. Most studies have reported that bone mineral density continues to decline steadily during long-term therapy. ADT significantly decreases muscle mass,[237] and treatment-related sarcopenia appears to contribute to frailty and increased risk of falls in older men.

The NCCN Guidelines Panel recommends screening and treatment for osteoporosis according to guidelines for the general population from the National Osteoporosis Foundation.[238] The National Osteoporosis Foundation guidelines include: 1) supplemental calcium (1200 mg daily) and vitamin D3 (800-1000 IU daily) for all men older than age 50 years; and 2) additional treatment for men when the 10-year probability of hip fracture is ≥3% or the 10-year probability of a major osteoporosis-related fracture is ≥20%. Fracture risk can be assessed using the algorithm FRAX®, recently released by WHO.[239] ADT should be considered "secondary osteoporosis" using the FRAX® algorithm.

Earlier randomized controlled trials have demonstrated that bisphosphonates increase bone mineral density, a surrogate for fracture risk, during ADT.[240-242] In 2011, the FDA approved denosumab as a treatment to prevent bone loss and fractures during ADT. Denosumab binds to and inhibits the receptor activator of NF-κB ligand (RANKL), thereby blunting osteoclast function and delaying generalized bone resorption and local bone destruction. Approval was based on a phase III study that randomized 1468 non-metastatic prostate cancer patients undergoing ADT to either biannual denosumab or placebo. At 24 months, denosumab increased bone mineral density by 6.7% and reduced fractures (1.5% vs. 3.9%) compared to placebo.[243] Denosumab

also was approved for prevention of SREs in patients with bone metastasis (see *Chemotherapy and Immunotherapy*).

Currently, treatment with denosumab (60 mg every 6 months), zoledronic acid (5 mg IV annually), or alendronate (70 mg PO weekly) is recommended when the absolute fracture risk warrants drug therapy. A baseline dual-energy x-ray absorptiometry (DEXA) scan before start of therapy and a follow-up DEXA scan after one year of therapy is recommended by the International Society for Clinical Densitometry to monitor response. Use of biochemical markers of bone turnover is not recommended. There are no existing guidelines on the optimal frequency of vitamin D testing, but vitamin D levels can be measured when DEXA scans are obtained.

Diabetes and Cardiovascular Disease

In a landmark population-based study, ADT was associated with higher incidence of diabetes and cardiovascular disease.[244] After controlling for other variables, including age and comorbidity, ADT with a GnRH agonist was associated with a greater risk for new diabetes (HR, 1.44; $P < .001$), coronary artery disease (HR, 1.16; $P < .001$), and myocardial infarction (HR, 1.11; $P = .03$). Studies that have evaluated the potential relationship between ADT and cardiovascular mortality produced mixed results.[209,244-250]

Several mechanisms may contribute to a greater risk for diabetes and cardiovascular disease during ADT. ADT increases fat mass and decreases lean body mass.[237,251,252] ADT with a GnRH agonist increases fasting plasma insulin levels[253,254] and decreases insulin sensitivity.[255] ADT also increases serum levels of cholesterol and triglycerides.[253,256]

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

Hormone Therapy for CRPC

Most men with advanced disease eventually stop responding to traditional ADT and are categorized as castration-recurrent (also known as castration-resistant). Research has shown enhancement of autocrine and/or paracrine androgen synthesis in the tumor microenvironment of men receiving ADT.[257,258] This demonstrates the importance of androgen signaling from non-gonadal sources in CRPC, previously thought to be resistant to further hormone therapies. The development of novel hormonal agents demonstrating efficacy in the metastatic CRPC setting dramatically changed the paradigm of CRPC treatment.

Abiraterone Acetate

In April 2011, the FDA approved the androgen synthesis inhibitor, abiraterone acetate, in combination with low-dose prednisone, for the treatment of men with metastatic CRPC who have received prior chemotherapy containing docetaxel.

FDA approval in the post-docetaxel setting was based on the results of a phase III, randomized, placebo-controlled trial (COU-AA-301) in men with metastatic CRPC previously treated with docetaxel-containing regimens.[259,260] Patients were randomized to receive either abiraterone acetate 1000 mg orally once daily (n=797) or placebo once daily (n=398), and both arms received daily prednisone. In the final analysis, the median survival was 15.8 vs. 11.2 months in the abiraterone and

placebo arm, respectively (HR, 0.74; 95% CI, 0.64-0.86; *P* < .0001).[260] Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone acetate.[260,261]

