National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer

Version 3.2024 — March 8, 2024

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NCCN Guidelines Panel Disclosures

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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.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 3.2024 of the NCCN Guidelines for Prostate Cancer from Version 2.2024 include:

PROS-15
- Footnote * added: An FDA-approved biosimilar is an appropriate substitute.

PROS-B
- Footnote a added: An FDA-approved biosimilar is an appropriate substitute.

PROS-I (6 of 8) and (7 of 8)
- Footnote f added: An FDA-approved biosimilar is an appropriate substitute.

Updates in Version 2.2024 of the NCCN Guidelines for Prostate Cancer from Version 1.2024 include:

PROS-11
- Radiation therapy recurrence:
  - Studies negative for regional lymph nodes and distant metastasis, treatment option modified: Monitoring ~~(preferred)~~
  - Studies positive for regional lymph nodes, treatment option modified: Monitoring ~~(preferred)~~

PROS-H 3 of 8
- Test name modified: 17-gene *Genomic Prostate Score (GPS)* assay ~~(Oncotype DX Prostate)~~

Updates in Version 1.2024 of the NCCN Guidelines for Prostate Cancer from Version 4.2023 include:

PROS-1
- Clinically localized, regional, and metastatic prostate cancer
  - Workup
    - ◊ 6th bullet modified: Inquire about known high-risk germline mutations *and family history*
      - – Sub-bullet added: Perform somatic and/or germline testing as appropriate
    - ◊ Bullet removed: Obtain family history
- Regional and metastatic prostate cancer
  - Workup
    - ◊ 2nd bullet added: Perform imaging for staging
- Footnote c added: See Principles of Bone Health in Prostate Cancer (PROS-B) (also on PROS-8A, PROS-10A)
- Footnote f added: See Principles of Imaging (PROS-E).
- Footnote g added to the page and modified: Bone imaging can be achieved by conventional technetium-99m-methylene diphosphonate (MDP) bone scan. ~~Plain films,~~ CT, MRI, PSMA-PET/CT or PSMA-PET/MRI... (also on PROS-2A)
- Footnote h added to the page and modified: Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (*eg,* CT, *bone scan* ~~MRI~~) at both initial staging... (also on PROS-2A, PROS-9A, PROS-10A, PROS-11A, PROS-12, PROS-13A, PROS-14)

PROS-2A
- Footnote i modified: Tumor-based molecular assays and germline genetic testing are other tools that can assist with risk stratification. *See CRIT-6 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and LS-1 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal*) ~~See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C)~~ to determine if a patient is an appropriate candidate for germline genetic testing, and see Principles of Risk Stratification (PROS-H) to determine if a patient is an appropriate candidate for tumor-based molecular assays.
- Footnote l added: Percentage of positive cores in the intermediate-risk groups is based on biopsies that include systematic biopsies with or without targeted MRI-guided biopsies.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Prostate Cancer from Version 4.2023 include:

PROS-3

- Very-low-risk group: Page extensively revised to indicate that active surveillance is the only recommendation for patients with life expectancy ≥10 y.

PROS-4

- Low-risk group
  - Expected patient survival ≥10 y
    - ◊ Initial therapy modified: ~~EBRT + brachytherapy~~ *Radiation therapy (RT)* (also for PROS-5 through PROS-8; details of definitive radiation therapy options in each setting are delineated in the Principles of Radiation Therapy)
    - ◊ Adjuvant therapy modified: Adverse feature(s): Monitoring *(category 1, preferred)* with consideration of early RT for a detectable and rising PSA or PSA >0.1 ng/mL (also for PROS-5, PROS-6, PROS-7, and PROS-8)

PROS-5

- Favorable intermediate-risk group
  - Expected patient survival >10 y
    - ◊ Adjuvant therapy modified: Lymph node metastasis: ADT ~~(category 1)~~ ± EBRT ~~(category 2B)~~ (also on PROS-6, PROS-7, and PROS-8)

PROS-8A

- Footnote q modified: *Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5).* If higher grade and/or higher T stage is found during confirmatory testing, see PROS-2.
- Footnote x added: Monitoring is not preferred for patients with positive nodes or multiple high-risk features
- Footnote y modified: *For details on the use of ADT and other hormonal agents, including information on their efficacy and safety,* see Principles of Androgen Deprivation Therapy (PROS-G)
- Footnote dd modified: PSA persistence/recurrence after RP is defined as *when PSA does not* ~~failure of PSA to~~ fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or that increases to PSA >0.1 ng/mL.*Trials indicating non-inferiority of early RT compared with adjuvant RT after RP have used a PSA threshold of 0.1 or 0.2 ng/mL to trigger treatment. Imaging and treatment at lower PSA levels may be appropriate in patients at high risk for progression based on pretreatment risk factors, pathologic parameters, timing of recurrence, and genomic classifier score, among other factors.* (see also PROS-9A, PROS-10A)
- Footnote removed: Decipher molecular assay should be considered if not previously performed to inform adjuvant treatment if adverse features are found post-RP.
- Footnote removed: For short-term ADT with prostate-only RT, concurrent/adjuvant ADT is preferred over neoadjuvant ADT.

PROS-9

- Monitoring
  - Initial definitive therapy
    - ◊ 2nd bullet modified: *Consider* DRE if suspicion of recurrence

PROS-9A

- Footnote ee modified: ... especially in candidates for ~~salvage~~ *secondary* 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 patients who are younger or healthier. (also on PROS-11A)
- Foonote mm modified: PSA as frequently as every 3 mo may be necessary to clarify disease status, especially in ~~high-risk patients~~ *patients at risk of recurrence.*
- Footnote nn modified: ... technetium-99m-MDP bone scan. ~~Plain films,~~ CT, MRI, PSMA-PET/CT or PSMA-PET/MRI... (see also PROS-10A, PROS-11A, PROS-12, PROS-13A, PROS-14)

PROS-10

- Radical prostatectomy PSA persistence/recurrence: Page extensively revised.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Prostate Cancer from Version 4.2023 include:

PROS-10A
- Footnote y modified: *For details on the use of ADT and other hormonal agents, including information on their efficacy and safety,* See Principles of Androgen Deprivation Therapy (PROS-G) (also on PROS-11A, PROS-12, PROS-13A, PROS-14, PROS-15, PROS-16A)
- Footnote pp modified: ~~PSADT can be calculated to inform nomogram use and counseling and/or Decipher molecular assay (category 2B) can be considered to inform counseling.~~ Principles of Risk Stratification (PROS-H).
- Footnote qq modified: ... scan. ~~Plain films,~~ CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine, can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. mpMRI is preferred over CT for pelvic staging *and its use is recommended in addition to PSMA-PET in the setting of RT recurrence.* (also on PROS-11A)
- Footnote rr added: Monitoring should include physical exam, PSA every 3–6 mo, and imaging for symptoms or increasing PSA. (also on PROS-11A, PROS-14)
- Footnote ss added: If considering treatment, reinitiate the PROS-10 algorithm

PROS-11
- Radiation therapy recurrence: Page extensively revised

PROS-11A
- Footnote vv modified: Intermittent ADT can be considered for patients with M0 or M1 disease *receiving ADT monotherapy* to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-G).
- Footnote ww added: Principles of Local Secondary Post-Recurrence Therapy (PROS-K)

PROS-12
- New page: Treatment and monitoring for progressive M0 castration-sensitive prostate cancer (CSPC) after maximal pelvic therapy

PROS-13
- Systemic therapy for M1 CSPC: Page extensively revised

PROS-13A
- Footnote bbb modified: Stereotactic body RT (SBRT) to metastases can be considered in ~~patients with oligometastatic progression where progression-free survival (PFS) is the goal~~. *appropriate clinical situations. See Principles of Radiation Therapy (PROS-I)*
- Footnote eee modified: ... The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy. *If ADT monotherapy is given, intermittent ADT can be considered to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-G)*
- Footnote fff added: High-volume disease in this setting is defined based on CHAARTED criteria (the presence of visceral metastasis or ≥4 bone lesions with ≥1 beyond the vetebral bodies and pelvis)
- Footnote removed: Tumor and germline testing for homologous recombination repair gene mutations (HRRm) is recommended and tumor testing for microsatellite instability (MSI) or deficient mismatch repair (dMMR) can be considered. See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
- Footnote removed: PSADT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease.
- Footnote removed: Patients with a life expectancy ≤5 years can consider observation. See Principles of Active Surveillance and Observation (PROS-F).
- Footnote removed: Intermittent ADT can be considered for patients with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-I).
- Footnote removed: The panel encourages ADT with docetaxel and either darolutamide or abiraterone for patients with high-volume de novo disease who are fit for chemotherapy. See Principles of Non-Hormonal Systemic Therapy (PROS-J).
- Footnote removed: Patients who were under monitoring for M0 disease should receive an appropriate therapy for castration-sensitive disease.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Prostate Cancer from Version 4.2023 include:

PROS-14
- Systemic therapy for M0 castration-resistant prostate cancer (CRPC)
  - Last node for M0 disease modified: Change or maintain current treatment and continue ~~monitoring~~ periodic disease assessment

PROS-15
- CRPC, imaging studies positive for metastases
  - Bullets combined and revised as: Somatic testing for homologous recombination repair (HRR), microsatellite instability/mismatch repair deficiency (MSI/dMMR), and tumor mutational burden (TMB) if not previously done.
- Footnote lll added: For details on the efficacy and safety of these agents, see Principles of Non-Hormonal Systemic Therapy (PROS-L) (also on PROS-16A)

PROS-16
- No prior docetaxel/no prior novel hormone therapy
  - Useful in certain circumstances
    - ◊ Regimen added: Pembrolizumab for MSI-H/dMMR (category 2B)
- Progression on prior docetaxel/no prior novel hormone therapy
  - Useful in certain circumstances
    - ◊ Regimen added: Pembrolizumab for MSI-H/dMMR (category 2B)
- Progression on prior novel hormone therapy/no prior docetaxel
  - Preferred regimens
    - ◊ Regimen added: Olaparib for BRCA mutation (category 1)
    - ◊ Regimen added: Rucaparib for BRCA mutation (category 1)
  - Useful in certain circumstances
    - ◊ Regimen modified: Olaparib for HRR mutation *other than BRCA1/2* ~~(category 1)~~
    - ◊ Regimen removed: Rucaparib for BRCA mutation
    - ◊ Regimen added: Pembrolizumab for MSI-H/dMMR (category 2B)
  - Other recommended regimens
    - ◊ Regimens removed: Abiraterone, Abiraterone + dexamethasone, Enzalutamide (see footnote aaaa)
- Progression on prior docetaxel and a novel hormone therapy
  - Statement removed: The following systemic therapies are category 2B if visceral metastases are present
  - Other recommended regimens
    - ◊ Regimens removed: Abiraterone, Enzalutamide (see footnote aaaa)

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PROS-16A
- Footnote ppp modified: Patients can continue through all treatment options listed. Best supportive care, *which can include androgen-directed therapy or steroid*, is always an appropriate option.
- Footnote aaaa added: Other secondary hormone therapies include abiraterone, fine-particle abiraterone, and enzalutamide for patients with disease progression on prior novel hormone therapy. In addition, switching from prednisone or methylprednisolone to dexamethasone 1 mg/day can be considered for patients with disease progression on either formulation of abiraterone. Also see Principles of Androgen Deprivation Therapy (PROS-G).
- Footnote removed: Switching from prednisone to dexamethasone 1 mg/day can be considered for patients with disease progression on either formulation of abiraterone. Trials show improved PSA responses and PFS and acceptable safety using this strategy. Romero-Laorden N, et al. Br J Cancer 2018;119:1052-1059 and Fenioux C, et al. BJU Int 2019;123:300-306.
- Footnote removed: 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.
- Footnote removed: Consider AR-V7 testing to help guide selection of therapy (See Discussion)

PROS-B
- New section added: Principles of Bone Health in Prostate Cancer

PROS-C 1 of 2
- Germline Testing
  - Pre-test Considerations
    - ◊ 1st sub-bullet modified: The panel recommends inquiring about family and personal history of cancer, and known germline variants at time of initial diagnosis. Criteria for germline testing *(see CRIT-6 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and LS-1 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal)* ~~(see PROS-C, 2 of 3)~~ should be reviewed at time of initial diagnosis and, if relevant, at recurrence.
  - Testing
    - ◊ 1st sub-bullet modified: If criteria are met ~~(see PROS-C, 2 of 3)~~, germline multigene testing that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended.
    - ◊ 2nd sub-bullet removed: Additional genes may be appropriate depending on clinical context. For example, HOXB13 is a prostate cancer risk gene that does not have therapeutic implications in advanced disease, but testing may have utility for family counseling.
- Page removed: Germline testing criteria for patients with prostate cancer

PROS-C 2 of 2
- Somatic Testing
  - Testing
    - ◊ 1st sub-bullet modified: Somatic ~~tumor~~ testing *for alterations in DNA damage response*: ~~in homologous recombination DNA repair genes such as~~
    - ◊ 1st 3rd order bullet modified: *Multigene tumor testing for alterations in homologous recombination DNA repair (HRR) genes, including but not limited to* BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12, is recommended in patients with metastatic prostate cancer. This testing can be considered in patients with regional prostate cancer.
  - Tumor Specimen and Assay Considerations
    - ◊ 1st sub-bullet modified: The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. *This could include lymph node biopsy for patients with N1 disease.* When unsafe or unfeasible, plasma ciculating tumor (ctDNA) assay is an option, preferably collected during...

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Prostate Cancer from Version 4.2023 include:

PROS-E 1 of 4
- Goals of Imaging
  - 1st sub-bullet modified: Anatomic imaging techniques include ~~plain film radiographs~~, ultrasound, CT, and MRI.

PROS-E 2 of 4
- Bone Imaging
  - 1st sub-bullet modified: ~~Plain films,~~ CT, MRI, or PET/CT or PET/MRI with F-18 piflufolastat PSMA, Ga-68 PSMA-11, F-18 flotufolastat PSMA, F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone scan.

PROS-E 3 of 4
- Positron Emission Tomography
  - 6th bullet modified: Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (*eg,* CT, *bone scan* ~~MRI~~) at both initial

PROS-E 4 of 4
- Positron Emission Tomography continued
  - 2nd bullet modified: F-18 flotufolastat PSMA is a PET imaging agent that is part of a ~~novel~~ class of tracers referred to as radiohybrid (rh) ligands. These *tracers* ~~rh ligands~~ have ~~the unique advantage of offering~~ two binding sites for radionuclides (ie, F-18 or Ga-68). *The significance of this remains to be determined.* ~~which increases its flexibility in imaging. In addition, the presence of a chelator in these *tracers* rh ligands also allows for chelation of Lu-177 for its use as a theranostic as well as imaging agent.~~
  - 3rd bullet modified: ...as the non-contrast CT component of PSMA-PET/CT is insufficient to detect ~~visceral metastatic~~ disease

PROS-F 1 of 5
- Candidacy for Active Surveillance
  - 2nd sub-bullet modified: ... *For some of these patients*, ~~In some of these cases,~~ upfront treatment with RP or prostate RT may be preferred based on shared decision-making ~~with the patient.~~

PROS-F 2 of 5
- Confirmatory Testing to Establish Appropriateness of Active Surveillance
  - 3rd sub-bullet modified: ... PSA density (and repeat biopsy as indicated), and/or molecular tumor analysis, see Principles of Risk Stratification (PROS-H). *Other forms of imaging are discouraged.*
- Active Surveillance Program
  - 3rd, 3rd order bullet modified: Repeat prostate biopsy no more often than every 12 months unless clinically indicated. While the intensity of surveillance may be tailored *based on patient and tumor factors (eg, grade, tumor volume)* ~~on an individual basis,~~ most patients should have prostate biopsies *every 2 to 5 years* ~~incorporated~~ as part of their monitoring.
  - 9th, 3rd order bullet added: A metastatic staging evaluation (PSMA PET, bone scan, CT scan, or whole body MRI) should not be performed.
- Considerations for Treatment of Patients on Active Surveillance
  - 1st sub-bullet modified: ... factor influencing a change ~~in management~~ from active surveillance to treatment.
  - 3rd sub-bullet modified: ... a change in *disease* management

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Prostate Cancer from Version 4.2023 include:

PROS-F 5 of 5
• Reference 11 updated

PROS-G
• Principles of Androgen Deprivation Therapy
  ▸ Section extensively revised

PROS-H
• Principles of Risk Stratification
  ▸ Section extensively revised

PROS-I
• Principles of Radiation Therapy
  ▸ Section extensively revised

PROS-K
• New Section
  ▸ Principles of Local Secondary Therapy Post-Radiation

PROS-L
• Principles of Non-Hormonal Systemic Therapy
  ▸ Section extensively revised

INITIAL PROSTATE CANCER DIAGNOSIS[a,b,c]

WORKUP

Clinically localized prostate cancer (Any T, N0, M0 or Any T, NX, MX)

- Perform physical exam
- Perform digital rectal exam (DRE) to confirm clinical stage
- Perform and/or collect prostate-specific antigen (PSA) and calculate PSA density
- Obtain and review diagnostic prostate biopsies
- Estimate life expectancy (Principles of Life Expectancy Estimation [PROS-A])
- Inquire about known high-risk germline mutations and family history[d]
  - Perform somatic and/or germline testing as appropriate[d]
- Assess quality-of-life measures[e]

→ See Initial Risk Stratification and Staging Workup for Clinically Localized Disease (PROS-2)

Regional prostate cancer (Any T, N1, M0)

Metastatic prostate cancer (Any T, Any N, M1)

- Perform physical exam
- Perform imaging for staging[f,g,h]
- Perform DRE to confirm clinical stage
- Perform and/or collect PSA and calculate PSA doubling time (PSADT)
- Estimate life expectancy (Principles of Life Expectancy Estimation [PROS-A])
- Inquire about known high-risk germline mutations and family history[d]
  - Perform somatic and/or germline testing as appropriate[d]
- Assess quality-of-life measures[e]

→ See Regional Prostate Cancer (PROS-8)

→ Systemic Therapy for M1 Castration-Sensitive Prostate Cancer (CSPC) (PROS-13)

[a] See NCCN Guidelines for Older Adult Oncology for tools to aid optimal assessment and management of disease in older adults.
[b] NCCN Guidelines for Prostate Cancer Early Detection.
[c] Principles of Bone Health in Prostate Cancer (PROS-B).
[d] Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[e] Principles of Quality-of-Life and Shared Decision-Making (PROS-D).
[f] Principles of Imaging (PROS-E).

[g] Bone imaging can be achieved by conventional technetium-99m-methylene diphosphonate (MDP) bone scan. CT, MRI, prostate-specific membrane antigen (PSMA)-PET/CT or PSMA-PET/MRI, or PET/CT or PET/ MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Multiparametric MRI (mpMRI) is preferred over CT for pelvic staging. Alternatively, PSMA-PET/CT or PSMA-PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E).

[h] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (eg, CT, bone scan) at both initial staging and biochemical recurrence (BCR), the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.

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.

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE[i]

Risk Group	Clinical/Pathologic Features (Staging, ST-1)			Additional Evaluation[f,m]	Initial Therapy
Very low[j]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • <3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[k] • PSA density <0.15 ng/mL/g			• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-3
Low[j]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-4
Intermediate[j]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[l]	• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[l]	Bone and soft tissue imaging[g,h] • If regional or distant metastases are found, see PROS-8 or PROS-13	PROS-6
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			Bone and soft tissue imaging[g,h] • If regional or distant metastases are found, see PROS-8 or PROS-13	PROS-7
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			Bone and soft tissue imaging[g,h] • If regional or distant metastases are found, see PROS-8 or PROS-13	PROS-7

Footnotes for Initial Risk Stratification and Staging Workup for Clinically Localized Disease (PROS-2A).

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.

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

[f] Principles of Imaging (PROS-E).

[g] Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/ MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. mpMRI is preferred over CT for pelvic staging. Alternatively, PSMA-PET/CT or PSMA-PET/ MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E).

[h] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (eg, CT, bone scan) at both initial staging and BCR, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/ MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.

[i] Tumor-based molecular assays and germline genetic testing are other tools that can assist with risk stratification. See CRIT-6 in the NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and LS-1 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal to determine if a patient is an appropriate candidate for germline genetic testing, and see Principles of Risk Stratification (PROS-H) to determine if a patient is an appropriate candidate for tumor-based molecular assays.

[j] For patients who are asymptomatic in very-low-, low-, and intermediate-risk groups with life expectancy ≤5 years, no imaging or treatment is indicated until the patient becomes symptomatic, at which time imaging can be performed, see Principles of Imaging (PROS-E) and androgen deprivation therapy (ADT) should be given, see Principles of Androgen Deprivation Therapy (PROS-G).

[k] An ultrasound- or MRI- or DRE-targeted lesion that is biopsied more than once and demonstrates cancer (regardless of percentage core involvement or number of cores involved) can be considered as a single positive core.

[l] Percentage of positive cores in the intermediate-risk group is based on biopsies that include systematic biopsies with or without targeted MRI-guided biopsies.

[m] Bone imaging should be performed for any patient with symptoms consistent with bone metastases.

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.

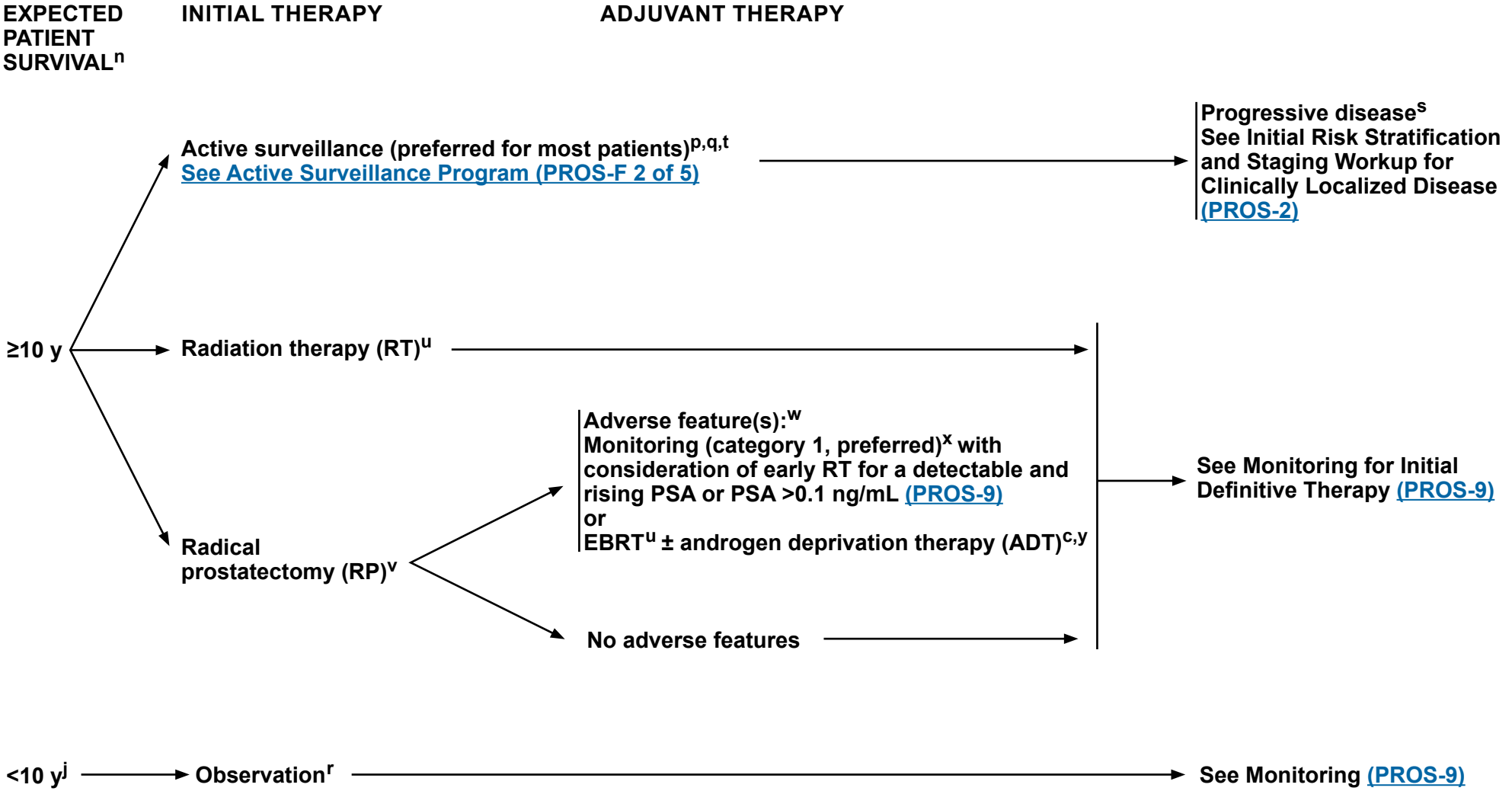
VERY-LOW-RISK GROUP

EXPECTED PATIENT SURVIVAL[n]	INITIAL THERAPY
≥10 y[o]	Active surveillance[p,q] See Active Surveillance Program (PROS-F 2 of 5) → Progressive disease[s] See Initial Risk Stratification and Staging Workup for Clinically Localized Disease (PROS-2)
<10 y[j]	Observation[r] → See Monitoring (PROS-9)

Footnotes for Risk Groups (PROS-8A).

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.

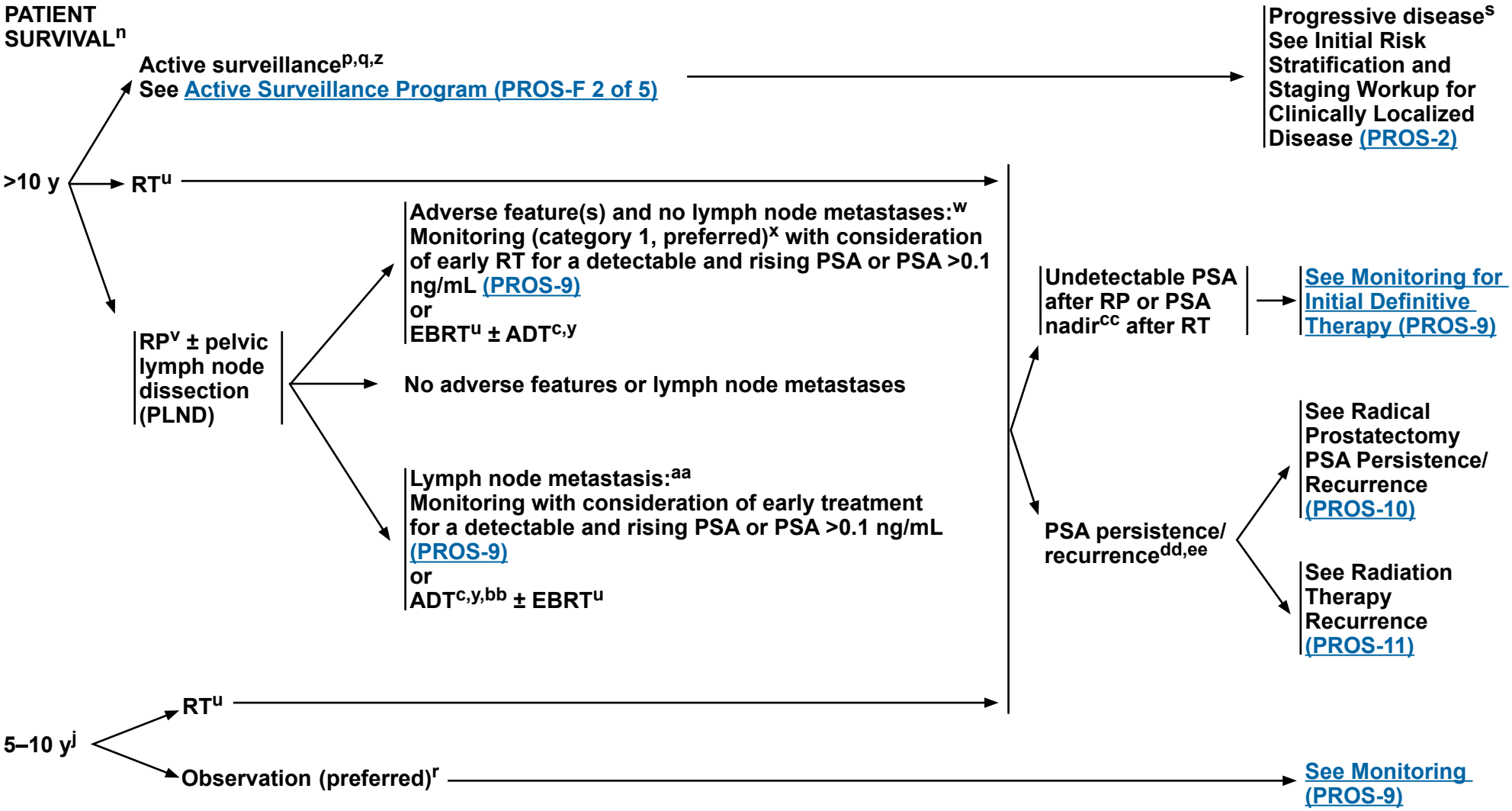
LOW-RISK GROUP



Footnotes for Risk Groups (PROS-8A).

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.

