NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer

Version 1.2017 — December 16, 2016

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NCCN Guidelines Version 1.2017
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NCCN Guidelines Panel Disclosures

Clinical Trials: NCCN believes that the best management for any patient with cancer 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.

NCCN Guidelines Version 1.2017 Prostate Cancer Updates

Updates in Version 1.2017 of the NCCN Guidelines for Prostate Cancer from Version 3.2016 include:

PROS-1
- Initial prostate cancer diagnosis, added a bullet for "Family history" with a new footnote: "The following should be considered: brother or father or multiple family members diagnosed with prostate cancer at less than 60 years of age, germline DNA repair gene abnormalities, especially BRCA2 mutation or Lynch syndrome (germline mutations in MLH1, MSH2, MSH6, or PMS2) and/or strong family history for breast or ovarian cancer (suggests possibility of BRCA2 mutation) or colorectal, endometrial, gastric, ovarian, pancreatic, small bowel, urothelial, kidney, or bile duct cancer (suggests possibility of Lynch syndrome)."
- Modified the following footnote: "Androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered in selected patients with high- or very-high-risk disease, where complications, such as hydronephrosis or metastasis, can be expected within 5 y. (See PROS-5 or PROS-6).
- Removed text box: "Preferred treatment for any therapy is approved clinical trial."
- Risk Group - added the ISUP/WHO Grade Groups. (See ST-3)

PROS-2, -3, -4, -5, -6
- Modified "Adverse feature(*s) and no lymph node metastases*."
- Added branch "No adverse features or lymph node metastases."

PROS-4
- Changed "Undetectable PSA or nadir" to "Undetectable PSA after RP or PSA nadir after RT."

PROS-5
- High and very high risk groups, initial therapy, removed "EBRT + ADT (2-3y) + docetaxel."
- Modified footnote: "Six cycles of docetaxel every 3 weeks without prednisone may be administered after the completion of radiation in selected patients who are fit for chemotherapy."

PROS-6
- Very high risk group, initial therapy, ADT replaced "in select patients" with "or observation for patients who are not candidates for definitive therapy."
- Added a new footnote "RP + PLND can be considered in younger, healthier patients without tumor fixation to the pelvic side-wall."
- Deleted footnote: "Primary therapy with ADT should be considered only for patients who are not candidates for definitive therapy."

PROS-7
- Changed "Advanced disease" to "Progression to metastatic disease *without biochemical failure*."
- N1 or M1, added "on ADT."
- Branches for recurrence after initial definitive therapy and N1 and M1 on ADT were separated
- Added *"Progression"* to bottom branch, with links to PROS-11 and PROS-12.

PROS-8
- Clarified "abdominal/pelvic" CT or MRI.
- "Progression" was split into separate pathways depending on previous treatment, with links to PROS-10, PROS-11, and PROS-12.
- Added a new footnote defining "castration-naive." The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.

PROS-9
- TRUS biopsy positive, studies negative for distant metastases: added the option for "high-intensity focused ultrasound (HIFU)."
- Not a candidate for local therapy, added "bone scan."
- Added a link to PROS-11 for patients who progress while on ADT.

PROS-10
- Systemic therapy for progressive castration-naive disease, M1, removed "Continuous" from "ADT."

PROS-11
- Moved the following footnote to the Principles of Androgen Deprivation Therapy (PROS-F). "DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/d and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited."
- No metastases, added "Change or maintain current treatment and continue monitoring."
- PSA rising, no, added "Maintain current treatment and continue monitoring."

PROS-12
- Removed the following footnote: "For patients who are not candidates for docetaxel-based regimens."

PROS-12, PROS-13 and PROS-14
- Ketoconazole ± hydrocortisone, added a footnote stating "Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone."

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Updates in Version 1.2017 of the NCCN Guidelines for Prostate Cancer from Version 3.2016 include:

PROS-13 and PROS-14
- Added a new footnote to prior therapy enzalutamide/abiraterone "Limited data suggest a possible role for AR-V7 testing to help guide selection of therapy."

PROS-B (2 of 3)
- Added the following bullets:
  - "Bone scans are helpful to monitor metastatic prostate cancer to determine the clinical benefit of systemic therapy. However, new lesions seen on an initial post-treatment bone scan, compared to the pre-treatment baseline scan, may not indicate disease progression."
  - "New lesions in the setting of a falling PSA or soft tissue response and in the absence of pain progression at that site may indicate bone scan flare or an osteoblastic healing reaction. For this reason, a confirmatory bone scan 8–12 weeks later is warranted to determine true progression from flare reaction. Additional new lesions favor progression. Stable scans make continuation of treatment reasonable. Bone scan flare is common, particularly on initiation of new hormonal therapy, and may be observed in nearly half of patients treated with the newer agents, enzalutamide and abiraterone. Similar flare phenomenon may exist with other imaging modalities, such as CT or PET/CT imaging."
  - "Bone scans and soft tissue imaging (CT or MRI) in men with metastatic prostate cancer or non-metastatic progressive prostate cancer may be obtained regularly during systemic therapy to assess clinical benefit. Bone scans should be performed for symptoms and as often as every 6–12 mo to monitor ADT. The need for soft tissue images remains unclear. In CRPC, 8- to 12-week imaging intervals appear reasonable."

PROS-B (3 of 3)
- Added "Whole body" to PET/CT.

PROS-D (1 of 2)
- Primary brachytherapy
  - Removed "low dose rate (LDR)."
  - Modified the last bullet "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 13 to 15 Gy x 1 fraction, 8 to 11.5 Gy x 2 fractions, 5.5 to 7.5 6.5 Gy x~~ 3 fractions, and 4.0 to 6.0 Gy x 4 fractions. A commonly used regimen for HDR treatment alone includes 9.5 Gy x 4 fractions, 10.5 Gy x 3 fractions, 13.5 Gy x 2 fractions, or 19 Gy x 1 fraction."

PROS-D (1 of 2) continued
- Salvage brachytherapy
  - Modified the first bullet, "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 *the pattern of recurrence, and* ranges from 100 to 110 Gy for LDR and 9 to 12 Gy x 2 fractions for HDR.

PROS-D (2 of 2)
- Post-Prostatectomy Radiation Therapy, added a new bullet "Two years instead of 6 months of ADT can be considered in addition to RT based on RTOG 9601 (presented at ASTRO 2015) for men with persistent PSA after RP or for PSA levels that exceed 1.0 ng/mL at the time of initiation of salvage therapy. Six months of ADT can be considered coadministered with salvage radiation based on the results of GETUG-16. An LHRH agonist should be used. For 2-year ADT, there is level 1 evidence to support 150 mg bicalutamide daily but an LHRH agonist could be considered as an alternative."

PROS-F (1 of 4)
- Added list of ADT agents for clarification.

PROS-F (3 of 4)
- Updated text from "There was a trend toward improvement in overall survival" to "An improvement in overall survival was demonstrated."
- Changed "Secondary hormonal manipulation" to "Secondary hormone therapy" for consistency with algorithm pages.
- Modified bullet, "In the setting in which patients ~~are docetaxel-naive and~~ have no or minimal symptoms, administration of secondary hormonal *therapy* including addition of, or switching to, a different anti-androgen (flutamide, bicalutamide, nilutamide, enzalutamide), addition of adrenal/paracrine androgen synthesis inhibitors (ketoconazole with or without hydrocortisone, *or* abiraterone with prednisone), or use of an estrogen, such as DES, can be considered. *Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.*"
- Added a new bullet, previously on page PROS-11: DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/d and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited."

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Updates in Version 1.2017 of the NCCN Guidelines for Prostate Cancer from Version 3.2016 include:

PROS-F (3 of 4)
- Added a new bullet: "Two randomized clinical trials (STRIVE and TERRAIN) showed that 160 mg/d enzalutamide improved progression-free survival compared with 50 mg/d bicalutamide in men with treatment-naïve CRPC and, therefore, enzalutamide may be the preferred option in this setting. However, bicalutamide can still be considered in some patients, given the different side-effect profiles of the agents and the increased cost of enzalutamide."

PROS-G (1 of 3)
- Added list of chemotherapy and immunotherapy agents for clarification.

PROS-G (2 of 3)
- Added "with prednisone" to cabazitaxel.
- Added "Patients who are not candidates for docetaxel or who are intolerant of docetaxel should be considered for cabazitaxel, based on recent results that suggest clinical activity of cabazitaxel in mCRPC. Cabazitaxel was associated with lower rates of peripheral neuropathy than docetaxel, particularly at 20 mg/m^2 (12% vs. 25%) and may be appropriate in patients with pre-existing mild peripheral neuropathy. Current data do not support greater efficacy of cabazitaxel over docetaxel."
- Added "Cabazitaxel at 25 mg/m² every 3 weeks with prednisone has been the standard of care in the post-docetaxel setting, with or without growth factor support. A recent trial, PROSELICA, compared cabazitaxel 25 mg/m² every 3 weeks to 20 mg/m² every 3 weeks. Cabazitaxel 20 mg/m² had less toxicity; febrile neutropenia, diarrhea, and fatigue were less frequent. Cabazitaxel at 20 mg/m² had a significantly lower PSA response rate but non-significantly lower radiographic response rate and non-significantly shorter progression-free and overall survival (13.4 vs 14.5 mo) compared to 25 mg/m². Cabazitaxel starting dose can be either 20 mg/m² or 25 mg/m² for men with mCRPC who have progressed despite prior docetaxel chemotherapy. Cabazitaxel 20 mg/m² with prednisone is recommended for frail or less chemo-fit men and those at high risk for neutropenic fever. Cabazitaxel 25 mg/m² with prednisone is recommended for healthy men who wish to be more aggressive."

PROS-G (2 of 3)
- Added the following bullets:
  - Docetaxel retreatment can be attempted for men who have not demonstrated definitive evidence of progression on prior docetaxel therapy.
  - Several systemic agents have shown palliative and radiographic response benefits in clinical trials.
  - Treatment decisions around off-label chemotherapy use in the treatment-refractory CRPC should be individualized based on comorbidities and functional status and after informed consent.
  - No benefits of combination approaches over sequential single-agent therapies have been demonstrated, and toxicity is higher with combination regimens.

PROS-G (3 of 3)
- Removed "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."
- Removed "Men who have not demonstrated definitive evidence of progression on prior docetaxel may be retreated with docetaxel."

ST-3
- Added Grade Group Definitions with references.

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INITIAL PROSTATE CANCER DIAGNOSIS

- DRE
- PSA
- Gleason primary and secondary grade
- Family history[a]

INITIAL CLINICAL ASSESSMENT

Life expectancy[b] ≤5 y and asymptomatic → No further workup or treatment until symptomatic, except in high- or very-high-risk groups[e]

Life expectancy[b] >5 y or symptomatic[c]

STAGING WORKUP[d]

Bone scan if any of these:
- T1 and PSA >20 ng/mL
- T2 and PSA >10 ng/mL
- Gleason score ≥8
- T3, T4
- Symptomatic

Pelvic CT or MRI if any of these:
- T3, T4
- T1-T2 and nomogram indicated probability of lymph node involvement >10%

→ Suspicious nodes → Consider biopsy →

All others: no additional imaging →

RISK GROUP [f]

Clinically Localized:

Very low:
- T1c
- Gleason score ≤6/grade group I
- PSA <10 ng/mL
- Fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core
- PSA density <0.15 ng/mL/g

→ See Initial Therapy (PROS-2)

Low:
- T1-T2a
- Gleason score ≤6/grade group I
- PSA <10 ng/mL

→ See Initial Therapy (PROS-3)

Intermediate:[f]
- T2b-T2c or
- Gleason score 3+4=7/grade group II or
- Gleason score 4+3=7/grade group III or
- PSA 10–20 ng/mL

→ See Initial Therapy (PROS-4)

High:[f]
- T3a or
- Gleason score 8/grade group IV or
- Gleason score 9–10/grade group V
- PSA >20 ng/mL

→ See Initial Therapy (PROS-5)

Locally Advanced:

Very high:
- T3b-T4 or
- Primary Gleason pattern 5/grade group V or
- >4 cores with Gleason score 8–10/grade group IV or V

→ See Initial Therapy (PROS-6)

Metastatic:
Any T, N1 or
Any T, Any N, M1

[a]The following should be considered: brother or father or multiple family members diagnosed with prostate cancer at less than 60 years of age, germline DNA repair gene abnormalities, especially BRCA2 mutation or Lynch syndrome (germline mutations in MLH1, MSH2, MSH6, or PMS2) and/or strong family history for breast or ovarian cancer (suggests possibility of BRCA2 mutation) or colorectal, endometrial, gastric, ovarian, pancreatic, small bowel, urothelial, kidney, or bile duct cancer (suggests possibility of Lynch syndrome).

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

[c]Men with clinically localized disease may consider the use of tumor-based molecular assays. Retrospective case cohort studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after radical prostatectomy or external beam therapy, and likelihood of developing metastasis after radical prostatectomy or salvage radiotherapy. See Discussion.

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

[e]Androgen deprivation therapy (ADT) or radiation therapy (RT) may be considered in selected patients with high- or very-high-risk disease, where complications, such as hydronephrosis or metastasis, can be expected within 5 y. (See PROS-5 or PROS-6).

[f]Patients with multiple adverse factors may be shifted into the next highest risk group.

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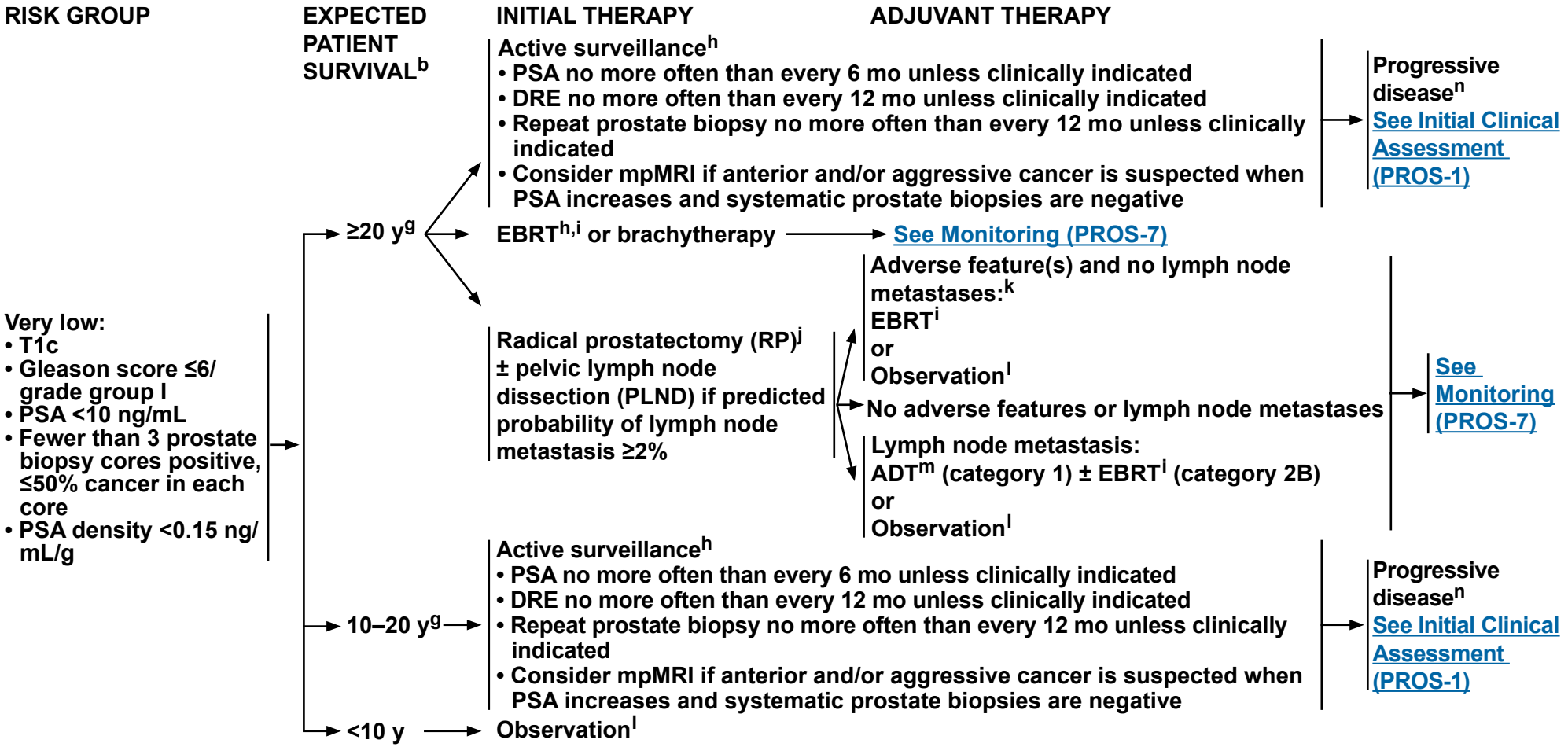

[b]See Principles of Life Expectancy Estimation (PROS-A).
[g]The panel remains concerned about the problems of over-treatment related to the increased diagnosis of early prostate cancer from PSA testing. See NCCN Guidelines for Prostate Cancer Early Detection. Active surveillance is recommended for these subsets of patients.
[h]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).
[i]See Principles of Radiation Therapy (PROS-D).
[j]See Principles of Surgery (PROS-E).
[k]Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.
[l]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).
[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[n]Criteria for progression are not well defined and require physician judgment; however, a change in risk group strongly implies disease progression. See Discussion.