FDA approval in the pre-docetaxel setting occurred December 10, 2012 and was based on a randomized phase 3 trial of abiraterone acetate and prednisone (n=546) versus prednisone alone (n=542) in men with asymptomatic or minimally symptomatic, metastatic CRPC.[262] Most men in this trial were not taking narcotics for cancer pain and none had visceral metastatic disease or prior ketoconazole exposure. The co-primary endpoint of radiographic progression-free survival was improved by treatment from 8.3 to 16.5 months (HR, 0.53; *P* < .001). Overall survival was improved by treatment from 27.2 months to not reached (HR, 0.75; *P* = .01), but this did not meet pre-specified statistical significance. Key secondary endpoints of time to symptomatic deterioration, time to chemotherapy initiation, time to pain progression, and PSA progression-free survival improved significantly with abiraterone treatment, and PSA declines (62% vs. 24% with >50% decline) and radiographic responses (36% vs. 16% RECIST responses) were more common.

The most common adverse reactions with abiraterone acetate/prednisone (>5%) were fatigue (39%); back or joint discomfort (28%-32%); peripheral edema (28%); diarrhea, nausea, or constipation (22%); hypokalemia (17%); hypophosphatemia (24%); atrial fibrillation (4%); muscle discomfort (14%); hot flushes (22%); urinary tract infection; cough; hypertension (22%, severe hypertension in 4%); urinary frequency and nocturia; dyspepsia; or upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase (11%-12%), or cardiac disorders (19%, serious in 6%). Thus, monitoring of liver function, potassium and phosphate levels, and blood pressure readings on a monthly basis, at least initially is warranted during abiraterone acetate/prednisone therapy. Symptom-directed assessment for cardiac disease also is warranted, particularly in patients with pre-existing cardiovascular disease.

Enzalutamide

On August 31, 2012, the FDA approved enzalutamide, an anti-androgen, for treatment of men with metastatic CRPC who had received prior docetaxel chemotherapy. Approval was based on the results of the randomized, phase 3, placebo-controlled trial (AFFIRM).[263] AFFIRM randomized 1199 men to enzalutamide or placebo in a 2:1 ratio and the primary endpoint was overall survival. Median survival was improved with enzalutamide from 13.6 to 18.4 months (HR, 0.63; *P* < .001). Survival was improved in all subgroups analyzed. Secondary endpoints also were improved significantly, which included the proportion of men with >50% PSA decline (54% vs. 2%), radiographic response (29% vs. 4%), radiographic progression-free survival (8.3 vs. 2.9 months), and time to first SRE (16.7 vs. 13.3 months). Quality of life measured using validated surveys was improved with enzalutamide compared to placebo. Adverse events were mild, and included fatigue (34% vs. 29%), diarrhea (21% vs. 18%), hot flushes (20% vs. 10%), headache (12% vs. 6%), and seizures (0.6% vs. 0%). The incidence of cardiac disorders did not differ between the arms. Enzalutamide is dosed at 160 mg daily. Patients in the AFFIRM study were maintained on GnRH agonist/antagonist therapy and could receive bone supportive care medications. The seizure risk in the enzalutamide FDA label was 0.9% versus 0.6% in the manuscript.[263,264]

Another phase III trial studied enzalutamide in the pre-chemotherapy setting. The PREVAIL study randomly assigned 1717 patients with chemotherapy-naïve metastatic prostate cancer to daily enzalutamide

or placebo.[265] The study was stopped early due to benefits shown in the active arm. Compared to the placebo group, the enzalutamide group showed improved progression-free survival (65% vs. 14%; *P* < .001) and overall survival (72% vs. 63%; *P* < .001). Improvements in all secondary end points also were observed (eg, the time until chemotherapy initiation or first skeletal-related event).

Thus, enzalutamide represents a treatment option for men in both the pre-docetaxel and post-docetaxel metastatic CRPC setting and is a reasonable choice in men who are not candidates for chemotherapy.

Chemotherapy and Immunotherapy

Recent research has expanded the therapeutic options for patients with metastatic CRPC depending on the presence or absence of symptoms.

Docetaxel

Two randomized phase III studies evaluated docetaxel-based regimens in symptomatic or rapidly progressive disease (TAX 327 and SWOG 9916).[266-268] TAX 327 compared docetaxel (every three weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1006 men.[267] Every 3-week docetaxel resulted in higher median overall survival than mitoxantrone (18.9 vs. 16.5 months; *P* = .009). This survival benefit was maintained at extended follow-up.[268] The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared to mitoxantrone plus prednisone.[266] Docetaxel is FDA-approved for metastatic CRPC. The standard regimen is every 3 weeks. An alternative to every 3 week docetaxel is a biweekly regimen of 50 mg/m^2. This regimen is based on a randomized large phase 2 trial of 346 men with metastatic CRPC randomized to either every 2 week docetaxel or every 3 week docetaxel, each with maintenance of ADT and prednisone. [269] Men treated with the every 2 week regimen survived an average of 19.5 months compared to 17.0 months with the every 3 week regimen (p=0.015). Time-to-progression and PSA decline rate favored every 2 week therapy. Tolerability was improved with every 2 week docetaxel; febrile neutropenia rate was 4% vs 14% and other toxicities and overall quality of life were similar.