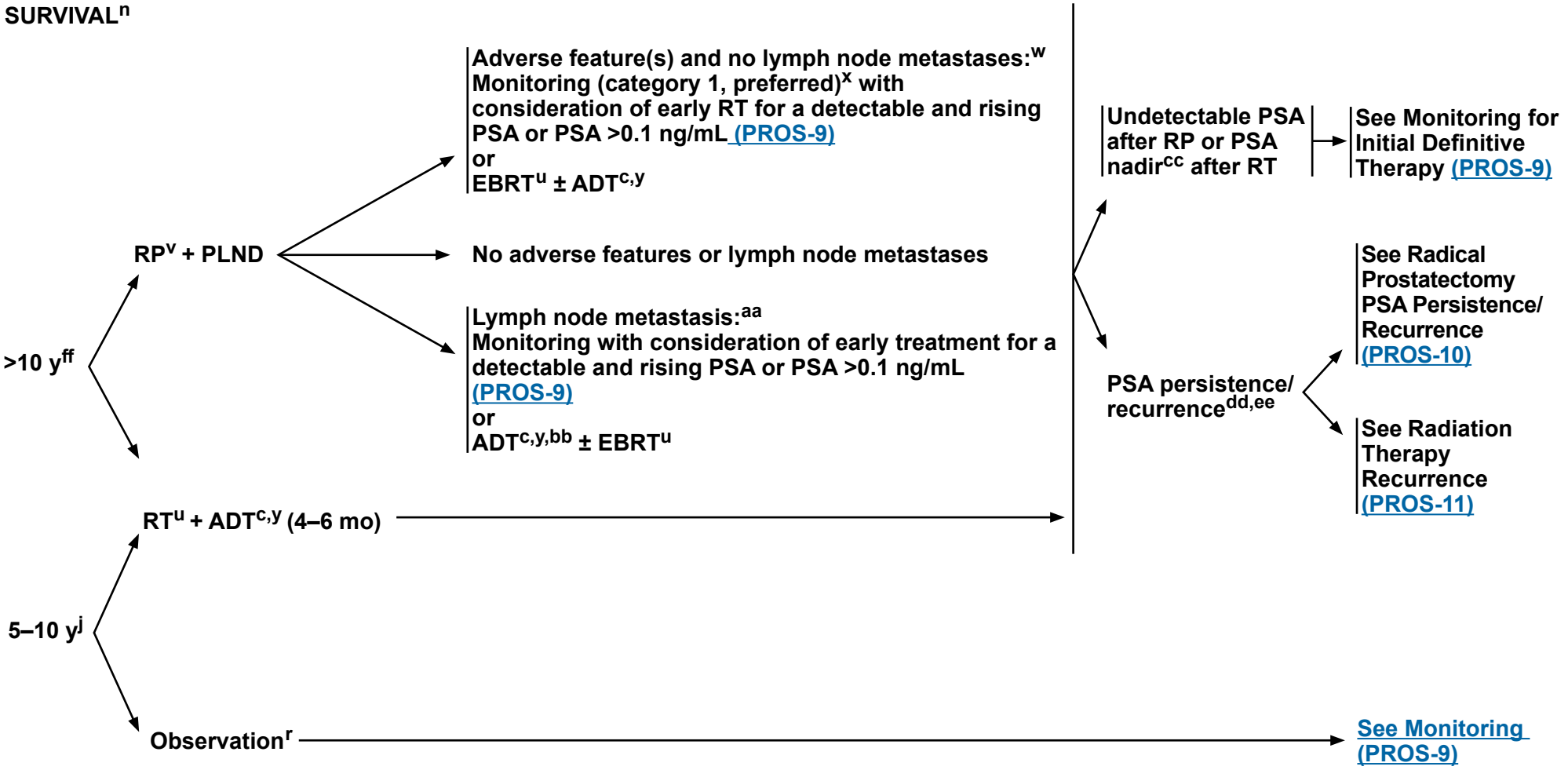
FAVORABLE INTERMEDIATE-RISK GROUP



Footnotes for Risk Groups (PROS-8A).

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.

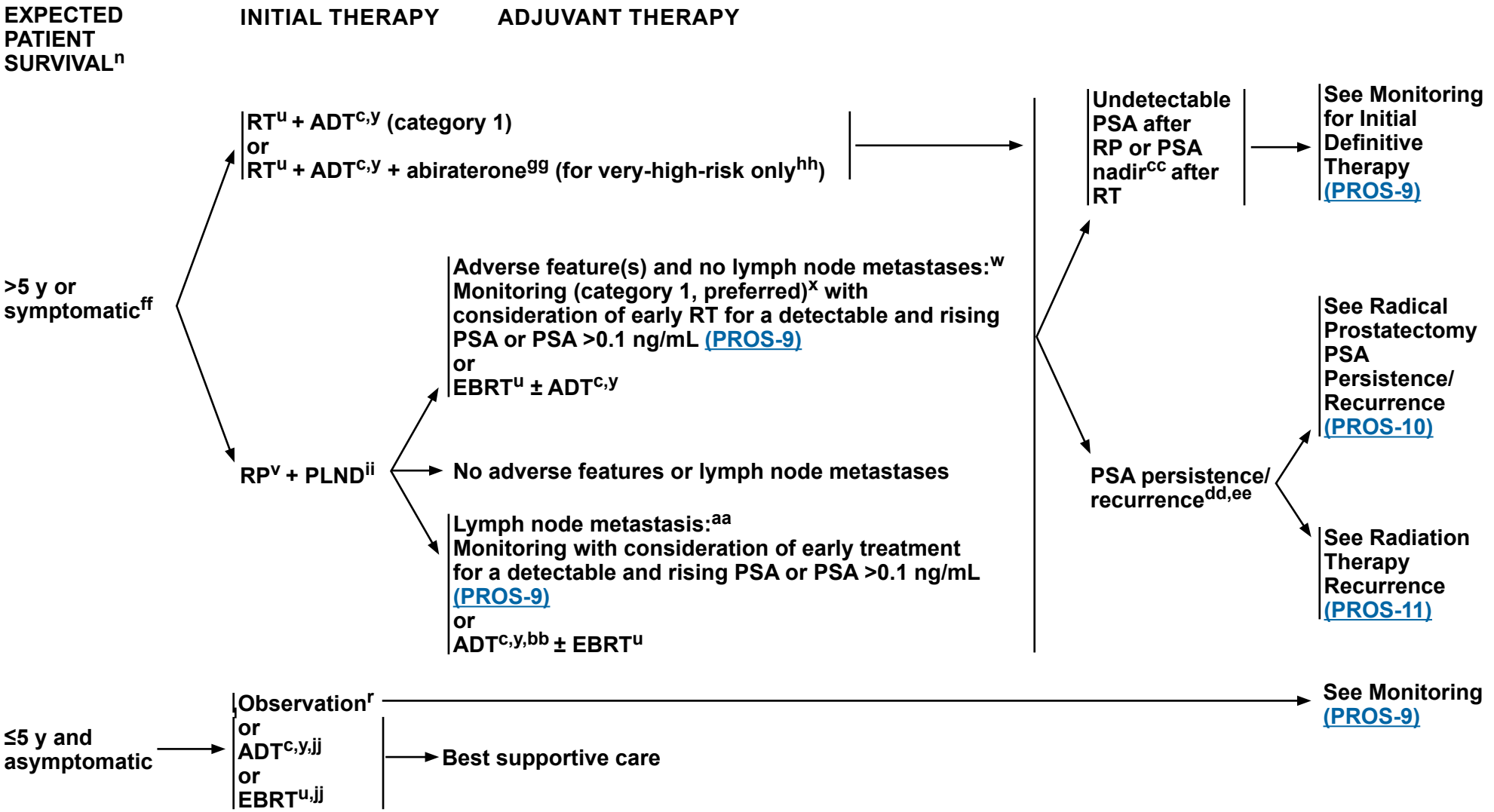
UNFAVORABLE INTERMEDIATE-RISK GROUP



Footnotes for Risk Groups (PROS-8A).

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.

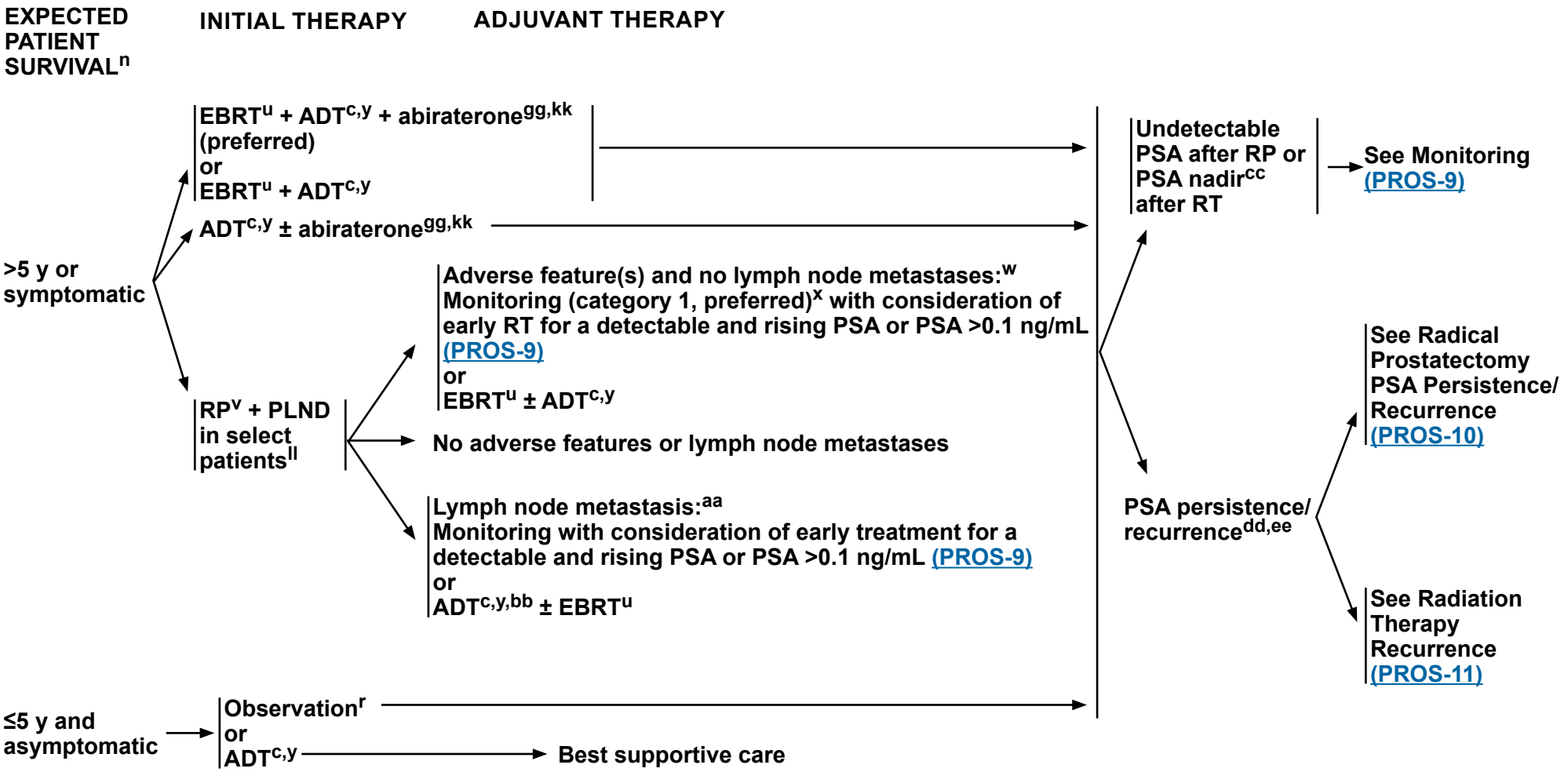
HIGH- OR VERY-HIGH-RISK GROUP



Footnotes for Risk Groups (PROS-8A).

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.

REGIONAL RISK GROUP (ANY T, N1, M0)



Footnotes for Risk Groups (PROS-8A).

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.

FOOTNOTES

[c] Principles of Bone Health in Prostate Cancer (PROS-B).

[j] For patients who are asymptomatic in very-low-, low-, and intermediate-risk groups with life expectancy ≤5 years, no imaging or treatment is indicated until the patient becomes symptomatic, at which time imaging can be performed, see Principles of Imaging (PROS-E) and ADT should be given, see Principles of Androgen Deprivation Therapy (PROS-G).

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

[o] The panel remains concerned about the problems of overtreatment 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 this subset of patients.

[p] 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-F).

[q] Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5). If higher grade and/or higher T stage is found during confirmatory testing, see PROS-2.

[r] 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-F).

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

[t] The panel recognizes that there is heterogeneity across the low-risk group, and that some factors may be associated with an increased probability of near-term grade reclassification, including high PSA density, a high number of positive cores (eg, ≥3), high genomic risk (from tissue-based molecular tumor analysis), and/or a known BRCA2 germline mutation. In some of these cases, upfront treatment with RP or prostate RT may be preferred based on shared decision-making with the patient. See Principles of Active Surveillance and Observation (PROS-F).

[u] Principles of Radiation Therapy (PROS-I).

[v] Principles of Surgery (PROS-J).

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

[x] Monitoring is not preferred for patients with positive nodes or multiple high-risk features.

[y] For details on the use of ADT and other hormonal agents, including information on their efficacy and safety, see Principles of Androgen Deprivation Therapy (PROS-G).

[z] Particular consideration to active surveillance may be appropriate for those patients in the favorable intermediate-risk group with a low percentage of Gleason pattern 4 cancer, low tumor volume, low PSA density, and/or low genomic risk (from tissue-based molecular tumor analysis). See Principles of Active Surveillance and Observation (PROS-F).

[aa] For patients with pN1 disease and PSA persistence, see PROS-10.

[bb] See monitoring for N1 on ADT (PROS-9).

[cc] PSA nadir is the lowest value reached after EBRT or brachytherapy.

[dd] PSA persistence/recurrence after RP is defined as when PSA does not fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or increases to PSA >0.1 ng/mL. Trials indicating non-inferiority of early RT compared with adjuvant RT after RP have used a PSA threshold of 0.1 or 0.2 ng/mL to trigger treatment. Imaging and treatment at lower PSA levels may be appropriate in patients at high risk for progression based on pretreatment risk factors, pathologic parameters, timing of recurrence, and genomic classifier (GC) score, among other factors.

[ee] 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 PSA recurrence after EBRT with or without hormone therapy; 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 secondary 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 patients who are younger or healthier.

[ff] Active surveillance of unfavorable intermediate and high-risk clinically localized cancers is not recommended in patients with a life expectancy >10 years (category 1).

[gg] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended option).

[hh] Patients in STAMPEDE had at least two of the following: cT3–4, Grade Group 4 or 5, and PSA >40 ng/mL.

[ii] RP + PLND can be considered in patients who are younger and healthier without tumor fixation to the pelvic sidewall.

[jj] ADT or EBRT 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 years.

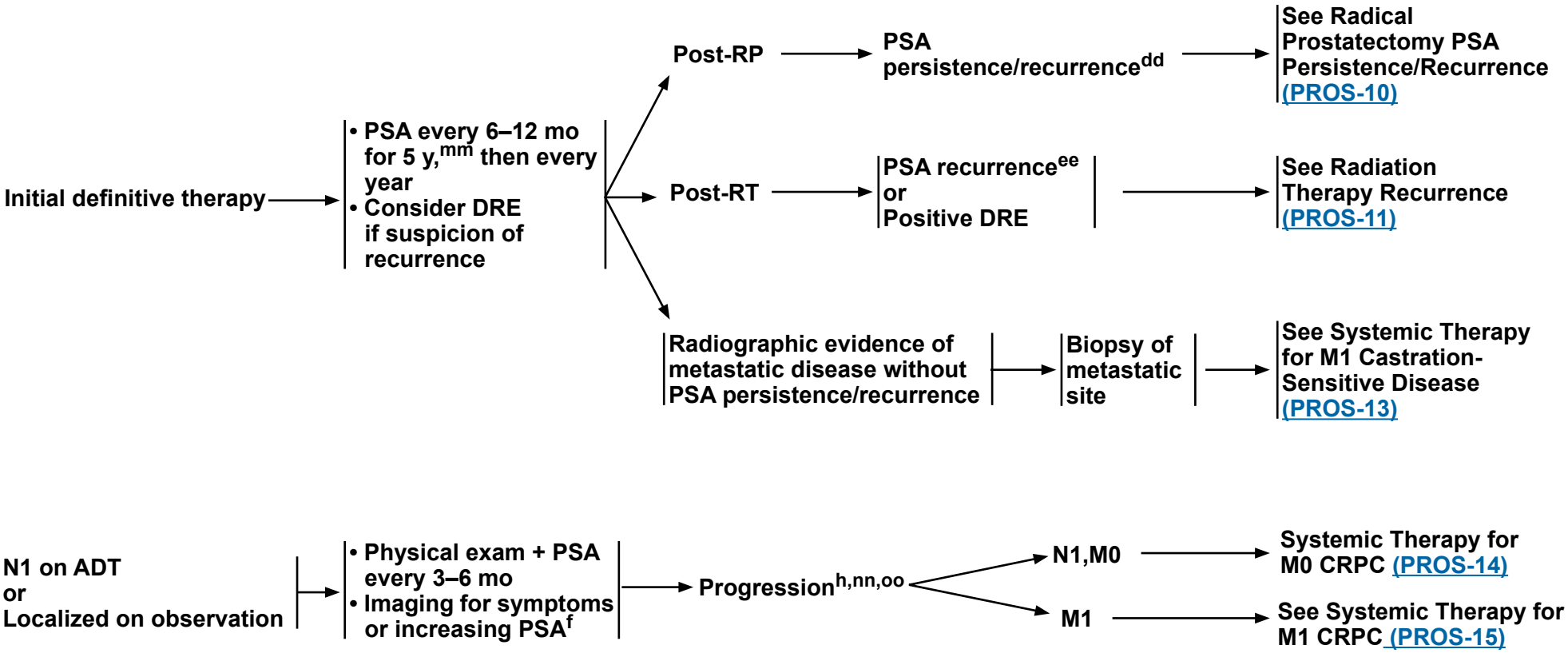
[kk] Abiraterone with ADT should be considered for a total of 2 years for those patients with N1 disease who are treated with radiation to the prostate and pelvic nodes (PROS-G).

[ll] There is limited evidence that RP + PLND is beneficial in the setting of node-positive disease. Use of this approach should be limited to patients with >10-year life expectancy and resectable disease and should be used in the context of a clinical trial or planned multimodality approach.

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.

MONITORING
See NCCN Guidelines for Survivorship

RECURRENCE



Footnotes for Monitoring (PROS-9A)

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.

RECURRENCE FOOTNOTES

[f] Principles of Imaging (PROS-E).

[h] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (eg, CT, bone scan) at both initial staging and BCR, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.

[dd] PSA persistence/recurrence after RP is defined as when PSA does not fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or increases to PSA >0.1 ng/mL. Trials indicating non-inferiority of early RT compared with adjuvant RT after RP have used a PSA threshold of 0.1 or 0.2 ng/mL to trigger treatment. Imaging and treatment at lower PSA levels may be appropriate in patients at high risk for progression based on pretreatment risk factors, pathologic parameters, timing of recurrence, and GC score, among other factors.

[ee] RTOG-ASTRO Phoenix Consensus: 1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for PSA recurrence after EBRT with or without hormone therapy; 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 secondary 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 patients who are younger or healthier.

[mm] PSA as frequently as every 3 mo may be necessary to clarify disease status, especially in patients at high risk of recurrence.

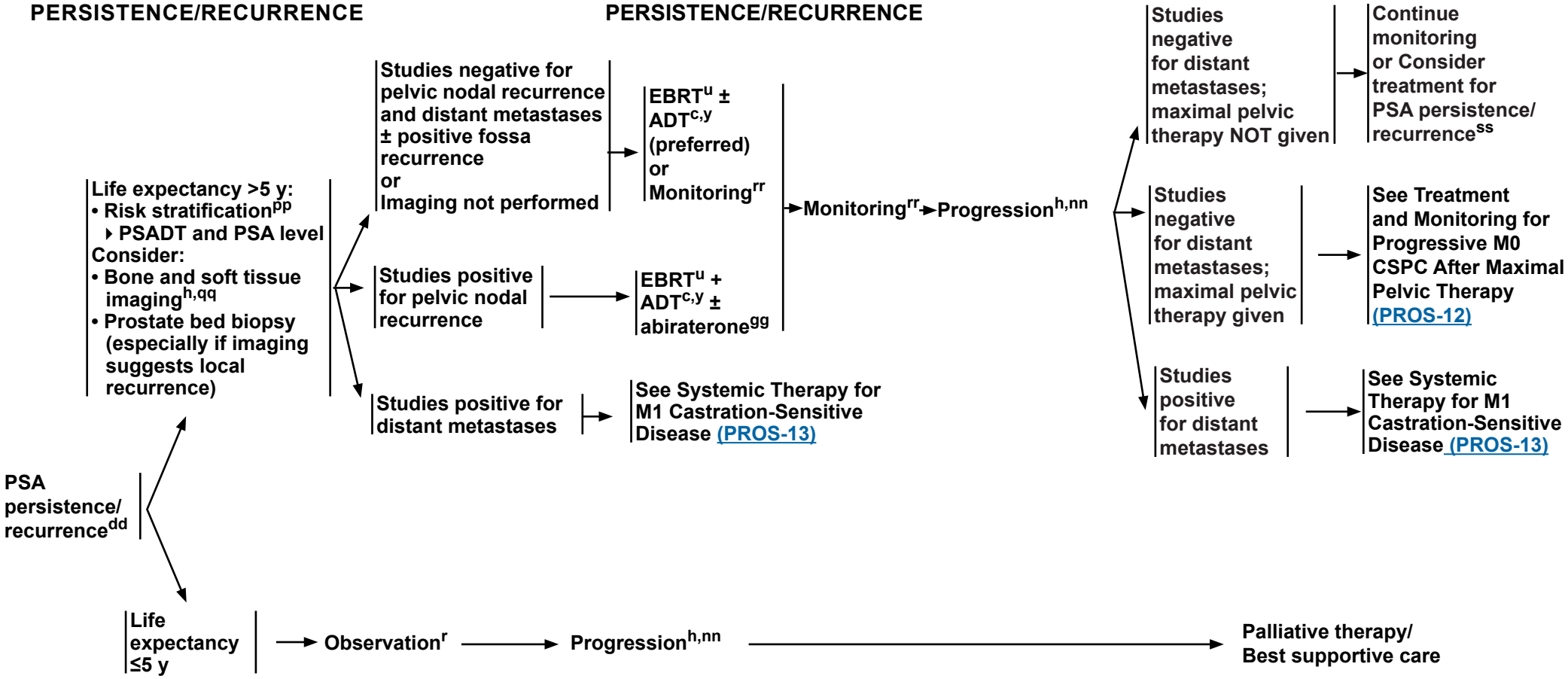
[nn] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, PSMA-PET/CT or PSMA-PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E).

[oo] Treatment for patients whose cancer progressed on observation of localized disease is ADT. See Principles of Androgen Deprivation Therapy (PROS-G).

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.

RADICAL PROSTATECTOMY PSA PERSISTENCE/RECURRENCE

TREATMENT FOR PSA PERSISTENCE/RECURRENCE



Radical Prostatectomy PSA Persistence/Recurrence Footnotes (PROS-10A)

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.

RADICAL PROSTATECTOMY PSA PERSISTENCE/RECURRENCE FOOTNOTES

[c] Principles of Bone Health in Prostate Cancer (PROS-B).

[h] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (eg, CT, bone scan) at both initial staging and BCR, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.

[r] 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-F).

[u] Principles of Radiation Therapy (PROS-I).

[y] For details on the use of ADT and other hormonal agents, including information on their efficacy and safety, see Principles of Androgen Deprivation Therapy (PROS-G).

[dd] PSA persistence/recurrence after RP is defined as when PSA does not fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or increases to PSA >0.1 ng/mL. Trials indicating non-inferiority of early RT compared with adjuvant RT after RP have used a PSA threshold of 0.1 or 0.2 ng/mL to trigger treatment. Imaging and treatment at lower PSA levels may be appropriate in patients at high risk for progression based on pretreatment risk factors, pathologic parameters, timing of recurrence, and GC score, among other factors.

[gg] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended option).

[nn] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, PSMA-PET/CT or PSMA-PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E).

[pp] Principles of Risk Stratification (PROS-H).

[qq] PSMA-PET/CT or PSMA-PET/MRI are preferred for bone and soft tissue (full body) imaging. Alternatively, bone imaging can be achieved by conventional technetium-99m-MDP bone scan. CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. mpMRI is preferred over CT for pelvic staging and its use is recommended in addition to PSMA-PET in the setting of RT recurrence. See Principles of Imaging (PROS-E).

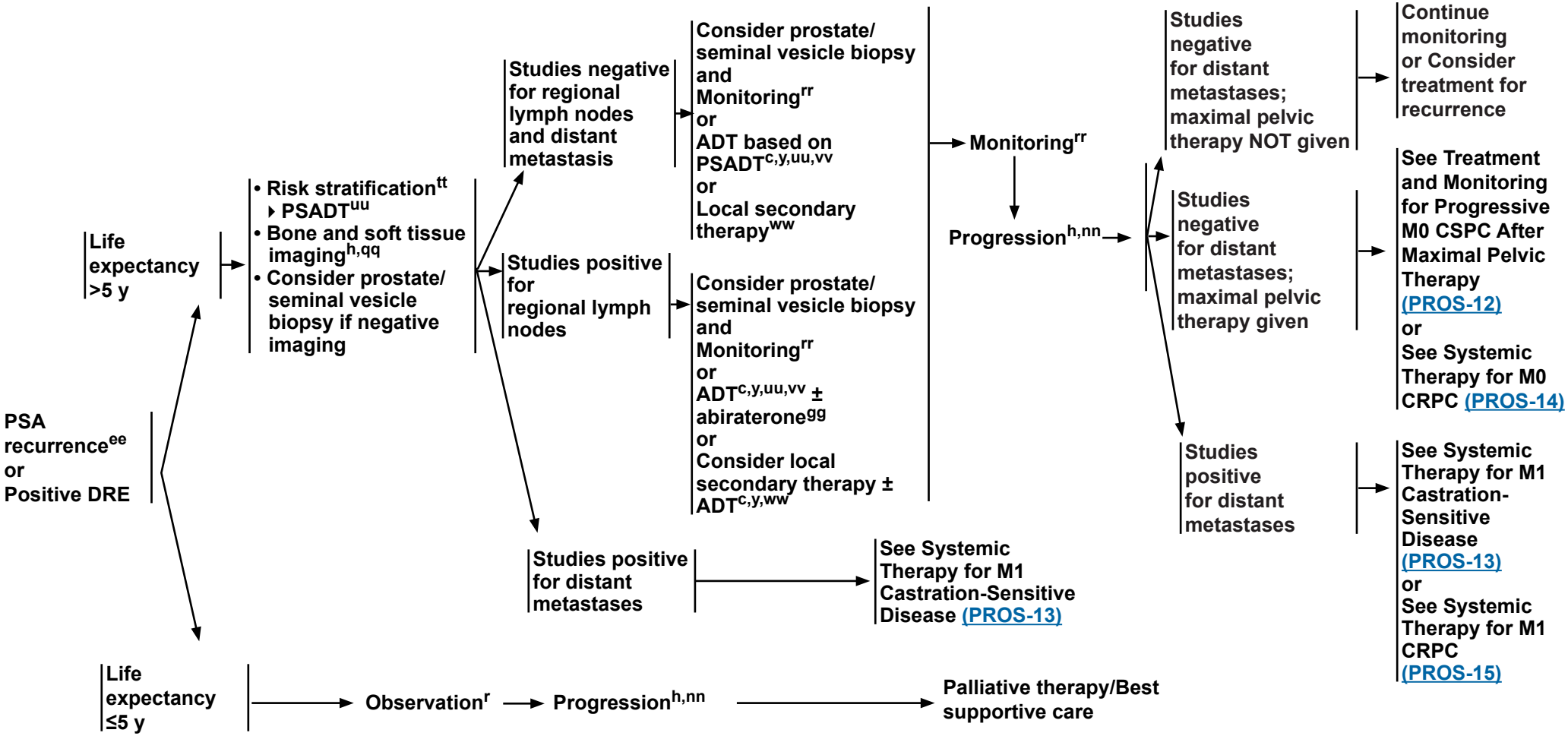
[rr] Monitoring should include physical exam, PSA every 3–6 mo, and imaging for symptoms or increasing PSA.

[ss] If considering treatment, reinitiate the PROS-10 algorithm.

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.

RADIATION THERAPY RECURRENCE

TREATMENT FOR RECURRENCE



Radiation Therapy recurrence Footnotes (PROS-11A)

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.

RADIATION THERAPY RECURRENCE
FOOTNOTES

[c] Principles of Bone Health in Prostate Cancer (PROS-B).

[h] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (eg, CT, bone scan) at both initial staging and BCR, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.

[r] 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-F).

[y] For details on the use of ADT and other hormonal agents, including information on their efficacy and safety, see Principles of Androgen Deprivation Therapy (PROS-G).

[ee] RTOG-ASTRO Phoenix Consensus: 1) PSA increase by 2 ng/mL or more above the nadir PSA is the standard definition for PSA recurrence after EBRT with or without hormone therapy; 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 secondary 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 patients who are younger or healthier.

[nn] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, PSMA-PET/CT or PSMA-PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E).

[qq] PSMA-PET/CT or PSMA-PET/MRI are preferred for bone and soft tissue (full body) imaging. Alternatively, bone imaging can be achieved by conventional technetium-99m-MDP bone scan. CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. mpMRI is preferred over CT for pelvic staging and its use is recommended in addition to PSMA-PET in the setting of RT recurrence. See Principles of Imaging (PROS-E).

[rr] Monitoring should include physical exam, PSA every 3–6 mo, and imaging for symptoms or increasing PSA.

[tt] PSADT can be calculated to inform nomogram use and counseling.

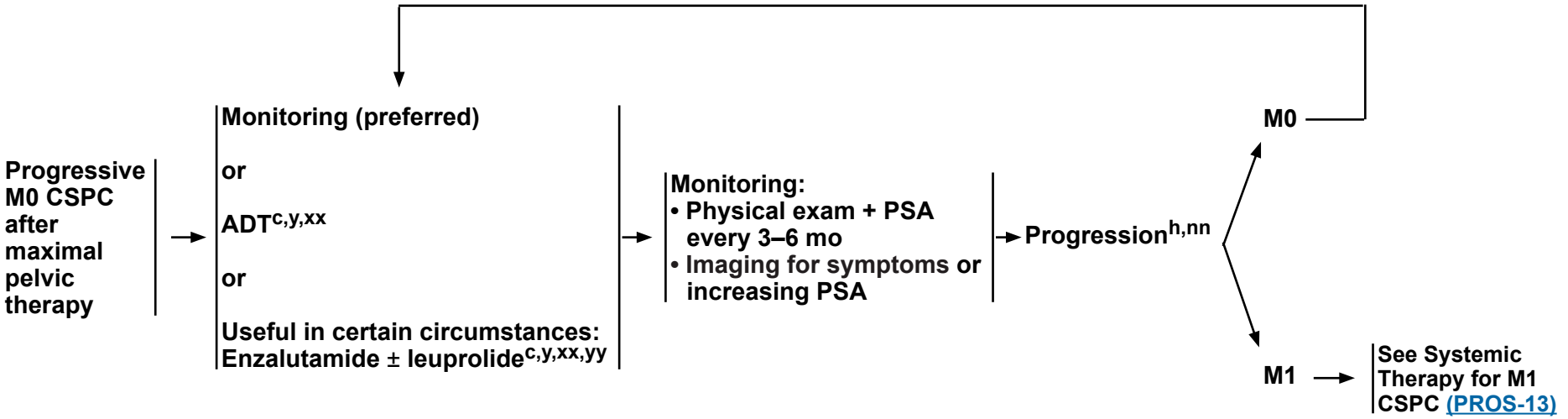
[uu] PSADT and Grade Group should be considered when deciding whether to begin ADT. See Principles of Androgen Deprivation Therapy (PROS-G).