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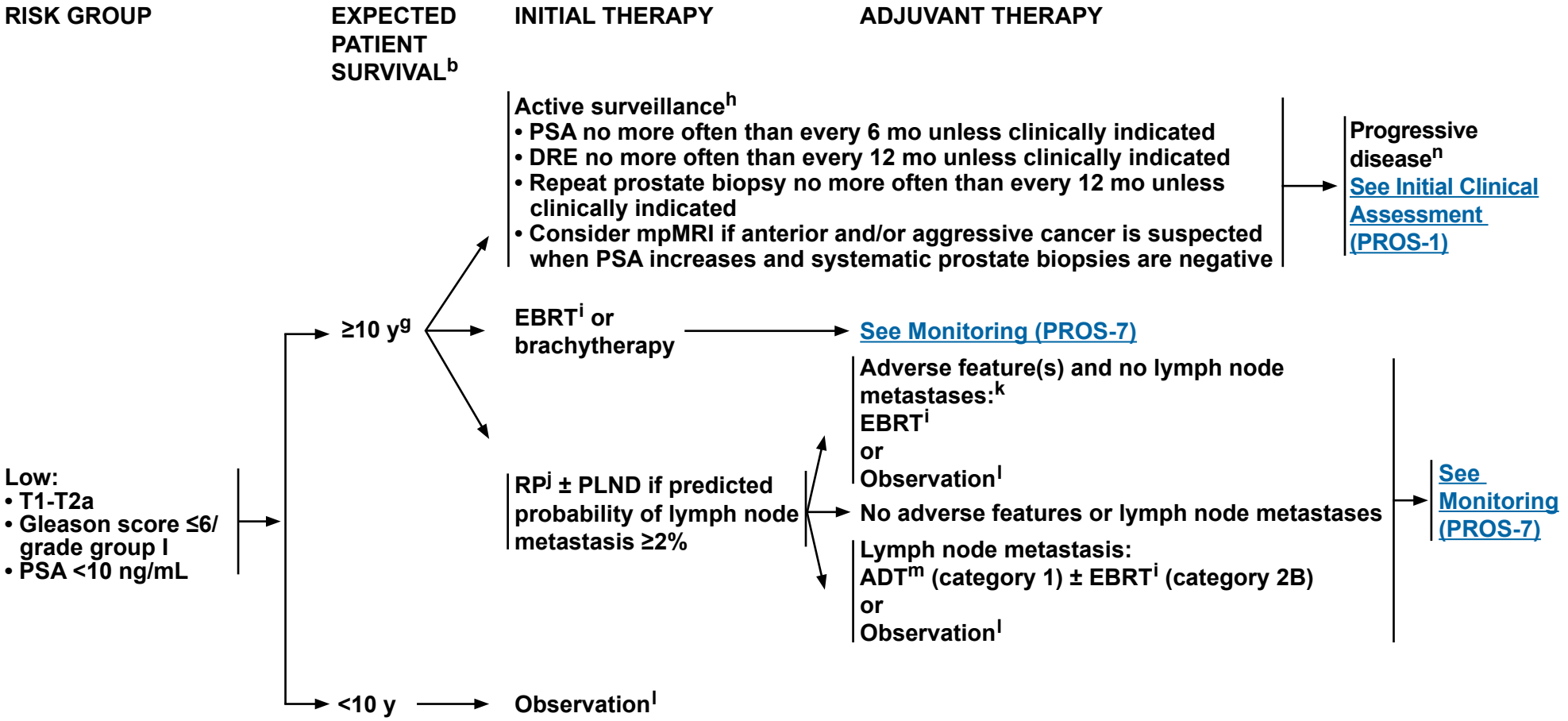

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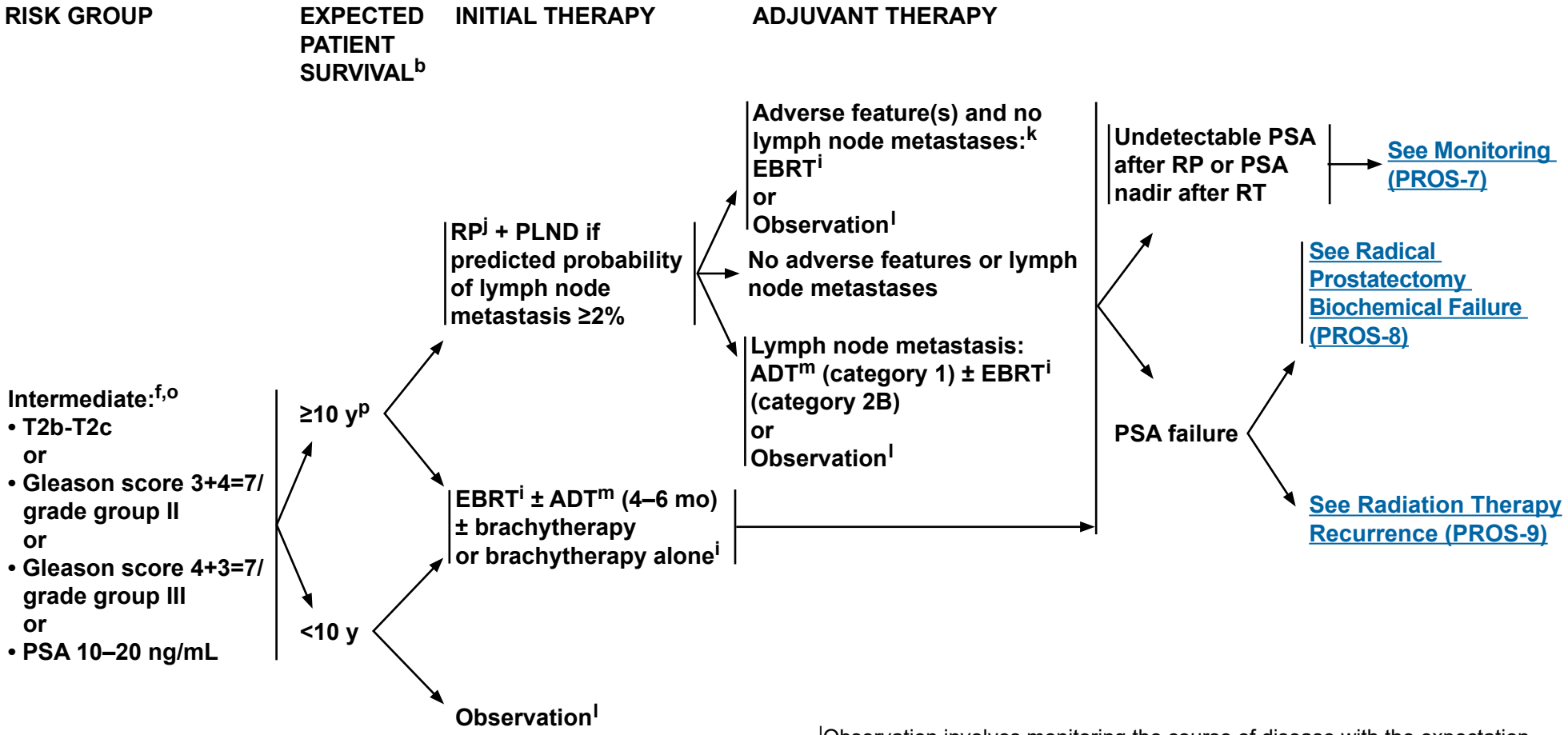

[b]See Principles of Life Expectancy Estimation (PROS-A).
[f]Patients with multiple adverse factors may be shifted into the next highest risk group.
[i]See Principles of Radiation Therapy (PROS-D).
[j]See Principles of Surgery (PROS-E).
[k]Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.

[l]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).
[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[o]Patients with favorable intermediate-risk prostate cancer (predominant Gleason grade 3 [ie, Gleason score 3 + 4 = 7/grade group II], and percentage of positive biopsy cores <50 percent, and no more than one NCCN intermediate risk factor) may be considered for active surveillance. See Discussion section.
[p]Active surveillance of unfavorable intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).

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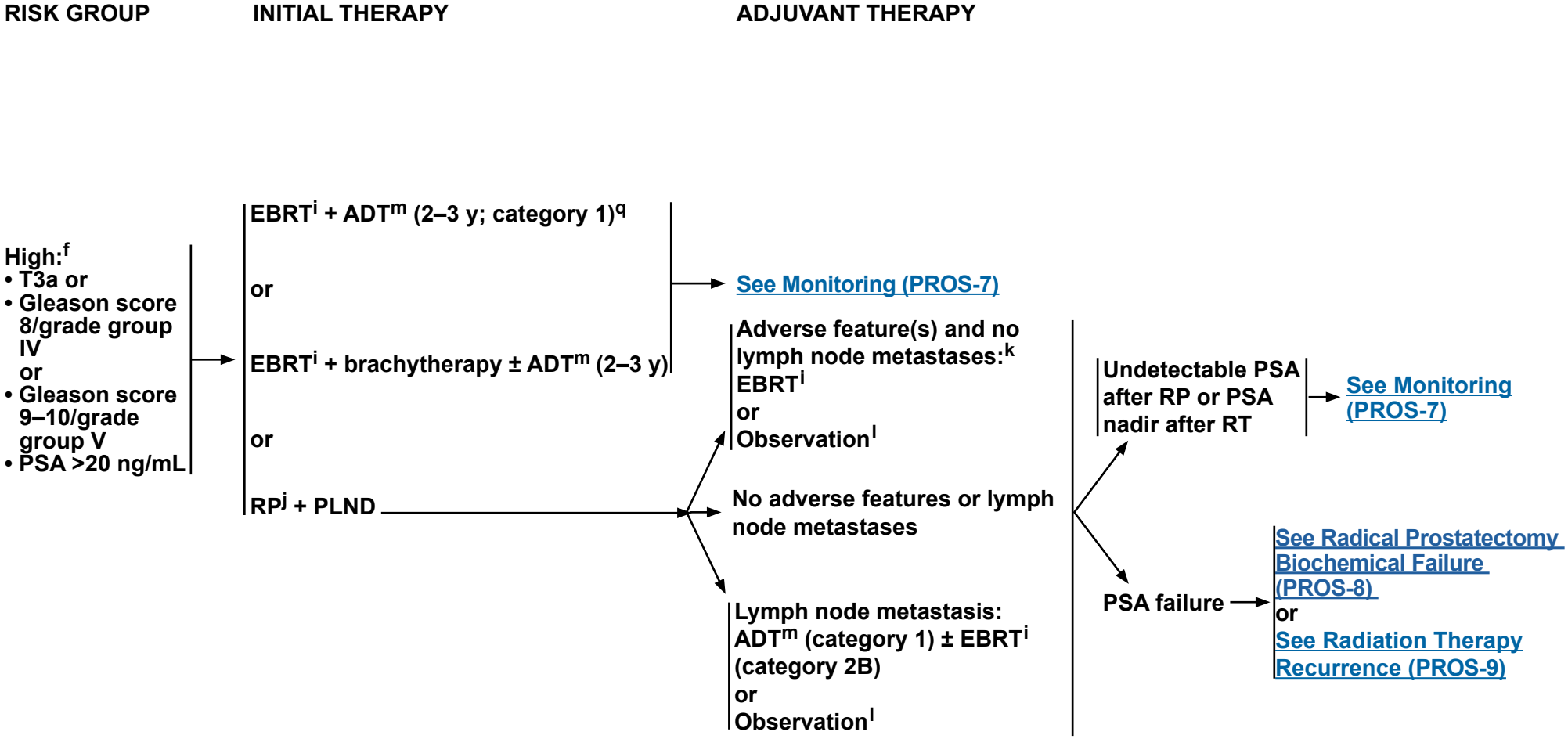

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[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[q]Six cycles of docetaxel every 3 weeks without prednisone may be administered after completion of radiation in selected patients who are fit for chemotherapy.

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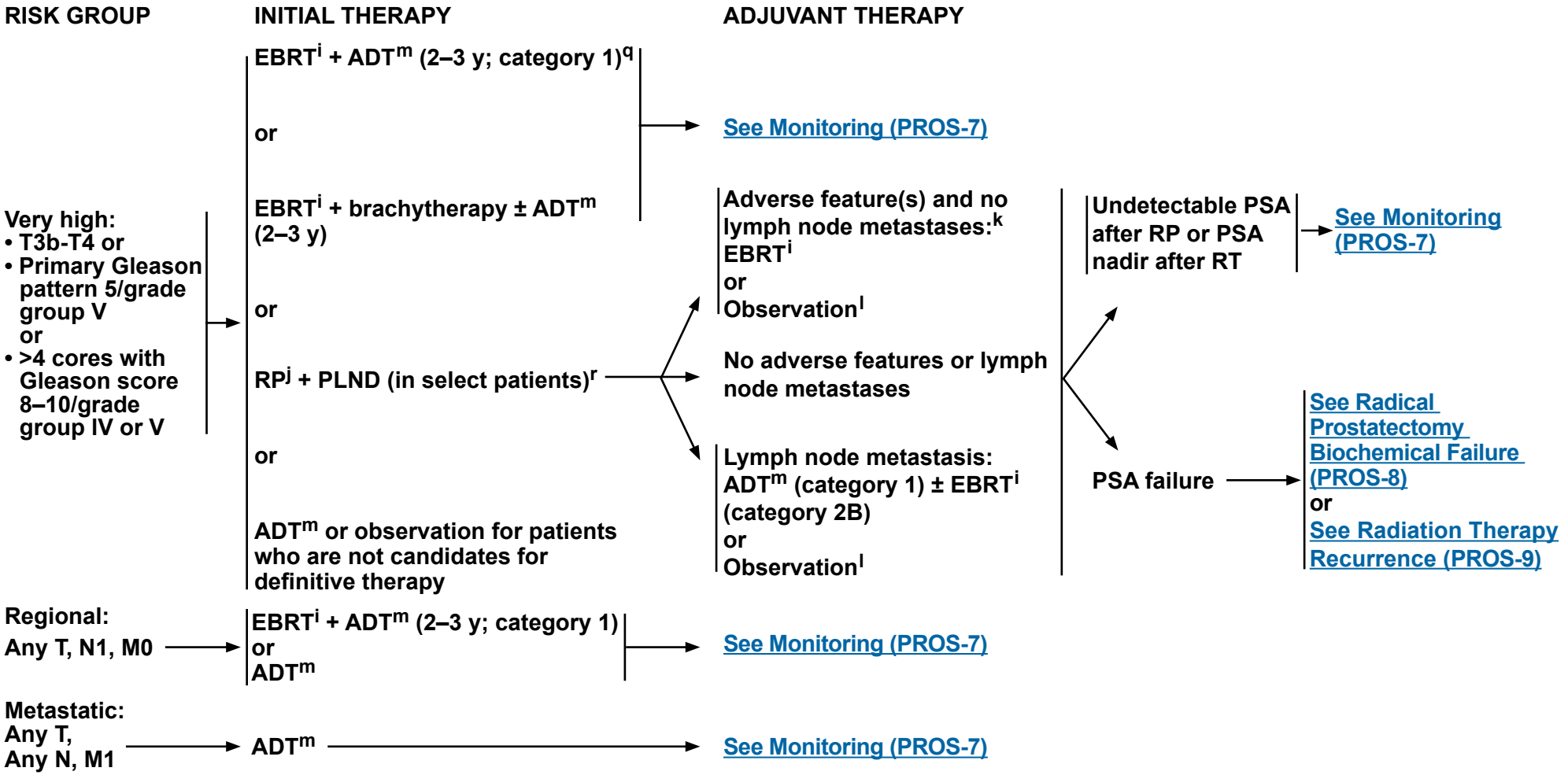

[l]Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).