Cabazitaxel

In June 2010, the FDA approved cabazitaxel, a semi-synthetic taxane derivative, for men with metastatic CRPC previously treated with a docetaxel-containing regimen. An international randomized phase III trial[271] randomized 755 men with progressive metastatic CRPC to receive cabazitaxel 25 mg/m^2 or mitoxantrone 12 mg/m^2, each with daily prednisone. A 2.4 month improvement in overall survival was demonstrated with cabazitaxel compared to mitoxantrone (HR, 0.72; *P* < .0001). The improvement in survival was balanced against a higher toxic death rate with cabazitaxel (4.9% vs. 1.9%), which was due, in large part, to differences in rates of sepsis and renal failure. Febrile neutropenia was observed in 7.5% of cabazitaxel-treated men vs. 1.3% of mitoxantrone-treated men. The incidences of severe diarrhea (6%), fatigue (5%), nausea/vomiting (2%), anemia (11%), and thrombocytopenia (4%) also were higher in cabazitaxel-treated men, which indicated the need for vigilance and treatment or prophylaxis in this setting to prevent febrile neutropenia. The survival benefit was sustained at an updated analysis with a median follow-up of 25.5 months.[272]

Sipuleucel-T

In April 2010, sipuleucel-T became the first in a new class of cancer immunotherapeutic agents to be approved by the FDA. This autologous cancer “vaccine” involves collection of the white blood cell fraction

containing antigen-presenting cells from each patient, exposure of the cells to the prostatic acid phosphatase -granulocyte macrophage colony-stimulating factor (PAP-GM-CSF recombinant fusion protein), and subsequent reinfusion of the cells. The pivotal study was a phase III, multicenter, randomized, double-blind trial (D9902B).[273] Five hundred and twelve patients with minimally symptomatic or asymptomatic metastatic CRPC were randomized 2:1 to receive sipuleucel-T or placebo. Median survival in the vaccine arm was 25.8 months compared to 21.7 months in the control arm. Sipuleucel-T treatment resulted in a 22% reduction in mortality risk (HR, 0.78; 95% CI, 0.61-0.98; *P* = .03). Common complications included mild to moderate chills (54.1%), pyrexia (29.3%), and headache (16.0%), which were usually transient.

Agents Related to Bone Health in CRPC

In a multicenter study, 643 men with CRPC and asymptomatic or minimally symptomatic bone metastases were randomized to intravenous zoledronic acid every 3 weeks or placebo.[274] At 15 months, fewer men in the zoledronic acid 4 mg group than men in the placebo group had SREs (33% vs. 44%; *P* =.02). An update at 24 months also revealed an increase in the median time to first SRE (488 days vs. 321 days; *P* = .01).[275] No significant differences were found in overall survival. Other bisphosphonates have not been shown to be effective for prevention of disease-related skeletal complications.

Denosumab was compared to zoledronic acid in a randomized, double-blind, placebo-controlled study in men with CRPC.[276] The absolute incidence of SREs was similar in the two groups; however, the median time to first SRE was delayed by 3.6 months by denosumab compared to zoledronic acid (20.7 vs. 17.1 months; *P* = .0002 for non-inferiority, *P* = .008 for superiority). The rates of important SREs with denosumab were similar to zoledronic acid and included spinal cord compression (3% vs. 4%), need for radiation (19% vs. 21%), and pathologic fracture (14% vs. 15%).

Treatment-related toxicities reported for zoledronic acid and denosumab were similar and included hypocalcemia (more common with denosumab 13% vs. 6%), arthralgias, and osteonecrosis of the jaw (ONJ, 1%-2% incidence). Most, but not all, patients who develop ONJ have preexisting dental problems.[277]

NCCN Recommendations

Initial Prostate Cancer Diagnosis

Initial suspicion of prostate cancer is based on an abnormal DRE or an elevated PSA level. A separate NCCN Guidelines Panel has written guidelines for prostate cancer early detection (see NCCN Guidelines for Prostate Cancer Early Detection). Definitive diagnosis requires biopsies of the prostate, usually performed by a urologist using a needle under transrectal ultrasound (TRUS) guidance. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Clinical staging is based on the TNM 2009 classification from the AJCC Staging Manual, 7th edition.[278] However, NCCN treatment recommendations are based on risk stratification rather than AJCC prognostic grouping.