[vv] Intermittent ADT can be considered for patients with M0 or M1 disease receiving ADT monotherapy to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-G).

[ww] Principles of Local Secondary Post-Recurrence Therapy (PROS-K).

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.

TREATMENT AND MONITORING FOR PROGRESSIVE M0 CASTRATION-SENSITIVE PROSTATE CANCER (CSPC) AFTER MAXIMAL PELVIC THERAPY



[c] Principles of Bone Health in Prostate Cancer (PROS-B).

[h] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (eg, CT, bone scan) at both initial staging and BCR, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.

[y] For details on the use of ADT and other hormonal agents, including information on their efficacy and safety, see Principles of Androgen Deprivation Therapy (PROS-G).

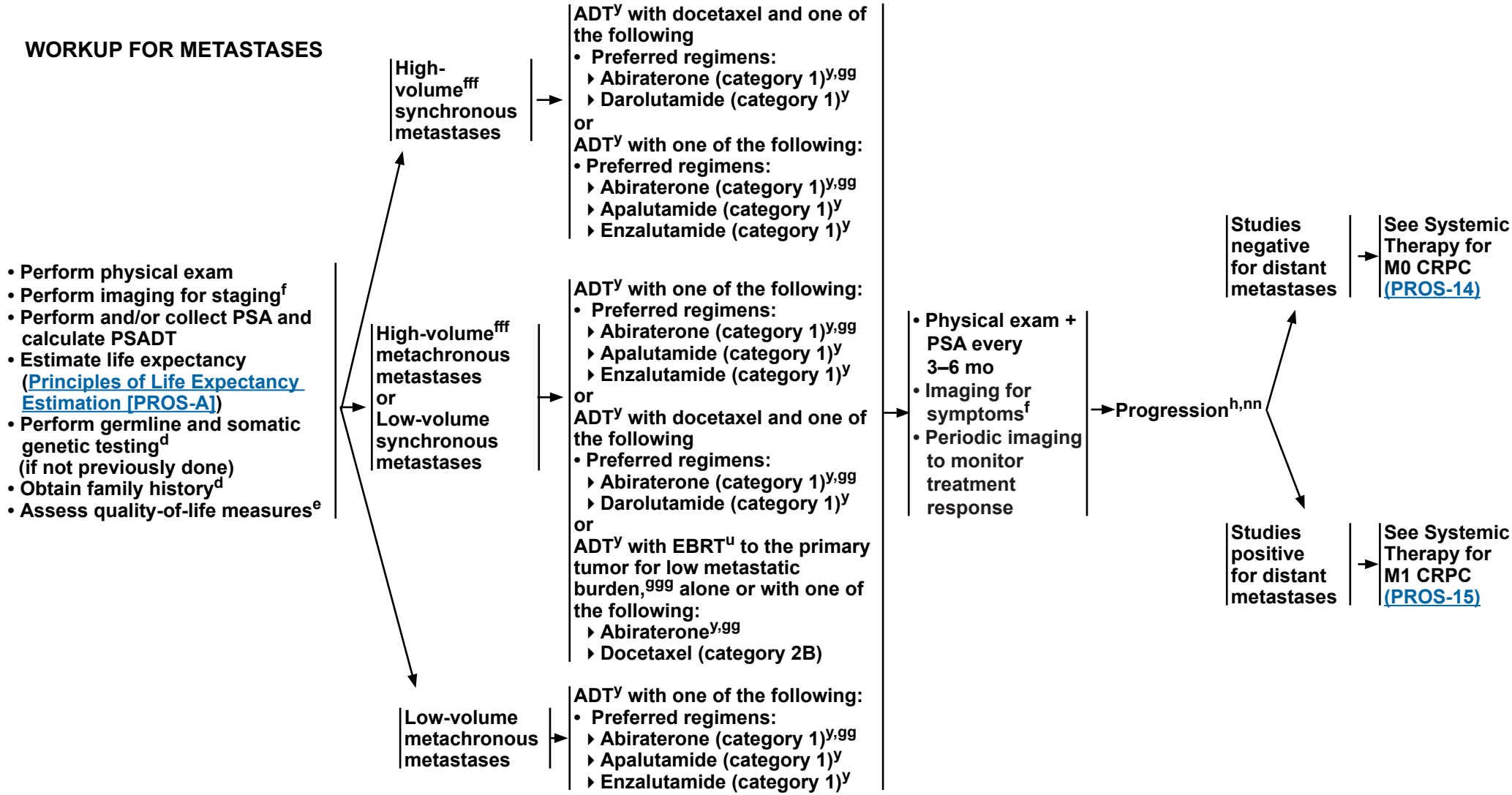
[nn] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, PSMA-PET/CT or PSMA-PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E).

[xx] For patients with non-metastatic castration-sensitive disease who are not candidates for pelvic therapy, monitoring until diagnosis of metastatic disease is preferred. PSADT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease. For ADT alone, intermittent ADT can be considered to reduce toxicity.

[yy] Enzalutamide with or without leuprolide is an option for patients who have the following high-risk criteria: M0 by conventional imaging; PSADT ≤9 months; PSA ≥2 ng/mL above nadir after RT or ≥1 ng/mL after RP with or without postoperative RT; and not considered a candidate for pelvic-directed therapy (Freedland SJ, et al. N Engl J Med 2023;389:1453-1465). See Principles of Androgen Deprivation Therapy (PROS-G).

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.

SYSTEMATIC THERAPY FOR M1 CSPC[c,zz,aaa,bbb,ccc,ddd,eee]



Systemic Therapy for M1 CSPC Footnotes (PROS-13A)

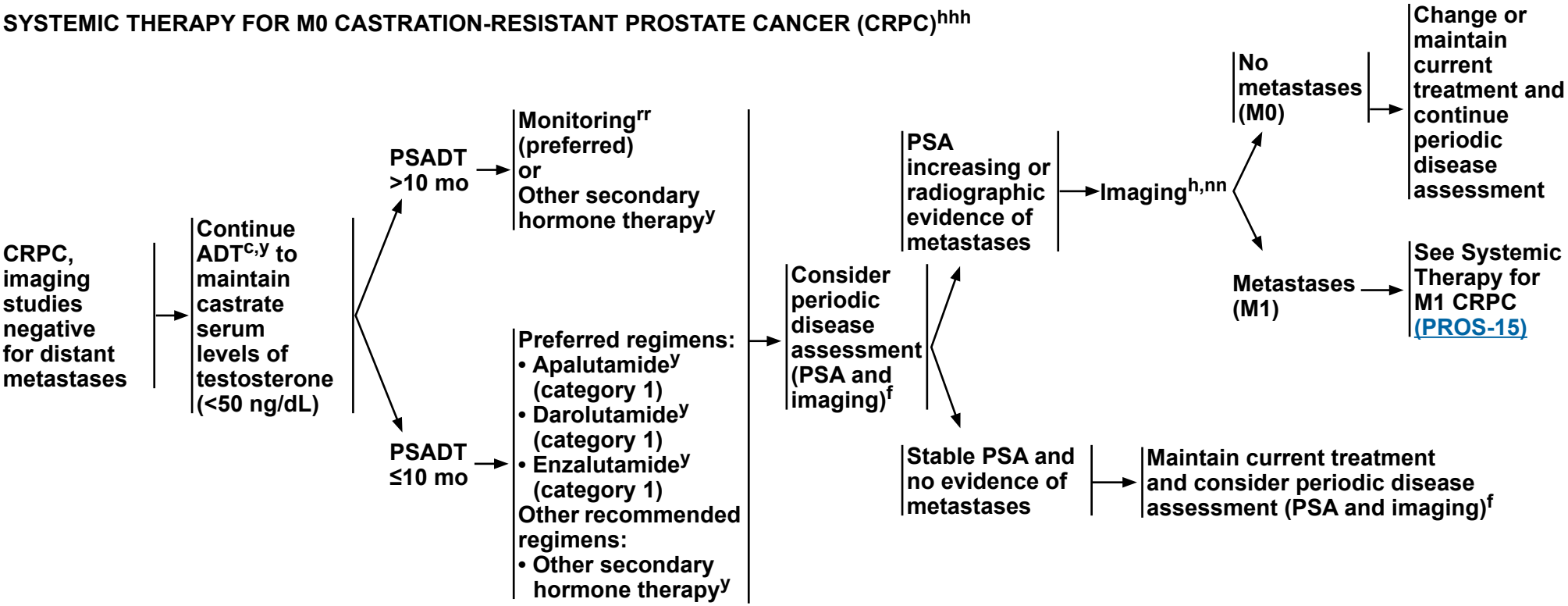
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOOTNOTES

[c] Principles of Bone Health in Prostate Cancer (PROS-B).
[d] Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[e] Principles of Quality-of-Life and Shared Decision-Making (PROS-D).
[f] Principles of Imaging (PROS-E).
[h] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (eg, CT, bone scan) at both initial staging and BCR, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.
[u] Principles of Radiation Therapy (PROS-I).
[y] For details on the use of ADT and other hormonal agents, including information on their efficacy and safety, see Principles of Androgen Deprivation Therapy (PROS-G).
[gg] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended option).
[nn] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, PSMA-PET/CT or PSMA-PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E).
[zz] EBRT to sites of bone metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.
[aaa] ADT alone (PROS-G) or observation are recommended for asymptomatic patients with metastatic disease and life expectancy ≤5 years.
[bbb] Stereotactic body RT (SBRT) to metastases can be considered in appropriate clinical situations. See Principles of Radiation Therapy (PROS-I).
[ccc] Bone antiresorptive therapy is indicated for elevated fracture risk based upon FRAX in the castration-sensitive setting. See PROS-B.
[ddd] The term "castration-sensitive" is used to define disease in patients who have not been treated with ADT and those who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-sensitive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of RT provided they have recovered testicular function.
[eee] ADT is strongly recommended in combination therapy for metastatic castration-sensitive disease. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy. If ADT monotherapy is given, intermittent ADT can be considered to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-G).
[fff] High-volume disease in this setting is defined based on CHAARTED criteria (the presence of visceral metastasis or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis).
[ggg] EBRT to the primary tumor is associated with an overall survival (OS) benefit in patients with low metastatic burden at the time of diagnosis of metastatic disease, which is defined by conventional imaging as either non-regional, lymph-node-only disease OR <4 bone metastases and without visceral/other metastasis (Ali A, et al. JAMA Oncol 2021;7:555-563). See Principles of Radiation Therapy (PROS-I).

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.

SYSTEMIC THERAPY FOR M0 CASTRATION-RESISTANT PROSTATE CANCER (CRPC)[hhh]



[c] Principles of Bone Health in Prostate Cancer (PROS-B).
[f] Principles of Imaging (PROS-E).
[h] Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (eg, CT, bone scan) at both initial staging and BCR, the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.
[y] For details on the efficacy and safety of these agents, see Principles of Androgen Deprivation Therapy (PROS-G).
[nn] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. CT, MRI, PSMA-PET/CT or PSMA-PET/MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. Alternatively, PSMA-PET/CT or PSMA-PET/MRI can be considered for bone and soft tissue (full body) imaging. See Principles of Imaging (PROS-E).
[rr] Monitoring should include physical exam, PSA every 3–6 mo, and imaging for symptoms or increasing PSA.
[hhh] CRPC is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, et al. J Clin Oncol 2008;26:1148-1159.

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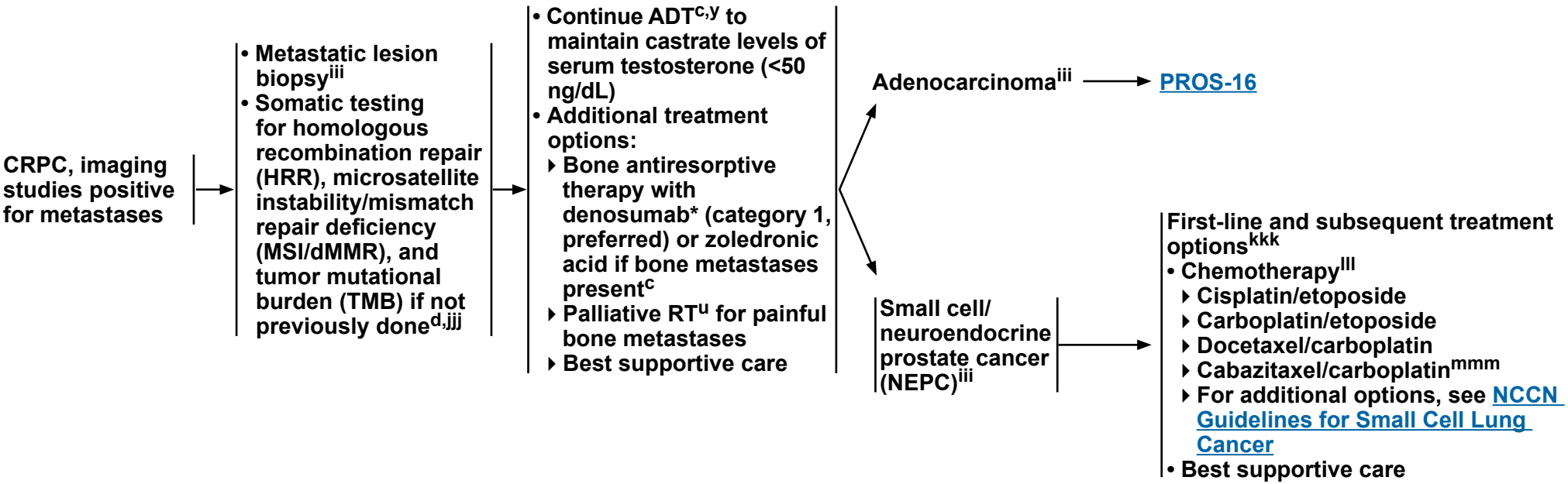
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC THERAPY FOR M1 CRPC[hhh]



[c] Principles of Bone Health in Prostate Cancer (PROS-B).
[d] Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[u] Principles of Radiation Therapy (PROS-I).
[y] For details on the use of ADT and other hormonal agents, including information on their efficacy and safety, see Principles of Androgen Deprivation Therapy (PROS-G).
[hhh] CRPC is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). Scher HI, et al. J Clin Oncol 2008;26:1148-1159.
[iii] Histologic evidence of both adenocarcinoma and small cell carcinoma may be present, in which case treatment can follow either pathway. Treat as adenocarcinoma if biopsy is not feasible or not performed.
[jjj] Germline testing for HRR mutations is recommended if not performed previously. See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[*] An FDA-approved biosimilar is an appropriate substitute.
[kkk] Document castrate levels of testosterone if progression occurs on ADT. Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT with contrast or abdominal/pelvic MRI with and without contrast. See Principles of Imaging (PROS-E) and Discussion.
[lll] For details on the efficacy and safety of these agents, see Principles of Non-Hormonal Systemic Therapy (PROS-L).
[mmm] Cabazitaxel 20 mg/m² plus carboplatin area under the curve [AUC] 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (ie, visceral metastases, low PSA and bulky disease, high lactate dehydrogenase [LDH], high carcinoembryonic antigen [CEA], lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of PTEN, *TP53*, and RB1). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.

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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.

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[nnn,ooo,ppp]

No prior docetaxel/no prior novel hormone therapy[qqq]	Progression on prior novel hormone therapy/no prior docetaxel[qqq]
• Preferred regimens ▸ Abiraterone[y,rrr] (category 1[sss]) ▸ Docetaxel[lll] (category 1) ▸ Enzalutamide[y] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation (category 1) ▸ Olaparib/abiraterone[y,lll,rrr,uuu] for *BRCA* mutation (category 1) ▸ Pembrolizumab for MSI-high (MSI-H)/dMMR[lll] (category 2B) ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[lll,www] (category 1) ▸ Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[y]	• Preferred regimens ▸ Docetaxel (category 1)[lll] ▸ Olaparib for *BRCA* mutation[yyy] (category 1) ▸ Rucaparib for *BRCA* mutation[zzz] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[lll,mmm] ▸ Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation (category 2B) ▸ Olaparib for HRR mutation other than *BRCA1/2*[yyy] ▸ Pembrolizumab for MSI-H/dMMR[lll] (category 2B) ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[lll,www] ▸ Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] (category 2B) • Other recommended regimens ▸ Other secondary hormone therapy[aaaa]
Progression on prior docetaxel/no prior novel hormone therapy[qqq]	**Progression on prior docetaxel and a novel hormone therapy[qqq]**
• Preferred regimens ▸ Abiraterone[y,rrr] (category 1) ▸ Cabazitaxel[lll] ▸ Enzalutamide[y] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[lll,mmm] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[lll] ▸ Niraparib/abiraterone[y,lll,ttt] for *BRCA* mutation ▸ Olaparib/abiraterone[y,lll,rrr,uuu] for *BRCA* mutation ▸ Pembrolizumab for MSI-H/dMMR[lll] (category 2B) ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[lll,www] ▸ Talazoparib/enzalutamide for HRR mutation[y,lll,xxx] • Other recommended regimens ▸ Other secondary hormone therapy[y]	• Preferred regimens ▸ Cabazitaxel[lll] (category 1) ▸ Docetaxel rechallenge[lll] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[lll,mmm] ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[bbbb] (category 1) ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[lll] ▸ Olaparib for HRR mutation[yyy] (category 1) ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[lll] ▸ Radium-223[u,vvv] for symptomatic bone metastases (category 1) ▸ Rucaparib for *BRCA* mutation[zzz] • Other recommended regimens ▸ Other secondary hormone therapy[aaaa]

Footnotes for Systemic Therapy M1 CRPC (PROS-16A)

Note: All recommendations are category 2A unless otherwise indicated.
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SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA
FOOTNOTES

[u] Principles of Radiation Therapy (PROS-I).

[y] For details on the use of ADT and other hormonal agents, including information on their efficacy and safety, see Principles of Androgen Deprivation Therapy (PROS-G).

[lll] For details on the efficacy and safety of these agents, see Principles of Non-Hormonal Systemic Therapy (PROS-L).

[mmm] Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant prostate cancer (ie, visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of *PTEN, TP53,* and RB1). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.

[nnn] Document castrate levels of testosterone if progression occurs on ADT. Workup for progression should include chest CT, bone imaging, and abdominal/pelvic CT with contrast or abdominal/pelvic MRI with and without contrast. Consider metastatic lesion biopsy. If small cell neuroendocrine is found, see PROS-15. See Principles of Imaging (PROS-E) and Discussion.

[ooo] Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases.

[ppp] Patients can continue through all treatment options listed. Best supportive care, which can include androgen-directed therapy or steroid, is always an appropriate option.

[qqq] Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior novel hormonal therapy.

[rrr] The fine-particle formulation of abiraterone can be used instead of the standard form (other recommended option).

[sss] The noted category applies only if there are no visceral metastases.

[ttt] Niraparib plus abiraterone (combination tablet) is a treatment option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet had treatment in the setting of mCRPC, depending on prior treatment in other disease settings (PROS-16). Use of niraparib/abiraterone for those who have received prior novel hormone therapy is controversial because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely. The fine-particle formulation of abiraterone can be given with single-agent niraparib as a substitute for the combination niraparib/abiraterone tablet (category 2B; other recommended option).

[uuu] Olaparib with abiraterone is an option for patients with a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received a novel hormone therapy and who have not yet had treatment in the setting of CRPC.

[vvv] Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT and should not be used in patients with visceral metastases. Concomitant use of denosumab or zoledronic acid is recommended. See Principles of Radiation Therapy (PROS-I).

[www] Sipuleucel-T is recommended only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 mo, and ECOG performance status 0–1. Benefit with sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. Sipuleucel-T also is not recommended for patients with small cell/NEPC.

[xxx] Talazoparib plus enzalutamide is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in an HRR gene (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2,* or RAD51C) who have not yet had treatment in the setting of CRPC, depending on prior treatment in other disease settings (PROS-16). There may be heterogeneity of response based on the specific gene mutation (Discussion). Use of talazoparib/enzalutamide for those who have received prior novel hormone therapy is controversial because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.

[yyy] Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a HRR gene (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* or *RAD54L*) who have been treated previously with androgen receptor-directed therapy. However, efficacy appears to be driven by the cohort of patients with at least one alteration in *BRCA2*, *BRCA1*, or *ATM*, and in particular by patients with *BRCA2* or BRCA1 mutations based on exploratory gene-by-gene analysis. There may be heterogeneity of response to olaparib for non-BRCA mutations based on the specific gene mutation (Discussion).

[zzz] Rucaparib is a treatment option for patients with mCRPC and a pathogenic BRCA1 or BRCA2 mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.

[aaaa] Other secondary hormone therapies include abiraterone, fine-particle abiraterone, and enzalutamide for patients with disease progression on prior novel hormone therapy. In addition, switching from prednisone or methylprednisolone to dexamethasone 1 mg/day can be considered for patients with disease progression on either formulation of abiraterone. Also see Principles of Androgen Deprivation Therapy (PROS-G).

[bbbb] Lu-177–PSMA-617 is a treatment option for patients with ≥1 PSMA-positive lesion and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with androgen receptor-directed therapy and a taxane-based chemotherapy. Sartor et al. N Engl J Med 2021; 385:1091-1103. See Principles of Radiation Therapy (PROS-I).

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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 patients but challenging for individuals.**
- **Life expectancy can be estimated using:**
  - **The Social Security Administration tables (www.ssa.gov/OACT/STATS/table4c6.html)**
  - **The WHO's Life Tables by country (http://apps.who.int/gho/data/view.main.60000?lang=en)**
  - **The Memorial Sloan Kettering Male Life Expectancy tool (https://www.mskcc.org/nomograms/prostate)**
- **If using a life expectancy table, life expectancy should 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**
- **Examples of upper, middle, and lower quartiles of life expectancy at selected ages are included in the NCCN Guidelines for Older Adult Oncology for life expectancy estimation.**

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PRINCIPLES OF BONE HEALTH IN PROSTATE CANCER

Treatment-Related Bone Loss

- ADT increases the risk of bone loss, and this risk is exacerbated with more potent androgen suppression, longer duration of therapy or delayed testosterone recovery, and concurrent prednisone use.
- The goal of osteoporosis screening is to identify patients at increased risk of sustaining a low-trauma fracture who would benefit from intervention to minimize the fracture risk. Risk assessment for treatment-related bone loss should take place for all patients initiating ADT of any duration. Fracture risk can be assessed using the Fracture Risk Assessment Tool (FRAX), the algorithm released by The University of Sheffield (https://frax.shef.ac.uk/FRAX/). FRAX was developed to estimate the 10-year probability of hip fracture or major osteoporotic fractures combined (hip, spine, shoulder, or wrist) for an untreated individual using easily obtainable clinical risk factors for fracture with or without information on bone mineral density. When utilizing the FRAX algorithm select YES for secondary osteoporosis for individuals with hypogonadism. ADT should be considered "secondary osteoporosis" when using the FRAX algorithm. A previous major osteoporotic fracture (hip fracture or spine fracture) is considered clinical osteoporosis and warrants bone antiresorptive drug therapy independent of bone mineral density.
- A baseline dual-energy x-ray absorptiometry (DEXA) scan should be obtained before starting ADT in patients at increased risk for fracture based on FRAX screening and being considered for antiresorptive therapy (see Table 1). For patients at low risk of fracture based on the FRAX risk assessment, baseline DEXA scan can be omitted. The exact FRAX fracture risk threshold has not been defined in this population. One approach is to set the threshold at 10-year risk of major osteoporotic fracture (calculated without DEXA) greater than that of a 65-year old white woman with no additional risk factors (defined as 8.4% in the United States).
- Treatment for osteoporosis is advised according to guidelines for the general population from the Bone Health and Osteoporosis Foundation.[1] These guidelines (see Table 1) include recommendations for: 1) calcium (1000–1200 mg daily from food, with supplements if intake is insufficient), 2) vitamin D3 (serum levels of 30 to 50 ng/mL with supplements prescribed if needed); and 3) pharmacologic treatment for men aged ≥50 years with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck or total hip by DEXA scan with a 10-year probability of hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20% based on FRAX screening (see Table 2).
- Antiresorptive medications which increase bone mineral density and reduce disease-related skeletal complications during ADT for prostate cancer include denosumab[a] (60 mg subcutaneously [SQ] every 6 months), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly) (see Table 2). Treatment with either denosumab[a], zoledronic acid, or alendronate sodium is recommended when the absolute fracture risk warrants drug therapy.
  - Choice of agent may depend on underlying comorbidities, whether the patient has been treated with zoledronic acid previously, logistics, and/or cost considerations.
  - Bisphosphonates (zoledronic acid or alendronate) can cause side effects of acute phase reaction, joint pain, hypocalcemia, osteonecrosis of the jaw, nephrotoxicity with need for dose modification for renal insufficiency, ocular toxicities, and atypical femoral fractures with prolonged use (>3–5 years).
  - Denosumab can cause side effects of hypocalcemia, osteonecrosis of the jaw, and atypical femoral fractures with prolonged use. The risk factors for denosumab-associated hypocalcemia include blastic bone metastases, renal impairment, vitamin D deficiency, the lack of prophylactic supplementation of calcium and/or vitamin D, preexisting hypoparathyroidism, hypomagnesemia, and gastric bypass. Although renal monitoring is not required, denosumab is not recommended in patients with a creatinine clearance <30 mL/min given risk of severe hypocalcemia. Calcium, creatinine, and vitamin D levels should be checked prior to initiating therapy. Periodic monitoring of serum calcium levels is recommended with denosumab use. Stopping denosumab therapy can result in rebound bone loss and fractures; therefore it is recommended to administer at least one dose of a potent bisphosphonate (zoledronic acid 4 or 5 mg) to prevent rebound bone loss and presumably rebound fracture.[2]

[a] An FDA-approved biosimilar is an appropriate substitute.

References (PROS-B 4 of 4)

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

PRINCIPLES OF BONE HEALTH IN PROSTATE CANCER

Treatment-Related Bone Loss Continued

- **The risk of osteonecrosis of the jaw is increased in patients who have tooth extractions, poor dental hygiene, or a dental appliance. To prevent osteonecrosis of the jaw, it is recommended that all patients have a comprehensive dental evaluation prior to initiating an osteoclast inhibitor.[3] 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). Stopping denosumab represents a dilemma is this context, and the clinician must carefully weigh the risk of rebound spine fractures versus the risk of osteonecrosis of the jaw.**

- **Annual assessment of fracture risk using the FRAX risk assessment tool is recommended for all patients on ADT or those who remain hypogonadal after completion of ADT (see Table 1). Depending on the fracture risk and prior DEXA scan results, repeat DEXA scan in 1 to 2 years is recommended for those patients on ADT. For individuals initiated on antiresorptive therapy, a follow-up DEXA scan after 1 year of treatment is recommended by the International Society for Clinical Densitometry, although there is no consensus on the optimal approach to monitoring the effectiveness of bone treatment. Use of biochemical markers of bone turnover to monitor response to therapy is not recommended. There are currently no guidelines on how often to monitor vitamin D levels.**
- **For patients receiving antiresorptive therapy, there are currently no consensus guidelines on duration of treatment. Due to concerns of long-term risks of antiresorptive therapy, a "drug holiday" at 3 to 5 years can be considered based on agent utilized, stability of bone mineral density, prior fracture history, and future fracture risk. Bone mineral density should be monitored approximately every 1 to 2 years after suspending therapy, and therapy should generally be resumed if bone mineral density declines significantly or if the patient develops a new fragility fracture.**

Table 1: Risk Assessment and Monitoring

Clinical Scenario	Recommendation
Baseline at ADT initiation	DEXA recommended for most patients. In select individuals at low probably of fracture based on FRAX risk assessment tool, DEXA can be omitted
On ADT	DEXA every 1–2 years, dependent on FRAX risk assessment tool
On antiresorptive therapy	DEXA at 1 year

References (PROS-B 4 of 4)

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Continued

PRINCIPLES OF BONE HEALTH IN PROSTATE CANCER

Prevention of Symptomatic Skeletal-Related Events (SREs) in Patients with Bone-Metastatic CRPC

- **In patients 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 SREs in patients with mCRPC, albeit with numerically higher hypocalcemia and osteonecrosis of the jaw risks. Initial studies investigated zoledronic acid and denosumab administered every 4 weeks. Subsequent studies demonstrated that every-12-week dosing of zoledronic acid compared to every-4-week dosing did not increase the risk of skeletal events.[4,5] Every-12-week dosing of zoledronic acid is recommended for symptomatic SRE reduction when indicated. Every-12-week dosing of denosumab is under investigation and current data suggest non-inferior symptomatic skeletal events compared to every-4-week dosing.[5] Utilization of zoledronic acid and denosumab for symptomatic SRE reduction requires consideration of degree of benefit and risk associated with therapy to optimize use, dose, and schedule. It is important to recognize that testing of zoledronic acid and denosumab in bone-metastatic CRPC was conducted during an era when treatment options for mCRPC were largely limited to docetaxel chemotherapy. Subsequent studies investigating abiraterone, enzalutamide, cabazitaxel, radium-223, and Lu-177–PSMA-617 have demonstrated improvement of SREs with treatment. While radium-223 did improve symptomatic SREs in patients with bone mCRPC, the combination of radium-223 with abiraterone was associated with increased frequency of bone fractures, particularly in individuals not receiving an antiresorptive agent.[6]**
- **A phase 3 clinical trial that assessed the role for zoledronic acid in patients with castration-sensitive disease beginning ADT for bone metastases was negative.[7] Therefore, use of osteoclast inhibitors for reduction of symptomatic SREs in metastatic castration-sensitive disease with bone metastases is not recommended. However, usage of these agents to prevent bone loss and fragility fractures at appropriate doses and dosing intervals should be utilized when clinically appropriate in this context (see Treatment-Related Bone Loss, PROS-B 1 of 4).**

Table 2: Optimization of Bone Health in Patients with Prostate Cancer

Patient Population	Category	Intervention
All patients receiving ADT	Lifestyle modifications	• Weight-bearing exercises (30 minutes per day), balance training, safe movement strategies • Limit alcohol consumption • Smoking cessation
	Calcium and vitamin D supplementation	• Calcium 1000–1200 mg daily from food with supplements if needed • Maintain serum vitamin D3 levels of 30 to 50 ng/mL with supplements if needed
For treatment-related bone loss in patients receiving ADT	Antiresorptive agents	• Alendronate 70 mg PO weekly • Denosumab[a] 60 mg SQ every 6 months • Zoledronic acid 5 mg IV annually
For prevention of symptomatic SREs in patients with bone-metastatic CRPC	Antiresorptive agents	• Denosumab[a] 120 mg SQ every 4 weeks • Zoledronic acid 4 mg IV every 12 weeks

[a] An FDA-approved biosimilar is an appropriate substitute.