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

[q]Six cycles of docetaxel every 3 weeks without prednisone may be administered after completion of radiation in selected patients who are fit for chemotherapy.

[r]RP + PLND can be considered in younger, healthier patients without tumor fixation to the pelvic side-wall.

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

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[k]Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.

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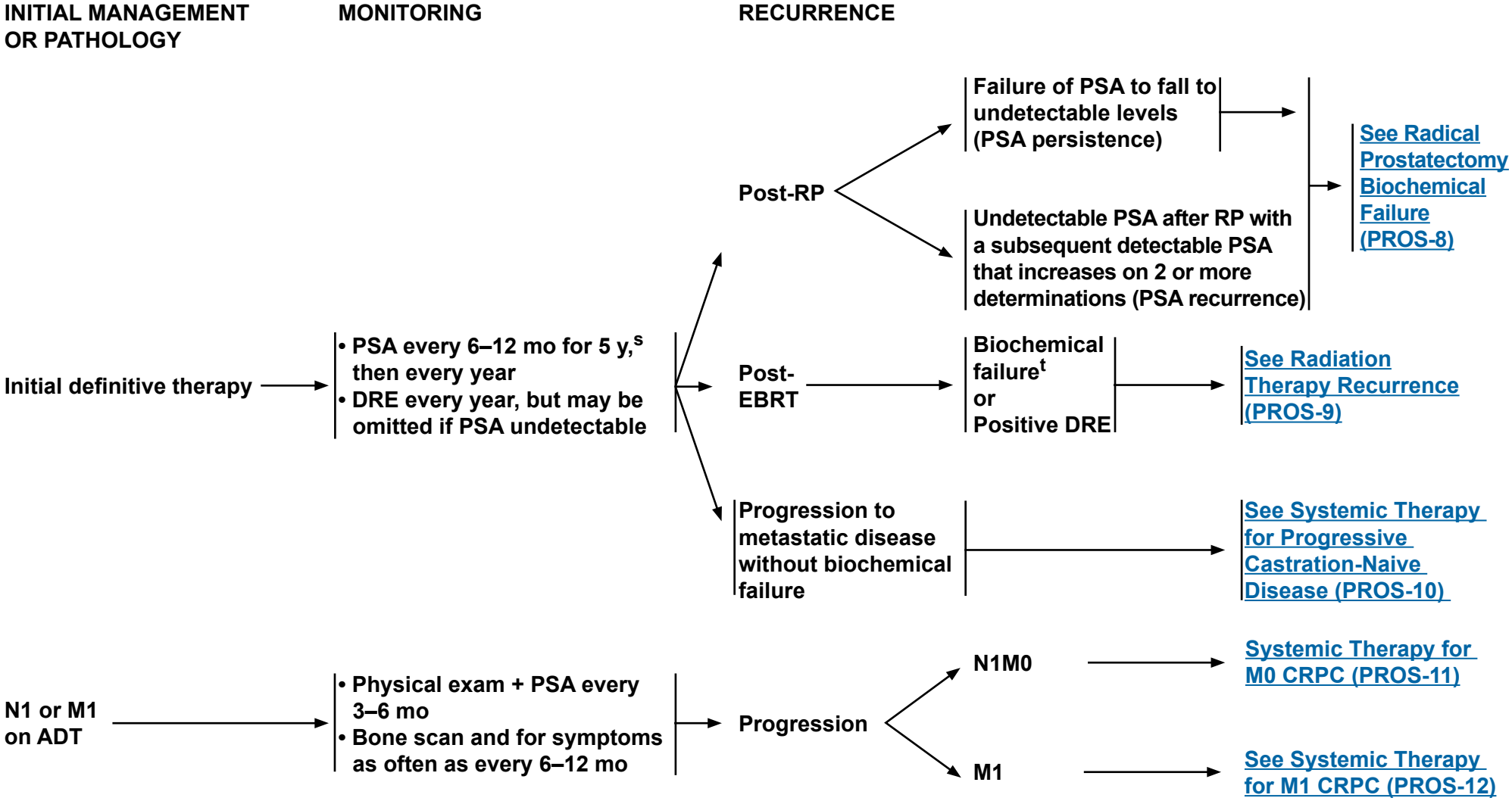

[s]PSA as frequently as every 3 mo may be necessary to clarify disease status, especially in high-risk men.

[t]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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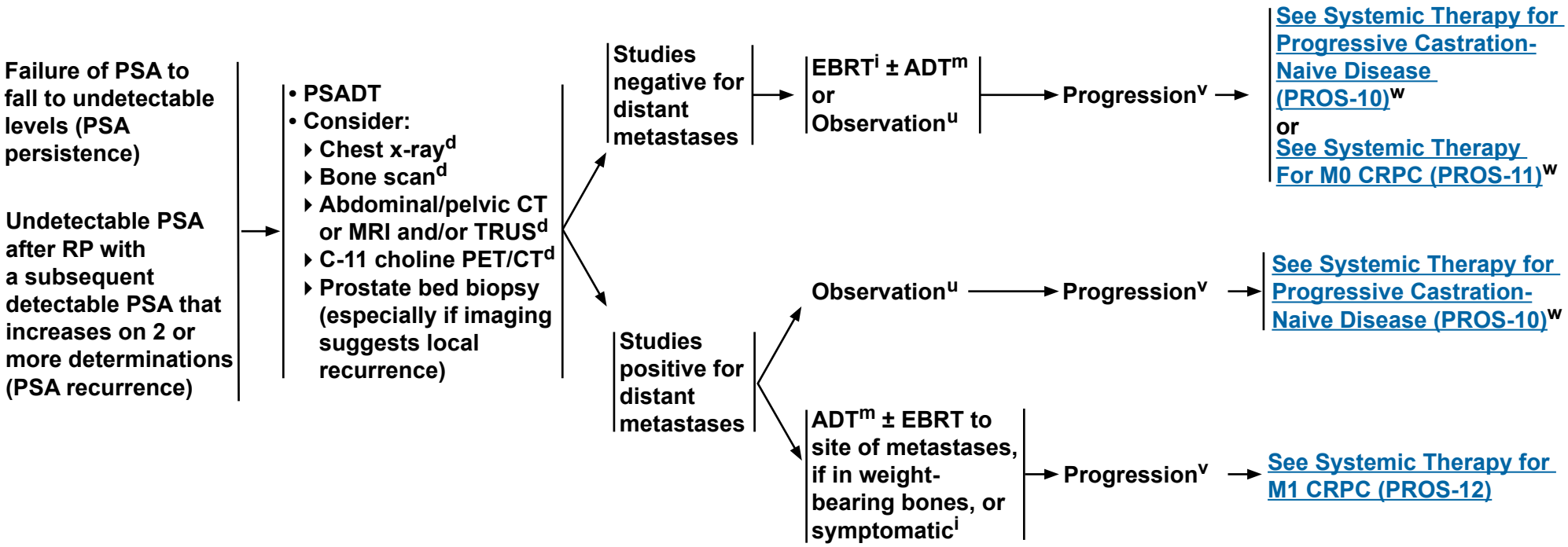
RADICAL PROSTATECTOMY BIOCHEMICAL FAILURE



[d]See Principles of Imaging (PROS-B).
[i]See Principles of Radiation Therapy (PROS-D).
[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[u]Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[v]Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT. See Principles of Imaging (PROS-B).
[w]The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.

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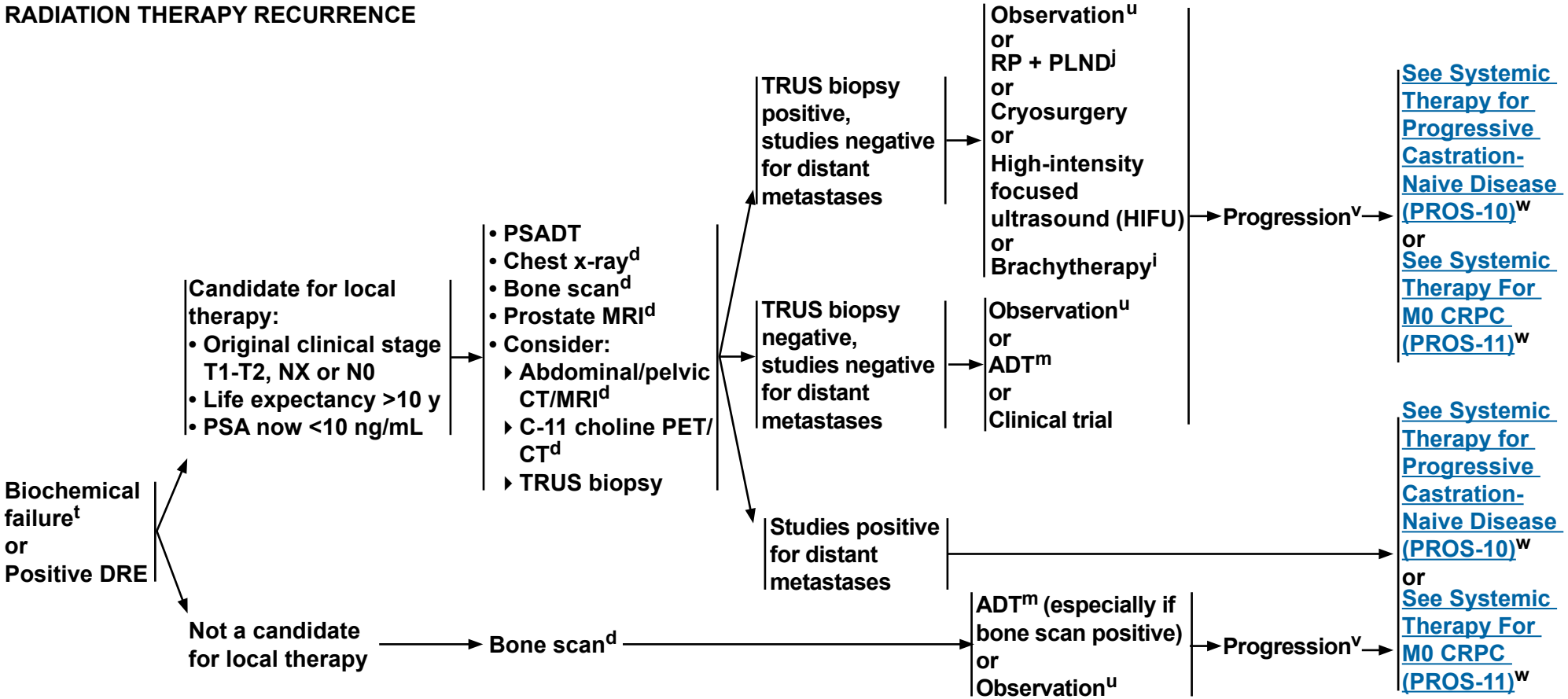
RADIATION THERAPY RECURRENCE



[d]See Principles of Imaging (PROS-B).
[i]See Principles of Radiation Therapy (PROS-D).
[j]See Principles of Surgery (PROS-E).
[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[t]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.
[u]Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[v]Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT. See Principles of Imaging (PROS-B).
[w]The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.

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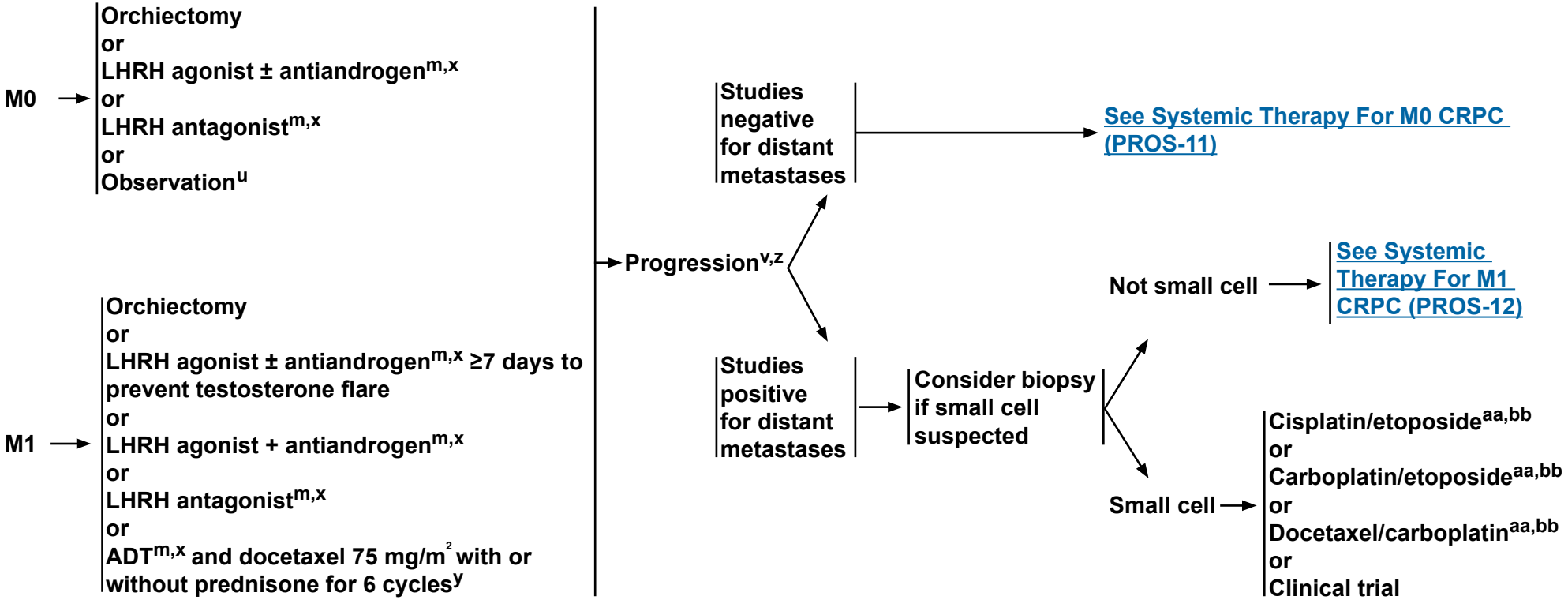
SYSTEMIC THERAPY FOR PROGRESSIVE CASTRATION-NAIVE DISEASE[w]



[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[u]Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[v]Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT. See Principles of Imaging (PROS-B).
[w]The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.
[x]Intermittent ADT can be considered for men with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-F)
[y]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. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.
[z]Assure castrate level of testosterone.
[aa]See Principles of Immunotherapy and Chemotherapy (PROS-G).
[bb]See NCCN Guidelines for Small Cell Lung Cancer.