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The NCCN Guidelines Panel favors pathology synoptic reports from the College of American Pathologists (CAP) that comply with the Commission on Cancer requirements.[279]

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 and/or those with a life expectancy of greater 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;[280] 2) a Gleason score of 8 or higher; 3) T3 to T4 tumors; or 4) symptomatic disease. Pelvic CT or MRI scanning is recommended if there is T3 or T4 disease, or if T1 or T2 disease and a nomogram indicate that there is 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%.[281] 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/recurrence into those with clinically localized disease at very low, low, intermediate, or high risk, or those with locally advanced 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, PSA <10 ng/mL, presence of disease in fewer than 3 biopsy cores, ≤50% prostate cancer involvement in any core, and PSA density <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 (monitoring no more often than every 6 months). 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) EBRT 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 Guidelines 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) EBRT with or without ADT (4 to 6 months), and with or without brachytherapy; 3) brachytherapy alone for selected patients with low-volume disease.

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) EBRT with or without 4 to 6 months of ADT, and with or without brachytherapy; 3) brachytherapy alone for selected patients with favorable factors (cT1c, Gleason score 7, low volume). Active surveillance is not recommended for patients with a life expectancy of >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 EBRT 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 (locally advanced) are defined by the NCCN Guidelines as those with clinical stage T3b to T4, primary Gleason pattern 5, or more than 4 cores with Gleason score 8 to 10.[282] The options for this group include: 1) EBRT 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.

Nodal and Metastatic Disease

ADT or RT of the primary tumor plus 2 or 3 years ADT are options for patients diagnosed with N1 disease on presentation. Positive nodal disease identified during prostatectomy is addressed under *Adjuvant or Salvage Therapy after Radical Prostatectomy*.

ADT is recommended for patients with M1 cancer.

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 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. MpMRI may be considered to exclude the presence of anterior cancer if the PSA level rises and systematic prostate biopsy remains negative.[283] PSA doubling time is not considered reliable enough to be used alone to detect disease progression.[284]

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 to12 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 and colleagues found that 45% of patients experienced recurrence within the first 2 years, 77% within the first 5 years, and 96% by 10 years.[285] 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. The relative risk for bone metastasis or death increases as PSADT falls. There appears to be a major inflection point at a PSADT of 8 months. Bone imaging should be performed more frequently in these men.[286]

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/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 or Salvage Therapy after Radical Prostatectomy

Adjuvant Therapy

Most patients who have undergone a radical prostatectomy are cured of prostate cancer. However, some men will suffer pathologic or biochemical failure. Selecting men appropriately for adjuvant or salvage radiation is difficult. However, recently published trials provide high-level evidence that can be used to counsel patients more appropriately. Thompson and colleagues reported the results of the SWOG 8794 trial enrolling 425 men with extraprostatic cancer treated with radical prostatectomy. Patients were randomized to receive either adjuvant RT or usual care, and follow-up has reached a median of 12.6 years.[287] The initial study report revealed that adjuvant RT reduced the risk of PSA relapse and disease recurrence.[288] An update reported improved 10-year biochemical failure-free survival for high-risk patients (seminal vesicle positive) receiving post-prostatectomy adjuvant radiation compared to observation (36% vs. 12%; P = .001).[289]

Another randomized trial conducted by the EORTC[290] compared post-prostatectomy observation and adjuvant RT in 1005 patients. All patients had extraprostatic extension and/or positive surgical margins. The 5-year biochemical progression-free survival significantly improved with RT compared to 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 and colleagues reported results on 268 patients.[291] All participants had pT3 disease and undetectable PSA levels after radical prostatectomy. Postoperative radiation improved 5-year biochemical progression-free survival compared to observation alone (72% vs. 54%; HR, 0.53; 95% CI, 0.37-0.79). Collectively, these trial results suggest that continued follow-up of these series of patients may show a survival advantage.

Although observation after radical prostatectomy is appropriate, adjuvant EBRT after recuperation from operation (usually within 1 year) is likely beneficial in men with adverse laboratory or pathologic features, which include positive surgical margin, seminal vesicle invasion, and/or extracapsular extension as recommended in the guideline by the American Urological Association (AUA) and ASTRO.[292] 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.[293] The value of whole pelvic irradiation is unclear due to a lack of benefit in progression-free survival in 2 trials (RTOG 9413 and GETUG 01);[294-296] it may be appropriate for selected patients.