References (PROS-B 4 of 4)

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Continued

PRINCIPLES OF BONE HEALTH IN PROSTATE CANCER
REFERENCES

[1] LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2022;33:2049-2102.
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[3] Yarom N, Shapiro CL, Peterson DE, et al. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO Clinical practice guideline. J Clin Oncol 2019;37:2270-2290.
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[6] Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:408-419.
[7] Smith MR, Halabi S, Ryan CJ, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). J Clin Oncol 2014;32:1143-1150.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

GERMLINE TESTING

For details regarding the nuances of genetic counseling and testing, see Principles of Cancer Risk Assessment and Counseling (EVAL-A) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

- **Pre-test Considerations**
  - **The panel recommends inquiring about family and personal history of cancer, and known germline variants at time of initial diagnosis. Criteria for germline testing (see CRIT-6 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and LS-1 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal) should be reviewed at time of initial diagnosis and, if relevant, at recurrence.**
  - **Germline testing should be considered in appropriate individuals where it is likely to impact the prostate cancer treatment and clinical trial options, management of risk of other cancers, and/or potential risk of cancer in family members.**
- **Testing**
  - **If criteria are met, germline multigene testing that includes at least *BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6,* and *PMS2* is recommended.**

- **Post-test Considerations**
  - **Post-test genetic counseling is strongly recommended if a germline mutation (pathogenic/likely pathogenic variant) is identified. Cascade testing for relatives is critical to inform the risk for familial cancers in all relatives.**
  - **Post-test genetic counseling is recommended if positive family history but no pathogenic variant OR if only germline variants of uncertain significance (VUS) are identified. This is to ensure accurate understanding of family implications and review indications for additional testing and/or follow-up (including clinical trials of reclassification).**
  - **Resources are available to review the available data supporting pathogenic consequences of specific variants (eg, https://www.ncbi.nlm.nih.gov/clinvar/; https://brcaexchange.org/about/app).**
  - **Individuals should be counseled to inform providers of any updates to family cancer history.**

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PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

SOMATIC TUMOR TESTING

- **Pre-test Considerations**
  - **At present, tumor molecular and biomarker analysis may be used for treatment decision-making, including understanding eligibility for biomarker-directed treatments, genetic counseling, early use of platinum chemotherapy, and eligibility for clinical trials. Clinical trials may include established and/or candidate molecular biomarkers for eligibility.**
  - **Tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making.**
  - **Patients should be informed that tumor molecular analysis by DNA sequencing has the potential to uncover germline findings. Confirmatory germline testing may be recommended [see Post-test Considerations (below) and Tumor Testing: Potential Implications for Germline Testing in the Principles of Cancer Risk Assessment and Counseling (EVAL-A) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic].**
- **Testing**
  - **Somatic testing for alterations in DNA damage response:**
    - **Multigene tumor testing for alterations in HRR genes, including but not limited to *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*, and *CDK12*, is recommended in patients with metastatic prostate cancer. This testing can be considered in patients with regional prostate cancer.**
    - **Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC and may be considered in patients with regional or castration-sensitive metastatic prostate cancer.**
    - **TMB testing may be considered in patients with mCRPC.**
- **Tumor Specimen and Assay Considerations**
  - **The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. This could include lymph node biopsy for patients with N1 disease. When unsafe or unfeasible, plasma circulating tumor (ctDNA) assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield.**
  - **Caution is needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP), which can result in a false-positive biomarker signal.**
  - **DNA analysis for MSI and immunohistochemistry for mismatch repair (MMR) are different assays measuring different biological effects caused by dMMR function. If MSI is used, testing using a next-generation sequencing assay validated for prostate cancer is preferred.**
- **Post-test Considerations**
  - **Post-test genetic counseling is recommended if pathogenic/likely pathogenic variant (mutation) identified in any gene that has clinical implications if also identified in germline (eg, *BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, PMS2*).**
  - **Post-test genetic counseling to assess for the possibility of Lynch syndrome is recommended if MSI-H or dMMR is found.**

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PRINCIPLES OF QUALITY-OF-LIFE AND SHARED DECISION-MAKING

- **Treatments for patients with localized prostate cancer have risks and side effects that must be considered in the context of the risk posed by the disease.[1-4]**
- **Baseline urinary, sexual, and bowel function are strongly associated with functional outcomes among patients undergoing treatment.[1-4]**
- **Thus, it is important to measure baseline disease-specific function (urinary, sexual, and bowel function), preferably using a standardized patient-reported outcomes instrument (eg, EPIC-26[5]).**
- **Shared decision-making regarding initial management of localized prostate cancer should include an explanation of the potential benefits and potential harms of each option. The provider should explain the likelihood of cure, recurrence, disease progression, and disease-specific mortality with each management option, taking into account disease severity and competing risks. In addition to the primary intended effects of treatment, the clinician should discuss the side effects of each treatment and predicted impact on quality of life, including urinary, sexual, and bowel function. Patient preferences should be elicited and should be incorporated into the disease management decision.[6]**

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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 disease management.
- Imaging techniques can evaluate anatomic or functional parameters.
  - Anatomic imaging techniques include ultrasound, CT, and MRI.
  - Functional imaging techniques include radionuclide bone scan, PET/CT, and advanced MRI techniques, such as spectroscopy and diffusion-weighted imaging (DWI).

Efficacy of Imaging

- The utility of imaging for patients with early PSA persistence/recurrence after RP depends on risk group prior to operation, pathologic Gleason grade and stage, PSA, and 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 patients with PSA <10 ng/mL. The relative risk for bone metastasis or death increases as PSADT shortens. Bone imaging should be performed more frequently when PSADT ≤8 months, 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 to guide prostate bed biopsy.
- Advanced ultrasound techniques for imaging of the prostate and for differentiation between prostate cancer and prostatitis are under evaluation.

Bone Imaging

- 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.
- Bone imaging is indicated in the initial evaluation of patients at high risk for skeletal metastases.
- Bone imaging can be considered for the evaluation of the patient post-prostatectomy when PSA does not 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 imaging 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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Continued

PRINCIPLES OF IMAGING

- 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 pretreatment 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 phenomena may exist with other imaging modalities, such as CT or PET/CT imaging.
- Bone scans and soft tissue imaging (CT or MRI) in patients with metastatic or non-metastatic 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.
- PET imaging for detection of bone metastatic disease
  - CT, MRI, or PET/CT or PET/MRI with F-18 piflufolastat prostate-specific membrane antigen (PSMA), Ga-68 PSMA-11, F-18 flotufolastat PSMA, F-18 sodium fluoride, C-11 choline, or F-18 fluciclovine can be considered for equivocal results on initial bone scan.
  - Ga-68 PSMA-11, F-18 piflufolastat PSMA, or F-18 flotufolastat PSMA PET/CT or PET/MRI (full body imaging) can be considered as an alternative to bone scan.

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 IV contrast, and CT technique should be optimized to maximize diagnostic utility while minimizing radiation dose.
- CT can be used for examination of the pelvis and/or abdomen for initial evaluation (PROS-2) and as part of workup for recurrence or progression (see PROS-11 through PROS-16).

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 IV contrast material.
  - Resolution of MRI images in the pelvis can be augmented using an endorectal coil.
- Standard MRI techniques can be used for examination of the pelvis and/or abdomen for initial evaluation (PROS-2) and as part of workup for recurrence or progression (see PROS-11 through PROS-16).
- MRI may be considered in patients after RP when PSA does not fall to undetectable levels or when an undetectable PSA becomes detectable and increases on 2 or more subsequent determinations, or after RT for increasing PSA or positive DRE if the patient is a candidate for additional local therapy. MRI-ultrasound fusion biopsy may improve the detection of higher grade (Grade Group ≥2) 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 patients who are considering active surveillance. Additionally, mpMRI may detect large and poorly differentiated prostate cancer (Grade Group ≥2) and detect extracapsular extension (T staging) and is preferred over CT for abdominal/pelvic staging. mpMRI has been shown to be equivalent to CT scan for pelvic lymph node evaluation.

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Continued

PRINCIPLES OF IMAGING

Positron Emission Tomography

- PSMA-PET refers to a growing body of radiopharmaceuticals that target PSMA on the surface of prostate cells. There are multiple PSMA radiopharmaceuticals at various stages of investigation. At this time, the NCCN Guidelines only recommend the currently FDA-approved PSMA agents: F-18 piflufolastat PSMA (also known as F-18 DCFPyL), F-18 flotufolastat PSMA (also known as rh-PSMA-7.3), and Ga-68 PSMA-11. Throughout these Guidelines, "PSMA-PET" refers to any of these FDA-approved PSMA ligands. See Table 2 in the Discussion section for more details.
- PSMA-PET/CT or PET/MRI can be considered as an alternative to standard imaging of bone and soft tissue for initial staging, the detection of biochemically recurrent disease, and as workup for progression.
- Synthesis of Ga-68 PSMA-11 requires that the PSMA-11 ligand is labeled with Ga-68 from a generator or cyclotron. Two commercial kits to perform this in nuclear pharmacies have been approved by the FDA.
- C-11 choline or F-18 fluciclovine PET/CT or PET/MRI may be used to detect small-volume recurrent disease in soft tissues and in bone.
- Studies suggest that PSMA-PET imaging have a higher sensitivity than C-11 choline or F-18 fluciclovine PET imaging, especially at very low PSA levels.
- Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (eg, CT, bone scan) at both initial staging and biochemical recurrence (BCR), the panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective frontline imaging tool for these patients.
- Histologic or radiographic confirmation of involvement detected by PET imaging is recommended whenever feasible due to the presence of false positives. Although false positives exist, literature suggests that these are outweighed by the increase in true positives detected by PET relative to conventional imaging. To reduce the false-positive rate, physicians should consider the intensity of PSMA-PET uptake and correlative CT findings in the interpretation of scans. Several reporting sytems have been proposed but will not have been validated or widely used.
- PSMA imaging should be done before initiation of ADT because ADT may affect detection sensitivity.
- High variability among PET/CT or PET/MRI equipment, protocols, interpretation, and institutions provides challenges for application and interpretation of the utility of PET/CT or PET/MRI.
- Table 2 in the Discussion section provides a summary of the main PET/CT or PET/MRI imaging tracers utilized for study in prostate cancer both before definitive therapy and at recurrence.
- PET/CT or PET/MRI results may change treatment but may not change oncologic outcome.
- When patients with the worst prognosis move from one risk group to the higher risk group, the average outcome of both risk groups will improve even if treatment has no impact on disease. This phenomenon is known as the Will Rogers effect, in which the improved outcomes of both groups could be falsely attributed to improvement in treatment, but would be due only to improved risk group assignment. As an example, F-18 sodium fluoride PET/CT may categorize some patients as M1b who would have been categorized previously as M0 using a bone scan (stage migration). Absent any change in the effectiveness of therapy, the overall survival (OS) of both M1b and M0 groups would improve. The definition of M0 and M1 disease for randomized clinical trials that added docetaxel or abiraterone to ADT was based on CT and conventional radionuclide bone scans. Results suggest that OS of M1 disease is improved, whereas progression-free but not OS of M0 disease is improved. Therefore, a subset of patients now diagnosed with M1 disease using F-18 sodium fluoride PET/CT might not benefit from the more intensive therapy used in these trials and could achieve equivalent OS from less intensive therapy aimed at M0 disease. Carefully designed clinical trials using proper staging will be necessary to prove therapeutic benefit, rather than making assumptions compromised by stage migration.

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Continued

PRINCIPLES OF IMAGING

Positron Emission Tomography (continued)

- **Fluorodeoxyglucose (FDG) PET/CT should not be used routinely for staging prostate cancer since data are limited in patients with prostate cancer.**
- **F-18 flotufolastat PSMA is a PET imaging agent that is part of a class of tracers referred to as radiohybrid (rh) ligands. These tracers have two binding sites for radionuclides (ie, F-18 or Ga-68). The significance of this remains to be determined.**
- **The increasing use of PSMA-PET has identified the potential for considerable biological diversity among disease foci within a given individual with prostate cancer, especially mCRPC, and that this heterogeneity can be detected with a combination of PSMA-PET and FDG-PET. Initial data suggest that metastases with PSMA-negative/FDG-positive mismatches may exist in patients with mCRPC undergoing Lu-PSMA radioligand therapy and that patients with these mismatches may have worse outcomes. Currently, no robust clinical trial data exist to support the incorporation of FDG-PET into routine clinical use alongside PSMA-PET. To overcome the limitations of PSMA-PET in PSMA-negative metastatic disease, the panel currently recommends the use of contrast-enhanced CT or MRI in these patients, as the non-contrast CT component of PSMA-PET/CT is insufficient to detect disease.**

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PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **The NCCN Prostate Cancer Panel and the NCCN Prostate Cancer Early Detection Panel (NCCN Guidelines for Prostate Cancer Early Detection) remain concerned about overdiagnosis and overtreatment of prostate cancer. The Prostate Cancer Panel recommends that patients and their physicians carefully consider active surveillance based on the patient's prostate cancer risk profile and estimated life expectancy. In settings where the patient's age and comorbidities suggest a shorter life expectancy, observation may be more appropriate. Shared decision-making, after appropriate counseling on the risks and benefits of the various options, is critical.**

ACTIVE SURVEILLANCE[1]

- **Active surveillance involves actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses.**

- **Life Expectancy:**
  - **Life expectancy is a key determinant for the choice between observation, active surveillance, and definitive treatment.**
  - **Consider incorporating a validated metric of comorbidity such as the Adult Comorbidity Evaluation-27 Index (ACE-27)[2] to differentiate between recommendations for observation versus active surveillance. Prior studies did not incorporate a validated metric of comorbidity to estimate life expectancy (Table 1 on PROS-F 4 of 5), which is a potential limitation when interpreting the data for a patient who is in excellent health.**
  - **Life expectancy can be challenging to estimate for individual patients (Principles of Life Expectancy Estimation, PROS-A).**

- **Candidacy for Active Surveillance:**
  - **Active surveillance is preferred for patients with very-low-risk prostate cancer (Risk Group Criteria [PROS-2]) and a life expectancy ≥10 years. (Observation is preferred for patients with a life expectancy <10 years and very-low-risk disease.)**
  - **Active surveillance is preferred for most patients with low-risk prostate cancer (Risk Group Criteria [PROS-2]) and a life expectancy ≥10 years. The panel recognizes that there is heterogeneity across this risk group, and that some factors may be associated with an increased probability of near-term grade reclassification including high PSA density, a high number of positive cores (eg, ≥3), and high genomic risk (from tissue-based molecular tumor analysis).[3] For some of these patients, upfront treatment with RP or prostate RT may be preferred based on shared decision-making.**
  - **Patients with favorable intermediate-risk prostate cancer (Risk Group Criteria [PROS-2]) and a life expectancy >10 years may also consider active surveillance. Particular consideration for active surveillance may be appropriate for those patients with a low percentage of Gleason pattern 4 cancer, low tumor volume, low PSA density, and/or low genomic risk (from tissue-based molecular tumor analysis). See Discussion.**
  - **Please see Table 1 (PROS-F 4 of 5) for a summary of major active surveillance cohorts, including their inclusion criteria.**

References on PROS-F 5 of 5

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Continued

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **Confirmatory Testing to Establish Appropriateness of Active Surveillance:**
  - **Goals of confirmatory testing are to help facilitate early identification of those patients who may be at a higher risk of future grade reclassification or cancer progression.**
  - **Since an initial prostate biopsy may underestimate tumor grade or volume, confirmatory testing is strongly recommended within the first 6 to 12 months of diagnosis for patients who are considering active surveillance.**
  - **Options for confirmatory testing include prostate biopsy, mpMRI with calculation of PSA density (and repeat biopsy as indicated), and/or molecular tumor analysis. See Principles of Risk Stratification (PROS-H). Other forms of imaging are discouraged.**
  - **Early confirmatory testing may not be necessary in patients who have had an mpMRI prior to diagnostic biopsy.**
  - **All patients should undergo a confirmatory prostate biopsy within 1–2 years of their diagnostic biopsy.**

- **Active Surveillance Program:**
  - **Patients who choose active surveillance should have regular follow-up, and key principles include:**
    - ◊ **PSA no more often than every 6 months unless clinically indicated.**
    - ◊ **DRE no more often than every 12 months unless clinically indicated.**
    - ◊ **Repeat prostate biopsy no more often than every 12 months unless clinically indicated. While the intensity of surveillance may be tailored based on patient and tumor factors (eg, grade, tumor volume), most patients should have prostate biopsies every 2 to 5 years as part of their monitoring.**
    - ◊ **Consider repeat mpMRI no more often than every 12 months unless clinically indicated.**
    - ◊ **In patients with a suspicious lesion on mpMRI, MRI-ultrasound fusion biopsy improves the detection of higher grade (Grade Group ≥2) cancers.**
    - ◊ **Patients should be transitioned to observation when life expectancy is <10 years.**
    - ◊ **Repeat molecular tumor analysis is discouraged.**
    - ◊ **The intensity of surveillance may be tailored based on patient life expectancy and risk of reclassification.**
    - ◊ **A metastatic staging evaluation (PSMA PET, bone scan, CT scan, or whole body MRI) should not be performed.**

- **Considerations for Treatment of Patients on Active Surveillance:**
  - **Grade reclassification on repeat biopsy is the most common factor influencing a change from active surveillance to treatment.**
  - **Other factors affecting decisions to actively treat include: increase in tumor volume, a rise in PSA density, and patient anxiety.**
  - **Considerations for a change in disease management strategy should be made in the context of the patient's life expectancy.**

References on PROS-F 5 of 5

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Continued

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **Advantages of Active Surveillance:**
  - **Between 50% and 68% of those eligible for active surveillance may safely avoid treatment for at least 10 years.[4-6]**
  - **Patients will avoid possible side effects of definitive therapy that may be unnecessary while on active surveillance.**
  - **Quality of life/normal activities will be less affected while on active surveillance.**
  - **Risk of unnecessary treatment of small, indolent cancers will be reduced.**

- **Limitations of Active Surveillance:**
  - **Between 32% and 50% of patients will undergo treatment by 10 years,[4-6] although treatment delays do not seem to impact cure rate.**
  - **Although the risk is very low (<0.5% in most series), it is possible for a cancer to progress to a regional or metastatic stage.[4-6]**

OBSERVATION

- **Observation involves monitoring with a history and physical exam no more often than every 12 months (without surveillance biopsies) until symptoms develop or are thought to be imminent.**
- **Observation is recommended for:**
  - **Asymptomatic patients in very-low-, low-, and intermediate-risk groups with life a expectancy ≤5 years.**
  - **Asymptomatic patients with very-low- and low-risk prostate cancer with a life expectancy 5–10 years.**
- **Observation is preferred for:**
  - **Asymptomatic patients with favorable and unfavorable intermediate-risk prostate cancer and a life expectancy between 5–10 years.**
- **Observation may be considered for:**
  - **Asymptomatic patients with high-risk, very-high-risk, regional, and metastatic prostate cancer and a life expectancy ≤5 years.**
- **Life expectancy can be challenging to estimate for individual patients (Principles of Life Expectancy Estimation, PROS-A). Consider incorporating a validated metric of comorbidity (see Life Expectancy, PROS-F 1 of 5).**
- **If patients under observation become symptomatic, an assessment of disease burden can be performed, and treatment or palliation can be considered (PROS-13).**

- **Advantages of Observation:**
  - **Patients will avoid possible side effects of unnecessary confirmatory testing and definitive therapy.**

- **Limitation of Observation:**
  - **There may be a risk of local or systemic symptoms (eg, urinary retention, pathologic fracture), without prior symptoms or concerning PSA levels.**

References on PROS-F 5 of 5

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Continued

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

Table 1: Selected Active Surveillace Experiences with Large Patient Cohorts

Cohort	Toronto[5,7,8]	Johns Hopkins[4,9-11]	UCSF		Canary PASS[14]	Cooley/Catalona Meta-Dataset[6]	PRIAS[15]
			Initial Cohort[12]	Newer Cohort[13]			
No. patients	993	1298	321	810	905	6775	5302
Median age (y)	68	66	63	62	63	64	66
Core involvement	% of cohort with ≤2 positive cores, 69 25% IR (D'Amico criteria)	Median # positive cores, 1	Mean % positive cores, 20.3%	Not available	% of cohort with ≤10% positive cores, 53 13% NCCN IR/HR	% of cohort with ≤2 positive cores, 77.6	% of cohort with ≤2 positive cores, 99
Median follow-up (months)	77	60	43	60	28	80	120
Conversion to treatment*	36.5% (10-y)	50% (10-y)	24% (3-y)	40% (5-y)	19% (28-mo)	33% (6.7-y)	52% (5-y) 73% (10-y)
Systemic progression Lymph node involvement and/or metastasis	3.1% (1.8% distant metastases; 1.3% positive lymph nodes) 6.6% systemic progression in IR group	0.15% distant metastases 0.08% positive lymph nodes	0% distant metastases 0.2% positive lymph nodes	0.1%	0% distant metastases 0.2% positive lymph nodes	0.4%	0.2%
Cancer-specific survival	98% (10-y)	99.9% (10-y)	100% (5-y)	100% (5-y)	100% (28-m)	99.8% (6.7-y)	>99% (10-y)
Overall survival	80% (10-y)	93% (10-y)	98% (10-y)	98% (5-y)	—	—	—
*Reason for conversion to treatment (% of entire cohort)							
Gleason grade change	9.5%	15.1%	38%	—	—	49%	34% (5-y) / 41% (20-y)[a]
PSA increase	11.7%	—	26%	—	—	8.5%	—
Tumor volume increase	—	—	—	—	—	7.2%	—
Personal choice	-1.6%	8%	8%	—	—	5% (anxiety)	5%

IR = intermediate risk; HR = high risk.

[a] Protocol-based reclassification (included change in Gleason grade, number of positive cores, or cT stage).

References on PROS-F 5 of 5

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Continued

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION
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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Clinically Localized (N0,M0) 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 unless there is a contraindication to definitive local therapy such as life expectancy ≤5 years and comorbidities. Under those circumstances, ADT may be used [see ADT for Patients on Observation Who Require Treatment and Those with Life Expectancy ≤5 Years (PROS-G, 5 of 5)].
- Giving ADT before, during, and/or after radiation (neoadjuvant, concurrent, and/or adjuvant ADT) prolongs survival in selected patients treated with radiation. For short-term ADT with prostate-only RT, concurrent/adjuvant ADT is preferred over neoadjuvant ADT. Options are:
  - Luteinizing hormone-releasing hormone (LHRH) agonist alone
    - ◊ Goserelin, leuprolide, or triptorelin
  - LHRH agonist (as above) plus first-generation antiandrogen
    - ◊ Nilutamide, flutamide, or bicalutamide
  - LHRH antagonist
    - ◊ Degarelix or relugolix
  - LHRH agonist or antagonist with abiraterone (very high risk only)
- For additional details on the use of RT with ADT by risk group, see PROS-I.
- Studies of short-term (4–6 mo) and long-term (2–3 y) neoadjuvant, concurrent, and/or adjuvant ADT all have used combined androgen blockade. Whether the addition of an antiandrogen is necessary requires further study.
- The largest randomized trial to date using the antiandrogen bicalutamide alone at high dose (150 mg) showed a delay in recurrence of disease but no improvement in survival; however, longer follow-up is needed.
- Abiraterone can be added to EBRT and 2 years of ADT in patients with very-high-risk prostate cancer. In the STAMPEDE trial, the hazard ratios for OS with the addition of abiraterone to EBRT and ADT in patients with node-negative disease was 0.69 (95% CI, 0.49–0.96). Severe hypertension or cardiac disorders were noted in 10% of patients in the abiraterone arm and grade 3–5 liver toxicity was noted in 7%.
  - Abiraterone should be given with concurrent steroid:
    - ◊ Prednisone 5 mg PO once daily for the standard formulation
    - ◊ Methylprednisolone 4 mg PO twice daily for the fine-particle formulation (category 2B)

ADT for Regional (N1,M0) Disease

- Patients with N1,M0 prostate cancer and a life expectancy >5 years or who are symptomatic can be treated with:
  - EBRT and neoadjuvant, concurrent, and/or adjuvant ADT as for patients with N0,M0 disease (see above) without abiraterone
  - EBRT and neoadjuvant, concurrent, and/or adjuvant LHRH agonist or antagonist with abiraterone
  - ADT alone or with abiraterone (see below)
- Abiraterone should be given with concurrent steroid:
  - Prednisone 5 mg PO once daily for the standard formulation
  - Methylprednisolone 4 mg PO twice daily for the fine-particle formulation (category 2B)
  - Abiraterone with ADT should be considered for a total of 2 years for those patients with N1 disease who are treated with radiation to the prostate and pelvic nodes.
- Options for ADT are:
  - Orchiectomy
  - LHRH agonist alone
    - ◊ Goserelin, leuprolide, or triptorelin
  - LHRH agonist (as above) plus first-generation antiandrogen
    - ◊ Nilutamide, flutamide, or bicalutamide
  - LHRH antagonist
    - ◊ Degarelix or relugolix
  - Orchiectomy plus abiraterone
  - LHRH agonist (as above) plus abiraterone
  - LHRH antagonist plus abiraterone
- The use of ADT plus abiraterone in patients with N1 M0 prostate cancer is based on the STAMPEDE trial, which demonstrated improved OS of the combination compared with ADT alone.
- Patients with regional disease and life expectancy ≤5 years who chose ADT can receive LHRH agonist, LHRH antagonist, or orchiectomy.

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Continued

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for pN1 Disease

- In one randomized trial, immediate and continuous use of ADT in patients with positive nodes following RP resulted in significantly improved OS compared to patients who received delayed ADT. Therefore, such patients should be considered for immediate LHRH agonist, LHRH antagonist, or orchiectomy. EBRT may be added (category 2B), in which case the ADT options are as for neoadjuvant, concurrent, and/or adjuvant ADT for clinically localized disease (see above). Many of the side effects of continuous ADT are cumulative over time on ADT.

ADT for M0 PSA Persistence/Recurrence After RP or RT (ADT for M0 Castration-Sensitive Disease)

- The timing of ADT for patients whose only evidence of cancer after definitive treatment is an increasing 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 secondary therapy after PSA persistence/recurrence. See PROS-10 and PROS-11.
- Patients with prolonged PSADTs (>12 months) and who are older are candidates for observation.
- Patients 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 patients with Grade Group 4 or 5 prostate cancer in the continuous arm had a median OS that was 14 months longer (8 years) than those in the intermittent arm (6.8 years).
- ADT options are:
  - M0 RP PSA persistence/recurrence:
    - ◊ EBRT +/- neoadjuvant, concurrent, and/or adjuvant ADT [see ADT for Clinically Localized (N0,M0) Disease, see PROS-G 1 of 5]
    - ◊ EBRT + LHRH agonist or antagonist with abiraterone (studies positive for pelvic nodal recurrence only)
  - M0 RT recurrence:
    - ◊ Orchiectomy
    - ◊ LHRH agonist alone
      - – Goserelin, leuprolide, or triptorelin
    - ◊ LHRH agonist (as above) plus first-generation antiandrogen
      - – Nilutamide, flutamide, or bicalutamide
    - ◊ LHRH antagonist
      - – Degarelix or relugolix
    - ◊ Orchiectomy, LHRH agonist (as above), or LHRH antagonist plus abiraterone (studies positive for pelvic nodal recurrence only)
  - Abiraterone should be given with concurrent steroid [see ADT for Regional (N1,M0) Disease, see PROS-G 1 of 5].

ADT for M0 Castration-Sensitive Disease After Maximal Pelvic Therapy

- Monitoring until diagnosis of metastatic disease is preferred for patients with non-metastatic castration-sensitive disease who are not candidates for pelvic therapy.
- PSADT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease.
- ADT monotherapy is an option for these patients, and intermittent ADT can be considered to reduce toxicity.
  - Options for ADT are the same as listed above for M0 RT recurrence.
- Enzalutamide with or without leuprolide is an option for patients who have the following high-risk criteria: M0 by conventional imaging; PSADT ≤9 months; PSA ≥2 ng/mL above nadir after RT or ≥1 ng/mL after RP with or without postoperative RT; and not considered a candidate for pelvic-directed therapy. In the EMBARK trial, metastasis-free survival (MFS) was improved in participants treated with enzalutamide plus leuprolide or with enzalutamide monotherapy compared with leuprolide alone. The most common adverse events associated with combination therapy and enzalutamide monotherapy were hot flashes and fatigue. Enzalutamide monotherapy was also significantly associated with gynecomastia (45% compared with 8% to 9% in the combination and leuprolide alone groups), nipple pain (15% compared with 1%–3%), and breast tenderness (14% compared with 1%).