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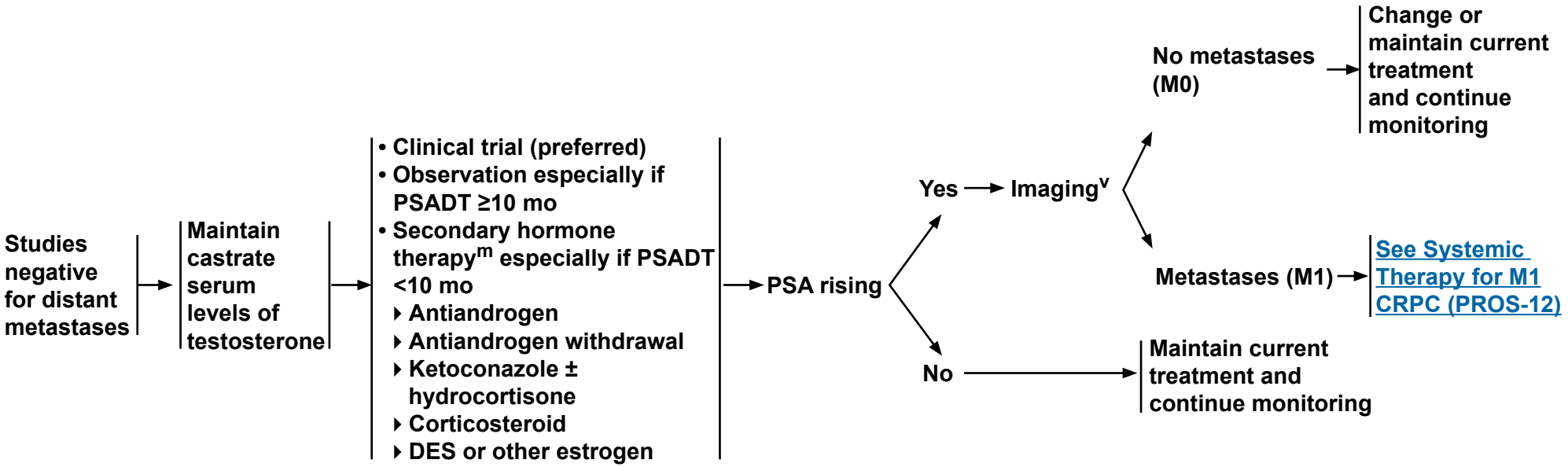
SYSTEMIC THERAPY FOR M0 CASTRATION-RECURRENT PROSTATE CANCER



[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[v]Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT. See Principles of Imaging (PROS-B).

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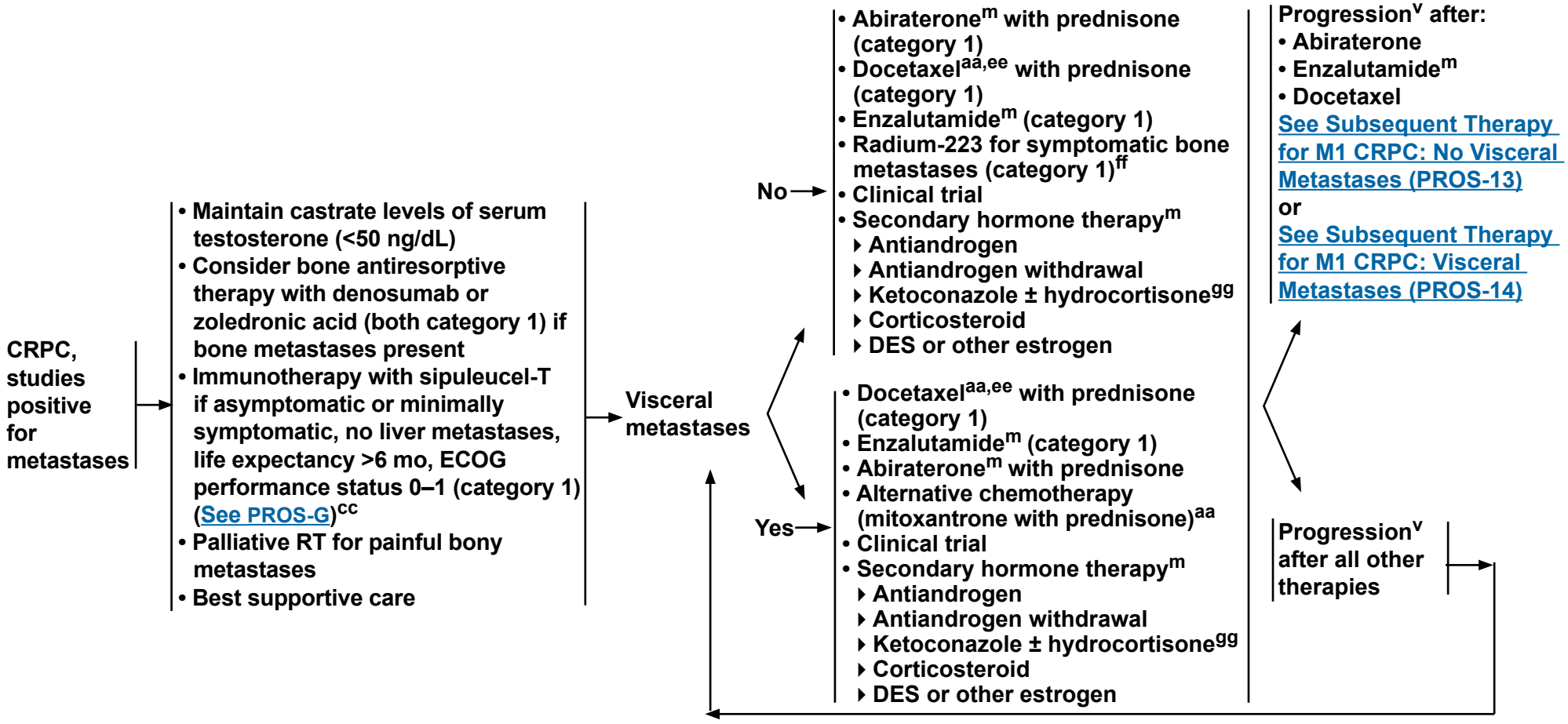
SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER



[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[v]Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT. See Principles of Imaging (PROS-B).
[aa]See Principles of Immunotherapy and Chemotherapy (PROS-G).
[cc]Sipuleucel-T has not been studied in patients with visceral metastases.
[ee]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.
[ff]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).
[gg]Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.

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SUBSEQUENT SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER[hh]

Prior therapy enzalutamide/abiraterone[ii]

- Docetaxel with prednisone (category 1)[aa]
- Abiraterone[m] with prednisone
- Enzalutamide[m]
- Radium-223 for symptomatic bone metastases (category 1)[ff]
- Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
- Clinical trial
- Other secondary hormone therapy[m]
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone[gg]
  - Corticosteroid
  - DES or other estrogen
- Best supportive care

No visceral metastases

Prior therapy docetaxel

- Enzalutamide (category 1)[m]
- Abiraterone[m] with prednisone (category 1)
- Radium-223 for symptomatic bone metastases (category 1)[ff]
- Cabazitaxel with prednisone (category 1)[aa]
- Sipuleucel-T if asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG 0–1
- Clinical trial
- Docetaxel rechallenge[aa]
- Alternative chemotherapy (mitoxantrone with prednisone)[aa]
- Other secondary hormone therapy[m]
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone[gg]
  - Corticosteroid
  - DES or other estrogen
- Best supportive care

[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[aa]See Principles of Immunotherapy and Chemotherapy (PROS-G).
[ff]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).

[gg]Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.
[hh]Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.
[ii]Limited data suggest a possible role for AR-V7 testing to help guide selection of therapy.

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SUBSEQUENT SYSTEMIC THERAPY FOR M1 CASTRATION-RECURRENT PROSTATE CANCER[hh]

Visceral metastases

Prior therapy enzalutamide/ abiraterone[ii] →

- Docetaxel with prednisone (category 1[aa]
- Clinical trial
- Abiraterone[m] with prednisone
- Enzalutamide[m]
- Other secondary hormone therapy[m]
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone[gg]
  - Corticosteroid
  - DES or other estrogen
- Best supportive care

Prior therapy docetaxel →

- Enzalutamide (category 1)[m]
- Abiraterone[m] with prednisone (category 1)
- Cabazitaxel with prednisone (category 1)[aa]
- Clinical trial
- Docetaxel rechallenge[aa]
- Alternative chemotherapy (mitoxantrone with prednisone)[aa]
- Other secondary hormone therapy[m]
  - Antiandrogen
  - Antiandrogen withdrawal
  - Ketoconazole ± hydrocortisone[gg]
  - Corticosteroid
  - DES or other estrogen
- Best supportive care

[gg]Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.
[hh]Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.
[ii]Limited data suggest a possible role for AR-V7 testing to help guide selection of therapy.

[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[aa]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) or the WHO's Life Tables by country (http://apps.who.int/gho/data/view.main.60000?lang=en).**
- **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 in the NCCN Guidelines for Older Adult Oncology for life expectancy estimation.**

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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/CT, and advanced MRI techniques, such as spectroscopy and spect (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 PSADT ≤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.

Bone Scan

- The use of the term “bone scan” refers to the conventional technetium-99m-MDP bone scan in which 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/CT scan or hybrid imaging bone scan can be used as a diagnostic staging study. These tests appear to have greater sensitivity than bone scan. However, there is controversy about how the results of 18F-NaF PET/CT bone scan should be acted upon since all phase 3 clinical trials to date have used progression criteria on 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.

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PRINCIPLES OF IMAGING

Bone Scan (continued)

- Bone scans are helpful to monitor metastatic prostate cancer to determine the clinical benefit of systemic therapy. However, new lesions seen on an initial post-treatment bone scan, compared to the pre-treatment baseline scan, may not indicate disease progression.
- New lesions in the setting of a falling PSA or soft tissue response and in the absence of pain progression at that site may indicate bone scan flare or an osteoblastic healing reaction. For this reason, a confirmatory bone scan 8–12 weeks later is warranted to determine true progression from flare reaction. Additional new lesions favor progression. Stable scans make continuation of treatment reasonable. Bone scan flare is common, particularly on initiation of new hormonal therapy, and may be observed in nearly half of patients treated with the newer agents, enzalutamide and abiraterone. Similar flare phenomenon may exist with other imaging modalities, such as CT or PET/CT imaging.
- Bone scans and soft tissue imaging (CT or MRI) in men with metastatic prostate cancer or non-metastatic progressive prostate cancer may be obtained regularly during systemic therapy to assess clinical benefit.
- Bone scans should be performed for symptoms and as often as every 6–12 mo to monitor ADT. The need for soft tissue images remains unclear. In CRPC, 8- to 12-week imaging intervals appear reasonable.

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 and 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.

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 and without the administration of intravenous contrast material.
  - Resolution of MRI 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.

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PRINCIPLES OF IMAGING

Magnetic Resonance Imaging

- 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. MRI-US fusion biopsy may improve the detection of higher grade (Gleason score ≥7) cancers.
- 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 ≥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

- Whole body PET/CT using C-11 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 18F-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 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).
- Patients with favorable intermediate-risk prostate cancer (predominant Gleason grade 3 [ie, Gleason score 3 + 4 = 7], and percentage of positive biopsy cores <50 percent, and no more than one NCCN intermediate risk factor) may be considered for active surveillance. See Discussion section. 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)
  - MRI-US fusion biopsy may improve the detection of higher grade (Gleason score ≥7) cancers.
  - A repeat prostate biopsy should be considered if prostate exam changes, MRI suggests more aggressive disease, or PSA increases, but no 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 mpMRI 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:**
  - **About 2/3 of men eligible for active surveillance will avoid treatment**
  - **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**

- **Disadvantages of active surveillance:**
  - **Chance of missed opportunity for cure although very low**
  - **About 1/3 of men will require treatment, although treatment delays do not seem to impact cure rate.**
  - **Periodic follow-up prostate biopsies may be necessary.**

- **Advantages of observation:**
  - **Avoidance of possible side effects of unnecessary definitive therapy and early initiation and/or continuous ADT**

- **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 an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.
- Patients with high-risk and very-high-risk cancers should receive neoadjuvant/concomitant/adjuvant ADT for a total of 2 to 3 y if comorbidities allow (category 1). Pelvic lymph node irradiation can be considered.
- 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 Brachytherapy

- Brachytherapy as monotherapy is indicated for patients with low-risk cancers and selected patients with low-volume intermediate-risk cancers. Intermediate-risk cancers may be treated by combining 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 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 TURP 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 in some men despite neoadjuvant ADT. Potential toxicity of ADT must be balanced against the potential benefit of target reduction.
- Post-implant dosimetry must be performed to document the quality of the low dose-rate implant.
- The recommended prescribed doses for brachytherapy 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). Commonly used boost regimens include 13 to 15 Gy x 1 fraction, 8 to 11.5 Gy x 2 fractions, 5.5 to 6.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions. Commonly used regimens for HDR treatment alone include 9.5 Gy x 4 fractions, 10.5 Gy x 3 fractions, 13.5 Gy x 2 fractions, or 19 Gy x 1 fraction.

Salvage Brachytherapy

- 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 the pattern of recurrence, 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. 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 more effective when pre-treatment PSA is low and PSADT is long.
- 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.
- Two years instead of 6 months of ADT can be considered in addition to RT based on RTOG 9601 (presented at ASTRO 2015) for men with persistent PSA after RP or for PSA levels that exceed 1.0 ng/mL at the time of initiation of salvage therapy. Six months of ADT can be considered coadministered with salvage radiation based on the results of GETUG-16. An LHRH agonist should be used. For 2-year ADT, there is level 1 evidence to support 150 mg bicalutamide daily but an LHRH agonist could be considered as an alternative.
- 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 castration-recurrent prostate cancer (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

- 8 Gy as a single dose should be used instead of 30 Gy 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.

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

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

Androgen Deprivation Therapy (ADT) for Clinically Localized Disease (PROS-2 through PROS-6), Biochemical Failure Without Metastases OR for Metastatic Castration-Naïve Disease (PROS-8 through PROS-10):

- LHRH agonist alone
  - Goserelin
  - Histrelin
  - Leuprolide
  - Triptorelin
- LHRH agonist (as above) plus first-generation antiandrogen
  - LHRH agonist plus nilutamide
  - LHRH agonist plus flutamide
  - LHRH agonist plus bicalutamide
- LHRH agonist (as above) plus second-generation antiandrogen
  - LHRH agonist plus enzalutamide
- LHRH antagonist
  - Degarelix

Secondary Hormone Therapy for M0 or M1 Castration-Recurrent Disease (PROS-11 through PROS-14):

- First-generation antiandrogen
  - Nilutamide
  - Flutamide
  - Bicalutamide
- Second-generation antiandrogen
  - Enzalutamide
- Ketoconazole
- Ketoconazole plus hydrocortisone
- Corticosteroids (hydrocortisone, prednisone, dexamethasone)
- DES or other estrogen

Systemic Therapy For M1 Castration-Recurrent Disease (PROS-12 through PROS-14):

- Second generation antiandrogen
  - Enzalutamide (category 1; category 2A if prior therapy with abiraterone)
- Androgen biosynthesis inhibitor
  - Abiraterone + prednisone (category 1; category 2A for initial treatment of disease with visceral metastases or if prior therapy with enzalutamide)

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.

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

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).