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 EBRT to ADT (category 2B). This is based on retrospective studies demonstrating improved biochemical recurrence-free survival and cancer-specific survival with post-prostatectomy RT and ADT compared to adjuvant ADT alone in patients with lymph node metastases.[297,298]

Biochemical Recurrence

Several retrospective studies have assessed the prognostic value of various combinations of pretreatment PSA levels, Gleason scores, PSA doubling time, and the presence or absence of positive surgical margins.[299-303] A large retrospective review of 501 patients who received salvage radiotherapy for detectable and increasing PSA after radical prostatectomy[302] showed that the predictors of progression were Gleason score 8 to 10, pre-RT PSA level greater than 2 ng/mL, seminal vesicle invasion, negative surgical margins, and PSA doubling time 10 months or less. However, separation of men into those likely to have local recurrence versus systemic disease, and hence response to postoperative radiation, has proven not possible for individual patients using clinical and pathological criteria.[304] Unfortunately, delivery of adjuvant or salvage RT becomes both therapeutic and diagnostic—PSA response indicates local persistence/recurrence. Delayed biochemical recurrence requires restaging and a nomogram[12,25] may prove useful to predict response, but it has not been validated.

Men who suffer biochemical recurrence after radical prostatectomy fall into 3 groups: 1) those whose PSA level fails to fall to undetectable levels after radical prostatectomy (persistent disease); 2) those who achieve an undetectable PSA after radical prostatectomy with a subsequent detectable PSA level that increases on 2 or more subsequent laboratory determinations (recurrent disease); or 3) the

occasional case with persistent but low PSA levels attributed to slow PSA metabolism or residual benign tissue. Consensus has not defined a threshold level of PSA below which PSA is truly "undetectable." Group 3 does not require further evaluation until PSA rises. Since PSA elevation alone does not necessarily lead to clinical failure,[305] the work-up for 1 and 2 must include an evaluation for distant metastases. The specific staging tests depend on the clinical history, but usually include a combination of PSA doubling time assessment, TRUS biopsy, bone scan, and prostate MRI. Other tests that may be useful include abdominal/pelvic CT/MRI and C-11 choline PET.

Bone scans are appropriate when patients develop symptoms or when PSA levels are increasing rapidly. In one study, the probability of a positive bone scan for a patient not on ADT after radical prostatectomy was less than 5% unless the PSA increased to 40 to 45 ng/mL.[306] A TRUS biopsy may be helpful when imaging suggests local recurrence.

The patient may be observed or undergo primary salvage RT with or without ADT if distant metastases are not suspected during biochemical recurrence.[292] The recommended post-prostatectomy RT dose is 64 to 72 Gy and may be increased for gross recurrence that has been proven by biopsy. The target volume includes the prostate bed and may include the whole pelvis in selected patients.[293] Treatment is most effective when pre-treatment PSA level is below 0.5 ng/mL.[25] Paradoxically, salvage RT was shown to be most beneficial when the PSA doubling time is less than 6 months in a cohort analysis of 635 men,[304] although another study of 519 men reported mortality reduction for both men with doubling time less than 6 months and those with doubling time more than or equal to 6 months.[307] Most men with prolonged PSA doubling time may be observed safely.[308]

ADT alone becomes the salvage treatment when there is proven or high suspicion for distant metastases. Radiation alone is not recommended but may be given to the site of metastasis or symptoms in addition to ADT in specific cases, such as to weight-bearing bone involvement. Observation remains acceptable for selected patients. In all cases, the form of primary or secondary systemic therapy should be based on the hormonal status of the patient.

Post-Irradiation Recurrence

According to the 2006 Phoenix definition revised by ASTRO and the Radiation Therapy Oncology Group in Phoenix:[309] 1) PSA rise by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical failure after EBRT with or without HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the rise above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid rise of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier men.

Further work-up is indicated in patients who are considered candidates for local therapy. These patients include those with original clinical stage T1-2, life expectancy greater than 10 years, and current PSA less than 10 ng/mL.[310] Work-up typically includes a PSA doubling time calculation, TRUS biopsy, bone scan, and additional tests, such as an abdominal/pelvic CT/MRI, prostate MRI, and/or C-11 choline PET. Local radiation failures are most responsive to salvage therapy when PSA levels at the time of treatment are low (<5 ng/ml). Biopsy should be encouraged at the time of biochemical radiation failure if staging work up does not reveal metastatic disease. When performing prostate

biopsy in the setting of suspected local recurrence following radiation, biopsy at the junction of the seminal vesicle and prostate should be considered since this is a common site of treatment failure.

Options for primary salvage therapy for those with positive biopsy but low suspicion of metastases to distant organs include observation or salvage prostatectomy in selected cases by highly experienced surgeons. Other options for localized interventions include cryotherapy[311] and brachytherapy (reviewed by Allen and colleagues[312]). Treatment, however, needs to be individualized based upon the patient's risk of progression, the likelihood of success, and the risks involved with salvage therapy.