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Continued

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Metastatic Castration-Sensitive Disease

- ADT with treatment intensification is strongly recommended for most patients with metastatic prostate cancer. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy. If ADT monotherapy is given, intermittent ADT can be considered to reduce toxicity.
- Treatment options for patients with M1 castration-sensitive disease are:
  - ADT alone (orchiectomy, LHRH agonist, LHRH agonist plus first-generation antiandrogen, or LHRH antagonist)
    - ◊ LHRH agonists: Goserelin, leuprolide, or triptorelin
    - ◊ First-generation antiandrogens: Nilutamide, flutamide, or bicalutamide
    - ◊ A first-generation antiandrogen must be given with LHRH agonist for ≥7 days to prevent testosterone flare if metastases are present in weight-bearing bone
  - Orchiectomy plus abiraterone, enzalutamide, or apalutamide
  - Orchiectomy plus docetaxel and abiraterone or darolutamide
  - LHRH agonist (as above) plus abiraterone, enzalutamide, or apalutamide
  - LHRH agonist (as above) plus docetaxel and abiraterone or darolutamide
  - LHRH antagonist plus abiraterone, enzalutamide, or apalutamide
  - LHRH antagonist plus docetaxel and abiraterone or darolutamide
- Abiraterone should be given with concurrent steroid [see ADT for Regional (N1,M0) Disease, see PROS-G 1 of 5].
- When EBRT to primary tumor is given with ADT in low metastatic burden M1, the options for ADT are:
  - Orchiectomy alone or with abiraterone or docetaxel
  - LHRH agonist alone or with abiraterone or docetaxel
  - LHRH antagonist alone or with abiraterone or docetaxel
- Two randomized phase 3 clinical trials of abiraterone with prednisone plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved OS over ADT alone. Adverse events were higher with abiraterone and prednisone but were generally mild in nature and were largely related to mineralocorticoid excess (ie, hypertension, hypokalemia, edema), hormonal effects (ie, fatigue, hot flushes), and liver toxicity.
- Cardiac events, severe hypertension, and liver toxicity were increased with abiraterone.
- A double-blind randomized phase 3 clinical trial of apalutamide plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved OS over ADT alone. Adverse events that were more common with apalutamide than with placebo included rash, hypothyroidism, and ischemic heart disease.
- An open-label randomized phase 3 clinical trial of enzalutamide plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved OS over ADT alone. In a separate double-blind randomized phase 3 clinical trial, enzalutamide reduced the risk of metastatic progression or death compared with placebo and showed an OS benefit. Adverse events associated with enzalutamide included fatigue, seizures, and hypertension.
- 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 did not 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.

Secondary Hormone Therapy for M0 or M1 CRPC

- Androgen receptor activation and autocrine/paracrine androgen synthesis are potential mechanisms of recurrence of prostate cancer during ADT (CRPC). Thus, castrate levels of testosterone (<50 ng/dL) should be maintained by continuing LHRH agonist or antagonist 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 conventional imaging, M0 CRPC vs. M1 CRPC, and whether or not the patient is symptomatic.

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Continued

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

- Administration of secondary hormonal therapy can include novel hormone therapy (ie, certain second-generation antiandrogens, androgen metabolism inhibitors) and certain novel hormone therapy/targeted therapy combinations (see PROS-14 and PROS-16). Other secondary hormone therapy options for M0 and M1 CRPC are:
  - ◊ First-generation antiandrogen (nilutamide, flutamide, or bicalutamide)
  - ◊ Corticosteroids (hydrocortisone, prednisone, or dexamethasone)
  - ◊ Antiandrogen withdrawal
  - ◊ Ketoconazole plus hydrocortisone
  - ◊ Abiraterone or enzalutamide following progression on other novel hormone therapies
  - ◊ Abiraterone plus dexamethasone following progression on either formulation of abiraterone
- Abiraterone should be given with concurrent steroid, either prednisone 5 mg PO twice daily for the standard formulation or methylprednisolone 4 mg PO twice daily for the fine-particle formulation.
- A phase 3 study of patients with M0 CRPC and a PSADT ≤10 months showed apalutamide (240 mg/day) improved the primary endpoint of MFS over placebo (40.5 months vs. 16.2 months). After a median follow-up of 52 months, final OS analysis showed an improved median OS with apalutamide versus placebo (73.9 months vs. 59.9 months). Adverse events included rash (24% vs. 5.5%), fracture (11% vs. 6.5%), and hypothyroidism (8% vs. 2%). Bone support should be used in patients receiving apalutamide.
- A phase 3 study of patients with M0 CRPC and a PSADT ≤10 months showed enzalutamide (160 mg/day) improved the primary endpoint of MFS over placebo (36.6 months vs. 14.7 months). Median OS was longer in the enzalutamide group than in the placebo group (67.0 months vs. 56.3 months). Adverse events included falls and nonpathologic fractures (17% vs. 8%), hypertension (12% vs. 5%), major adverse cardiovascular events (5% vs. 3%), and mental impairment disorders (5% vs. 2%). Bone support should be used in patients receiving enzalutamide.
- A phase 3 study of patients with M0 CRPC and a PSADT ≤10 months showed darolutamide (600 mg twice daily) improved the primary endpoint of MFS over placebo (40.4 months vs. 18.4 months). OS at 3 years was 83% (95% CI, 80–86) in the darolutamide group compared with 77% (95% CI, 72–81) in the placebo group. Adverse events that occurred more frequently in the treatment arm included fatigue (12.1% vs. 8.7%), pain in an extremity (5.8% vs. 3.2%), and rash (2.9% vs. 0.9%). The incidence of fractures was similar between darolutamide and placebo (4.2% vs. 3.6%).
- In a randomized controlled trial in the setting of M1 CRPC prior to docetaxel chemotherapy, abiraterone 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 OS 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-sensitive patients with M1 CRPC showed that enzalutamide (160 mg daily) resulted in significant improvement in rPFS and OS. 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 patients on enzalutamide).
- In the post-docetaxel M1 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/day enzalutamide improved progression-free survival (PFS) compared to 50 mg/day bicalutamide in patients with treatment-naïve M1 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.
- Although the optimal sequence of therapies remains undefined, some data are emerging that can help with treatment selection in some cases. See Discussion.

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Continued

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Patients on Observation Who Require Treatment and Those with Life Expectancy ≤5 Years

- Treatment for patients whose cancer progressed on observation of localized disease is LHRH agonist or antagonist or orchiectomy.

Optimal ADT

- Medical castration (ie, LHRH agonist or antagonist) and surgical castration (ie, bilateral orchiectomy) are equally effective.
- Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides modest to no benefit over castration alone in patients with metastatic disease.
- Antiandrogen therapy should precede or be coadministered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.
- Antiandrogen monotherapy appears to be less effective than medical or surgical castration and is not recommended.
- No clinical data support the use of finasteride or dutasteride with combined androgen blockade.
- Patients who do not achieve adequate suppression of serum testosterone (<50 ng/dL) with medical or surgical castration can be considered for additional hormonal manipulations (with antiandrogens, LHRH antagonists, or steroids), although the clinical benefit remains uncertain. Consider monitoring testosterone levels 12 weeks after first dose of LHRH therapy, then upon increase in PSA. The optimal level of serum testosterone to affect "castration" has yet to be determined.
- Data are limited on long-term adherence to oral relugolix and the potential effects on optimal ADT. Ongoing monitoring for sustained suppression of testosterone (<50 ng/dL) can be considered, and relugolix may not be a preferred agent if adherence to the prescribed regimen is uncertain.

Monitor/Surveillance

- ADT has a variety of adverse effects, including hot flashes, loss of libido, erectile dysfunction, shrinkage of penis and testicles, loss of muscle mass and strength, fatigue, anemia, breast enlargement and tenderness/soreness, depression and mood swings, hair loss, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease. The intensity and spectrum of these side effects vary greatly, and many are reversible or can be avoided or mitigated. For example, physical activity can counter many of these symptoms and should be recommended (NCCN Guidelines for Survivorship). Use of statins also should be considered. Patients and their medical providers should be advised about these risks prior to treatment.

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PRINCIPLES OF RISK STRATIFICATION

General Principles of Clinical Risk Stratification:

- The purpose of NCCN risk groups is to provide a method for risk stratification to allow standardized treatment recommendations to be provided.
  - It is acknowledged that there are methods of risk stratification with superior performance to NCCN risk groups, but they have not been routinely used in clinical trials. This limits the ability to provide evidence-based guideline treatment recommendations using these methods. See Table 1 on PROS-H 2 of 8.
  - Thus, the NCCN Guidelines continue to use NCCN risk groups as a framework. However, the panel acknowledges the ability to personalize treatment decisions through improved tools for risk stratification and has created this section to assist.
- Current treatment recommendations for localized and recurrent prostate cancer are based on prognosis, rather than use of predictive biomarkers. Prognosis is estimated through risk stratification.
- Clinical trials that have established the benefit of various treatments in localized and recurrent prostate cancer often enrolled patients across a spectrum of disease risk, and most trials have not restricted enrollment to a single NCCN risk group. Subgroup analyses, absolute benefit estimates, and expert opinion are used to provide treatment recommendations for each NCCN risk group.
  - Given the moderate prognostic performance of NCCN risk groups to risk stratify localized prostate cancer, there is intrinsic heterogeneity in prognosis within a given NCCN risk group. Thus, treatment recommendations for adjacent risk groups may be appropriate when using more accurate risk stratification methods in addition to NCCN risk group assignments.
- Multivariable models should be used for risk stratification.
  - Multivariable risk stratification models, such as NCCN and STAR-CAP, incorporate routine clinical (ie, PSA, T stage) and pathologic variables (ie, Grade Group, percent positive cores), and outperform a single clinical or pathologic feature for risk stratification.
  - Multivariable models, such as gene expression classifiers or artificial intelligence (AI)-derived digital histopathology biomarkers, can combine clinical, pathologic, and other biomarkers to further improve risk stratification.
- There are newer clinical risk stratification models that have been shown to outperform NCCN risk groups. There are also common histopathology variables that are prognostic (ie, cribriform, intraductal carcinoma, percent Gleason pattern 4) and clinical variables (ie, PSA density); however, they have rarely been reported in the context of clinical trials.
- The prognostic impact of germline mutations in localized disease has inconsistent results from generally low-quality retrospective studies with moderate to high risk of bias. Germline mutations should be considered independently to inform screening recommendations for other cancers, treatment implications in advanced disease, and cascade germline testing for family members.
- Imaging (ie, MRI and PSMA-PET/CT) can also aid in risk stratification. See Principles of Imaging (PROS-E).

Advanced Risk Stratification Tools:

- There are advanced risk stratification tools (ie, gene expression biomarkers, AI digital pathology) that have been variably demonstrated to independently improve risk stratification beyond NCCN or CAPRA risk stratification. See Table 2 on PROS-H 3 of 8.
  - These tools are recommended to be used when they have the potential ability to change disease management. These tools should not be ordered reflexively.
    - ◊ The most common treatment decisions in localized prostate cancer to use these tests include the use and/or intensity of active surveillance versus radical therapy, RT versus RT + short-term (ST)-ADT, and RT + ST-ADT versus long-term (LT)-ADT.
    - ◊ The most common treatment decisions in biochemically recurrent prostate cancer post-RP to use these tests include secondary RT versus secondary RT + ADT.
    - ◊ These tools are not recommended for patients with very-low-risk prostate cancer.
  - There are an extensive number of these tools created with substantial variability in quality of reporting and model design, endpoint selection, and quality and caliber of validation. It is recommended to use models that have high-quality and robust validation, ideally with high-quality, long-term clinical trial data, which usually comes from randomized trials and across multiple clinical trials.

Footnotes (PROS-H 7 of 8) References (PROS-H 8 of 8)

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PRINCIPLES OF RISK STRATIFICATION

Table 1. Risk Stratification: Selected Clinical Variables and Models

Disease State	Method	Predictive	Prognostic	Endpoint Trained For[a]	Simon Level of Evidence[1,d]	Comments
Localized						
	D'Amico[2]	No	Yes	See footnote[b]	IB	Not a trained model. Created from review of the literature.
	NCCN	No	Yes	See footnote[b]	IB	Not a trained model. Adapted from D'Amico risk groups.
	CAPRA[3]	No	Yes	BCR	IIC	Model excludes cT3b–T4 and cN1
	MSKCC nomograms[4]	No	Yes	BCR and PCSM	IVD	Trained and validated for surgically treated patients.
	STAR-CAP[5]	No	Yes	PCSM	IIC	Outperformed NCCN, AJCC, and CAPRA.
	AJCC 8th Edition[6]	No	Yes	See footnote[c]	IIC	Not a trained model. Created from expert opinion.
Post-RP						
	CAPRA-S[7]	No	Yes	BCR	IIC	Patients with cT3a, cT3b, cT4, and cN1 were not included.
BCR Post-RP						
	Multicenter nomogram[8]	No	Yes	BCR	IVD	Retrospective multicenter study
	Pre-RT PSA[9]	Yes	Yes	—	IB Predictive IB Prognostic	Predictive for hormone therapy benefit in NRG/RTOG 9601.
mCSPC						
	Volume (low vs. high)[10]	Yes	Yes	—	IIB Predictive IB Prognostic	See footnote[e]
	Number of bone metastasis	Yes	Yes	—	IIB Predictive IB Prognostic	Predictive for benefit of RT to primary.[11]

PCSM = prostate cancer-specific mortality

Footnotes (PROS-H 7 of 8)
References (PROS-H 8 of 8)

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PRINCIPLES OF RISK STRATIFICATION

Table 2. Risk Stratification: Selected Advanced Tools for Localized Prostate Cancer

Category	Tool	Predictive	Prognostic	Prognostic Endpoint Trained For[f]	Simon Level of Evidence[1,d]	Treatment Implications
Gene Expression						
	22-gene genomic classifier (GC) (Decipher)	No	Yes	Metastasis	IB	See Table 3
	31-gene cell cycle progression (CCP) assay (Prolaris)	No	Yes	See footnote[g]	IIIC[i]	
	17-gene Genomic Prostate Score (GPS) assay	No	Yes	Adverse pathology	IIIC	
AI Pathology						
	Multimodal artificial intelligence (ArteraAI Prostate)	Yes	Yes	BCR, DM, PCSM[h]	IB Predictive IB Prognostic	See Table 3
Germline						
	HRD	No	Unclear	—	VD	
Risk Stratification: Selected Advanced Tools Post-RP						
Gene Expression						
	22-gene GC	No	Yes	Metastasis	IB	See Table 3
	31-gene CCP assay	No	Yes	See footnote[g]	IVD	
	17-gene GPS assay	No	Yes	Adverse pathology	IVD	

HRD = Homologous recombination deficiency, DM= distant metastases, PCSM = Prostate cancer-specific mortality

Footnotes (PROS-H 7 of 8)
References (PROS-H 8 of 8)

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PRINCIPLES OF RISK STRATIFICATION

Table 3. Treatment Implications for Advanced Tools: 22-Gene Genomic Classifier (GC) Assay

Population	Score	Treatment Decision	Treatment Implications
NCCN Low-Risk	**≥0.6**	**Active surveillance Intensity vs. Radical therapy**	**Evidence:** In a prospective multicenter statewide registry, GC high risk (≥0.6) was associated with shorter time on active surveillance and shorter time to treatment failure (TTF) for those who underwent radical therapy.[12] **Evidence synthesis:** More intensive active surveillance frequency should be considered for patients with NCCN low-risk disease and a high GC score, given the higher probability of transitioning off active surveillance and subsequent progression.
NCCN Intermediate-Risk	**≤0.45 vs. ≥0.60**	**RT vs. RT with ST-ADT**	**Evidence:** NRG/RTOG 0126 phase III randomized trial was profiled post-hoc with a pre-specified analysis plan.[13] The study demonstrated the independent prognostic effect of GC on biochemical failure, secondary therapy, DM, PCSM, MFS, and OS. Patients receiving RT alone with low GC scores had 10-year DM rates of 4%, compared with 16% for GC high risk. **Evidence synthesis:** RT alone should be considered for patients with a low GC score and NCCN intermediate-risk disease. The addition of ST-ADT should be considered for patients with a high GC score given their increased risk of DM and significant benefit of ST-ADT on DM, even with dose-escalated RT or brachytherapy boost.
NCCN High-Risk	**≤0.45 vs. ≥0.60**	**RT + LT-ADT vs. RT + ST-ADT**	**Evidence:** A meta-analysis of three phase III randomized trials (NRG/RTOG 9202, 9413, and 9902) were profiled post-hoc with a prespecified analysis plan.[14] The study demonstrated the independent prognostic effect of GC on biochemical failure, DM, MFS, PCSM, and OS. Patients with low GC scores had 10-year DM rates of 6%, compared with 26% for GC high risk. The absolute benefit of LT-ADT over ST-ADT was 11% for patients with high GC scores (NNT of 9), and 3% for patients with low GC scores (NNT of 33). **Evidence synthesis:** RT + LT-ADT should be recommended for most patients with NCCN high-risk disease regardless of the GC score outside of a clinical trial, even with dose-escalated RT or brachytherapy boost. However, patients with a GC low risk score should be counseled that the absolute benefit of LT-ADT over ST-ADT is smaller than for patients with GC high risk scores and when accounting for patient age, comorbidities, and patient preferences, it may be reasonable with shared decision-making to use a duration shorter than LT-ADT.

NNT = number needed to treat, PCSS = prostate cancer-specific survival

Footnotes (PROS-H 7 of 8)
References (PROS-H 8 of 8)

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Continued

PRINCIPLES OF RISK STRATIFICATION

Table 3. Treatment Implications for Advanced Tools: 22-Gene Genomic Classifier (GC) Assay

Population	Score	Treatment Decision	Treatment Implications
Post-RP BCR	**<0.6 vs. ≥0.60[j]**	**RT vs. RT + ADT**	**Evidence:** Two phase III randomized trials post-RP were profiled post-hoc with prespecified analysis plans. NRG/RTOG 9601 demonstrated the independent prognostic effect of GC on DM, PCSM, and OS, and found that for patients with lower entry PSAs (<0.7 ng/mL), the 12-year DM rate benefit from hormone therapy for patients with GC lower risk vs. GC higher risk was 0.4% vs. 11.2%.[15] The SAKK 09/10 phase III trial tested post-RP lower vs. higher dose RT alone. The study demonstrated the independent prognostic effect of GC on biochemical progression, clinical progression, secondary hormone therapy, DM, and MFS.[16] **Evidence synthesis:** For patients with node-negative disease post-RP planned for early secondary RT (PSA ≤0.5 ng/mL) with GC low or intermediate risk, use of RT alone should be considered. For patients planned for early secondary RT with a GC high-risk tumor, use of secondary RT with ADT is recommended. Currently, it is unclear how best to use GC for patients receiving late post-RP secondary RT (PSA >0.5 ng/mL). Optimal ADT duration (ie, 6 vs. 24 months) based on GC score is unknown at this time.

Footnotes (PROS-H 7 of 8)
References (PROS-H 8 of 8)

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Continued

PRINCIPLES OF RISK STRATIFICATION

Table 3. Treatment Implications for Advanced Tools: Multi-Modal Artificial Intelligence (MMAI) Assay

Population	Score	Treatment Decision	Treatment Implications
NCCN Low-, Intermediate-, and High-Risk	**Continuous**	**See Evidence synthesis**	**Evidence:** Five phase III randomized trials were profiled post-hoc (NRG/RTOG 9202, 9408, 9413, 9910, and 0126).[17] The MMAI model was superior for discrimination of BCR, DM, PCSM, and OS than 3-tier NCCN risk groups in the validation cohort and in individual validation trial subsets [5-year DM AUC was 0.83 vs. 0.72 for MMAI vs. NCCN, respectively (P < .001)]. **Evidence synthesis:** Given the superior discrimination of the MMAI model for multiple oncologic endpoints over NCCN risk groups, this test may be used to provide more accurate risk stratification to inform shared decision-making regarding absolute benefit from various treatment approaches. Specific score cut points have not been published to date for specific treatment decisions.
NCCN Intermediate-Risk	**Biomarker (+)**	**RT vs. RT +/- ST-ADT**	**Evidence:** A predictive biomarker for benefit of ST-ADT to RT was trained in five phase III radiotherapy randomized trials and validated in NRG/RTOG 9408, a randomized trial of RT +/- 4 months of ST-ADT.[18] On validation, there was a significant biomarker-treatment interaction for DM (P interaction 0.01). In patients with biomarker-positive disease, ST-ADT significantly reduced the risk of DM compared to RT alone (sHR = 0.34, 95% CI [0.19–0.63], P < .001). There were no significant differences between treatment arms in the biomarker negative subgroup (sHR = 0.92, 95% CI [0.59–1.43], P = .71). **Evidence synthesis:** Patients with intermediate-risk prostate cancer planning to receive RT, those with biomarker positive disease, and especially those with unfavorable intermediate risk disease should be recommended for the addition of ST-ADT regardless of RT dose or type, notwithstanding contraindications to ADT. Those with biomarker (-) tumors, especially tumors with more favorable prognostic risk, may consider the use of RT alone.

sHR = subdistribution hazard ratio, ST-ADT = short term adrogen deprivation therapy, BCR = Biochemical recurrence, DM= distant metastases, PCSM = Prostate cancer-specific mortality, OS = overall survival, AUC = area under the curve

Footnotes (PROS-H 7 of 8)
References (PROS-H 8 of 8)

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PRINCIPLES OF RISK STRATIFICATION FOOTNOTES

[a] The listed models or variables may have demonstrated they are prognostic for additional endpoints. This column indicates what the original model was trained for.

[b] The D'Amico risk groups were created from review of the literature at the time and were validated initially for BCR. NCCN risk groups were adapted from the D'Amico risk groups. The expanded NCCN risk groups that currently include subcategories of low, intermediate, and high risk were created from subdividing the existing three-tier NCCN risk groups individually.

[c] AJCC 8th edition was not trained for an endpoint and was made by expert opinion.

[d] Simon level of evidence criteria are as follows[1]:

- **1A,** Prospective clinical trial(s) designed to address tumor marker
- **1B,** Prospective clinical trial(s) using archived samples with design that accommodates tumor marker utility, ≥1 validation study available with consistent results
- **IIB** Prospective clinical trial(s) using archived samples with design that accommodates tumor marker utility, no validation studies available, or validation studies have inconsistent results
- **IIC,** Prospective observational registry, ≥2 validation studies available with consistent results
- **IIIC,** Prospective observational registry, no validation studies available, or 1 validation study with consistent or inconsistent results
- **IVD,** Small retrospective/observational studies with no prospective aspect
- I**VD,** Small retrospective/observational pilot studies with no prospective aspect, designed to determine biomarker marker levels in a population.

[e] Predictive for benefit of RT to primary, less clear predictive ability for docetaxel, and not predictive of androgen receptor signaling inhibitor benefit.[19-21]

[f] The listed models and biomarkers may have demonstrated they are prognostic for additional endpoints. This column indicates what the original model or biomarker was trained for.

[g] CCP was not specifically trained for a clinical endpoint.

[h] Separate models were trained and validated for each endpoint.

[i] The CCP biomarker is level IVD except for grade group 1 cancer where it is level IIIC, where CCP was independently associated with minor upgrading, but was not significantly associated with major upgrading or biochemical recurrence. Cooperberg MR, et al. Eur Urol 2021;79:141-149.

[j] SAKK 09/10 combined GC low and intermediate risk due to relatively similar prognosis. NRG/RTOG 9601 dichotomized patients by GC low versus intermediate and high risk. However, due to the age of the tissue from NRG/RTOG 9601 (>20 years old) there is a known shifting of GC scores, and a more contemporary distribution of score distribution would approximate closer to combining GC low and intermediate risk together.

References (PROS-H 8 of 8)

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PRINCIPLES OF RISK STRATIFICATION
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PRINCIPLES OF RADIATION THERAPY

Definitive Radiation Therapy General Principles

- Highly conformal RT techniques should be used for the treatment of primary prostate cancer. Selection of treatment approach should balance trade-offs in biochemical disease control, toxicity, logistics burden for the patient, and patient preferences.
- External Beam RT (EBRT):
  - Photon and proton RT are both forms of EBRT that appear to have generally comparable biochemical control (Discussion).
  - The accuracy of EBRT should be verified by daily prostate localization to address interfraction setup uncertainty, with any of the following: techniques of image-guided RT (IGRT) using CT, MRI, ultrasound, implanted fiducials, or electromagnetic targeting/tracking. Endorectal balloons may be used to improve prostate immobilization. Advanced image guidance with real-time intrafraction tracking may allow further precision for margin reduction and reduction in toxicity but requires quality validation.
  - Biocompatible and biodegradable perirectal spacer materials may be implanted between the prostate and rectum in patients undergoing external radiotherapy with organ-confined prostate cancer in order to displace the rectum from high radiation dose regions for the purpose of toxicity reduction. Patients with grossly apparent posterior extraprostatic extension should not undergo perirectal spacer implantation. Marginal or suspected early extension is not a clear contraindication.
  - Various fractionation and dose regimens can be considered depending on the clinical scenario (Table 1 on PROS-I 4 of 8). Whole gland dose escalation improves biochemical control while modestly increasing toxicity. Alternately, targeted dose escalation of imaging-defined (eg, MRI) intraprostatic dominant disease, using a simultaneous integrated micro-boost, improves biochemical disease control, without added toxicity when using an isotoxic approach that prioritizes normal organ constraints over boost target coverage.[1]
  - Stereotactic body RT (SBRT; also known as stereotactic ablative radiotherapy, SAbR) refers to a delivery of ultra-hypofractionated RT with high precision treatment setup and image guidance techniques. SBRT is acceptable for treatment of primary prostate cancer across all risk groups and for locoregional and/or distant metastases in practices with appropriate technology and expertise. Advanced imaging guidance with intrafraction tracking when using intensified doses and/or especially tight treatment margins should be considered when available and validated, based on data showing acute toxicity reduction. For primary site and/or regional nodal treatment with SBRT, simultaneous integrated boost for dosing of prostate, intraprostatic, seminal vesicle, and/or regional nodal targets to differing doses may be used. In select patients, SBRT to the prostate may also be used as a boost in combination with fractionated EBRT. Based upon data for improved durability of disease control and pain reduction compared to historical palliative regimens, SBRT is recommended for metastasis-directed therapy in the following circumstances:
    - ◊ In a patient with limited metastatic disease (eg, oligometastatic) when ablation is the goal.
    - ◊ In a patient with limited progression (eg, oligoprogression) or limited residual disease on otherwise effective systemic therapy (eg, consolidation) where PFS is the goal.
    - ◊ In a symptomatic patient where the lesion occurs in or immediately adjacent to a previously irradiated treatment field.
    - ◊ At physician discretion for more durable control of pain than achieved with typical palliative regimens used in some randomized trial data, which should be considered particularly in prostate cancer where natural history of advanced disease can be very long. Regardless of SBRT or other planning methods, hypofractionated palliative regimens are favored given long-established data for equivalent or superior pain control with minimization of logistics burden to patients.[2,3]
- Biologically effective dose (BED) modeling with the linear-quadratic equation may not be accurate for ultra-hypofractionated (eg, SBRT) radiation.
- Brachytherapy:
  - Interstitial implantation of prostate +/- proximal seminal vesicles with temporary (high dose-rate, HDR) or permanent (low dose-rate, LDR) radioactive sources for monotherapy or as boost when added to EBRT should be performed in practices with adequate training, experience, and quality assurance measures.
  - Patient selection should consider aspects of gland size, baseline urinary symptoms, and prior procedures (ie, transurethral resection of prostate) that may increase risk of adverse effects. Neoadjuvant ADT to shrink a

References PROS-I 8 of 8

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PRINCIPLES OF RADIATION THERAPY

gland to allow treatment should balance its additional toxicity with this benefit.
- Post-implant dosimetry must be performed for LDR implants to verify dosimetry.
- Brachytherapy boost, when added to EBRT and ADT, improves biochemical control. To address historical trial data concerns for increased toxicity incidence, careful patient selection and contemporary planning associated with lesser toxicity, such as use of recognized organ at risk (OAR) dose constraints, use of high-quality ultrasound and other imaging, and prescription of dose as close as possible to the target without excessive margins should be implemented. Moreover, given trial data showing similar cancer control with lower toxicity with brachytherapy alone in unselected cohorts with intermediate-risk prostate cancer, the use of combination EBRT with brachytherapy boost is best reserved for higher risk disease and unfavorable intermediate-risk disease with several risk factors.[4]

Definitive Radiation Therapy by Risk Group

- Very low risk and low risk[a,b]
  - Patients with NCCN very-low-risk and low-risk prostate cancer are encouraged to pursue active surveillance.
  - Those electing treatment with RT may receive EBRT or brachytherapy but should not be treated with combination brachytherapy boost with EBRT ADT or antiandrogen therapy should NOT be used.
- Favorable intermediate risk[a,b]
  - RT options include either EBRT or brachytherapy. Combination brachytherapy boost with EBRT should not be routinely used. ADT or antiandrogen therapy is not used routinely but can be considered if additional risk assessments suggest aggressive tumor behavior.
- Unfavorable intermediate risk[a,b]
  - RT options include EBRT, brachytherapy boost combined with EBRT, or brachytherapy alone. ADT should be used unless additional risk assessments suggest less aggressive tumor behavior or if medically contraindicated. Whether the duration of ADT can be reduced when combined with EBRT and brachytherapy remains unclear and controversial.
- High and very high risk[a,b]
  - RT options include EBRT or brachytherapy boost combined with EBRT. Brachytherapy alone should not be routinely used. ADT (level 1 data for long-term ADT; see PROS-7) is required unless medically contraindicated. Use of intensified androgen receptor pathway inhibition strategies should be considered in select patients (see PROS-7 and PROS-G 1 of 5). Addition of abiraterone should be used very selectively as the benefit in contemporary practice with modern staging is uncertain.
- Regional disease
  - Prostate, seminal vesicle, and nodal radiation should be performed. Clinically positive nodes should be dose-escalated as dose-volume histogram parameters allow. ADT is required unless medically contraindicated.The addition of abiraterone is preferred (see PROS-8 and PROS-G 1 of 5).
- Low metastatic burden, castration-sensitive disease
  - RT to the prostate should be considered in patients with lower metastatic burden castration-sensitive metastatic disease according to conventional imaging when added to ADT. The definition of this cohort is evolving with study updates, concurrent use of intensified systemic therapies, and the introduction of advanced PET imaging. The strongest data are for a survival benefit of adding RT in patients receiving either ADT alone, ADT+ docetaxel, or ADT + abiraterone for those with <4 bony metastases but should be noted to favor a benefit for up to 7 bony metastases, as reviewed:
    - ◊ High metastatic burden originally was defined according to the CHAARTED trial using conventional imaging by presence of visceral metastasis OR ≥4 bone metastasis with at least one outside the vertebral bodies or pelvis. Low metastatic burden disease is defined by lesser volume or extent of disease than high burden. Metastatic burden thus is defined by conventional imaging, whereas PET imaging should not be used to exclude a patient from treatment of the primary tumor.
    - ◊ This recommendation is based on the STAMPEDE phase 3 randomized trial's Arm H, which randomized 2061 patients to standard systemic therapy with or without radiotherapy to the primary. The overall cohort had a significant improvement from the addition of radiotherapy to the primary in failure-free survival (FFS), but not OS. The prespecified low-volume subset had a significant improvement in both FFS and OS.[5] A meta-analysis with two other studies confirmed this benefit for primary RT to the primary tumor in lower volume disease.[6]

Footnotes (PROS-I 7 of 8) References (PROS-I 8 of 8)

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PRINCIPLES OF RADIATION THERAPY

- ◊ A subsequent update of the STAMPEDE study delineated with more granularity who benefits from treatment of the primary more simply based on number of bone metastases,[15] given the practical challenges with using the CHAARTED definition. In this analysis, the survival benefit of primary RT added to ADT continuously decreased with increasing bone lesion number for up to 7 metastases, with the strongest statistical association remaining for those with <4 metastases. Thus, conventional imaging defined number of bony metastases without visceral involvement may be preferred to define candidacy for treatment of the primary tumor.
- ▸ Minimizing toxicity is paramount when delivering RT to the primary in patients with metastatic disease. As such, it is unclear if routine treatment of regional nodes in addition to the primary tumor or if substantial dose escalation beyond regimens used in prospective studies such as STAMPEDE Arm H improves outcomes; nodal treatment should be performed in the context of a clinical trial.
- ▸ Brachytherapy is not recommended outside of a clinical trial, as safety and efficacy have not been established in this patient population.
- ▸ At present, the use of primary RT cannot be used in itself to omit ADT intensification, and conversely, the use of ADT intensification does not clearly obviate the benefit of primary RT.