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 could not demonstrate non-inferiority for survival. However, quality-of-life measures for erectile function and mental health were better in the intermittent ADT arm after 3 months of ADT compared to the continuous ADT arm.
- In addition, three meta-analyses of randomized controlled trials failed to show a difference in survival between intermittent and continuous ADT.
- 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 co-administered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.
- 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.

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Secondary Hormone Therapy

- Androgen receptor activation and autocrine/paracrine androgen synthesis are potential mechanisms of recurrence of prostate cancer during ADT (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, M0 CRPC (non-metastatic) vs. M1 CRPC (metastatic), and whether or not the patient is symptomatic.
- In the setting in which patients have no or minimal symptoms, administration of secondary hormonal therapy including addition of, or switching to, a different anti-androgen (flutamide, bicalutamide, nilutamide, enzalutamide), addition of adrenal/paracrine androgen synthesis inhibitors (ketoconazole with or without hydrocortisone or abiraterone with prednisone), or use of an estrogen, such as DES, can be considered. Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.
- DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/d and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.
- In a randomized controlled trial in the setting of M1 CRPC 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. An improvement in overall survival was demonstrated. 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 rPFS 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 M1 CRPC. 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.
- Two randomized clinical trials (STRIVE and TERRAIN) showed that 160 mg/d enzalutamide improved progression-free survival compared with 50 mg/d bicalutamide in men with treatment-naïve CRPC and, therefore, enzalutamide may be the preferred option in this setting. However, bicalutamide can still be considered in some patients, given the different side-effect profiles of the agents and the increased cost of enzalutamide.
- Evidence-based guidance on the sequencing of these agents in either pre- or post-docetaxel remains unavailable.

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Monitor/Surveillance

- ADT has a variety of adverse effects including hot flashes, loss of libido and erectile dysfunction, shrinkage of penis and testicles, loss of muscle mass and strength, fatigue, depression, hair loss, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease. Patients and their medical providers should be advised about these risks prior to treatment.
- Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation (www.nof.org). The National Osteoporosis Foundation guidelines include recommendations for: 1) supplemental calcium (1200 mg 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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PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

Systemic Therapy for M1 Castration-Recurrent Disease

- Chemotherapy
  - Docetaxel + prednisone (category 1; category 2A for rechallenge)
  - Cabazitaxel + prednisone (category 1 post-docetaxel)
- Immunotherapy
  - Sipuleucel-T (category 1)
    - Only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, ECOG performance status 0-1

- 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
- 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. (See PROS-F, 3 of 4). Mitoxantrone and prednisone may provide palliation but have not been shown to extend survival.
- 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.

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PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

- Patients who are not candidates for docetaxel or who are intolerant of docetaxel should be considered for cabazitaxel with prednisone, based on recent results that suggest clinical activity of cabazitaxel in mCRPC. Cabazitaxel with prednisone was associated with lower rates of peripheral neuropathy than docetaxel, particularly at 20 mg/m² (12% vs. 25%) and may be appropriate in patients with pre-existing mild peripheral neuropathy. Current data do not support greater efficacy of cabazitaxel over docetaxel.
- 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.
- Cabazitaxel at 25 mg/m² every 3 weeks with prednisone has been the standard of care in the post-docetaxel setting, with or without growth factor support. A recent trial, PROSELICA, compared cabazitaxel 25 mg/m² every 3 weeks to 20 mg/m² every 3 weeks. Cabazitaxel 20 mg/m² had less toxicity; febrile neutropenia, diarrhea, and fatigue were less frequent. Cabazitaxel at 20 mg/m² had a significantly lower PSA response rate but non-significantly lower radiographic response rate and non-significantly shorter progression-free and overall survival (13.4 vs 14.5 mo) compared to 25 mg/m². Cabazitaxel starting dose can be either 20 mg/m² or 25 mg/m² for men with mCRPC who have progressed despite prior docetaxel chemotherapy. Cabazitaxel 20 mg/m² with prednisone is recommended for frail or less chemo-fit men and those at high risk for neutropenic fever. Cabazitaxel 25 mg/m² with prednisone is recommended for healthy men who wish to be more aggressive.
- Docetaxel retreatment can be attempted in men who have not demonstrated definitive evidence of progression on prior docetaxel therapy.
- No chemotherapy regimen to date has demonstrated improved survival or quality of life after cabazitaxel, and trial participation should be encouraged. Several systemic agents have shown palliative and radiographic response benefits in clinical trials.
- Treatment decisions around off-label chemotherapy use in the treatment-refractory CRPC should be individualized based on comorbidities and functional status and after informed consent.
- No benefits of combination approaches over sequential single-agent therapies have been demonstrated, and toxicity is higher with combination regimens.
- See NCCN Guidelines for Myeloid Growth Factors for recommendations on growth factor support.

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PRINCIPLES OF IMMUNOTHERAPY AND CHEMOTHERAPY

- 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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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.

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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.

Continue

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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)

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GRADE GROUP DEFINITIONS

Grade group 1: Gleason score ≤6
Only individual discrete well-formed glands

Grade group 2: Gleason score 3+4=7
Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands

Grade group 3: Gleason score 4+3=7
Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands*

Grade group 4: Gleason score 4+4=8; 3+5=8; 5+3=8
- **Only poorly-formed/fused/cribriform glands or**
- **Predominantly well-formed glands and lesser component lacking glands[1] or**
- **Predominantly lacking glands and lesser component of well-formed glands[1]**

Grade group 5: Gleason score 9-10
Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands[2]

[1]Poorly-formed/fused/cribriform glands can be a more minor component
[2]For case with >95% poorly-formed/fused/cribriform glands or lack of glands on a core or at RP, the component of <5% well-formed glands is not factored into the grade

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- Rubin MA, Girelli G, Demichelis F. Genomic correlates to the newly proposed grading prognostic groups for prostate cancer. Eur Urol 2016;69:557-560.
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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/27/16

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

An estimated 220,800 new cases of prostate cancer will be diagnosed in 2015, accounting for 26% of new cancer cases in men.[1] However, the age-adjusted death rates from prostate cancer have declined (-3.8% annually from 1994–2004). Researchers have estimated prostate cancer to account for 27,540 deaths in 2015.[1] The decreasing and comparatively low death rate suggests that increased public awareness with earlier detection and treatment has affected mortality from this prevalent cancer. The alternative hypothesis is that prostate cancer is becoming biologically less aggressive, but evidence is lacking. Early detection can lead to overtreatment of prostate cancers that do not threaten life expectancy, which results in unnecessary side effects that impair quality of life and increase health care expenditures. Over the past several years, the incidence of prostate cancer has declined, likely in part a result of decreased rates of prostate-specific antigen (PSA) screening.[2,3] Better use of PSA for early detection of potentially fatal prostate cancer (see the NCCN Guidelines for Prostate Cancer Early Detection, available at www.NCCN.org) should decrease the risk of over-detection and over-treatment AND preserve the decrease in prostate cancer mortality.

Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature in prostate cancer published between September 4, 2014 and April 15, 2015, which used the search term prostate cancer, prior to the update of this version of the NCCN Guidelines® for Prostate Cancer. The PubMed database was chosen because 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 97 citations and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed relevant to these guidelines and discussed by the panel have been included in this updated Discussion section. Recommendations for which high-level evidence was lacking were based on panel review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Estimates of Life Expectancy

Estimates of life expectancy have emerged as a key determinant of primary treatment, particularly when considering active surveillance or observation. Life expectancy can be estimated for groups of men, but it is difficult to extrapolate these estimates to an individual patient. Life expectancy can be estimated using the Minnesota Metropolitan Life Insurance Tables, the Social Security Administration Life Insurance Tables,[4] or the WHO's Life Tables by Country,[5] and adjusted for individual patients by adding or subtracting 50% based on whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively.[6] As an example, the Social Security Administration Life Expectancy for a 65-year-old American man is 17.7 years. If judged to be in the upper quartile of health, a life expectancy of 26.5 years is assigned. If judged to be in the lower quartile of health, a life expectancy of 8.8 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 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 spread to the regional lymph nodes? How likely is the cancer to progress or metastasize after treatment? How likely is adjuvant or salvage radiation to control cancer after an unsuccessful radical prostatectomy? Prostate cancers are best characterized by the digital rectal exam (DRE)- and radiographically determined clinical T stage, Gleason score and extent of cancer 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 and to predict the probability of biochemical failure after definitive local therapy.[7] Risk group stratification has been published widely and validated, and provides a better basis for treatment recommendations than clinical stage alone.[8,9]

The NCCN Guidelines Panel recognized that heterogeneity exists within each risk group. For example, an analysis of 12,821 patients showed 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).[10] 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. Other studies have reported differences in outcomes in the high-risk group depending on risk factors.[11] Evidence also shows heterogeneity in the low-risk group, with PSA levels and percent positive cores affecting pathologic findings after radical prostatectomy.[12,13]

In a retrospective study, 1024 patients with intermediate-risk prostate cancer were treated with radiation with or without neoadjuvant and concurrent ADT.[14] Multivariate analysis revealed that primary Gleason pattern 4, percentage of positive biopsy cores ≥50, and presence of >1 intermediate-risk factors (ie, T2b-c, PSA 10-20ng/mL, Gleason score 7) were significant predictors of increased incidence of distant metastasis. The authors used these factors to separate the patients into unfavorable and favorable intermediate-risk groups and determined that the unfavorable intermediate-risk group had worse PSA recurrence-free survival, distant metastasis, and prostate cancer-specific mortality than the favorable intermediate-risk group.

Nomograms

The more clinically relevant information that is used in the calculation of time to PSA failure, the more accurate the result. The Partin tables[15-17] 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,[18,19] radical prostatectomy,[20-23]

neurovascular bundle preservation[24-26] or omission of pelvic lymph node dissection (PLND) during radical prostatectomy,[27,28] brachytherapy,[20,29-31] or external beam radiation therapy (EBRT).[20,32] Biochemical progression-free survival can be reassessed postoperatively using age, diagnostic serum PSA, and pathologic grade and stage.[20,33] Potential success of adjuvant or salvage radiation therapy (RT) after unsuccessful radical prostatectomy can be assessed using a nomogram.[20,34]

None of the current models predicts with perfect accuracy, and only some of these models predict metastasis[19,20,33,35,36] and cancer-specific death.[21,23,37,38] 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.[39] 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 National Academy of Medicine has described several lessons that should accelerate the development of useful biomarkers[40] to inform men and their physicians about proper choices for treatment of clinically localized prostate cancer. Dr. Hayes has warned us that a “bad tumor marker is as bad as a bad drug.”[41,42] 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. Although risk groups, life expectancy estimates, and nomograms help inform decisions, uncertainty about the risk of disease progression persists. American men continue to under-select active surveillance and their physicians may under-recommend it, likely as a result of this uncertainty.[43]

Several tissue-based molecular assays have been developed in an effort to improve decision-making in newly diagnosed men considering active surveillance and in treated men considering adjuvant therapy or treatment for recurrence. Uncertainty about the risk of disease progression can be reduced if such molecular assays can provide accurate and reproducible prognostic or predictive information beyond NCCN risk group assignment and currently available life expectancy tables and nomograms. Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or radiotherapy, and likelihood of developing metastasis after operation or salvage radiotherapy.[44-48] No randomized controlled trials have studied the utility of these tests. Several of these assays are available, and 3 have received positive reviews by the Molecular Diagnostic Services Program (MolDX) and are likely to be covered by CMS (Centers for Medicare & Medicaid Services). Several other tests are under development, and the use of these assays is likely to increase in the coming years.

Table 1 lists these tests in alphabetical order and provides an overview of each test, populations where each test independently predicts outcome, and supporting references. These molecular biomarker tests

listed have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with clinically localized disease may consider the use of tumor-based molecular assays at this time. Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of men with 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*.

The guidelines recommend CT or MRI imaging as part of staging workup for men with longer life expectancies and T3 or T4 disease or nomogram-predicted probability of lymph node involvement >10%. Multivariate analysis of retrospective data on 643 men with newly diagnosed prostate cancer who underwent staging CT found that PSA, Gleason score, and clinical T stage were associated independently with a positive finding ($P < .05$ for all).[49] Bone scans are recommended as part of staging for patients with longer life expectancies and higher Gleason grade, higher T stage, or higher PSA values as delineated in the algorithm. Retrospective evidence suggests that Gleason score and PSA levels are associated with positive bone scan findings.[50]

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 operation or radiation.

The utility of imaging for men with an early biochemical recurrence after radical prostatectomy depends on disease risk before operation and pathologic stage, Gleason grade, PSA, and PSA doubling time after recurrence. Patients with low- and intermediate-risk disease and low postoperative serum PSA levels have a very low risk of positive bone scans or CT scans.[51,52] In a series of 414 bone scans performed in 230 men with biochemical recurrence after radical prostatectomy, the rate of a positive bone scan for men with PSA >10 ng/mL was only 4%.[53] Serial PSA measurements can be helpful for 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.[54,55]

The use of multiparametric MRI (mpMRI) in the staging and characterization of prostate cancer has increased in the last few years. To be considered “multi-parametric,” MRI images must be acquired with at least one more sequence apart from the anatomical T2-weighted one, such as DWIs or dynamic contrast-enhanced (DCE) images. 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 cancers (ie, Gleason score ≥7).[56] MpMRI has been incorporated into MRI-TRUS fusion-targeted biopsy protocols, which has led to an increase in the diagnosis of high-grade cancers with fewer biopsy cores, while reducing detection of low-grade and insignificant cancers.[57-59] Second, mpMRI aids in the detection of extracapsular

extension (T staging), with high negative predictive values in low-risk men.[60] MpMRI results may inform decision-making regarding nerve-sparing operation.[61] Third, mpMRI has been shown to be equivalent to CT scan for staging of pelvic lymph nodes.[62,63] Finally, mpMRI out-performs bone scan and targeted x-rays for detection of bone metastases, with sensitivity 98% to 100% and specificity of 98% to 100% (vs. sensitivity of 86% and specificity of 98%–100% for bone scan plus targeted x-rays).[64]

C-11 choline PET/CT has been used to detect and differentiate prostate cancer from benign tissue.[65,66] The sensitivity and specificity of the technique in restaging patients with biochemical failure were 85% and 88%, respectively.[67] C-11 choline PET/CT may be useful to detect distant metastases in these patients. FDG-PET/CT, in contrast, is not recommended for routine use for prostate cancer management because data remain insufficient.

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 clear. 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 and radiation burns. No effect is seen below the dose threshold. Medical imaging is always performed almost below the threshold for deterministic effects. Stochastic effects tend to occur late, increase in likelihood as dose increases, and have no known lower “safe” limit. 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 using other models (such as from atomic bomb survivors). The literature is conflicting with regards to the precise risk of secondary malignancies in patients undergoing medical imaging procedures. There is a small but finite risk of developing secondary malignancies as a result of medical imaging procedures, and 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.[68] Efforts should be made to minimize dose from these procedures, which begin with judicious use of imaging only when justified by the clinical situation. Harm may 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 may 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 (eg, hives, itching) but occasionally severe reactions can be life-threatening (bronchospasm or anaphylactoid). The risk of severe reaction is low with non-ionic contrast materials and may be about 1:170,000 injections.[69] Both iodinated CT contrast material and gadolinium-based MR contrast materials can affect renal function, particularly when renal function is impaired. 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 limitations for sensitivity, specificity, and accuracy, which are modulated further by the expertise of the interpreting physician. Harm can arise from failure to detect a tumor or tumor recurrence (ie, false negative), but 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 malignant can lead to significant patient anxiety, additional and unnecessary imaging, and invasive procedures that carry their own risks for adverse outcomes.

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 in 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 also has been identified as a significant contributor to health care costs in the United States and worldwide. Therefore, imaging should be performed only when medically appropriate, and in a manner that 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,[70] can assist 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 noncurative 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. However, patients may develop urinary retention or pathologic fracture without prior symptoms or increasing PSA level.