A negative TRUS biopsy following post-radiation biochemical recurrence poses clinical uncertainties. Observation, ADT, or enrolling in clinical trials are viable options. Alternatively, the patients may undergo more aggressive work-up, such as repeat biopsy, MR spectroscopy, and/or prostate MRI.[313,314]

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

Management of ADT-Naïve Advanced Disease

Options for patients with advanced disease who have not been treated with ADT include: 1) orchiectomy; 2) LHRH agonist with or without anti-androgen for at least 7 days to prevent flare; 3) LHRH antagonist; 4) CAB; 5) observation for asymptomatic patients without metastasis; or 6) continuous ADT and docetaxel (75 mg/m^2) without prednisone for 6 cycles for high-volume metastatic disease. The last option of upfront docetaxel combined with ADT is based on results from a phase III trial (ECOG 3805, or CHAARTED) reported in abstract form and is anticipated to become the new standard for patients with high-burden metastases.[270] The Panel has opted to discuss the trial in detail when it is published after peer review.

Docetaxel should not be offered to men without metastatic prostate cancer or to men with low volume metastatic prostate cancer, as this subgroup has not been shown to have improved survival outcomes in the ECOG study or a similar European trial (GETUG-AFU 15).[270]

In the setting of biochemical relapse after local therapy, one should first determine whether or not the patient is a candidate for salvage therapy. Men who opt for ADT should consider the intermittent approach. The timing of ADT initiation should be individualized according to PSA velocity, patient anxiety, and potential side effects. Patients with shorter PSA doubling time or rapid PSA velocity and long life expectancy should be encouraged to consider early ADT. Men with prolonged PSA doubling times who are older can be excellent candidates for observation.

Metastatic patients should be queried about adverse effects related to ADT. Intermittent ADT should be used for those who experience significant side effects of ADT. Some men who have no ADT-related morbidity may find the uncertainty of intermittent ADT not worthwhile. Intermittent ADT requires close monitoring of PSA and testosterone levels especially during off-treatment periods and patients may need to switch to continuous therapy upon signs of disease progression.

CAB therapy adds to cost and side effects, and prospective randomized evidence is lacking that CAB is more efficacious than ADT.

Progression to CRPC

Patients who progress during primary ADT to CRPC should receive a laboratory assessment to assure a castrate level of testosterone. In addition, imaging tests may be indicated to monitor for signs of distant metastases. Factors affecting the frequency of imaging include individual risk, age, PSA velocity, Gleason grade, and overall patient health.

A number of options for systemic therapy should be considered based on metastasis status, as discussed in the following sections.

CRPC without Signs of Metastasis

Clinical trial is the preferred choice for patients without signs of distant metastasis (M0). Observation is another option especially if the PSA doubling time is 10 months or longer since these patients will have a relatively indolent disease history.[315] Secondary hormone therapy is an option mainly for patients with a shorter PSA doubling time (<10 months) since the androgen receptor may remain active. Patients who progress on CAB should have the anti-androgen discontinued to exclude an "anti-androgen withdrawal response."[316,317] Secondary hormone therapy can be an anti-androgen for patients who initially received medical or surgical castration, ketoconazole (adrenal enzyme inhibitor), corticosteroids, diethylstilbestrol (DES), or other estrogens.[318,319] However, none of these strategies has yet been shown to prolong survival in randomized clinical trials in men who have not yet received docetaxel-based chemotherapy.

Small Cell Carcinoma of the Prostate

Small cell carcinoma of the prostate should be considered in patients who no longer respond to ADT and test positive for metastases. Those with initial Gleason score 9 or 10 are especially at risk. These relatively rare tumors are typically associated with low PSA levels despite large metastatic burden and visceral disease.[320] Thus, a biopsy of accessible lesions should be considered to identify patients with small cell histomorphologic features.[321] These cases may be managed by cytotoxic chemotherapy, such as cisplatin/etoposide, carboplatin/etoposide, or a docetaxel-based regimen.[322,323] Participation in a clinical trial is another option. Physicians should consult the NCCN Guidelines for Small Cell Lung Cancer since the behavior of small cell carcinoma of the prostate is similar to that of small cell carcinoma of the lung. Small cell carcinomas of the prostate differ from neuroendocrine prostate cancers; the latter histology may be more common and should not alter treatment.

Metastatic CRPC

All patients with metastatic CRPC should maintain castrate levels of serum testosterone and receive best supportive care. Treatment options for specific settings are discussed below.