• High-metastatic burden
- ▸ RT to the prostate should NOT be used in patients with high-volume metastatic disease outside the context of a clinical trial unless for palliative intent.
- ▸ This recommendation is based on two randomized trials, HORRAD and STAMPEDE, neither of which showed an improvement in OS from the addition of radiotherapy to the primary when combined with standard systemic therapy.

References (PROS-I 8 of 8)

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PRINCIPLES OF RADIATION THERAPY

Table 1: Below are examples of regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.
See PROS-3, PROS-4, PROS-5, PROS-6, PROS-7, PROS-8, PROS-13, and PROS-I for other recommendations, including recommendations for neoadjuvant/concomitant/adjuvant ADT.

Regimen	Preferred Dose/Fractionation	NCCN Risk Group (✓ indicates an appropriate regimen option if RT is given)					
		Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High	Regional N1[e]	Low Metastatic Burden M1[e]
EBRT							
Moderate Hypofractionation[c]	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓	✓	
	2.75 Gy x 20 fx						✓
Conventional Fractionation[c]	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓	✓	
	2.2 Gy x 35 fx + micro-boost[d] to MRI-dominant lesion to up to 95 Gy (fractions up to 2.7 Gy)		✓	✓	✓		
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 fx[c] 6.1 Gy x 7 fx[c]	✓	✓	✓	✓		
	6 Gy x 6 fx[c]						✓
Brachytherapy Monotherapy							
LDR Iodine 125[c] Palladium 103[c] Cesium 131	145 Gy[c] 125 Gy[c] 115 Gy	✓	✓				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓				
Boost Brachytherapy or SBRT with EBRT (combined with 45–50.4 Gy x 25–28 fx or 37.5 Gy x 15 fx)							
LDR Iodine 125[c] Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			✓	✓		
HDR Iridium-192	15 Gy x 1 fx[c] 10.75 Gy x 2 fx			✓	✓		
EBRT + SBRT Boost	19 Gy x 2 fx for SBRT boost			✓	✓		

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Footnotes (PROS-I 7 of 8)

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PRINCIPLES OF RADIATION THERAPY

Radiotherapy for Recurrent Prostate Cancer After Definitive Radiotherapy:
See Principles of Local Secondary Post-Recurrence Therapy (PROS-K)

Post-Prostatectomy Radiation Therapy

- The panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, PSADT, and 22-gene GC molecular assay to individualize treatment discussion.
- Postoperative radiotherapy should be instituted in patients with sufficient life expectancy when an undetectable PSA becomes subsequently detectable and increases on two measurements or when a PSA remains persistently detectable after RP. Treatment is more effective when pretreatment PSA is low and PSADT is long. This is based on trial data, as reviewed:
  - Historically, indications for adjuvant RT based on randomized trial data include pT3a disease, positive margin(s), or seminal vesicle involvement, regardless of PSA status. Adjuvant RT is usually given within 1 year after RP and after operative side effects have improved/stabilized.
  - Currently, for most patients, institution of early postoperative radiotherapy for rising serum PSA levels at low levels is associated with best cancer control outcomes and minimization of overtreatment. This is based upon a meta-analysis of three randomized studies in which adjuvant RT was not superior in event-free survival, compared to institution of early postoperative radiotherapy at low PSA (eg, after confirmation of ≥0.1–0.2 ng/mL).[7]
  - Notably, these studies did not well represent patients with very-high-risk features such as nodal involvement or particularly adverse features, where individualized risk-based decision-making should be favored.
- Use of ADT: Selection for ADT addition to postoperative RT continues to evolve based on clinicopathologic, patient-specific, and GC based selection factors. Patients with high 22-gene GC scores (GC >0.6) should be strongly considered for the addition of ADT to EBRT, particularly when the opportunity for early EBRT has been missed. Data for ADT use in patients with rising PSA after prostatectomy without metastases or pathologic lymph node involvement is detailed:
  - EBRT with 2 years of 150 mg/day of bicalutamide demonstrated improved OS and MFS on a prospective randomized trial (RTOG 9601) versus radiation alone in the secondary treatment setting. A secondary analysis of RTOG 9601 found that patients with PSA ≤0.6 ng/mL had no OS improvement with the addition of the antiandrogen to EBRT. In addition, results of a retrospective analysis of RP specimens from patients in RTOG 9601 suggest that those with low PSA and a low GC score derived less benefit (development of distant metastases, OS) from bicalutamide than those with a high GC score.[8,9]
  - EBRT with 6 months of ADT (LHRH agonist) improved biochemical or clinical progression at 5 years on a prospective randomized trial (GETUG-16) versus radiation alone in patients with rising PSA levels between 0.2 and 2.0 ng/mL after RP.[10]
  - The SPPORT (RTOG 0534) trial included patients with PSA levels between 0.1 and 2.0 ng/mL after RP. The primary outcome measure of freedom from progression was 70.9% at 5 years (95% CI, 67.0–74.9) for those who received RT to the prostate bed and 81.3% (95% CI, 78.0–84.6) for those who also received 4–6 months of ADT (LHRH agonist plus antiandrogen). In a group that received RT to pelvic lymph nodes and the prostate bed and 4–6 months of ADT, freedom from progression at 5 years was 87.4% (95% CI, 84.7–90.2).[11]
- The panel recommends consultation with the American Society for Radiation Oncology (ASTRO)/American Urological Association (AUA) Guidelines. Evidence supports offering adjuvant/secondary RT in most patients with adverse pathologic features or detectable PSA and no evidence of disseminated disease.

References PROS-I 8 of 8

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Continued

PRINCIPLES OF RADIATION THERAPY

Post-Prostatectomy Radiation Therapy (Continued)

- Typical prescribed doses for adjuvant RT or secondary post-prostatectomy RT for rising PSA are 64–72 Gy in standard fractionation. Biopsy-proven and/or imaging-defined gross recurrence may require higher doses. Notably, randomized trial data for those without gross evident disease demonstrated no benefit but higher physician-reported toxicity with dose escalation for 70 Gy versus 64 Gy. Treatment volumes and OAR tolerances thus should be carefully considered and prioritized. Hypofractionated post-prostatectomy RT remains under prospective study with data from large studies such as RADICALS-RT (52.5 Gy/20 fractions vs. 64 Gy/32 fractions) suggesting no excess toxicity in post hoc comparison for at least fossa alone treatment.[12,13]
- Nuclear medicine advanced imaging techniques with improved sensitivity can be useful for localizing disease with PSA levels at low absolute levels, as low as 0.2 ng/mL (Discussion).
- Target volumes include the prostate bed and may include the pelvic nodes according to physician discretion.

Radiopharmaceutical Therapy

- Radiopharmaceutical therapies for prostate cancer are suitable options for improving survival and/or PFS in select patients with advanced castration-resistant disease. Due to prior therapy exposure, specific targets, and hematologic effects of these therapies, careful selection and sequencing strategy with other therapies is important. This section discusses the two currently FDA-approved agents in use (Ra-223, Lu-177 PSMA-617).
- Radium-223 is an alpha-emitting radiopharmaceutical that has been shown to extend survival in patients who have CRPC with symptomatic bone metastases, but no visceral metastases. Radium-223 alone has not been shown to extend survival in patients with visceral metastases or bulky nodal disease (>3–4 cm). Radium-223 causes double-strand DNA breaks and has a short radius of activity.
  - Radium-223 is administered IV once a month for 6 months by an appropriately licensed facility. Concurrent use with systemic therapies other than ADT should be pursued only on clinical trial due to potential for myelosuppression.
  - Hematologic toxicities: Selection includes verification of baseline marrow reserve by CBC testing per label. Grade 3–4 hematologic toxicity (ie, 2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency. Verification of suitable counts per label prior to subsequent doses is important, and extended delays without sufficient recovery (eg, >6–8 weeks) should lead to discontinuation.
  - Bone fracture risk: Radium-223 may increase fracture risk when given concomitantly with abiraterone acetate/prednisone. Concomitant use of denosumab[f] or zoledronic acid is recommended; it does not interfere with the beneficial effects of radium-223 on survival.
- Lu-177–PSMA-617[14]
  - Lu-177–PSMA-617 is a beta-emitting radiopharmaceutical that selectively binds to PSMA receptors on prostate cancer cells. In patients with PSMA-positive disease, Lu-177–PSMA-617 has been shown to improve OS in patients with progressive mCRPC previously treated with androgen receptor inhibitors and taxane chemotherapy.
  - Lu-177–PSMA-617 is not recommended in patients with dominant PSMA-negative lesions. PSMA-negative lesions are defined as metastatic disease that lacks PSMA uptake including bone with soft tissue components ≥1.0 cm, lymph nodes ≥2.5 cm in short axis, and solid organ metastases ≥1.0 cm in size.
  - Lu-177–PSMA-617 is typically administered IV 200 mCi (7.4 GBq) every 6 weeks for a total of 6 treatments by an appropriately licensed facility, usually in nuclear medicine or RT departments. Patients should be well-hydrated during treatment. Because Lu-177 also emits gamma radiation, appropriate precautions should be taken to minimize exposure to personnel administering the radiopharmaceutical. Treatment rooms should be monitored for potential contamination following treatments, and patients should be provided written instructions regarding radiation safety precautions following treatment.
  - The most frequently reported side effects from Lu-177–PSMA-617 include fatigue (43%), dry mouth (39%), nausea (35%), and anemia (32%).
  - Although the FDA has approved Ga-68 PSMA-11 for use with Lu-177–PSMA-617, the panel believes that F-18 piflufolastat PSMA and F-18 flotufolastat PSMA can also be used in the same space due to multiple reports describing the equivsalency of these imaging agents in:
    - ◊ PSMA molecular recognition motifs,
    - ◊ normal organ biodistribution, and
    - ◊ detection accuracy of prostate cancer lesions.

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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.

Footnotes (PROS-I 7 of 8)
References PROS-I 8 of 8
Continued

PRINCIPLES OF RADIATION THERAPY
FOOTNOTES

[a] Micro-boost to MRI-dominant disease improved biochemical control in patients with intermediate- and high-risk prostate cancer in a randomized phase III study in the setting of conventionally fractionated EBRT. If using micro-boost, it is critical to restrict dose to OARs to meet constraints that would normally have been achieved without such boost, sacrificing dose coverage of the boost as needed. Further, careful IGRT and delivery procedures should be developed in line with the technical demands of this approach. Kerkmeijer LGW, Groen VH, Pos FJ, et al. J Clin Oncol 2021;39:787-796.

[b] Prophylactic nodal radiotherapy (PNRT): The addition of PNRT in non-metastatic prostate cancer has not demonstrated consistent benefit in unselected populations. PNRT reduced relapse and distant/regional progression in one randomized trial focusing on patients with high-risk features and negative metabolic (PET PSMA) staging imaging. While awaiting pending trial data to mature in other cohorts, the panel recommends PNRT in patients with high-risk and regionally metastatic (cN+) prostate cancer, while deferring to physician discretion according to patient-specific factors in those with intermediate-risk disease. PNRT should not used in patients with lower risk disease. Murthy V, et al. J Clin Oncol 2021;39:1234-1242.

[c] Regimen supported by level 1 prospective data in multicenter trials.

[d] The micro-boost technique with level 1 data was established for a modestly hypofractionated regimen but has been extrapolated reasonably to other regimens in ongoing clinical trials. Care must be taken in doing so outside of clinical trials in order to respect normal tissue toxicity risk and above all prioritizing normal organ tolerances over micro-boost coverage.

[e] Regional N1 and M1 are defined by conventional imaging. Metabolic imaging (PET)-defined disease management is evolving with a preference for definitive therapy absent conventional imaging confirmation of metastases. That said, clear PET evidence of disease amenable to safe concurrent treatment, such as nodal boosts during nodal irradiation, are supported by the panel, with focus being stressed on respecting normal organ tolerances.

[f] An FDA-approved biosimilar is an appropriate substitute.

References PROS-I 8 of 8

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Continued

PRINCIPLES OF RADIATION THERAPY
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PRINCIPLES OF SURGERY

Pelvic Lymph Node Dissection

- Extended PLND provides more complete staging and may cure some patients 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.
- While PLND at the time of RP has not been shown to improve oncologic outcomes, it can provide staging and prognostic information.[1]
- A PLND can be excluded in patients with low predicated probability of nodal metastases by nomograms, although some patients with lymph node metastases will be missed. There is no single evidence-based threshold for performing PLND. Based on the risk of complications with PLND and extra time to perform the procedure, the published thresholds range from 2% to 7%.[2-5]
- A patient who is above the threshold for performing a PLND, but has a negative PSMA PET scan should still undergo PLND. In two studies, the sensitivity of PSMA PET for pelvic lymph node involvement among patients undergoing RP and PLND was low (about 40%), and the negative predictive value was about 81%.[6,7] Thus, basing the decision to perform PLND on a negative PSMA PET scan could result in missing 19% of patients with positive lymph nodes.
- 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 who has no serious comorbid conditions that would contraindicate an elective operation.
- High-volume surgeons in high-volume centers generally provide better outcomes.
- Blood loss can be substantial with RP, but can be reduced by using laparoscopic or robotic assistance or by careful control of the dorsal vein complex and periprostatic vessels when performed as open surgery.
- 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.

Secondary Radical Prostatectomy

- Secondary 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 secondary RP.

References (PROS-J 2 of 2)

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Continued

PRINCIPLES OF SURGERY
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PRINCIPLES OF LOCAL SECONDARY THERAPY POST-RADIATION

Local Secondary Therapy for Recurrent Prostate Cancer After Definitive Radiotherapy:

- **Patients with biopsy-proven recurrence in the prostate after prior RT and without distant metastatic disease can be considered for local therapy.**
- **The panel recommends that patients receive multidisciplinary counseling about the risks and benefits of each of these options in the context of the available comparative literature on this topic.[1,2]**
- **Local therapy options for patients with recurrence in the prostate only include:**
  - **RP + PLND**
  - **Non-surgical strategies**
    - **Cryotherapy**
    - **High-intensity focused ultrasound (HIFU) (category 2B)**
    - **Reirradiation**
- **Local therapy options for patients with recurrence in the regional nodes with or without prostate recurrence include:**
  - **ADT + pelvic lymph node radiation (if not previously done)**
  - **ADT + pelvic lymph node reirradiation (category 2B)**
  - **ADT + PLND (category 2B)**
  - **Pelvic lymph node radiation**
  - **PLND**
- **Reirradiation options include LDR brachytherapy, HDR brachytherapy, and SBRT.[1-7]**
- **There is no consensus as to the most appropriate reirradiation volume, and there are published experiences for both focal/partial and whole gland reirradiation. The panel recommends that patients receiving local therapy for RT recurrence are treated within the context of clinical trials when available and/or at experienced centers.**

References (PROS-K 2 of 2)

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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 LOCAL POST-RECURRENCE THERAPY
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PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

Non-Hormonal Systemic Therapy for M1 Castration-Sensitive Prostate Cancer

- Patients with high-volume castration-sensitive metastatic prostate cancer who are fit for chemotherapy should be considered for ADT plus docetaxel and either abiraterone or darolutamide based on phase 3 studies:
  - ADT with docetaxel and abiraterone was compared to ADT alone or with docetaxel in an open-label, randomized, phase 3 study. Radiographic PFS was longer in patients who received abiraterone than in those who did not. The populations receiving the triplet and doublet therapies experienced similar rates of neutropenia, febrile neutropenia, fatigue, and neuropathy, although grade ≥3 adverse events occurred in 63% of patients who received the triplet combination compared with 52% of those receiving ADT and docetaxel.
  - ADT with docetaxel and darolutamide was compared with ADT with docetaxel and placebo in a randomized phase 3 trial. OS, time to CRPC, skeletal event-free survival, and time to initiation of subsequent systemic antineoplastic therapy were improved in the patients who received darolutamide. Adverse events of any grade, grade 3 to 5 adverse events, and serious adverse events occurred at similar incidence levels between the two arms. Many of these were known effects of docetaxel. Exceptions were rash (16.6% vs. 13.5%) and hypertension (13.7% vs. 9.2%), which are known effects of androgen receptor pathway inhibitors and were more frequent in the darolutamide group.
- The use of myeloid growth factors should follow the NCCN Guidelines for Hematopoietic Growth Factors, based on risk of neutropenic fever

Non-Hormonal Systemic Therapy for M1 CRPC

Chemotherapy

- Docetaxel with concurrent steroid
  - Concurrent steroid includes daily prednisone, which may be omitted on the day of chemotherapy administration when dexamethasone is given.
  - Every-3-week docetaxel with concurrent steroid is the preferred first-line chemotherapy treatment based on phase 3 clinical trial data for patients with symptomatic mCRPC. Adverse events associated with docetaxel include neutropenia, leukopenia, febrile neutropenia, neutropenic infections, fluid retention, hypersensitivity reaction, hepatic function impairment, neuropathy, and other low-grade adverse events (eg, fatigue, nausea, vomiting, alopecia, diarrhea).
  - 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.
  - Docetaxel retreatment can be attempted after progression on a novel hormone therapy in patients with mCRPC whose cancer has not demonstrated definitive evidence of progression on prior docetaxel therapy in the castration-sensitive setting.
- Cabazitaxel with concurrent steroid
  - Concurrent steroid includes daily prednisone, which may be omitted on the day of chemotherapy administration when dexamethasone is given.
  - Patients who are not candidates for docetaxel or who are intolerant of docetaxel should be considered for cabazitaxel with concurrent steroid, based on results that suggest clinical activity of cabazitaxel in mCRPC. Cabazitaxel 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.
  - Cabazitaxel at 25 mg/m² with concurrent steroid has been shown in a randomized phase 3 study (TROPIC) to prolong OS, PFS, PSA response, and radiologic response when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second-line setting. Toxicity at this dose was significant and included febrile neutropenia, severe diarrhea, fatigue, nausea/vomiting, anemia, thrombocytopenia, sepsis, and renal failure. 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 PFS and OS (13.4 months vs. 14.5 months) compared to 25 mg/m².
  - Cabazitaxel at 25 mg/m² with concurrent steroid improved rPFS and reduced the risk of death compared with abiraterone or enzalutamide in patients with prior docetaxel treatment for mCRPC in the CARD study.

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Continued

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

- No chemotherapy regimen to date has demonstrated improved survival or quality of life after cabazitaxel, and trial participation should be encouraged.

- Cabazitaxel/carboplatin with concurrent steroid
  - Concurrent steroid includes daily prednisone, which may be omitted on the day of chemotherapy administration when dexamethasone is given.
  - Cabazitaxel starting dose can be either 20 mg/m² or 25 mg/m² for patients with mCRPC whose cancer has progressed despite prior docetaxel chemotherapy. Cabazitaxel 25 mg/m² with concurrent steroid may be considered for healthy patients who wish to be more aggressive. Growth factor support may be needed with either dose.
  - Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per minute with growth factor support can be considered for fit patients with aggressive variant prostate cancer (ie, visceral metastases, low PSA and bulky disease, high LDH, high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of *PTEN*, *TP53*, and *RB1*). The most common grade 3 to 5 adverse events were fatigue, anemia, neutropenia, and thrombocytopenia. Corn PG, et al. Lancet Oncol 2019;20:1432-1443.
- Mitoxantrone with prednisone
  - Mitoxantrone with prednisone may provide palliation but has not been shown to extend survival in two randomized trials. Adverse events associated with mitoxantrone are similar to docetaxel, but with lower rates of grade 3 or 4 neutropenic fevers, cardiovascular events, nausea and vomiting, metabolic disturbances, and neurologic events.
- Increasing PSA should not be used as the sole criteria for progression. Assessment of response should incorporate clinical and radiographic criteria.
- See NCCN Guidelines for Hematopoietic Growth Factors for recommendations on growth factor support.

PARP Inhibitors With or Without Novel Hormone Therapies

- Olaparib is an option for patients with mCRPC who have an HRR mutation and whose cancer has progressed on prior treatment with androgen receptor-directed therapy regardless of prior docetaxel therapy based on results of a randomized phase 3 study in patients with HRR mutations. Radiographic PFS was improved over physician's choice of abiraterone or enzalutamide. In the pre-docetaxel setting, olaparib is a preferred treatment option for patients with a pathogenic mutation (germline and/or somatic) in *BRCA1* or *BRCA2*, and is also an option in this setting for patients with other HRR gene alterations *(ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* or *RAD54L*). Adverse events that may occur with olaparib treatment include anemia (including that requiring transfusion), fatigue, nausea or vomiting, anorexia, weight loss, diarrhea, thrombocytopenia, neutropenia, creatinine elevation, cough, and dyspnea. Rare but serious side effects may include thromboembolic events (including pulmonary emboli), drug-induced pneumonitis, and a theoretical risk of myelodysplasia or acute myeloid leukemia.

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Continued

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

- **Rucaparib is an option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy based on results from a phase 2 trial. Results from the confirmatory randomized phase 3 trial showed that the median duration of imaging-based PFS was significantly longer in the group that received rucaparib than in those who received a control medication (abiraterone, enzalutamide, or docetaxel). In the pre-docetaxel setting, rucaparib is a prefered option for patients with *BRCA1* or *BRCA2* mutations. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given. Adverse events that may occur with rucaparib include anemia (including that requiring transfusion), fatigue, asthenia, nausea or vomiting, anorexia, weight loss, diarrhea or constipation, thrombocytopenia, neutropenia, increased creatinine, increased liver transaminases, and rash. Rare but serious side effects of rucaparib include a theoretical risk of myelodysplasia or acute myeloid leukemia, as well as fetal teratogenicity.**
- **Olaparib with abiraterone is an option for certain patients with mCRPC (PROS-16) and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received a novel hormone therapy and who have not yet had treatment in the setting of CRPC based on results of an international, double-blind, phase 3 trial. Imaging-based PFS in the ITT population was significantly longer in the olaparib group than in the placebo group. The safety profile of the olaparib/abiraterone combination was as expected based on the known safety profiles of the individual drugs, with the most common adverse events being anemia, fatigue/asthenia, and nausea.**
- **Talazoparib plus enzalutamide is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in an HRR gene *(BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C*) who have not yet had treatment in the setting of CRPC, depending on prior treatment in other disease settings (PROS-16) based on results from a randomized, double-blind, phase 3 trial. Median radiographic PFS was improved in the talazoparib group compared with the control group. The safety profile of enzalutamide plus talazoparib was consistent with the known safety profiles of the individual drugs, with the most common adverse events in those who received talazoparib being anemia, neutropenia, and fatigue. However, hematologic adverse events were of higher grades and occurred more frequently than would be expected with talazoparib alone.**
- **There may be heterogeneity of response based on the specific gene mutation (Discussion). Use of talazoparib/enzalutamide for those who have received prior novel hormone therapy is controversial because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.**
- **Niraparib plus abiraterone (combination tablet) is a treatment option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet had treatment in the setting of mCRPC, depending on prior treatment in other disease settings (PROS-16) based on results of a randomized, double-blinded phase 3 trial. Radiographic PFS was improved for those receiving niraparib in the HRR mutation group overall and in the *BRCA* mutation subgroup. The incidence of grade 3/4 adverse events was higher in the niraparib group than in the placebo group, with anemia and hypertension as the most reported grade ≥3 adverse events. Use of niraparib/abiraterone for those who have received prior novel hormone therapy is controversial because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.**

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Continued

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

Immunotherapy

- **Patients with asymptomatic or minimally symptomatic mCRPC may consider immunotherapy.**
- **Sipuleucel-T**
  - **Sipuleucel-T is only for asymptomatic or minimally symptomatic patients with no liver metastases, life expectancy >6 months, and ECOG performance status 0–1.**
  - **Sipuleucel-T is not recommended for patients with small cell/NEPC.**
  - **Sipuleucel-T has been shown in a phase 3 clinical trial to extend mean survival from 21.7 months in the control arm to 25.8 months in the treatment arm, which constitutes a 22% reduction in mortality risk.**
  - **Sipuleucel-T is well-tolerated; common complications include chills, pyrexia, and headache.**
- **Pembrolizumab is an option for certain patients with mCRPC and MSI-H, dMMR, or TMB ≥10 mut/Mb (PROS-16).**
  - **Pembrolizumab may cause severe, life-threatening immune-mediated adverse reactions, which may include but are not limited to: pneumonitis, colitis, hepatitis, myocarditis, endocrinopathies, exfoliative dermatologic conditions, renal failure and nephritis, and ocular toxicities. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.**

Other Targeted Agents

- **Pan-cancer, tumor-agnostic treatments can be considered for patients with actionable mutations.**

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American Joint Committee on Cancer (AJCC)
TNM Staging System For Prostate Cancer (8th ed., 2017)
***Table 1.* Definitions for T, N, M**
Clinical T (cT)

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
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 found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.

Pathological T (pT)

T	Primary Tumor
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Note: There is no pathological T1 classification.
Note: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional 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. M1c is most advanced.

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Table 2. **AJCC Prognostic Groups**

Group	T	N	M	PSA (ng/mL)	Grade Group
Stage I	cT1a-c	N0	M0	PSA <10	1
	cT2a	N0	M0	PSA <10	1
	pT2	N0	M0	PSA <10	1
Stage IIA	cT1a-c	N0	M0	PSA ≥10 <20	1
	cT2a	N0	M0	PSA ≥10 <20	1
	pT2	N0	M0	PSA ≥10 <20	1
	cT2b	N0	M0	PSA <20	1
	cT2c	N0	M0	PSA <20	1
Stage IIB	T1-2	N0	M0	PSA <20	2
Stage IIC	T1-2	N0	M0	PSA <20	3
	T1-2	N0	M0	PSA <20	4
Stage IIIA	T1-2	N0	M0	PSA ≥20	1-4
Stage IIIB	T3-4	N0	M0	Any PSA	1-4
Stage IIIC	Any T	N0	M0	Any PSA	5
Stage IVA	Any T	N1	M0	Any PSA	Any
Stage IVB	Any T	Any N	M1	Any PSA	Any

Note: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

Histopathologic Type

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

Definition of Histologic Grade Group (G)

Recently, the Gleason system has been compressed into so-called Grade Groups.

Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

ABBREVIATIONS

ADT	androgen deprivation therapy
AI	artificial intelligence
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
AUC	area under the curve
BCR	biochemical recurrence
BED	biologically effective dose
CCP	cell cycle progression
CEA	carcinoembryonic antigen
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
ctDNA	circulating tumor DNA
DEXA	dual-energy x-ray absorptiometry
DM	distant metastases
dMMR	mismatch repair deficient
DRE	digital rectal exam
DWI	diffusion-weighted imaging
EBRT	external beam radiation therapy
FDG	Fluorodeoxyglucose
FFS	failure-free survival
FRAX	Fracture Risk Assessment Tool
GC	genomic classifier
HIFU	high-intensity focused ultrasound
HDR	high dose-rate
HRR	homologous recombination repair gene
IGRT	image-guided radiation therapy
IRF	intermediate risk factor
LDH	lactate dehydrogenase
LDR	low dose-rate
LHRH	luteinizing hormone-releasing hormone
LT-ADT	long-term androgen deprivation therapy
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MFS	metastasis-free survival
MMAI	multi-modal artificial intelligence
mpMRI	multiparametric MRI
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
NEPC	neuroendocrine prostate cancer
OAR	organ at risk
OS	overall survival
PCSM	prostate cancer-specific mortality
PCSS	prostate cancer-specific survival
PFS	progression-free survival
PLND	pelvic lymph node dissection
PNRT	prophylactic nodal radiotherapy
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PSMA	prostate-specific membrane antigen
rh	radiohybrid
RP	radical prostatectomy
rPFS	radiographic progression-free survival
RTOG	Radiation Therapy Oncology Group

ABBREVIATIONS

SBRT	**stereotactic body radiation therapy**
SPECT	**single-photon emission CT**
SQ	**subcutaneously**
SRE	**skeletal-related event**
ST-ADT	**short-term androgen deprivation therapy**
TMB	**tumor mutational burden**
TTF	**time to treatment failure**
VUS	**variant of uncertain significance**

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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Prostate Cancer. Sections on metastatic castration-sensitive prostate cancer and castration-resistant prostate cancer were updated on September 7, 2023. The remaining text was updated on May 10, 2022.

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Overview

An estimated 288,300 new cases of prostate cancer will be diagnosed in the United States in 2023, accounting for 29% of new cancer cases in men.[1] It is the most common cancer in men in the United States, who currently have a 1 in 8 lifetime risk of developing prostate cancer.[1] The incidence of prostate cancer declined by approximately 40% from 2007 to 2014, but since that time has increased at a rate of 3% annually. This increase is driven by a rise in the diagnosis of regional and metastatic disease, which may be a result of declining rates of prostate-specific antigen (PSA) testing that followed the 2012 USPSTF recommendations against testing.[2-10]

Researchers further estimate that prostate cancer will account for 11% of male cancer deaths in the United States in 2023, with an estimated 34,700 deaths.[1] The age-adjusted death rate from prostate cancer declined by 52% from 1993 to 2017, but the death rate has become more stable in recent years, with a 0.6% annual decrease from 2013 through 2020.[1] For all stages combined, the 5-year relative survival rate for prostate cancer is 97%.[1] The comparatively low death rate suggests that increased public awareness with earlier detection and treatment has affected mortality from this prevalent cancer, but is also complicated by screening-related lead-time bias and detection of indolent cancers. Maintenance of this low death rate is threatened by the rising prostate cancer incidence and diagnosis of advanced disease.