Observation is applicable to elderly or frail men with comorbidity that will likely out-compete prostate cancer. Johansson and colleagues[71] 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 deliver curative therapy 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.

In one study, approximately two thirds of eligible men avoided treatment, and thus the possible associated side effects of treatment, after 5 years of active surveillance.[72] In another study, 55% of the

population remained untreated at 15 years.[73] Although a proportion of men will eventually undergo treatment, the delay does not appear to impact cure rates, and several studies have shown active surveillance is safe.[72-76] In fact, a 2015 meta-analysis of 26 active surveillance cohort studies that included 7627 men identified only 8 prostate cancer deaths and 5 cases of metastasis.[77] In addition, studies have shown that active surveillance does not adversely impact psychologic well-being or quality of life.[78-81] Possible disadvantages of active surveillance are listed in the *Principles* section of these guidelines and include the possible necessity of follow-up prostate biopsies.

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[82]; the high frequency of positive prostate biopsies in men with normal DREs and serum PSA values[83]; 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[84,85] or 100 men with low-risk prostate cancer[86] to prevent one death from the disease. The controversy regarding over-treatment of prostate cancer and the value of prostate cancer early detection[84-90] has been informed further by publication of the Goteborg study, a subset of the European Randomized Study of Screening for Prostate Cancer (ERSPC).[91] 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 managed initially using active surveillance 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 men 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.[92]

The best models of prostate cancer detection and progression estimate that 23% to 42% of all U.S. screen-detected cancers were overtreated[93] and that PSA detection was responsible for up to 12.3 years of lead-time bias.[94] 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[95] 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 insignificant using the Epstein criteria were not organ-confined based on postoperative findings.[96,97] A new nomogram may be better.[98] Although many variations upon this definition have been proposed (reviewed by Bastian and colleagues[99]), 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.[94]

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[100]). 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, particularly for African-American men. Multiple studies have shown that African Americans with very-low-risk prostate cancer may harbor high-grade (Gleason sum ≥7) cancer that is not detected by pre-treatment biopsies. Compared to Caucasian Americans matched on clinical parameters, African Americans have been reported to have 1.7- to 2.3-fold higher change of pathologic upgrading.[101,102] Several studies have reported that, among men with low-risk prostate cancer who are enrolled in active surveillance programs, African Americas have higher risk of disease progression to higher Gleason grade or volume cancer than Caucasian Americans.[103-105] African Americans in the low- to intermediate-risk categories also appear to suffer from an increased risk of biochemical recurrence after treatment.[106] Reasons for these clinical disparities are under investigation and may include difference in tumor location within the prostate that may reflect different prostate cancer subtypes related to differences in gene expression.[107-110] Strategies to improve risk-stratification for African Americans considering active surveillance may include mpMRI in concert with targeted image-guided biopsies, which has been reported to improve detection of clinically significant tumors in some men.[111]

Surveillance Program and Reclassification Criteria

Each of the major active surveillance series has used different criteria for reclassification.[73,75,112-116] Reclassification criteria were met by 23% of men with a median follow-up of 7 years in the Toronto experience,[114] 36% of men with a median follow-up of 5 years in the Johns Hopkins experience,[75] and 16% of men with a median follow-up of 3.5 years in the University of California, San Francisco (UCSF) experience[113] (Table 2). 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/y.[117] The Johns Hopkins group used biopsy-demonstrated reclassification to Gleason pattern 4 or 5 or increased tumor volume on biopsy as their criteria for reclassification. Of 290 men on an annual prostate biopsy program, 35% demonstrated reclassification at a median follow-up of 2.9 years.[118] Neither PSA doubling time (area under the curve [AUC] 0.59) nor PSA velocity (AUC 0.61) was associated with prostate biopsy reclassification. Both groups have concluded that PSA kinetics cannot replace regular prostate biopsy, although 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.[119,120]

A repeat prostate biopsy should be considered if prostate exam changes, if mpMRI (if done) suggests more aggressive disease, or if PSA increases, but no parameter is very reliable for detecting prostate cancer progression. Repeat biopsy is useful to determine whether higher Gleason grade elements, which may influence prognosis and hence the decision to continue active surveillance or to proceed to definitive local therapy, are evolving although the risk appears small.[121] Treatment of all men who developed Gleason pattern 4 on annual prostate biopsies has thus far resulted in only 2 prostate cancer deaths among 1298 men (0.15%) in the Johns Hopkins study.[75] However, it remains uncertain whether treatment of all who progress to Gleason pattern 4 was necessary. 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.[114] These 3 deaths led them to revise their criteria for offering men active surveillance, because each of these 3 men probably had metastatic disease at the time of entry on 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%.[114] Of the 30% (n = 145) of men who progressed, 8% had an increase in Gleason grade, 14% had PSA doubling time <3 years, 1% developed a prostate nodule, and 3% were treated because of anxiety. One hundred thirty-five of these 145 men were treated: 35 by radical prostatectomy, 90 by EBRT 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 62% for those undergoing radical prostatectomy and 43% for those undergoing radiation. Longer-term follow-up of this cohort was reported in 2015.[73] The 10- and 15-year actuarial cause-specific survival rates for the entire cohort were 98.1% and 94.3 %, respectively. Only 15 of 993 (1.5%) patients had died of prostate cancer, an additional 13 men (1.3%) had developed metastatic disease, and only 36.5% of the cohort had received treatment by 10 years.

In comparison, among 192 men on active surveillance who underwent delayed treatment at a median of 2 years after diagnosis in the Johns Hopkins experience, 5-year biochemical progression-free survival was 96% for those who underwent radical prostatectomy and 75% for those who underwent radiation.[116] 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 of 37.5 months, compared to 97% of men in the primary radical prostatectomy group at median follow-up of 35.5 months. A later publication from this

group showed that 23 of 287 men who were treated after active surveillance (8%) experienced biochemical recurrence, and the rate was independent of the type of treatment.[75] Several studies have shown that delayed radical prostatectomy does not increase the rates of adverse pathology.[122-125]

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 pose an increasing burden. Literature suggests that as many as 7% of men undergoing prostate biopsy will suffer an adverse event,[88] and those who develop urinary tract infection are often fluoroquinolone-resistant.[126] Radical prostatectomy may become technically challenging after multiple sets of biopsies, especially as it pertains to potency preservation.[127]

Radical Prostatectomy

Radical prostatectomy is appropriate for any patient whose cancer appears clinically localized 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[23] reported a low 15-year prostate cancer-specific mortality of 12% in patients who underwent radical prostatectomy (5% for patients with low-risk disease), 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).[128,129] 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.[128] The reduction in mortality was confirmed at 23 years of follow-up, with an absolute difference of 11%.[129] 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 for clinically localized prostate cancer.

Some patients at high or very high risk may 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.[130] 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 an option for men with high-risk disease and in select patients with very high-risk disease.

Radical prostatectomy is a salvage option for patients experiencing biochemical recurrence after primary EBRT, but morbidity (incontinence, erectile dysfunction, and bladder neck contracture) remains significantly higher than when radical prostatectomy is used as initial therapy.[131,132] Overall and cancer-specific 10-year survival ranged from 54% to 89% and 70% to 83%, respectively.[131] 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 to radical prostatectomy;

high-volume surgeons in high-volume centers generally achieve superior outcomes.[133,134] Laparoscopic and robot-assisted radical prostatectomy are used commonly and are considered comparable to conventional approaches in experienced hands.[135,136] 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.[137] A second large study reported no difference in overall complications, readmission, and additional cancer therapies between open and robot-assisted radical prostatectomy, although the robotic approach was associated with higher rates of genitourinary complications and lower rates of blood transfusion.[138] Oncologic outcome of a robotic versus open approach was similar when assessed by use of additional therapies[137] or rate of positive surgical margins,[139] 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.[139] 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[140] and potency recovery.[141]

An analysis of the Prostate Cancer Outcomes Study on 1655 men with localized prostate cancer compared long-term functional outcomes after radical prostatectomy or EBRT.[142] At 2 and 5 years, patients who underwent radical prostatectomy reported higher rates of urinary incontinence and erectile dysfunction 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, those who received EBRT 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.[143]

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.[144] Anastomotic strictures that increase the risk of long-term incontinence are less frequent with modern surgical techniques. Recovery of erectile function is related directly to the degree of preservation of the cavernous nerves, age at surgery, and preoperative erectile function. Improvement in urinary function was reported with nerve-sparing techniques.[145] Replacement of resected nerves with nerve grafts does not appear to be effective for patients undergoing wide resection of the neurovascular bundles.[146] The ability of mpMRI to detect extracapsular extension can aid in decision-making in nerve-sparing surgery.[61]

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.[28] The panel recommends use of a nomogram developed at Memorial Sloan Kettering Cancer Center that uses pretreatment PSA, clinical stage, and Gleason sum to predict the risk of pelvic lymph node metastases.[28]

PLND should be performed using an extended technique.[147,148] 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 increased likelihood of finding lymph node metastases, thereby providing more complete staging.[149-151] A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to elimination of microscopic metastases.[150,152-154] PLND can be performed safely laparoscopically, robotically, or open, and complication rates should be similar among 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. Three-dimensional (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.[35,155-157] The second-generation 3D technique, intensity-modulated radiation therapy (IMRT), is used increasingly in practice[158] because IMRT reduced the risk of gastrointestinal toxicities and rates of salvage therapy compared to 3D-CRT in some but not all studies, although treatment cost is increased.[159-162]

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.[163-168] Kuban and colleagues[166] published an analysis of their dose-escalation trial of 301 patients with stage T1b to T3 prostate cancer. Freedom from biochemical or clinical failure was higher in the group randomized to 78 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%, $P = .001$). An analysis of the National Cancer Data Base found that dose escalation (75.6–90 Gy) resulted in a dose-dependent improvement in overall survival for men with intermediate- or high-risk prostate cancer.[169] 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.[159,170,171]

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 in most[172,173] but not all trials.[174] These RT techniques can be considered as an alternative to conventionally fractionated regimens when clinically indicated.

Data suggested that EBRT and radical prostatectomy were effective for the treatment of localized prostate cancer.[175] EBRT of the primary prostate cancer shows several distinct advantages over radical prostatectomy. EBRT 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 has a low risk of urinary incontinence and stricture and a good chance of short-term preservation of erectile function.[176]

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.[176,177] In addition, if the cancer recurs, salvage radical prostatectomy is associated with a higher risk of complications than primary radical prostatectomy.[178] Contraindications to EBRT 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 principal treatment options for clinically localized prostate cancer. The NCCN Guidelines Panel consensus was that modern EBRT and surgical series show similar progression-free survival in patients with low-risk disease treated with radical prostatectomy or EBRT. 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.[179]

EBRT for Patients with High-Risk or Very High-Risk Disease

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.[180] In another study (RTOG 8531), 977 patients with T3 disease treated with EBRT were randomized to adjuvant ADT or ADT at relapse.[181] Two other randomized phase III trials evaluated long-term ADT with or without radiation in a population of patients who mostly had T3 disease.[182-184] 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 *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,[185] 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 radiation, appropriately designed radiation treatment fields and schedules using extremely hypofractionated regimens should result in similar cancer control rates without 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.[186] 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.[185-191] According to a pooled analysis of phase II trials, the 5-year biochemical relapse-free survival is 95%, 84%, and 81% for patients with low-, intermediate-, and high-risk disease, respectively.[192] 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%; $P = .001$).[193]

Brachytherapy

Brachytherapy is used traditionally for low-risk cases since earlier studies found it less effective than EBRT for high-risk disease.[9,194] 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.[195] 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, with excessive irradiation of the bladder and rectum 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 prostate cancer with medium-term follow-up.[196] 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.[177] 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.[197,198]

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.[199,200] 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, prostate size may not decline in some men and the risks of potentially increased toxicity of ADT must be weighed against the possible benefit of target reduction.

Post-implant dosimetry should be performed to document the quality of the implant.[201] 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.[202-205] Studies have demonstrated reduced risk of recurrence with the addition of brachytherapy to EBRT.[206-208] An analysis

of a cohort of 12,745 patients with high-risk disease 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.[209] 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.[210,211] 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.[212] 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.[213,214]

Two groups have observed a lower risk of urinary frequency, urgency, and rectal pain with HDR brachytherapy compared with LDR brachytherapy (permanent seed implant).[215,216] Vargas and colleagues[217] reported that HDR brachytherapy results in a lower risk of erectile dysfunction than LDR brachytherapy.

Salvage Brachytherapy

Brachytherapy can be considered in men with biochemical recurrence after EBRT. In a retrospective study of 24 men who had EBRT as primary therapy and permanent brachytherapy after biochemical failure, the cancer-free and biochemical relapse-free survival rates were 96% and 88%, respectively, after a median follow-up of 30 months.[218] Results of a phase II study of salvage HDR brachytherapy after EBRT included relapse-free survival, distant metastases-free survival, and cause-specific survival rates of 68.5%, 81.5%, and 90.3%, respectively, at 5 years.[219] Toxicities were mostly grade 1 and 2 and included gastrointestinal toxicity and urethral strictures, and one case of Grade 3 urinary incontinence.

Data on the use of brachytherapy after permanent brachytherapy are limited, but the panel agrees that it can be considered for carefully selected patients. Decisions regarding the use of brachytherapy in the recurrent-disease setting should consider comorbidities, extent of disease, and potential complications. Brachytherapy in this setting is best performed at high-volume centers.

Proton Therapy

Proton beam RT has been used to treat patients with cancer since the 1950s. Proponents of proton therapy argue that this form of RT could have advantages over x-ray (photon)-based radiation in certain clinical circumstances. Proton therapy and x-ray-based therapies like IMRT 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 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 higher dose parts of the exposure. These studies suffer from the biases and talents of the investigators who plan and create computer models of dose deposition for one therapy or the other.[220] 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.

Comparative effectiveness studies have been published in an attempt to compare toxicity and oncologic outcomes between proton and photon therapies. Two comparisons between men treated with proton therapy or EBRT report similar early toxicity rates.[221,222] 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 follow-up.[223] A Medicare analysis of 421 men treated with proton therapy and a matched cohort of 842 men treated with IMRT showed less genitourinary toxicity at 6 months for protons, although the difference disappeared after 1 year.[222] No other significant differences were seen between the groups. In contrast, a single-center report of prospectively collected quality-of-life data revealed significant problems with incontinence, bowel dysfunction, and impotence at 3 months, 12 months, and >2 years after treatment with proton therapy.[221] In that report, only 28% of men with normal erectile function maintained it after therapy. The largest retrospective comparative effectiveness analysis to date comparing IMRT to proton therapy was 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.[224] With follow-up 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. However, firm conclusions regarding differences in toxicity or effectiveness of proton and photon therapy cannot be drawn because of the limitations inherent in retrospective/observational studies.