Bone Metastases

Zoledronic acid every 3 to 4 weeks or denosumab 120 mg every 4 weeks is recommended for men with CRPC and bone metastases to prevent or delay disease-associated SREs (category 1 recommendation). SREs include pathologic fractures, spinal cord compression, operation, or RT to bone. The optimal duration of zoledronic acid or denosumab in men with CRPC and bone metastases remains unclear.

Oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce the risk of ONJ.[324] If invasive dental surgery is necessary, therapy should be deferred until the dentist confirms that the patient has healed completely from the dental procedure. Supplemental calcium

and vitamin D treatment is recommended to prevent hypocalcemia in patients receiving either denosumab or zoledronic acid.

Monitoring of creatinine clearance is required to guide dosing of zoledronic acid. Zoledronic acid should be dose reduced in men with impaired renal function (estimated creatinine clearance 30-60 mL/min), and held for creatinine clearance <30 mL/min.[325] Denosumab may be administered to men with impaired renal function or even men on hemodialysis; however, the risk for severe hypocalcemia and hypophosphatemia is greater in this population, and the dose, schedule, and safety of denosumab has not yet been defined for this group. A single study of 55 patients with creatinine clearance less than 30 mL/min or on hemodialysis evaluated the use of a 60 mg dose of denosumab.[326] Hypocalcemia should be corrected before starting denosumab, and serum calcium monitoring is required for denosumab and recommended for zoledronic acid, with appropriate repletion as needed.

Clinical research continues on the prevention or delay of disease spread to bone. A phase III randomized trial involving 1432 patients with non-metastatic CRPC at high risk of bone involvement showed that denosumab delayed bone metastasis by 4 months compared to placebo.[327] Overall survival did not improve and the FDA did not approve this indication for denosumab.

Radium-223 is a category 1 option to treat symptomatic bone metastases without visceral metastases. Hematologic evaluation should be performed according to the FDA label before treatment initiation and before each subsequent dose.[328] Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial has the potential for additive myelosuppression.[328] Radium-223 can be used with denosumab or a bisphosphonate.

The use of systemic radiotherapy with either 89Sr or 153Sm occasionally benefits patients with widely metastatic, painful, skeletal involvement that is not responding to palliative chemotherapy or systemic analgesia and who are not candidates for localized EBRT.[188] The risk of bone marrow suppression, which might influence the ability to provide additional systemic chemotherapy, should be considered before this therapy is initiated.

Asymptomatic or Minimally Symptomatic

Based on phase III randomized trial evidence, sipuleucel-T is a category 1 recommendation for patients with metastatic CRPC who are asymptomatic or minimally symptomatic, and has good performance level (ECOG 0-1), more than 6 months of estimated life expectancy, and no liver metastases. Sipuleucel-T has not been studied in patients with visceral metastases. Clinicians and patients should be aware that the usual markers of benefit (decline in PSA and improvement in bone or CT scans) are not usually seen, and therefore benefit to the individual patient cannot be ascertained using currently available testing. Treatment subsequent to sipuleucel-T treatment should proceed as clinically indicated, particularly in the occurrence of symptoms.

No Visceral Metastases

Enzalutamide and abiraterone acetate with prednisone are 2 newer therapies that received category 1 recommendation as first-line therapy for patients with asymptomatic, chemotherapy-naïve, metastatic CRPC. Abiraterone acetate should be given with oral prednisone 5 mg twice daily. It should not be taken with food to abrogate signs of mineralocorticoid excess that can result from treatment. These signs can include hypertension, hypokalemia, and peripheral edema. Serum electrolytes and blood pressure should be monitored closely during therapy. Patients receiving enzalutamide have no restrictions for food intake and concurrent prednisone is permitted but not required.[263]

Docetaxel with prednisone is the traditional mainstay of treatment for symptomatic metastases (category 1). Docetaxel is not used commonly for asymptomatic patients, but may be considered when the patient shows signs of rapid progression or visceral metastases despite lack of symptoms. Radium-223 is a category 1 option to treat symptomatic bone metastases without visceral metastases.

Other options include clinical trial participation and secondary hormone therapy (antiandrogen, antiandrogen withdrawal, ketoconazole, corticosteroids).

Visceral Metastases

Every 3-week docetaxel and prednisone is the preferred first-line chemotherapy treatment for symptomatic CRPC with visceral metastases (category 1). PSA rise alone does not define docetaxel failure; the patient may benefit from continued chemotherapy if clinical progression is not apparent. The addition of estramustine to docetaxel has been shown to increase side effects without enhancing efficiency and is not recommended.[329] Enzalutamide is another category 1 recommendation in this setting. Abiraterone acetate has not been assessed formally in symptomatic men with CRPC prior to docetaxel. Therefore, its use in these patients is a category 2A recommendation. Use of abiraterone is reasonable for men who are not candidates for docetaxel or who decline chemotherapy.