Unfortunately, large inequities exist in incidence of and mortality from prostate cancer across racial and ethnic groups. The incidence rate in Black individuals is 70% higher than in white individuals, and the mortality rate in this population is two to four times higher than all other racial and ethnic groups.[1] In addition, the mortality rate for American Indian/Alaska Native populations is higher than for white individuals.

The USPSTF released updated recommendations in 2018 that include individualized, informed decision-making regarding prostate cancer screening in males aged 55 to 69 years.[11] These updated recommendations may allow for a more balanced approach to prostate cancer early detection, and evidence suggests that PSA testing rates increased after the USPSTF's draft statement was released in 2017.[12] Better use of PSA for early detection of potentially fatal prostate cancer coupled with the use of imaging and biomarkers to improve the specificity of screening should decrease the risk of overdetection (see the NCCN Guidelines for Prostate Cancer Early Detection, available at www.NCCN.org). This reduced overdetection along with the use of active surveillance in appropriate patients should reduce overtreatment AND preserve the relatively low rates of prostate cancer mortality.

Guidelines Update Methodology

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

Literature Search Criteria

Prior to the update of the NCCN Guidelines for Prostate Cancer, an electronic search of the PubMed database was performed to obtain key literature in prostate cancer published since the previous Guidelines update, using the search term "prostate cancer." The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[13]

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; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these

guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[14] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Initial Prostate Cancer Diagnosis

Initial suspicion of prostate cancer is based on an abnormal digital rectal exam (DRE) or an elevated PSA level. A separate NCCN Guidelines Panel has written guidelines for prostate cancer early detection (see the NCCN Guidelines for Prostate Early Detection, available at www.NCCN.org). Definitive diagnosis requires biopsies of the prostate, usually performed by a urologist using a needle under transrectal ultrasound (TRUS) guidance. A pathologist assigns a Gleason primary and secondary grade to the biopsy specimen. Clinical staging is based on the TNM (tumor, node, metastasis) classification from the AJCC Staging Manual, Eighth Edition.[15] NCCN treatment recommendations are based on risk stratification that includes TNM staging rather than on 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 (CoC) requirements.[16]

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 individuals, 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,[17] the WHO's Life Tables by Country,[18] or the Memorial Sloan Kettering Male Life Expectancy tool[19] 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.[20] As an example, the Social Security Administration Life Expectancy for a 65-year-old American male 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 patient was judged to be in either poor or excellent health.

Prostate Cancer Genetics

Family history of prostate cancer raises the risk of prostate cancer.[21-24] In addition, prostate cancer has been associated with hereditary breast and ovarian cancer (HBOC) syndrome (due to germline mutations in homologous DNA repair genes) and Lynch syndrome (resulting from germline mutations in DNA mismatch repair [MMR] genes).[24-29] In fact, approximately 11% of patients with prostate cancer and at least 1 additional primary cancer carry germline mutations associated with increased cancer risk.[30] Therefore, the panel recommends a thorough review of personal and family history for all patients with prostate cancer.[31,32]

The newfound appreciation of the frequency of germline mutations has implications for family genetic counseling, cancer risk syndromes, and assessment of personal risk for subsequent cancers. Some patients with prostate cancer and their families may be at increased risk for breast and ovarian cancer, melanoma, and pancreatic cancer (HBOC); colorectal cancers (Lynch syndrome); and other cancer types. Data also suggest that patients with prostate cancer who have *BRCA1/2* germline mutations have increased risk of progression on local therapy and decreased overall survival (OS).[33-35] This information should be discussed with such patients if they are considering active surveillance. Finally, there are possible treatment implications for patients with DNA repair defects (see *Treatment Options for Patients with DNA Repair Gene Mutations*, below).

Prostate cancer is often associated with somatic mutations that occur in the tumor but not in the germline. An estimated 89% of metastatic castration-resistant prostate cancer (CRPC) tumors contain a potentially actionable mutation, with only about 9% of these occurring in the germline.[36] Both germline and tumor mutations are discussed herein.

Homologous DNA Repair Genes

Somatic mutations in DNA repair pathway genes occur in up to 19% of localized prostate tumors and 23% of metastatic CRPC tumors, with most mutations found in *BRCA2* and *ATM*.[36,37] These tumor mutations are often associated with germline mutations. For example, 42% of patients with metastatic CRPC and somatic mutations in *BRCA2* were found to carry the mutation in their germlines.[36] In localized prostate cancer, that number was 60%.[37]

Overall, germline DNA repair mutations have been reported with the lowest frequencies seen in patients with lower-risk localized prostate cancer (1.6%–3.8%), higher frequencies in those with higher-risk localized disease (6%–8.9%), and the highest frequencies in those with metastatic disease (7.3%–16.2%).[36,38-44] One study found that 11.8% of patients with metastatic prostate cancer have germline mutations in 1 of 16 DNA repair genes: *BRCA2* (5.3%), *ATM* (1.6%), *CHEK2* (1.9%), *BRCA1* (0.9%), *RAD51D* (0.4%), *PALB2* (0.4%), *ATR* (0.3%), and *NBN*, *PMS2*, *GEN1*, *MSH2*, *MSH6*, *RAD51C*, *MRE11A*, *BRIP1*, or *FAM175A*.[43]

An additional study showed that 9 of 125 patients with high-risk, very-high-risk, or metastatic prostate cancer (7.2%) had pathogenic germline mutations in *MUTYH* (4), *ATM* (2), *BRCA1* (1), *BRCA2* (1), and *BRIP1* (1).[40] In this study, the rate of metastatic disease among those with a mutation identified was high (28.6%, 2 of 7 patients). Although having a relative with breast cancer was associated with germline mutation identification (P = .035), only 45.5% of the mutation carriers in the study had mutations that were concordant with their personal and family history. Another study also found that a family history of breast cancer increased the chances of identifying a germline DNA repair gene mutation in patients with prostate cancer (OR, 1.89; 95% CI, 1.33–2.68; P = .003).[45] In a study of an unselected cohort of 3607 patients with a personal history of prostate

cancer who had germline genetic testing based on clinician referral, 11.5% had germline mutations in *BRCA2*, *CHEK2*, *ATM*, *BRCA1*, or *PALB2*.[46]

More than 2% of Ashkenazi Jews carry germline mutations in *BRCA1* or *BRCA2*, and these carriers have a 16% chance (95% CI, 4%–30%) of developing prostate cancer by the age of 70.[47] In a study of 251 unselected Ashkenazi Jewish patients with prostate cancer, 5.2% had germline mutations in *BRCA1* and *BRCA2*, compared with 1.9% of control Ashkenazi Jewish males.[48]

Germline *BRCA1* or *BRCA2* mutations have been associated with an increased risk for prostate cancer in numerous reports.[28,29,48-58] In particular, *BRCA2* mutations have been associated with a 2- to 6-fold increase in the risk for prostate cancer, whereas the association of *BRCA1* mutations and increased risks for prostate cancer are less consistent.[28,29,48,50,52,57,59,60] In addition, limited data suggest that germline mutations in *ATM, PALB2,* and *CHEK2* increase the risk of prostate cancer.[61-64] Furthermore, prostate cancer in individuals with germline *BRCA* mutations (*BRCA*m) appears to occur earlier, has a more aggressive phenotype, and is associated with significantly reduced survival times than in non-carrier patients.[34,35,59,65-69]

DNA Mismatch Repair Genes

Tumor mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* may result in tumor microsatellite instability (MSI) and deficient MMR (dMMR; detected by immunohistochemistry) and are sometimes associated with germline mutations and Lynch syndrome. Patients with Lynch syndrome may have an increased risk for prostate cancer. In particular, studies show an increased risk for prostate cancer in patients who are older and have germline *MSH2* mutations.[70,71]

In a study of more than 15,000 patients with cancer treated at Memorial Sloan Kettering Cancer Center who had their tumor and matched normal DNA sequenced and tumor MSI status assessed, approximately 5% of 1048 patients with prostate cancer had MSI-high (MSI-H) or MSI-indeterminate tumors, 5.6% of whom were found to have Lynch syndrome (0.29% of patients with prostate cancer).[25] In another prospective case series, the tumors of 3.1% of 1033 patients with prostate cancer demonstrated MSI-H/dMMR status, and 21.9% of these patients had Lynch syndrome (0.68% of the total population).[72] In a study of an unselected cohort of 3607 patients with a personal history of prostate cancer who had germline genetic testing based on clinician referral, 1.7% had germline mutations in *PMS2*, *MLH1, MSH2,* or *MSH6*.[46]

Effect of Intraductal/Cribriform or Ductal Histology

Ductal prostate carcinomas are rare, accounting for approximately 1.3% of prostate carcinomas.[73] Intraductal prostate cancer may be more common, especially in higher risk groups, and may be associated with a poor prognosis.[74] It is important to note that there is significant overlap in diagnostic criteria and that intraductal, ductal, and invasive cribriform features may coexist in the same biopsy. By definition, intraductal carcinoma includes cribriform proliferation of malignant cells as long as they remain confined to a preexisting gland that is surrounded by basal cells. These features are seen frequently with an adjacent invasive cribriform component and would be missed without the use of basal cell markers.

Limited data suggest that acinar prostate adenocarcinoma with invasive cribriform pattern, intraductal carcinoma of prostate (IDC-P), or ductal adenocarcinoma component y have increased genomic instability.[75-78] In particular, tumors with these histologies may be more likely to harbor somatic MMR gene alterations than those with adenocarcinoma histology.[78-80] In addition, limited data suggest that germline homologous DNA repair gene mutations may be more common in prostate tumors of ductal or intraductal origin[81,82] and that intraductal histology is common in

germline *BRCA2* mutation carriers with prostate cancer.[83] Overall, the panel believes that the data connecting histology and the presence of genomic alterations are stronger for intraductal than ductal histology at this time. Therefore, patients with presence of intraductal carcinoma on biopsy should have germline testing as described below.

Genetic Testing Recommendations

Germline Testing Based on Family History, Histology, and Risk Groups

The panel recommends inquiring about family and personal history of cancer and known germline variants at time of initial diagnosis. Germline testing should be considered in appropriate individuals where it is likely to impact the prostate cancer treatment and clinical trial options, management of risk of other cancers, and/or potential risk of cancer in family members. Based on the data discussed above, the panel recommends *germline* genetic testing for patients with prostate cancer and any of the following[31,32]:

- A positive family history (see definition in the guidelines above)
- High-risk, very-high-risk, regional, or metastatic prostate cancer, regardless of family history
- Ashkenazi Jewish ancestry
- A personal history of breast cancer

In addition, germline genetic testing should be considered in patients with a personal history of prostate cancer and 1) intermediate-risk prostate cancer and intraductal/cribriform histology or 2) a personal history of exocrine pancreatic cancer, breast cancer, colorectal, gastric, melanoma, pancreatic cancer, upper tract urothelial cancer, glioblastoma, biliary tract cancer, and small intestinal cancer.

Germline testing, when performed, should include *MLH1, MSH2, MSH6*, and *PMS2* (for Lynch syndrome) and the homologous recombination genes *BRCA1, BRCA2, ATM, PALB2,* and *CHEK2*. Additional genes may be appropriate depending on clinical context. For example, *HOXB13* is a prostate cancer risk gene and, whereas there are not currently clear therapeutic implications in the advanced disease setting, testing may have utility for family counseling.[84,85]

Genetic counseling resources and support are critical, and post-test genetic counseling is recommended if a germline mutation (pathogenic variant) is identified. Cascade testing for relatives is critical to inform the risk for familial cancers in all relatives. Post-test genetic counseling is recommended if positive family history but no pathogenic variant OR if only germline variants of unknown significance (VUS) are identified. This is to ensure accurate understanding of family implications and review indications for additional testing and/or follow up (including clinical trials of reclassification). Resources are available to check the known pathologic effects of genomic variants (eg, https://brcaexchange.org/about/app; https://www.ncbi.nlm.nih.gov/clinvar/). Information regarding germline mutations in patients with metastatic disease can be used to inform future treatments or to determine eligibility for clinical trials.

Somatic Tumor Testing Based on Risk Groups

Tumor testing recommendations are as follows:

1. Tumor testing for somatic homologous recombination gene mutations (eg, *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D*, *CHEK2, CDK12*) can be considered in patients with regional (N1) prostate cancer and is recommended for those with metastatic disease.
2. Tumor testing for MSI or dMMR can be considered in patients with regional or metastatic castration-naïve prostate cancer and is recommended in the metastatic CRPC setting.
3. Tumor mutational burden (TMB) testing may be considered in patients with metastatic CRPC.
4. Multigene molecular testing can be considered for patients with low-, intermediate-, and high-risk prostate cancer and life

expectancy ≥10 years (see *Tumor Multigene Molecular Testing*, below).

5. The Decipher molecular assay is recommended to inform adjuvant treatment if adverse features are found post-radical prostatectomy, and can be considered as part of counseling for risk stratification in patients with PSA resistance/recurrence after radical prostatectomy (category 2B). See *Tumor Multigene Molecular Testing*, below).

The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. When unsafe or unfeasible, plasma ctDNA assay is an option, preferably collected during biochemical (PSA) and/or radiographic progression in order to maximize diagnostic yield. Caution is needed when interpreting ctDNA-only evaluation due to potential interference from clonal hematopoiesis of indeterminate potential (CHIP), which can result in a false-positive biomarker signal.[86]

If MSI testing is performed, testing using an NGS assay validated for prostate cancer is preferred.[87-89] If MSI-H or dMMR is found, the patient should be referred for genetic counseling to assess for the possibility of Lynch syndrome. MSI-H or dMMR indicate eligibility for pembrolizumab for certain patients with metastatic CRPC (see *Pembrolizumab*, below).

Post-test genetic counseling is recommended if pathogenic/likely pathogenic somatic mutations in any gene that has clinical implications if also identified in germline (eg, *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2).* Post-test genetic counseling to assess for the possibility of Lynch syndrome is recommended if MSI-H or dMMR is found. Virtually none of the NGS tests is designed or validated for germline assessment. Therefore, over-interpretation of germline findings should be avoided. If a germline mutation is suspected, the patient should be recommended for genetic counseling and follow-up dedicated germline testing.

Additional Testing

Tumors from a majority of patients with metastatic CRPC harbor mutations in genes involved in the androgen receptor signaling pathway.[36] Androgen receptor splice variant 7 (AR-V7) testing in circulating tumor cells (CTCs) can be considered to help guide selection of therapy in the post-abiraterone/enzalutamide metastatic CRPC setting (discussed in more detail below, under *AR-V7 Testing*).

Risk Stratification for Clinically Localized Disease

Optimal treatment of prostate cancer requires estimation 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 post-recurrence radiation to control cancer after an unsuccessful radical prostatectomy?

NCCN and other risk classification schemas are prognostic and have not been shown to be predictive of benefit to a specific treatment. Thus, recommendations of when to offer conservative management versus radical therapy and the use of short-term versus long-term ADT are based on expert opinion and estimates of absolute benefit and harm from a given therapy in the context of NCCN risk groups.

There are newer risk classification schemas that have been shown to outperform NCCN risk groups,[90,91] as well as tools (ie, imaging, gene expression biomarkers, germline testing) that together improve risk stratification. These tools should not be ordered reflexively. They are recommended only when they will have the ability to change management (eg, active surveillance vs. radical treatment). Improved risk stratification can better identify patients who may derive greater or lesser absolute benefit from a given treatment.

NCCN Risk Groups

The NCCN Guidelines have, for many years, incorporated a risk stratification scheme that uses a minimum of stage, Gleason 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 recurrence after definitive local therapy.[92] Risk group stratification has been published widely and validated, and provides a better basis for treatment recommendations than clinical stage alone.[93,94]

A new prostate cancer grading system was developed during the 2014 International Society of Urological Pathology (ISUP) Consensus Conference.[95] Several changes were made to the assignment of Gleason pattern based on pathology. The new system assigns Grade Groups from 1 to 5, derived from the Gleason score.

- 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
  - For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well-formed glands is not factored into the grade.
- 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 (poorly formed/fused/cribriform glands can be a more minor component); or
  - Predominantly lacking glands and lesser component of well-formed glands (poorly formed/fused/cribriform glands can be a more minor component)
- Grade Group 5: Gleason score 9–10; lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands
  - For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well-formed glands is not factored into the grade.

Many experts believe that ISUP Grade Groups will enable patients to better understand their true risk level and thereby limit overtreatment. The new Grade Group system was validated in two separate cohorts, one of >26,000 patients and one of 5880 patients, treated for prostate cancer with either radical prostatectomy or radiation.[96,97] Both studies found that Grade Groups predicted the risk of recurrence after primary treatment. For instance, in the larger study, the 5-year biochemical recurrence-free progression probabilities after radical prostatectomy for Grade Groups 1 through 5 were 96% (95% CI, 95–96), 88% (95% CI, 85–89), 63% (95% CI, 61–65), 48% (95% CI, 44–52), and 26% (95% CI, 23–30), respectively. The separation between Grade Groups was less pronounced in the radiation therapy (RT) cohort, likely because of increased use of neoadjuvant/concurrent/adjuvant androgen deprivation therapy (ADT) in the higher risk groups. In another study of the new ISUP Grade Group system, all-cause mortality and prostate cancer-specific mortality were higher in patients in Grade Group 5 than in those in Grade Group 4.[98] Additional studies have supported the validity of this new system.[99-104] The NCCN Panel has accepted the new Grade Group system to inform better treatment discussions compared to those using Gleason score. Patients remain divided into very-low-, low-, intermediate-, high-, and very-high-risk groups.

The NCCN Guidelines Panel recognized that heterogeneity exists within each risk group. For example, an analysis of 12,821 patients showed that those assigned to the intermediate-risk group by clinical stage (T2b–T2c) had a lower risk of recurrence than those categorized according to Gleason score (7) or PSA level (10–20 ng/mL).[105] A similar trend of superior recurrence-free survival was observed in patients 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 or primary Gleason pattern.[106,107] Evidence also shows heterogeneity in the low-risk group, with PSA levels and percent positive cores affecting pathologic findings after radical prostatectomy.[108,109]

In a retrospective study, 1024 patients with intermediate-risk prostate cancer were treated with radiation with or without neoadjuvant and concurrent ADT.[110] Multivariate analysis revealed that primary Gleason pattern 4, number of positive biopsy cores ≥50%, and presence of >1 intermediate-risk factors (IRFs; ie, T2b-c, PSA 10–20 ng/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 and higher rates of distant metastasis and prostate cancer-specific mortality than the favorable intermediate-risk group. The use of active surveillance in patients with favorable intermediate-risk prostate cancer is discussed below (see *Active Surveillance in Favorable Intermediate Risk*). The NCCN Panel has included the separation of intermediate risk group into favorable and unfavorable subsets in their risk stratification scheme.

Nomograms

The more clinically relevant information that is used in the calculation of time to PSA recurrence, the more accurate the result. 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. The Partin tables were the first to achieve widespread use for counseling patients with clinically localized prostate cancer.[111-114] The tables give the probability (95% CI) that a patient with a certain clinical stage, Gleason score, and PSA will have a cancer of each pathologic stage. Nomograms can be used to inform treatment decision-making for patients contemplating active surveillance,[115-117] radical prostatectomy,[118-121] neurovascular bundle preservation[122-124] or omission of pelvic lymph node dissection (PLND) during radical prostatectomy,[125-128] brachytherapy,[118,129-131] or external beam RT (EBRT).[118,132] Biochemical progression-free survival (PFS) can be reassessed postoperatively using age, diagnostic serum PSA, and pathologic grade and stage.[118,133-135] Potential success of adjuvant or post-recurrence RT after unsuccessful radical prostatectomy can be assessed using a nomogram.[118,136]

None of the current models predicts with perfect accuracy, and only some of these models predict metastasis[117,118,133,137,138] and cancer-specific death.[119,121,139-141] Given the competing causes of mortality, many patients who sustain PSA recurrence will not live long enough to develop clinical evidence of distant metastases or to die from prostate cancer. Those with a short PSA doubling time (PSADT) are at greatest risk of death. Not all PSA recurrences are clinically relevant; thus, PSADT may be a more useful measure of risk of death.[142] 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.

Tumor Multigene Molecular Testing

Personalized or precision medicine is a goal for many translational and clinical investigators. Molecular testing of a tumor offers the potential of added insight into the "biologic behavior" of a cancer that could thereby aid in the clinical decision-making. The NCCN Prostate Cancer Guidelines Panel strongly advocates for use of life expectancy estimation, nomograms, and other clinical parameters such as PSA density as the foundations for augmented clinical decision-making. Whereas risk groups, life expectancy estimates, and nomograms help inform decisions, uncertainty about disease progression persists, and this is where the prognostic multigene molecular testing can have a role.

Several tissue-based molecular assays have been developed in an effort to improve decision-making in newly diagnosed patients considering active surveillance and in treated patients 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 or CAPRA risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT, likelihood of adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after operation, definitive EBRT, or post-recurrence EBRT.[143-155] Evaluation of diagnostic biopsy tissue from patients enrolled in the Canary PASS multicenter active surveillance cohort suggested that results of a molecular assay were not associated with adverse pathology either alone or in combination with clinical variables.[156]

Clinical utility studies on the tissue-based molecular assays have also been performed.[157-159] One prospective, clinical utility study of 3966 patients newly diagnosed with localized prostate cancer found that the rates of active surveillance increased with use of a tissue-based gene expression classifier.[157] Active surveillance rates were 46.2%, 75.9%, and 57.9% for those whose classifier results were above the specified threshold, those whose classifier results were below the threshold, and those who did not undergo genomic testing, respectively ($P < .001$). The authors estimate that one additional patient may choose active surveillance for every nine patients with favorable-risk prostate cancer who undergo genomic testing.

Another clinical utility study used two prospective registries of patients with prostate cancer post-radical prostatectomy (n = 3455).[158] Results of molecular testing with Decipher changed management recommendations for 39% of patients. This study also evaluated clinical benefit in 102 patients. Those who were classified as high risk by the assay had significantly different 2-year PSA recurrence rates if they received adjuvant EBRT versus if they did not (3% vs. 25%; hazard ratio [HR], 0.1; 95% CI, 0.0–0.6; $P = .013$). No differences in 2-year PSA recurrence were observed between those who did and did not receive adjuvant therapy in those classified as low or intermediate risk by the assay. Based on these results, the panel recommends that the Decipher molecular assay should be used to inform adjuvant treatment if adverse features are found post-radical prostatectomy.

Several of these assays are available, and four 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 have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous U.S. Food and Drug Administration (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 patients with low or favorable intermediate disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate, or Prolaris during initial risk stratification. Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris. In addition, Decipher may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence (category 2B for the latter setting). Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of patients with prostate cancer.

Initial Clinical Assessment and Staging Evaluation

For patients with very-low-, low-, and intermediate-risk prostate cancer and a life expectancy of 5 years or less and without clinical symptoms, further imaging and treatment should be delayed until symptoms develop, at which time imaging can be performed and ADT should be given. Those with a life expectancy less than or equal to 5 years who fall into the high- or very-high-risk categories should undergo bone imaging and, if indicated by nomogram prediction of lymph node involvement, pelvic +/- abdominal imaging.

For symptomatic patients and/or those with a life expectancy of greater than 5 years, bone and soft tissue imaging is appropriate for patients with unfavorable intermediate-risk, high-risk, and very-high-risk prostate cancer:

- Bone imaging can be achieved by conventional technetium-99m-MDP bone scan.
  - Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 prostate-specific membrane antigen (PSMA)-11, or F-18 piflufolastat PSMA can be considered for equivocal results on initial bone imaging.
- Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. mpMRI is preferred over CT for pelvic staging.
- Alternatively, Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging.
  - Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.

Retrospective evidence suggests that Gleason score and PSA levels are associated with positive bone scan findings.[160] Multivariate analysis of retrospective data on 643 patients 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).[161] mpMRI may detect large and poorly differentiated prostate cancer (Grade Group ≥2) and detect extracapsular extension (T staging) and is preferred over CT for abdominal/pelvic staging. mpMRI has been shown to be equivalent to CT scan for pelvic lymph node evaluation.

See *Imaging Techniques* below for a more detailed discussion.

Imaging Techniques

Imaging techniques are useful for staging and for detecting metastases and tumor recurrence. Current clinical imaging techniques for prostate cancer include conventional radiography (ie, x-rays), ultrasound, CT, MRI, single photon emission computed tomography (SPECT, scintigraphy), and PET. Some of these modalities have the ability to assess both anatomy and tumor function/biology. For example, functional MR sequences can be added to conventional anatomic MR sequences in a clinical examination such as diffusion-weighted imaging (DWI) to assess tumor cellularity or MR spectroscopy (MRS) to assess tumor metabolism.

Different modalities can also be merged to maximize prostate cancer assessment. For example, the functional information obtained with PET can be combined with the spatial and anatomic information with either CT (ie, PET/CT) or MRI (ie, PET/MRI) to inform about the locations of tumor foci for diagnosis or therapy response. Another example of the advantage of combining modalities is MR-ultrasound fusion guided biopsy (eg, MR-TRUS) where MRI datasets containing information on suspicious lesions identified by the radiologist are used by the urologist to navigate ultrasound-guided biopsies of the prostate for more accurate diagnosis.[162] More details on each technique are outlined in the algorithm under *Principles of Imaging*.

Multiparametric MRI (mpMRI)

The use of mpMRI in the staging and characterization of prostate cancer has increased in the last few years. mpMRI examinations typically include three sequences: T2-weighted imaging, DWI, and dynamic contrast enhancement (DCE) imaging. There has been increased interest in biparametric imaging that excludes the use of gadolinium contrast in prostate MRI examinations; however, more data are needed to identify the risk groups who would benefit most from this approach.[163] In general, it is recommended that mpMRI be performed on a 3 Tesla (3T) magnetic strength MRI scanner. This is the highest strength scanner in routine clinical use and provides the best possible evaluation of prostate cancer.

Additional instrumentation can be used, such as an endorectal coil (ERC) to improve image quality. If a lower strength 1.5T MRI cancer is required for a patient because of indwelling medical device incompatibility with 3T MRI, an ERC is recommended. Use of ERC in routine prostate imaging is controversial. Current data suggest that a 3T exam with ERC may not be significantly better than a 3T exam without ERC. Moreover, there may not be a significant difference in image interpretation between a 1.5T with ERC and 3T without ERC.[164] The use of ERC in prostate MRI also introduces new problems into the clinical workflow including patient discomfort, prostate distortion, increased scanner time and expense, and requirement of someone experienced to place the ERC.

Evidence supports the implementation of mpMRI in several aspects of prostate cancer management.[162] ***First,*** mpMRI helps detect larger and/or more poorly differentiated cancers (ie, Grade Group ≥2).[165] 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.[166-168] In fact, a recently published clinical study identified that MRI-targeted biopsy synergized with conventional systematic biopsy to identify

more clinically significant cancers.[169] ***Second,*** mpMRI aids in better assessment of extracapsular extension (T staging), with high negative predictive values (NPVs) in patients with low-risk disease.[170] mpMRI results may inform decision-making regarding nerve-sparing operation.[171] ***Third,*** mpMRI is equivalent to CT scan for staging of pelvic lymph nodes.[172,173] Finally, mpMRI outperforms bone scan and targeted x-rays for detection of bone metastases, with a sensitivity of 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).[174]

PET Imaging

The use of PET/CT or PET/MRI imaging using tracers other than F-18 fluorodeoxyglucose (FDG) for staging of small-volume recurrent or metastatic prostate cancer has rapidly expanded in recent years.[162] Currently, there are five PET tracers that are FDA approved for use in patients with prostate cancer: Ga-68 PSMA-11 (PSMA-HBED-CC), F-18 piflufolastat (DCFPyL), C-11 choline, F-18 fluciclovine, and F-18 sodium fluoride. Although these tracers are approved for the evaluation of patients with biochemical recurrence, the PSMA tracers Ga-68 PSMA-11 and F-18 piflufolastat are also approved for patients at initial staging with suspected metastatic disease. Tracer distribution in patients with prostate cancer can be imaged with either PET/CT or PET/MRI modalities. Although CT and MRI are equivalent in the assessment of lymphadenopathy, PET/MRI has the added advantage over PET/CT with enhanced tissue contrast that is especially important in evaluation of pelvic anatomy and prostate cancer assessment. Table 2 summarizes the FDA-cleared PET imaging tracers studied in prostate cancer. F-18 FDG PET should not be used routinely, because data are limited in patients with prostate cancer and suggest that its sensitivity is significantly lower than that seen with the above described tracers.[175-177]

PSMA-PET refers to a growing body of radiopharmaceuticals that target prostate specific membrane antigen (PSMA) on the surface of prostate cells. Because of the high density of PSMA receptors on the surface of cancer cells relative to adjacent prostate, PSMA-PET has the advantage of high signal-to-noise relative to adjacent tissues. The mechanistic role of androgen receptor signaling in PSMA regulation is still being investigated, as multiple reports in animals and humans suggest that androgen modulation can affect PSMA expression and may even be dichotomous in patients with castration-naïve versus castrate-resistant disease.[178-180] There are multiple PSMA radiopharmaceuticals at various stages of investigation. At this time, the NCCN Guidelines only recommend two PSMA tracers: the currently FDA-approved PSMA agents, F-18 piflufolastat and Ga-68 PSMA-11. F-18 piflufolastat PSMA or Ga-68 PSMA-11 PET/CT or PET/MRI can be considered as an alternative to standard imaging of bone and soft tissue for initial staging, the detection of biochemically recurrent disease, and as workup for progression with bone scan plus CT or MRI for the evaluation of bone, pelvis, and abdomen.

Studies suggest that PSMA PET imaging has a higher sensitivity than C-11 choline or F-18 fluciclovine PET imaging, especially at very low PSA levels.[181-186] The reported sensitivity and specificity for PSMA-11 PET/CT in the detection of nodal involvement in primary staging of patients with intermediate-, high-, and very-high-risk disease is 40% and 95%, respectively.[187] The patient-level positive predictive value (PPV) in detection of lesions in patients with biochemical recurrence (BCR) is 92%.[188] Similarly, the reported sensitivity and specificity for piflufolastat PET/CT in the detection of nodal involvement in primary staging of patients with unfavorable intermediate-, high-, and very-high-risk disease is 31% to 42% and 96% to 99%, respectively.[189,190] The patient-level correct localization rate (CLR; patient-level PPV validated by anatomic lesion co-localization) for piflufolastat PET/CT is 85% to 87%.[191] Thus, PSMA-11 and piflufolastat are considered equivalent. Because of the

increased sensitivity and specificity of PSMA PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.