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.[222] 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.”[225,226]

An ongoing prospective randomized trial is accruing patients to compare prostate proton therapy and prostate IMRT. The NCCN panel believes no clear evidence supports 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. 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.[227] 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).[228] 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.[229] 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.[230]

In May 2013, the U.S. 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) that included 921 men with symptomatic CRPC, 2 or more bone metastases, and no known visceral disease.[231] 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 SRE (median 15.6 months vs. 9.8 months). Preplanned subset analyses showed that the survival benefit of radium-223 was maintained regardless of prior docetaxel use.[232] Intention-to-treat analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic skeletal-related events (SREs).[233] Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), likely due to the short range of radioactivity.[231] Fecal elimination of the agent led to generally mild non-hematologic 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.[230] 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) or samarium-153 (153Sm).[234]

Other Local Therapies

Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that damages tumor tissue through local freezing. The reported 5-year biochemical disease-free rate following cryotherapy ranged from 65% to 92% in patients with low-risk disease using different definitions of biochemical failure.[235] A report suggests

that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer.[236] A study by Donnelly and colleagues[237] randomly assigned 244 men with T2 or T3 disease to either cryotherapy or EBRT. 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.[238] 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.[239]

Other emerging local therapies, such as high intensity focused ultrasound (HIFU) and vascular-targeted photodynamic (VTP), also warrant further study.[240]

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. Castrate levels of serum testosterone (<50 ng/dL) should be achieved, because low nadir serum testosterone levels were shown to be associated with improved cause-specific survival in the PR-7 study.[241]

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.[242,243] LHRH antagonists rapidly and directly inhibit the release of androgens, unlike LHRH agonists that initially stimulate LHRH receptors prior 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. No prospective randomized studies have demonstrated a survival advantage with combined androgen blockade over the serial use of an LHRH agonist and an anti-androgen.[244] 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.[245,246] More complete disruption of the androgen axis (finasteride or dutasteride or anti-androgen, in addition to medical or surgical castration) provides little if any benefit over castration alone.[247] Anti-androgen monotherapy appears to be less effective than medical or surgical castration and is not recommended for primary ADT.

Diethylstilbestrol (DES) can produce safe chemical castration in many men. Gynecomastia and cardiovascular side effects occur with increasing frequency with increasing dose. Side effects are rare, and survival appears equivalent to that of other means of ADT at a 1-mg daily dose. The mechanism of action of DES remains uncertain because a 1-mg dose does not render some men castrate and DES produces responses when used in CRPC.[248] Transdermal estradiol may provide similar cancer control with fewer side effects.[249] An ongoing clinical trial demonstrated similar rates of castrate levels of testosterone, PSA response, and side effects in 85 men treated with LHRH agonist and 168 men treated with 100 mcg/24 hours estrogen patches twice

weekly[250]; the PATCH trial continues enrollment in order to assess survival.

ADT for Patients with Low-Risk Disease

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.[251] 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.[252] Placing patients with early prostate cancer on ADT should not be routine practice.

ADT for Patients with Intermediate-Risk Disease

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 (Trans Tasman Radiation Oncology Group [TROG] 9601, Dana Farber Cancer Institute [DFCI] 95096, and Radiation Therapy Oncology Group [RTOG] 9408).[253-255] Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly high-risk men (RTOG 8610).[256] Results from the RTOG 9910 trial showed that a longer course of ADT (36 weeks vs. 16 weeks) did not improve outcomes.[257] The addition of short-course ADT to EBRT in men with intermediate-risk disease is an option.

ADT for Patients with High-Risk or Very-High-Risk Disease

ADT combined with EBRT is an effective primary treatment for patients at high risk or very high risk, as discussed in the *Radiation Therapy* section. Combination therapy was associated consistently with improved disease-specific and overall survival compared to single-modality treatment in randomized phase III studies.[180,181,183,184]

Increasing evidence favors long-term over short-term neoadjuvant/concurrent/adjuvant ADT for patients with high- and very-high-risk disease. The RTOG 9202 trial included 1521 patients with T2c-T4 prostate cancer who received 4 months of ADT before and during EBRT.[258] 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 EBRT given with 6 months of ADT in 970 patients, most of whom had T2c-T3, N0 disease.[259] The DART01/05 GICOR trial also reported similar results in men with high-risk disease.[260] 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.[261]

Adjuvant ADT after Radical Prostatectomy

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 who were found to have positive lymph nodes at the time of radical prostatectomy to immediate ADT or observation.[262] At median follow-up 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.[244] 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.[263]

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.[264,265]

ADT for Biochemical Recurrence

Patients with an increasing 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 increasing PSA is influenced by PSA velocity, patient and physician anxiety, the short-term and long-term side effects of ADT, and underlying comorbidities of the patient. Early ADT is acceptable, but 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. The benefit of early ADT is unclear[244]; treatment should be individualized until definitive clinical trials 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.[266,267]

The Canadian-led PR.7 trial was a phase III trial of intermittent versus continuous ADT in patients with non-metastatic prostate cancer who experienced biochemical failure after radical prostatectomy.[268] One thousand three hundred eighty-six patients with PSA >3 ng/mL after RT were randomly assigned 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).[268] In this situation, patients should be given the option to weigh the effects of ADT on quality of life against a possible impact on survival, although pathology was not centrally reviewed and the study was not powered to detect small differences in survival based on Gleason sum.[269]

The multinational European ICELAND trial randomized 702 participants with locally advanced or biochemically recurrent prostate cancer to continuous or intermittent ADT.[270] Clinical outcomes, which included time to PSA progression, PSA PFS, OS, mean PSA levels over time, quality of life, and adverse events, were similar between the arms. A 2015 meta-analysis identified 6 randomized controlled trials comparing continuous with intermittent ADT in men with locally advanced prostate cancer and found no difference in mortality and progression and an advantage of the intermittent approach in terms of quality of life and adverse effects.[271]

ADT for Nodal or Metastatic Disease

The EORTC 30846 trial randomized 234 treatment-naïve patients with node-positive prostate cancer to immediate versus delayed ADT.[272] 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.[244] 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.[273]

Intermittent versus Continuous ADT (Metastatic)

Hussain and colleagues[274] conducted the SWOG (Southwest Oncology Group) 9346 trial to compare intermittent and continuous ADT in patients with metastatic disease. 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 may have returned to 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).[274] 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.

Several meta-analyses of randomized controlled trials reported no difference in survival between intermittent ADT and continuous ADT.[275-277] Another recent analysis concluded that the non-inferiority of intermittent to continuous ADT in terms of survival has not been demonstrated clearly.[278] Still, the intermittent approach leads to marked improvement in quality of life compared to the continuous approach in most studies, and the panel believes that intermittent ADT should be considered strongly.

A more personalized approach could treat all patients with metastatic disease with ADT. After 7 months of ADT, patients can be assigned a risk category based on the PSA value at that time point[273]: low risk is defined by a PSA less than 0.2 ng/mL (median survival of 75 months); intermediate risk is defined by a PSA between 0.2 and 4.0 ng/mL (median survival of 44 months), and high risk is defined by a PSA

higher than 4.0 ng/mL (median survival of 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 because it is easier to administer.[269] 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. 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 therapy than intermittent therapy.

Adverse Effects of Traditional ADT

ADT has a variety of adverse effects including hot flashes, 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.[279-281] Recent evidence suggests that there could be a link between ADT and cognitive decline or future Alzheimer's disease, although the risk is low and the link remains to be proven.[282,283] 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.[284-286] 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,[287-290] 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,[291] 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.[292] 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.[293] ADT should be considered "secondary osteoporosis" using the FRAX® algorithm.

Earlier randomized controlled trials demonstrated that bisphosphonates increase bone mineral density, a surrogate for fracture risk, during ADT.[294-296] 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) to blunt osteoclast function and delay generalized bone resorption and local bone destruction. Approval was based on a phase III study that randomized 1468 patients with non-metastatic prostate cancer 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.[297] 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.[298] After controlling for other variables, which included age and comorbidity, ADT with a GnRH agonist was associated with increased 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 evaluated the potential relationship between ADT and cardiovascular mortality have produced mixed results.[256,298-304] In a Danish cohort of 31,571 patients with prostate cancer, medical castration was associated with an increased risk for myocardial infarction (HR, 1.31; 95% CI, 1.16–1.49) and stroke (HR, 1.19; 95% CI, 1.06–1.35) whereas surgical castration was not.[305] An analysis based on SEER data resulted in similar findings.[306] Men with recent history of cardiovascular disease appear to have higher risk,[307] and increased physical activity may decrease the symptoms and cardiovascular side effects of men treated with ADT.[308]

Several mechanisms may contribute to greater risk for diabetes and cardiovascular disease during ADT. ADT increases fat mass and decreases lean body mass.[291,309,310] ADT with a GnRH agonist increases fasting plasma insulin levels[311,312] and decreases insulin sensitivity.[313] ADT also increases serum levels of cholesterol and triglycerides.[311,314]

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.[315,316] Androgen signaling from non-gonadal sources in CRPC refutes earlier beliefs that CRPC was 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 (abiraterone), 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.[317,318] Patients were randomized to receive either abiraterone 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; $P < .0001$).[318] Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone.[318,319]

FDA approval in the pre-docetaxel setting occurred December 10, 2012 and was based on the randomized phase 3 COU-AA-302 trial of abiraterone and prednisone (n=546) versus prednisone alone (n=542) in men with asymptomatic or minimally symptomatic, metastatic CRPC.[320] Most men in this trial were not taking narcotics for cancer pain and none had visceral metastatic disease or prior ketoconazole exposure. The coprimary 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 at final analysis with a median follow-up of 49.2 months (34.7 months vs. 30.3 months; HR, 0.81; 95% CI, 0.70–0.93; $P = .003$).[321] 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/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/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).[322,323] 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.[322,324]

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.[325] The study was stopped early due to benefits shown in the treatment 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 endpoints also were observed (eg, the time until chemotherapy initiation or first SRE).

Thus, enzalutamide represents a treatment option for men in both the pre-docetaxel and post-docetaxel metastatic CRPC setting and is a reasonable choice for 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).[326-328] TAX 327 compared docetaxel (every 3 weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1006 men.[327] 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.[328] The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared to mitoxantrone plus prednisone.[326] 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 large randomized 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.[329] 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 ($P = .015$). 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% versus 14% and other toxicities and overall quality of life were similar.

Docetaxel is included as an upfront option for men with progressive androgen-stimulated prostate cancer and distant metastases based on results from 2 phase III trials (ECOG 3805/CHAARTED and STAMPEDE).[330,331] CHAARTED randomized 790 men with metastatic, androgen-stimulated prostate cancer to docetaxel plus ADT or ADT alone.[331] The patients in the combination arm experienced a longer OS than those in the ADT arm (57.6 months vs. 44.0 months; HR, 0.61; 95% CI, 0.47–0.80; $P<.001$). Subgroup analysis showed that the survival benefit was more pronounced in the 65% of participants with high-volume disease (HR, 0.60; 95% CI, 0.45–0.81; $P<.001$). Men with low-volume disease in CHAARTED may have derived a survival benefit from the inclusion of docetaxel (HR, 0.60; 95% CI, 0.32–1.13; $P=.11$), although median OS was not reached for either arm, and the number of patients was low.

The STAMPEDE trial, a multi-arm, multistage phase III trial, included patients with both M0 and M1 androgen-stimulated prostate cancer.[330] The results in the M1 population essentially confirmed the survival advantage of adding docetaxel to ADT seen in the CHAARTED trial. In STAMPEDE, extent of disease was not evaluated in the 1087 men with metastatic disease, but the median OS for all patients with M1 disease was 5.4 years in the ADT-plus-docetaxel arm versus 3.6 years in the ADT-only arm (a difference of 1.8 years between groups compared with a 1.1-year difference in CHAARTED). The results of the STAMPEDE trial seem to confirm the results of the CHAARTED trial.

The panel added the use of docetaxel in combination with ADT and EBRT in fit men with high- and very-high-risk localized disease in the 2016 version of these guidelines. This recommendation is based on unpublished data, panel consensus, and the expectation that stronger data on this strategy are likely to emerge in the future.

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[332] 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 median follow-up 25.5 months.[333]

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).[334] Five hundred 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 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 usually were 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.[335] 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; $P = .01$).[336] 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.[337] The absolute incidence of SREs was similar in the 2 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.[338]

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 TRUS guidance. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Clinical staging is based on the TNM 2010 classification from the AJCC Staging Manual, 7th edition.[339] 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.[340]

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- or very high-risk factors (bulky T3-T4 cancers or Gleason score 8–10) for developing hydronephrosis or metastases within 5 years are present, ADT or EBRT 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;[341] 2) Gleason score 8 or higher; 3) T3 to T4 disease; or 4) symptomatic disease. Pelvic CT or MRI scanning is recommended for T3 or T4 disease, or T1 or T2 disease when a nomogram indicates that 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%.[342] Alternative approaches to imaging based on the likelihood of a positive study rather than by risk group alone have been proposed based on data from a quality improvement collaborative in the state of Michigan.[49] For pelvic CT, the following criteria would identify almost all men with a positive study and reduce the number of negative studies: 1) PSA level >20 ng/mL, or 2) Gleason score ≥8, or 3) clinical stage ≥T3. For bone scan, the recommended criteria include: 1) PSA level >20 ng/mL, or 2) Gleason score ≥8.[50] Use of these criteria may reduce the number of negative study results without missing a significant number of positive studies. 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. 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 life expectancy 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, EBRT or brachytherapy, or radical prostatectomy are all viable options and should be discussed thoroughly.

Low Risk

The NCCN Guidelines define the low-risk group as patients with clinical stage T1 to T2a, Gleason score 6, and serum PSA level <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%. ADT as a primary treatment for localized prostate cancer does not improve survival and is not recommended by the NCCN Guidelines Panel.

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 clinical stage T2b to T2c, Gleason score 7, or PSA value 10 ng/mL to 20 ng/mL. Patients with multiple adverse factors may be shifted to the high-risk group.

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; and 3) brachytherapy alone for selected patients with low-volume disease.

Initial treatment options for patients with an expected survival ≥10 years include: 1) radical prostatectomy and PLND if the predicted probability of lymph node metastasis is ≥2%; 2) EBRT with or without 4 to 6 months of ADT, and with or without brachytherapy; and 3) brachytherapy alone for selected patients with low-volume disease. In addition, the panel defines a favorable subset of men with intermediate-risk prostate cancer for whom active surveillance may be considered (ie, predominant Gleason grade 3 [ie, Gleason score 3+4=7], percentage of positive biopsy cores <50, and ≤1 NCCN intermediate risk factor).[14] Active surveillance is not recommended for patients with a life expectancy >10 years (category 1) if they fall in the unfavorable subset of intermediate risk.

The literature on outcomes of active surveillance in men with intermediate-risk prostate cancer is limited. In the PIVOT trial, men with clinically localized prostate cancer and life expectancy ≥10 years were randomized to radical prostatectomy or observation.[343] Of the 120

participants with intermediate-risk disease who were randomized to observation, only 13 died from prostate cancer, a non-significant difference compared with 6 prostate-cancer deaths in 129 participants with intermediate-risk disease in the radical prostatectomy arm (HR, 0.50; 95% CI, 0.21–1.21; *P* = .12). The median 10-year follow-up and less-than-average health of men in the PIVOT study suggest only men with competing risks may safely be offered active surveillance. Other prospective studies of active surveillance that included men with intermediate-risk prostate cancer resulted in prostate cancer-specific survival rates of 94% to 100% for the full cohorts.[73,74,76] The panel interpreted these data to show that a subset of men with intermediate-risk prostate cancer may be considered for active surveillance, although longer term follow-up is needed in these and others studies to increase confidence about the risks and benefits of active surveillance in this population.

The panel believes that active surveillance may be considered for men with favorable intermediate-risk prostate cancer, but should be approached with caution, include informed decision-making, and use close monitoring for progression.

High Risk

Men with prostate cancer that is clinical stage T3a, Gleason score 8 to 10, or PSA level greater than 20 ng/mL are categorized by the panel as high risk. Patients with multiple adverse factors may be shifted to the very high-risk category. The preferred treatment is EBRT in conjunction with 2 to 3 years of neoadjuvant/concurrent/adjuvant 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 neoadjuvant/concurrent/adjuvant ADT. Fit men in the high-risk group can consider 6 cycles of docetaxel without prednisone after EBRT is completed and while continuing ADT. The combination of EBRT and brachytherapy, with or without neoadjuvant/concurrent/adjuvant ADT, is another primary treatment option. However, the optimal duration of ADT in this setting remains unclear.

Radical prostatectomy with PLND remains an option because a subset of younger and healthier men in the high-risk group may benefit from operation.