Radium-223 alone has not been shown to extend survival in men with visceral metastases or bulky nodal disease greater than 3 to 4 cm and is not recommended in this setting.

Mitoxantrone may provide palliative benefit for symptomatic patients who cannot tolerate docetaxel.[330,331] Clinical trial is another option.

Progression Following Enzalutamide or Abiraterone Acetate

Patients with disease progression after enzalutamide or abiraterone acetate have the following options: docetaxel with prednisone (category 1), abiraterone acetate if previously given enzalutamide therapy, enzalutamide if previously given abiraterone acetate, radium-223 for bone-predominant disease without visceral metastases (category 1), sipuleucel-T if asymptomatic or minimally symptomatic and without visceral or liver metastases (life expectancy >6 months and ECOG score 0–1), clinical trial, or secondary hormone therapy. All patients should receive best supportive care.

Progression Following Docetaxel

No consensus exists for the best additional therapy for metastatic CRPC patients after docetaxel failure. Options include abiraterone acetate (category 1), enzalutamide (category 1), radium-223 for bone-predominant disease without visceral metastases (category 1), cabazitaxel with prednisone (category 1), sipuleucel-T if asymptomatic or minimally symptomatic and without visceral or liver metastases (life expectancy >6 months and ECOG score 0–1), clinical trial, docetaxel rechallenge, alternative chemotherapy (mitoxantrone), and secondary ADT. All patients should receive best supportive care.

Both abiraterone acetate/prednisone and enzalutamide represent a new standard of care after failure of docetaxel chemotherapy for metastatic CRPC (category 1), provided these agents were not used pre-docetaxel.

The NCCN Guidelines Panel included cabazitaxel as an option for second-line therapy after docetaxel failure for patients with symptomatic metastatic CRPC. This recommendation is category 1 based on randomized phase III study data; however, extension of survival is relatively short and side effects are relatively high.[271] Physicians should

follow current guidelines for prophylactic white blood cell growth factor use, particularly in this heavily pre-treated, high-risk population. In addition, supportive care should include antiemetics (prophylactic antihistamines, H2 antagonists, and corticosteroids prophylaxis), and symptom-directed antidiarrheal agents. Cabazitaxel has not been tested in patients with hepatic dysfunction and therefore should not be used in these patients. Cabazitaxel should be stopped upon clinical disease progression or intolerance.

The decision to initiate therapy in the post-docetaxel CRPC setting should be based on the available high-level evidence of safety, efficacy, and tolerability of these agents and the application of this evidence to an individual patient. Prior exposures to these agents should be considered. No data informs the proper sequence for delivery of these agents in men with metastatic CRPC, and some data suggest cross-resistance between abiraterone and enzalutamide.[332-334] No randomized trials have been reported that compared these agents, and no predictive models or biomarkers help to identify patients who are likely to benefit from any of these agents. Choice of therapy is based largely on clinical considerations, which include patient preferences, prior treatment, presence or absence of visceral disease, symptoms, and potential side effects. NCCN recommends that patients be monitored closely with radiological imaging (ie, CT, bone scan), PSA tests, and clinical exams for evidence of progression. Therapy should be continued until clinical progression or intolerability in cases where PSA or bone scan changes may indicate flare rather than true clinical progression.[335] The sequential use of these agents is reasonable in a patient who remains a candidate for further systemic therapy.

NCCN panelists agreed that docetaxel rechallenge may be useful in some patients (category 2A instead of category 1 in this setting). Some patients with metastatic CRPC may be deemed unsuitable for taxane chemotherapy; such patients could be considered for radium-223 or a second-line hormonal agent. In addition, mitoxantrone remains a palliative treatment option for men who are not candidates for taxane-based therapy based on older randomized studies that showed palliative benefit. [330,331] Limited evidence suggests potential palliative benefits with mitoxantrone and a variety of chemotherapeutic or hormonal agents, but no randomized studies have demonstrated improved survival with these agents after docetaxel failure. Treatment with these agents could be considered after an informed discussion between the physician and an individual patient about treatment goals and risks/side effects and alternatives, which must include best supportive care.

In the phase III sipuleucel-T trial, 18.2% of patients had received prior chemotherapy, which included docetaxel, since eligibility requirements included no chemotherapy for 3 months and no steroids for 1 month prior to enrollment.[273] These men were asymptomatic or minimally symptomatic. In a subset analysis, both those who did and those who did not receive prior chemotherapy benefited from sipuleucel-T treatment.

Summary

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

Table 1. Active Surveillance Experience in North America

Center	Toronto[83]	Johns Hopkins[81,84,85]	UCSF[82]
No. patients	450	769	531
Age (yr)	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

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