Very High Risk

Patients at very high risk (locally advanced) are defined by the NCCN Guidelines as men with clinical stage T3b to T4, primary Gleason pattern 5, or more than 4 biopsy cores with Gleason score 8 to 10.[344] 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) EBRT plus ADT and docetaxel; 4) radical prostatectomy plus PLND in selected patients with no fixation to adjacent organs; or 5) ADT for patients not eligible for definitive therapy.

Nodal and Metastatic Disease

ADT or EBRT of the primary tumor plus 2 or 3 years neoadjuvant/concurrent/adjuvant ADT are options for patients diagnosed with N1 disease on presentation. Positive nodal disease identified during radical 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 PSA measurement no more often than

every 6 months unless clinically indicated, 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. Change in prostate exam or increase in PSA level may prompt consideration for repeat biopsy at the discretion of the physician. 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.[345] PSA doubling time is not considered reliable enough to be used alone to detect disease progression.[346]

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

For patients initially treated with intent to cure, serum PSA levels should be measured every 6 to12 months for the first 5 years and then annually. PSA testing every 3 months may be better 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.[347] Local recurrence may result in substantial morbidity and can, in rare cases, occur in the absence of a PSA elevation. Therefore, annual DRE is appropriate to monitor for prostate cancer recurrence and to detect colorectal cancer. Similarly, after EBRT, 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 lymph-node-positive or metastatic disease is determined by the response to initial ADT, radiotherapy, or both. Follow-up evaluation of these patients should include history and physical examination, DRE, and PSA measurement every 3 to 6 months based on clinical judgment. The relative risk for bone metastasis or death increases as PSADT falls; a major inflection point appears at PSADT 8 months. Bone imaging should be performed more frequently in these men.[348]

Patients treated with either medical or surgical ADT have increased risk for 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 denosumab, zoledronic acid, or alendronate.

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

Most patients who have undergone 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.

Adjuvant Therapy

Recently published trials provide high-level evidence that can be used to counsel patients more appropriately. Thompson and colleagues reported the results of SWOG 8794, which enrolled 425 men with extraprostatic cancer found at radical prostatectomy. Patients were randomized to receive either adjuvant EBRT or usual care, and follow-up has reached a median of 12.6 years.[349] The initial study report revealed that adjuvant EBRT reduced the risk of PSA relapse and disease recurrence.[350] An update reported improved 10-year biochemical failure-free survival for patients with high-risk disease (seminal vesicle positive) receiving post-prostatectomy adjuvant radiation compared to observation (36% vs. 12%; $P = .001$).[351]

Another randomized trial conducted by EORTC[352] compared post-prostatectomy observation and adjuvant EBRT in 1005 patients. All patients had extraprostatic disease and/or positive surgical margins. The 5-year biochemical progression-free survival significantly improved with EBRT 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.[353] All participants had extraprostatic 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 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.[354] 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.[355] 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)[356-358]; whole pelvic radiation 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, as discussed above (see *Adjuvant ADT after Radical Prostatectomy*).[262] Another option is observation, which is a category 2A recommendation for patients with very-low-risk or low-risk prostate cancer but category 2B for patients with intermediate, high, or very high risk. Retrospective data show that initial observation may be safe in some men with N1 disease at radical prostatectomy, because 28% of a cohort of 369 patients remained free from biochemical recurrence at 10 years.[359] A third option is the addition of pelvic EBRT to ADT (category 2B). This last recommendation is based on retrospective studies and a National Cancer Data Base analysis that demonstrated improved biochemical recurrence-free survival, cancer-specific survival, and all-cause survival with post-prostatectomy EBRT and ADT compared to adjuvant ADT alone in patients with lymph node metastases.[360-363]

Biochemical Recurrence After Radical Prostatectomy

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.[364-368] A large retrospective review of 501 patients who received salvage radiotherapy for detectable and increasing PSA after radical

prostatectomy[367] showed that the predictors of progression were Gleason score 8 to 10, pre-EBRT PSA level >2 ng/mL, seminal vesicle invasion, negative surgical margins, and PSA doubling time ≤10 months. However, prediction of systemic disease versus local recurrence and hence responsiveness to postoperative radiation has proven unfeasible for individual patients using clinical and pathological criteria.[369] Delivery of adjuvant or salvage EBRT becomes both therapeutic and diagnostic—PSA response indicates local persistence/recurrence. Delayed biochemical recurrence requires restaging, and a nomogram[20,34] 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."[54] Group 3 does not require further evaluation until PSA increases. Since PSA elevation alone does not necessarily lead to clinical failure,[370] the workup 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. Abdominal/pelvic CT/MRI and C-11 choline PET may be useful.

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.[371] A TRUS biopsy may be helpful when imaging suggests local recurrence.

The patient may be observed or undergo primary salvage EBRT with or without ADT if distant metastases are not suspected during biochemical recurrence.[354] Large retrospective cohort studies support the use of EBRT in this setting, because it is associated with decreased all-cause and prostate cancer-specific survival.[369,372] The recommended post-radical prostatectomy EBRT 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.[355] Treatment is most effective when pre-treatment PSA level is below 0.5 ng/mL.[34] Paradoxically, salvage EBRT was shown to be most beneficial when the PSA doubling time was <6 months in a cohort analysis of 635 men,[369] although another study of 519 men reported mortality reduction for both men with PSA doubling time <6 months and those with PSA doubling time ≥6 months.[372] Most men with prolonged PSA doubling time may be observed safely.[373]

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, with ADT delayed until symptoms develop or PSA levels suggest that symptoms are imminent. In all cases, the form of primary or secondary systemic therapy should be based on the hormonal status of the patient.

Post-Irradiation Recurrence

The 2006 Phoenix definition was revised by ASTRO and the Radiation Therapy Oncology Group in Phoenix:[374] 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 workup is indicated in patients who are considered candidates for local therapy. These patients include those with original clinical stage T1-2, life expectancy >10 years, and current PSA <10 ng/mL.[375] Workup typically includes PSA doubling time calculation, bone scan, and prostate MRI; additional tests, such as an abdominal/pelvic CT/MRI, TRUS biopsy, and/or C-11 choline PET can be considered. 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 radiation biochemical failure if staging workup does not reveal metastatic disease. Prostate biopsy in the setting of suspected local recurrence after radiation should be considered, including biopsy at the junction of the seminal vesicle and prostate, because 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 radical prostatectomy with PLND in selected cases by highly experienced surgeons. Other options for localized interventions include cryotherapy[376] and brachytherapy (reviewed by Allen and colleagues[377] and discussed in *Salvage Brachytherapy*). Treatment, however, needs to be individualized based on the patient's risk of progression, the likelihood of success, and the risks involved with salvage therapy.

Negative TRUS biopsy after post-radiation biochemical recurrence poses clinical uncertainties. Observation, ADT, or enrolling on clinical trials are viable options.

Patients with radiographic evidence of distant metastases or patients who are not initial candidates for local therapy should be treated with ADT or observed.

Progressive Castration-Naïve Disease

Options for patients with progressive castration-naïve disease depend on the presence of distant metastases. Men with M0 disease can undergo orchiectomy or ADT with LHRH antagonist or combined androgen blockade or they can be observed until symptoms develop or are imminent. Options for men with M1 disease include: 1) orchiectomy; 2) LHRH agonist with or without anti-androgen for at least 7 days to prevent flare; 3) LHRH antagonist; 4) combined androgen blockade; or 5) continuous ADT and docetaxel (75 mg/m^2) with or without prednisone for 6 cycles. The last option of upfront docetaxel and ADT is based on results from the phase III CHAARTED and STAMPEDE trials (as discussed under *Docetaxel)*.[330,331]

Docetaxel should not be offered to men with M0 progressive castration-naïve prostate cancer based on results of pre-planned subgroup analysis of the STAMPEDE trial that showed no OS benefit for participants with M0 disease.[330] Men with low-volume metastatic disease can be offered early treatment with docetaxel combined with ADT; however they have less certain benefit from treatment than men with higher-volume disease, as this subgroup did not have definitively improved survival outcomes in the ECOG CHAARTED study or a similar European trial (GETUG-AFU 15).[331,378,379] Meta-analyses of randomized controlled trials also concluded that docetaxel provides a

significant OS benefit in this setting, with no evidence that the benefit was dependent on the volume of disease.[380,381]

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 are excellent candidates for observation.

Patients with metastatic disease 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.

Combined androgen blockade therapy adds to cost and side effects, and prospective randomized evidence is lacking that combined androgen blockade is more efficacious than ADT.

Progression to CRPC

Patients whose disease progresses to CRPC during primary ADT should receive a laboratory assessment to assure a castrate level of testosterone (<50 ng/dL). Imaging tests may be indicated to monitor for signs of distant metastases. Factors affecting the frequency of imaging include individual risk, age, overall patient health, PSA velocity, and Gleason grade.

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 with CRPC and no signs of distant metastasis (M0). Observation is another option especially if PSA doubling time is ≥10 months since these patients will have a relatively indolent disease history.[382] Secondary hormone therapy is an option mainly for patients with shorter PSA doubling time (<10 months), because the androgen receptor may remain active. Patients whose disease progresses on combined androgen blockade should have the anti-androgen discontinued to exclude an “anti-androgen withdrawal response.”[383,384] Secondary hormone therapy can be an anti-androgen for patients who initially received medical or surgical castration, anti-androgen withdrawal, ketoconazole (adrenal enzyme inhibitor) with or without hydrocortisone, corticosteroid, diethylstilbestrol (DES), or other estrogen.[385,386] 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 associated with low PSA levels despite large metastatic burden and visceral disease.[387] Biopsy of accessible lesions should be considered to identify patients with small cell histomorphologic features.[388] These cases may be managed by cytotoxic chemotherapy (ie, cisplatin/etoposide, carboplatin/etoposide, docetaxel/carboplatin).[389,390] 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 (<50 ng/dL) 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 EBRT 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.[391] 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 are 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.[392] 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, and the dose, schedule, and safety of denosumab have not yet been defined. A single study of 55 patients with creatinine clearance <30 mL/min or on hemodialysis evaluated the use of 60 mg dose denosumab.[393] Hypocalcemia should be corrected before starting denosumab, and serum calcium monitoring is required for denosumab and recommended for zoledronic acid, with repletion as needed.

Clinical research continues on the prevention or delay of disease spread to bone. A phase III randomized trial of 1432 patients with non-metastatic CRPC at high risk of bone involvement showed that denosumab delayed bone metastasis by 4 months compared to placebo.[394] Overall survival was not improved, 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.[395] Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial has the potential for additive myelosuppression.[395] Radium-223 can be used with denosumab or zoledronic acid.

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.[234] 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 have good performance level (ECOG 0-1), estimated life expectancy >6 months, and no liver metastases.[334] 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 if symptoms develop.

No Visceral Metastases

Enzalutamide and abiraterone 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 not be taken with food. Abiraterone acetate should be given with oral prednisone 5 mg twice daily to abrogate signs of mineralocorticoid excess that can result from treatment. These signs 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.[322]

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 with or without hydrocortisone, corticosteroid, DES, or other estrogens).

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.[396] Enzalutamide is another category 1 recommendation in this setting. Abiraterone 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 with prednisone 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 lymph node metastases (>3 to 4 cm) and is not recommended in this setting.

Mitoxantrone may provide palliative benefit for symptomatic patients who cannot tolerate docetaxel.[397,398] Clinical trial and secondary hormone therapy are options.

Progression After Enzalutamide or Abiraterone

Patients with disease progression after enzalutamide or abiraterone have the following options: docetaxel with prednisone (category 1), abiraterone with prednisone if previously given enzalutamide therapy, enzalutamide if previously given abiraterone, 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 can continue through all treatment options and should receive best supportive care.

Progression After Docetaxel

No consensus exists for the best additional therapy for patients with metastatic CRPC after docetaxel failure. Options include abiraterone with prednisone (category 1), enzalutamide (category 1), radium-223 for symptomatic bone metastases 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 can continue through all treatment options and should receive best supportive care.

Both abiraterone/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 before 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.[332] 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 inform the proper sequence for delivery of these agents in men with metastatic CRPC, and some data suggest cross-resistance between abiraterone and enzalutamide.[399-401] 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. The panel awaits validation of exciting data that suggest AR-V7 may be helpful for selecting treatments.[402] 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 closely monitored 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.[403] 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), especially in those who have not shown definitive evidence of progression on prior docetaxel therapy. 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.[397,398] No chemotherapy regimen has demonstrated improved survival or quality of life after cabazitaxel, although several systemic agents other than mitoxantrone have shown palliative and radiographic response benefits in clinical trials (ie, carboplatin, cyclophosphamide, doxorubicin, vinorelbine, carboplatin/etoposide, docetaxel/carboplatin, gemcitabine/oxaliplatin, paclitaxel/carboplatin[404-413]). Prednisone or dexamethasone at low doses may provide palliative benefits in the chemotherapy-refractory setting.[414] No survival benefit for combination regimens over sequential single agent regimens has been demonstrated and toxicity is higher with combination regimens. 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. Participation in a clinical trial is encouraged.

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.[334] 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 adjusted life expectancy, disease characteristics, predicted outcomes, and patient preferences) must be considered by the patient and physician to tailor prostate cancer therapy for the individual patient.

Table 1. Available Tissue-Based Tests for Prostate Cancer Prognosis

Test	Platform	Populations studied	Outcome Reported (Test independently predicts)	References	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (44,000 genes) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	Metastasis Prostate cancer-specific mortality	110,415-424	Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
		Post RP, biochemical recurrence	Metastasis Biochemical failure		
		Post RP, adjuvant or salvage radiotherapy	Metastasis		
Ki-67	IHC	Biopsy, intermediate- to high-risk treated with EBRT	Metastasis	425-428	Not recommended
		Biopsy, conservatively managed (active surveillance)	Prostate cancer-specific mortality		
Onco*type* DX	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, low- to intermediate-risk treated with RP	Non-organ-confined pT3 or Gleason grade 4 disease on RP	48,429	Cover post-biopsy for NCCN very-low- and low-risk prostate cancer at diagnosis with 10-20 years life expectancy
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)	Prostate cancer-specific mortality	44-47,430,431	Cover post-biopsy for NCCN very-low- and low-risk prostate cancer at diagnosis with at least 10 years life expectancy
		Biopsy, conservatively managed (active surveillance)	Prostate cancer-specific mortality		
		Biopsy, localized prostate cancer	Biochemical recurrence Metastasis		
		Biopsy, intermediate-risk treated with EBRT	Biochemical failure		
		RP, node-negative localized prostate cancer	Biochemical recurrence		
ProMark	Multiplex immunofluorescent staining of 8 proteins	Biopsy, Gleason grade 3+3 or 3+4	Non-organ-confined pT3 or Gleason pattern 4 disease on RP	432	Not reviewed
PTEN	Fluorescent in situ hybridization or IHC	Transurethral resection of the prostate (TURP), conservatively managed (active surveillance)	Prostate cancer-specific mortality	433-435	Not recommended
		Biopsy, Gleason grade 3+3	Upgrading to Gleason pattern 4 on RP		
		RP, high-risk localized disease	Biochemical recurrence		

Table 2. Selected Active Surveillance Experiences in North America

Center	Toronto[73,114]	Johns Hopkins[75,112,115,116]	UCSF[113]
No. patients	993	1298	321
Median age (y)	68	66	63
Median follow-up (months)	77	60	43
10-year overall survival	80%	93%	98%
Cancer-specific survival	98% (10-y)	99.9% (10-y)	100% (5-y)
Conversion to treatment	36.5% (10-y)	50% (10-y)	24% (3-y)
Reason for treatment (% of entire cohort)			
Gleason grade change	9.5%	15.1%	38%
PSA increase	11.7%*	-	26%†

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