PET/CT or PET/MRI detect small-volume disease in bone and soft tissues.[192,193] The reported sensitivity and specificity of C-11 choline PET/CT in restaging patients with biochemical recurrence ranges from 32% to 93% and from 40% to 93%, respectively.[194-203] The reported sensitivity and specificity of F-18 fluciclovine PET/CT ranges from 37% to 90% and from 40% to 100%, respectively.[200,204,205] A prospective study compared F-18 fluciclovine and C-11 choline PET/CT scans in 89 patients, and agreement was 85%.[200] Thus, choline and fluciclovine are considered equivalent in the evaluation of patients with biochemical recurrence. The panel believes that F-18 fluciclovine PET/CT or PET/MRI or C-11 choline PET/CT or PET/MRI may be used in patients with biochemical recurrence after primary treatment for further soft tissue and/or bone evaluation after bone scan, chest CT, and abdominal/pelvic CT or abdominal/pelvic MRI.

The use of these PET tracers can lead to changes in clinical management. The FALCON trial showed that results of F-18 fluciclovine PET/CT in 104 patients with biochemical recurrence after definitive therapy resulted in a change in disease management for 64% of patients.[206] In addition, the LOCATE trial demonstrated that fluciclovine frequently changed disease management plans in patients with biochemical recurrence.[207] In a similar fashion, data also show that PSMA PET has the ability to change radiation treatment planning in 53% (N = 45) of patients with high- and very-high-risk prostate cancer using PSMA-11 as well as change disease management in over half of a prospective cohort of 635 patients with BCR.[208,209] However, whether changes to treatment planning because of PET tracers have an impact on long-term survival remains to be studied.

F-18 sodium fluoride targets osteoblast activity where the fluoride is deposited into new bone formation, thus limiting use of this agent to the detection of osseous metastases. Fluoride PET/CT has greater sensitivity than standard bone scintigraphy in the detection of bone metastases, with 77% to 94% sensitivity, 92% to 99% specificity, and 82% to 97% PPV.[210] However, emerging evidence indicates that other tracers such as PSMA are at least equivalent to fluoride in the detection of osseous metastases with the added advantage of soft tissue metastasis detection.[211]

The Panel believes that bone imaging can be achieved by conventional technetium-99m-MDP bone scan. Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 PSMA-11, or F-18 piflufolastat PSMA can be considered for equivocal results on initial bone imaging. Alternatively, Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging. [212-215]

Histologic or radiographic confirmation of involvement detected by PET imaging is recommended whenever feasible due to the presence of false positives. Although false positives exist, literature suggests that these are outweighed by the increase in true positives detected by PET relative to bone scintigraphy. To reduce the false-positive rate, physicians should consider the intensity of PSMA-PET uptake and correlative CT findings in the interpretation of scans. Several reporting systems have been proposed but will not have been validated or widely used.[216,217] Moreover, although PET imaging may change treatment,[207] it may not change oncologic outcome. Earlier detection of bone metastatic disease, for instance, may result in earlier use of newer and more expensive therapies, which may not improve oncologic outcomes or OS.

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 overdetection.

Exposure to Ionizing Radiation

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 survivors of radiation exposure). The literature is conflicting with regard 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.[218] 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 from erroneous staging.

Adverse Reaction to Contrast Media

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, urticaria, pruritus) but occasionally severe reactions can be life-threatening (bronchospasm or anaphylaxis). The risk of severe reaction is low with non-ionic contrast materials.[219] Both iodinated CT contrast material and gadolinium-based MR contrast materials can be problematic in patients with reduced renal function. Gadolinium MR contrast media, in particular, is contraindicated in patients with acute renal failure or stage V chronic kidney disease (glomerular filtration rate [GFR] <15).[220] Patients in this category are significantly more likely to develop nephrogenic systemic fibrosis (NSF). Centers performing imaging studies with contrast materials should have policies in place to address the use of contrast in these patients.

False-Positive Scans and Overdetection

Every imaging test has limitations for sensitivity, specificity, and accuracy that involve both the nature of the imaging modality as well as the interpreting physician. Harm can arise when a tumor or tumor recurrence is not detected (ie, false negative), but harm to the patient and added expense to the medical system also can result from false-positive scans. Extensive workup of imaging findings that may otherwise be benign or indolent (ie, overdetection) 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 comprehensive care 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,[221] can assist in medical decision-making.

Observation

Observation involves monitoring the course of prostate cancer with a history and physical exam no more often than every 12 months (without surveillance biopsies) until symptoms develop or are thought to be imminent. If patients under observation become symptomatic, an assessment of disease burden can be performed, and treatment or palliation can be considered. Observation thus differs from active surveillance. The goal of observation is to maintain quality of life (QOL) 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 patients who are older or frail with comorbidity that will likely out-compete prostate cancer for cause of death. Johansson and colleagues[222] observed that only 13% of patients developed metastases 15 years after diagnosis of T0–T2 disease and only 11% had died from prostate cancer. Because prostate cancer will not be treated for cure for patients with shorter life expectancies, observation for as long as possible is a reasonable option based on physician discretion. Monitoring should include PSA and physical exam no more often than every 6 months, but will not involve surveillance biopsies or radiographic imaging. When symptoms develop or are imminent, patients can begin palliative ADT.

Active Surveillance

Active surveillance (formerly 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 patients with seemingly indolent cancer with the goal to defer or avoid 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.

Several large active surveillance cohort studies have shown that between 50% and 68% of those eligible for active surveillance may safely avoid treatment, and thus the possible associated side effects of treatment, for at least 10 years.[223-225] For example, in one study, 55% of the population remained untreated at 15 years.[224] Although a proportion of patients on active surveillance will eventually undergo treatment, the delay does not appear to impact cure rates, and numerous studies have shown that active surveillance can be a safe option for many patients.[223-233] In fact, a 2015 meta-analysis of 26 active surveillance cohort studies that included 7627 patients identified only 8 prostate cancer deaths and 5 cases of metastasis.[234]

Further, the ProtecT study, which randomized 1643 patients with localized prostate cancer to active surveillance, radical prostatectomy, or RT, found no significant difference in the primary outcome of prostate cancer mortality at a median of 10 years follow-up.[235] Of 17 prostate cancer deaths (1% of study participants), 8 were in the active surveillance group, 5 were in the operation group, and 4 were in the radiation group (P = .48 for the overall comparison). However, a 12.2% absolute increase in the rate of disease progression and a 3.4% absolute increase in the rate of metastases or prostate cancer death were seen in the active surveillance group.[235,236] Approximately 23% of participants had Gleason scores 7–10, and 5 of 8 deaths in the active surveillance group were in this subset. Patient-reported outcomes were compared among the 3 groups.[237] The operation group experienced the greatest negative effect on sexual function and urinary continence, whereas bowel function was worst in the radiation group.

In addition, studies have shown that active surveillance does not adversely impact psychological well-being or QOL.[237-242]

The proportion of patients with low-risk prostate cancer choosing active surveillance in the Veterans Affairs Integrated Health Care System increased from 2005 to 2015: from 4% to 39% of those <65 years and from 3% to 41% of those ≥65 years.[243] An analysis of the SEER database found a similar trend, with the use of active surveillance in patients with low-risk prostate cancer increasing from 14.5% in 2010 to 42.1% in 2015.[244] An international, hospital-based, retrospective analysis of greater than 115,000 patients with low-risk prostate cancer reported that active surveillance utilization increased, but the proportions were lower at 7% in 2010 and 20% in 2014.[245]

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. Shared decision-making, after appropriate counseling on the risks and benefits of the various options, is critical.

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. One important ongoing study that can help answer these questions is the prospective multi-institutional Canary PASS cohort study, which has been funded by the NCI.[230] Nine hundred five patients, median age 63 years and median follow-up 28 months, demonstrated 19% conversion to therapy. Much should be learned about the criteria for selection of and progression on active surveillance as this cohort and research effort mature.

Rationale

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

The debate about the need to diagnose and treat every individual who has prostate cancer is fueled by the high prevalence of prostate cancer upon autopsy of the prostate[246]; the high frequency of positive prostate biopsies in individuals with normal DREs and serum PSA values[247]; the contrast between the incidence and mortality rates of prostate cancer; and the need to treat an estimated 37 patients with screen-detected prostate cancer[248,249] or 100 patients with low-risk prostate cancer[250] to prevent one death from the disease. The controversy regarding overtreatment of prostate cancer and the value of prostate cancer early detection[248-254] has

been further informed by publication of the Goteborg study, a subset of the European Randomized Study of Screening for Prostate Cancer (ERSPC).[255,256] Many believe that this study best approximates proper use of PSA for early detection because it was population-based and involved a 1:1 randomization of 20,000 participants who received PSA every 2 years and used thresholds for prostate biopsy of PSA >3 and >2.5 since 2005. The 14-year follow-up reported in 2010 was longer than the European study as a whole (9 years) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial (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%).[255] Most impressively, 40% of the patients were initially on active surveillance and 28% were still on active surveillance at the time these results were analyzed. To prevent a prostate cancer death, 12 individuals would need to be diagnosed and treated as opposed to the ERSPC as a whole where 37 individuals needed to be treated. Analysis of 18-year follow-up data from the Goteborg study reduced the number needed to be diagnosed to prevent 1 prostate cancer death to 10.[257] Thus, early detection, when applied properly, should reduce prostate cancer mortality. However, that reduction comes at the expense of overtreatment that may occur in as many as 50% of patients treated for PSA-detected prostate cancer.[258]

The best models of prostate cancer detection and progression estimate that 23% to 42% of all U.S. screen-detected cancers were overtreated[259] and that PSA detection was responsible for up to 12.3 years of lead-time bias.[260] The NCCN Guidelines Panel responded to these evolving data with careful consideration of which patients 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-, low-, and favorable intermediate-risk prostate cancer; the ability to detect disease progression without compromising chance of cure; and the chance and consequences of treatment side effects.

Patient Selection

Epstein and colleagues[261] introduced clinical criteria to predict pathologically “insignificant” prostate cancer. Insignificant, or very-low-risk, prostate cancer is identified by: clinical stage T1c, biopsy Grade Group 1, 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.[262,263] A new nomogram may be better.[264] Although many variations upon this definition have been proposed (reviewed by Bastian and colleagues[265]), a consensus of the NCCN Guidelines Panel was reached that insignificant prostate cancer, especially when detected early using serum PSA, poses little threat to individuals with a life expectancy of 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 individual to 6 years in a 75-year-old individual.[260]

At this time, the NCCN Panel consensus is that active surveillance is preferred for all patients with very-low-risk prostate cancer and life expectancy greater than 10 years.

Active Surveillance in Low-Risk Disease

Panel consensus is that active surveillance is preferred for most patients with low-risk prostate cancer and a life expectancy greater than or equal to 10 years. However, the panel recognizes that there is heterogeneity

across the low-risk group, and that some factors may be associated with an increased probability of near-term grade reclassification including high PSA density, a high number of positive cores (eg, ≥3), high genomic risk (from tissue-based molecular tumor analysis), and/or a known *BRCA2* germline mutation.[266-268] Of note, core involvement in the major active surveillance cohort studies was generally low (see *Table 1* in the *Principles of Active Surveillance and Observation*, in the algorithm above). Therefore, in some of patients with low-risk prostate cancer, upfront treatment with radical prostatectomy or prostate RT may be preferred based on shared decision-making with the patient.

Active Surveillance in Favorable Intermediate-Risk Disease

The literature on outcomes of active surveillance in patients with intermediate-risk prostate cancer is limited.[269] In the PIVOT trial, patients with clinically localized prostate cancer and a life expectancy greater than or equal to 10 years were randomized to radical prostatectomy or observation.[270] Of the 120 participants with intermediate-risk disease who were randomized to observation, 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). After longer follow-up (median 12.7 years), a small difference was seen in all-cause mortality in those with intermediate-risk disease (absolute difference, 14.5 percentage points; 95% CI, 2.8–25.6), but not in those with low-risk disease (absolute difference, 0.7 percentage points; 95% CI, -10.5–11.8).[271] Urinary incontinence and erectile and sexual dysfunction, however, were worse through 10 years in the radical prostatectomy group. These results and the less-than-average health of participants in the PIVOT study[272] suggest that patients with competing risks may safely be offered active surveillance.

Other prospective studies of active surveillance that included patients with intermediate-risk prostate cancer resulted in favorable prostate cancer-specific survival rates of 94% to 100% for the full cohorts.[224,227,228] However, with extended follow-up, the Toronto group has demonstrated inferior metastasis-free survival for patients with intermediate-risk prostate cancer (15-year metastasis-free survival for cases of Gleason 6 or less with PSA <10 ng/mL, 94%; Gleason 6 or less with PSA 10–20 ng/mL, 94%; Gleason 3+4 with PSA 20 ng/mL or less, 84%; and Gleason 4+3 with PSA 20 ng/mL or less, 63%).[273]

Overall, the Panel interpreted these data to show that a subset of patients with favorable intermediate-risk prostate cancer and life expectancy greater than 10 years may be considered for active surveillance. However, the precise inclusion criteria and follow-up protocols need continued refinement. Patients must understand that a significant proportion of those clinically staged as having favorable intermediate-risk prostate cancer may have higher risk disease.[274-277] Particular consideration to active surveillance may be appropriate for those patients with a low percentage of Gleason pattern 4 cancer, low tumor volume, low PSA density, and/or low genomic risk (from tissue-based molecular tumor analysis), but should be approached with caution, include informed decision-making, and use close monitoring for progression.

Role of Race in Decisions Regarding Active Surveillance

Race is emerging as an important factor to consider when contemplating active surveillance, particularly for African-American patients. A CDC analysis of population-based cancer registries found that from 2003 to 2017, the incidence of prostate cancer was higher in black individuals than in white individuals, Hispanic individuals, American Indian/Alaska natives, and Asian/Pacific islanders.[278] Five-year survival for all stages combined was higher for white patients than for black or Hispanic patients, but survival for distant stage disease was higher for black patients than white patients. In an analysis that spanned 2010 to 2012, African Americans had a higher lifetime risk of developing (18.2% vs. 13.3%) and dying from

(4.4% vs. 2.4%) prostate cancer compared to Caucasian Americans.[279] In one study, the increase in prostate-cancer-specific mortality in African American patients was limited to those with grade group 1.[280] Multiple studies have shown that African Americans with very-low-risk prostate cancer may harbor high-grade (Grade Group ≥2) cancer that is not detected by pre-treatment biopsies. Compared to Caucasian Americans matched on clinical parameters, African Americans have been reported to have a 1.7- to 2.3-fold higher change of pathologic upgrading.[281,282] However, other studies have not seen different rates of upstaging or upgrading.[283,284] For example, in a retrospective study of 895 patients in the SEARCH database, no significant differences were seen in the rates of pathologic upgrading, upstaging, or biochemical recurrence between African American and Caucasian Americans.[283]

Several studies have reported that, among patients with low-risk prostate cancer who are enrolled in active surveillance programs, African Americans have higher risk of disease progression to higher Gleason grade or volume cancer than Caucasian Americans.[285-288] African Americans in the low- to intermediate-risk categories also appear to suffer from an increased risk of biochemical recurrence after treatment.[289] In addition, African American patients with low-risk or favorable intermediate-risk prostate cancer have an increase in all-cause mortality after treatment, mainly due to cardiovascular complications after ADT.[290]

Reasons for these clinical disparities are under investigation, but treatment disparities and access to health care may play a significant role.[291,292] In fact, results of some studies suggest that racial disparities in prostate cancer outcomes are minimized when health care access is equal.[293-296] Strategies to improve risk-stratification for African Americans considering active surveillance may include mpMRI in concert with targeted image-guided biopsies, which have been reported to improve detection of clinically significant tumors in some individuals.[297]

Confirmatory Testing

Confirmatory testing can help facilitate early identification of those patients who may be at a higher risk of future grade reclassification or cancer progression. Since an initial prostate biopsy may underestimate tumor grade or volume, confirmatory testing is strongly recommended within the first 6 to 12 months of diagnosis for patients who are considering active surveillance.

Before starting on an active surveillance program, mpMRI with calculation of PSA density should be considered to confirm candidacy for active surveillance if not performed during initial workup.[298] Patients with PI-RADS 4 or 5 on mpMRI have an increased risk of biopsy progression during active surveillance.[299]

In patients with low and favorable intermediate risk, molecular tumor analysis can also be considered before deciding whether to pursue active surveillance (see *Tumor Multigene Molecular Testing*, above). One study examined the role of molecular tumor analysis for predicting upgrading on surveillance biopsy or the presence of adverse pathology on eventual radical prostatectomy in patients in an active surveillance cohort.[156] In this study, results of the molecular testing did not significantly improve risk stratification over the use of clinical variables alone.

If results of mpMRI and/or molecular testing are concerning, a repeat biopsy may be appropriate.

Early confirmatory testing may not be necessary in patients who have had a complete workup including mpMRI prior to diagnostic biopsy, advanced PSA-based bloodwork, and/or molecular tumor analysis. However, all patients should undergo a confirmatory prostate biopsy within 1 to 2 years of their diagnostic biopsy.

Active Surveillance Program

The current NCCN recommendations for the active surveillance program include PSA no more often than every 6 months unless clinically indicated; DRE no more often than every 12 months unless clinically indicated; repeat prostate biopsy no more often than every 12 months unless clinically indicated; and repeat mpMRI no more often than every 12 months unless clinically indicated. Repeat molecular tumor analysis is discouraged during active surveillance. Results of a study of 211 patients with Grade Group 1 prostate cancer who had initial and repeat mpMRIs and PSA monitoring suggest that a negative initial mpMRI predicts a low risk of Gleason upgrading by systematic biopsy.[300] In addition, PSA velocity was significantly associated with subsequent progression in those with an initial negative mpMRI. In contrast, those with high-risk visible lesions on mpMRI before initiation of active surveillance had an increased risk of progression. A meta-analysis of 43 studies found the sensitivity and NPV for mpMRI to be 0.81 and 0.78, respectively.[301] An analysis of patients in Canary PASS found that mpMRI had an NPV and PPV for detecting Grade Group ≥2 cancer of 83% and 31%, respectively.[302] Another study found the NPV of mpMRI to be 80%.[303]

Whereas the intensity of surveillance may be tailored on an individual basis (eg, based on life expectancy and risk of reclassification), most patients should have prostate biopsies incorporated as part of their monitoring, but no more often than every 12 months, because PSA kinetics may not be reliable for predicting progression. Repeat biopsy is useful to determine whether higher Gleason grade exists, which may influence prognosis and hence the decision to continue active surveillance or proceed to definitive local therapy.[304] A repeat prostate biopsy should also be considered if the prostate exam changes, if mpMRI (if done) suggests more aggressive disease, or if PSA increases. However, literature suggests that as many as 7% of patients undergoing prostate biopsy will suffer an adverse event,[252] and those who develop urinary tract infection are often fluoroquinolone-resistant.[305] Radical prostatectomy may become technically challenging after multiple sets of biopsies, especially as it pertains to potency preservation.[306] Therefore, many clinicians choose to wait 2 years for a biopsy if there are no signs of progression.

If the PSA level increases and systematic prostate biopsy remains negative, mpMRI may be considered to exclude the presence of anterior cancer.[307]

In patients with a suspicious lesion on mpMRI, MRI-US fusion biopsy improves the detection of higher grade (Grade Group ≥2) cancers. Early experience supports the utilization of mpMRI in biopsy protocols to better risk stratify patients under active surveillance.[308-310] However, more recent studies have shown that a significant proportion of high-grade cancers are detected with systematic biopsy and not targeted biopsy in patients on active surveillance.[311-313]

Patients should be transitioned to observation (see Observation, above) when life expectancy is less than 10 years.

Considerations for Treatment of Patients on Active Surveillance

Reliable parameters of prostate cancer progression await the results of ongoing clinical trials. PSADT is not considered reliable enough to be used alone to detect disease progression.[314] If repeat biopsy shows Grade Group ≥3 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. Grade reclassification on repeat biopsy is the most common factor influencing a change in management from active surveillance to treatment. Other factors affecting decisions to actively treat include: increase in tumor volume, a rise in PSA density, as well as patient anxiety. Considerations for a change in management strategy should be made in the context of the patient's life expectancy.

Each of the major active surveillance series has used different criteria for reclassification.[223,224,229-232,315-318] Reclassification criteria were met by 23% of patients with a median follow-up of 7 years in the Toronto experience,[316] 36% of patients with a median follow-up of 5 years in the Johns Hopkins experience,[223] and 16% of patients with a median follow-up of 3.5 years in the University of California, San Francisco (UCSF) experience[232] (Table 3). Uncertainty regarding reclassification criteria and the desire to avoid missing an opportunity for cure drove several reports that dealt with the validity of commonly used reclassification criteria. The Toronto group demonstrated that a PSA trigger point of PSADT less than 3 years could not be improved upon by using a PSA threshold of 10 or 20, PSADT calculated in various ways, or PSA velocity greater than 2 ng/mL/y.[319] 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 patients on an annual prostate biopsy program, 35% demonstrated reclassification at a median follow-up of 2.9 years.[320] Neither PSADT (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 patients who demonstrate reclassification on prostate biopsy prevents evaluation of biopsy reclassification as a criterion for treatment or reduction of survival. Treatment of all patients who developed Gleason pattern 4 on annual prostate biopsies has thus far resulted in only 2 prostate cancer deaths among 1298 patients (0.15%) in the Johns Hopkins study.[223] However, it remains uncertain whether treatment of all who progressed 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 findings on three patients who died of prostate cancer in their experience with 450 patients on active surveillance.[316] These three deaths led them to revise their criteria for offering active surveillance, because each of these three patients probably had metastatic disease at the time of entry on active surveillance. The 450 patients were followed for a median of 6.8 years; OS was 78.6% and prostate cancer-specific survival was 97.2%.[316] Of the 30% (n = 145) of patients who progressed, 8% had an increase in Gleason grade, 14% had a PSADT less than 3 years, 1% developed a prostate nodule, and 3% were treated because of anxiety. One hundred thirty-five of these 145 patients were treated: 35 by radical prostatectomy, 90 by EBRT with or without ADT, and 10 with ADT alone. Follow-up is available for 110 of these patients, and 5-year biochemical PFS is 62% for those undergoing radical prostatectomy and 43% for those undergoing radiation. Longer-term follow-up of this cohort was reported in 2015.[224] 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 patients (1.3%) had developed metastatic disease, and only 36.5% of the cohort had received treatment by 10 years. In an analysis of 592 patients enrolled in this cohort who had 1 or more repeat prostate biopsies, 31.3% of cases were upgraded. Fifteen percent of upgraded cases were upgraded to Gleason ≥8, and 62% of total upgraded cases proceeded to active treatment.[321] Another analysis of this cohort revealed that metastatic disease developed in 13 of 133 patients with Gleason 7 disease (9.8%) and 17 of 847 patients with Gleason ≤6 disease (2.0%).[322] PSADT and the number of positive scores were also predictors of increased risk for the development of metastatic disease.

In comparison, among 192 patients on active surveillance who underwent delayed treatment at a median of 2 years after diagnosis in the Johns Hopkins experience, 5-year biochemical PFS was 96% for those who underwent radical prostatectomy and 75% for those who underwent radiation.[318] The two groups were similar by pathologic Gleason grade, pathologic stage, and margin positivity. All patients treated by radical

prostatectomy after progression on active surveillance had freedom from biochemical progression at a median follow-up of 37.5 months, compared to 97% of those in the primary radical prostatectomy group at a median follow-up of 35.5 months. A later publication from this group showed that 23 of 287 patients who were treated after active surveillance (8%) experienced biochemical recurrence, and the rate was independent of the type of treatment.[223] Several studies have shown that delayed radical prostatectomy does not increase the rates of adverse pathology.[230,323-325]

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 generally be reserved for patients whose life expectancy is 10 years or more. Stephenson and colleagues[121] 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).[326,327] With a median follow-up of 12.8 years, those assigned to the radical prostatectomy group had significant improvements in disease-specific survival, OS, and risk of metastasis and local progression.[326] The reduction in mortality was confirmed at 18 years of follow-up, with an absolute difference of 11%.[327] Overall, 8 patients needed to be treated to avert one death; that number fell to 4 for patients <65 years of age. Longer follow-up results were also reported, in which the cumulative incidence of death from prostate cancer was 19.6% and 31.3% in the radical prostatectomy and watchful waiting groups, respectively, at 23 years, with a mean increase of 2.9 years of life in the radical prostatectomy group.[328] 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 patients 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.[329] 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 patients with high-risk disease and in select patients with very-high-risk disease.

Retrospective data and population-based studies suggest that radical prostatectomy with PLND can be an effective option for patients with cN1 disease.[330-332] Extrapolation of results of STAMPEDE arm H, in which EBRT to the primary tumor improved OS and other endpoints in patients with low-volume metastatic disease, also suggests that local treatment to the prostate may be beneficial in patients with advanced disease.[333]

Radical prostatectomy is a treatment 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.[334,335] Overall and cancer-specific 10-year survival ranged from 54% to 89% and 70% to 83%, respectively.[334] Patient selection is important, and post-RT recurrence radical 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.[336,337] Laparoscopic and robot-assisted radical prostatectomy are commonly used and are considered comparable to conventional approaches in experienced hands.[338-340] In a cohort study using 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.[341] 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.[342] Oncologic outcome of a robotic versus open approach was similar when assessed by use of additional therapies[341] or rate of positive surgical margins,[343] 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.[343] Risk of positive surgical margins was the same. Two more recent meta-analyses showed a statistically significant advantage in favor of a robotic approach compared to an open approach in 12-month urinary continence[344] and potency recovery.[345] Early results from a randomized controlled phase 3 study comparing robot-assisted laparoscopic radical prostatectomy and open radical retropubic prostatectomy in 326 patients were published in 2016.[346,347] Urinary function and sexual function scores and rates of postoperative complications did not differ significantly between the groups at 6, 12, and 24 months after surgery. Rates of positive surgical margins were similar, based on a superiority test (10% in the open group vs. 15% in the robotic group). Assessment of oncologic outcomes from this trial will be limited because postoperative management and additional cancer therapies were not standardized between the groups.[346]

An analysis of the Prostate Cancer Outcomes Study on 1655 patients with localized prostate cancer compared long-term functional outcomes after radical prostatectomy or EBRT.[348] 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 urologic procedures than those who underwent radical prostatectomy, but higher incidence for hospital admissions, rectal or anal procedures, open surgical procedures, and secondary malignancies.[349]

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.[350] 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 and sexual function has been reported with nerve-sparing techniques.[351,352] Replacement of resected nerves with nerve grafts does not appear to be effective for patients undergoing wide resection of the neurovascular bundles.[353] The ability of mpMRI to detect extracapsular extension can aid in decision-making in nerve-sparing surgery.[171]

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 because this avoids 47.7% of PLNDs at a cost of missing 12.1% of positive pelvic lymph nodes.[126] A more recent analysis of 26,713 patients in the SEER database treated with radical prostatectomy and PLND between 2010 and 2013 found that the 2% nomogram threshold would avoid 22.3% of PLNDs at a cost of missing 3.0% of positive pelvic lymph nodes.[354] 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.[126]

PLND should be performed using an extended technique.[355,356] An extended PLND includes removal of all node-bearing tissue from an area bounded by the external iliac vein anteriorly, the pelvic side wall laterally, the bladder wall medially, the floor of the pelvis posteriorly, Cooper's ligament distally, and the internal iliac artery proximally. Removal of more lymph nodes using the extended technique has been associated with increased likelihood of finding lymph node metastases, thereby providing more complete staging.[357-359] A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to elimination of microscopic metastases,[358,360-362] although definitive proof of oncologic benefit is lacking.[363] PLND can be performed safely laparoscopically, robotically, or as an open procedure, and complication rates should be similar among the three approaches.

Radiation Therapy

RT techniques used in prostate cancer include EBRT, proton radiation, and brachytherapy. EBRT techniques include IMRT and hypofractionated, image-guided SBRT. An analysis that included propensity-score matching of patients showed that, among younger patients with prostate cancer, stereotactic body RT (SBRT) and intensity-modulated RT (IMRT) had similar toxicity profiles whereas proton radiation was associated with reduced urinary toxicity and increased bowel toxicity. The cost of proton therapy was almost double that of IMRT, and SBRT was slightly less expensive.[364]

The panel believes that highly conformal RT (CRT) techniques should be used to treat localized prostate cancer. Photon and proton beam radiation are both effective at achieving highly CRT with acceptable and similar biochemical control and long-term side effect profiles. Radiation techniques are discussed in more detail below.

External Beam Radiation Therapy

Over the past several decades, EBRT techniques have evolved to allow higher doses of radiation to be administered safely. Three-dimensional (3D) CRT (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.[137,365-367] The second-generation 3D technique, IMRT, has been used increasingly in practice.[368] IMRT reduced the risk of gastrointestinal toxicities and rates of post-recurrence therapy compared to 3D-CRT in some but not all older retrospective and population-based studies, although treatment cost is increased.[369-372]

More recently, moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) have been tested in randomized trials, and their efficacy has been similar or non-inferior to conventionally fractionated IMRT, with one trial showing fewer treatment failures with a moderately fractionated regimen.[373-382] Toxicity was similar between moderately hypofractionated and conventional regimens in some[373,377,380,381] but not all of the trials.[375,378,379] In addition, efficacy results varied among the trials, with some showing noninferiority or similar efficacy and others showing that hypofractionation may be less effective than conventional fractionation schemes. These safety and efficacy differences are likely a result of differences in fractionation schedules.[383] In addition, results of a

large cohort study showed no differences in QOL or urinary or bowel function between those that received hypofractionated versus conventional regimens.[384] Overall, the panel believes that hypofractionated IMRT techniques, which are more convenient for patients, can be considered as an alternative to conventionally fractionated regimens when clinically indicated. The panel lists fractionation schemes that have shown acceptable efficacy and toxicity on PROS-F page 3 of 5 in the algorithm above. An ASTRO/ASCO/AUA evidence-based guideline regarding the use of hypofractionated radiation in patients with localized prostate cancer concluded that moderately fractionated regimens are justified for routine use in this setting and provides more detail on the topic.[385]

Daily prostate localization using image-guided RT (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.[386-391] Kuban and colleagues[389] published an analysis of their dose-escalation trial of 301 patients with stage T1b to T3 prostate cancer. Freedom from biochemical or clinical recurrence 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). A longer follow-up (mean 14.3 years) found that improvements in biochemical and clinical recurrences were sustained, with lower rates of additional cancer treatment and better prostate cancer-specific mortality.[392] OS was not improved.

An analysis of the National Cancer Database found that dose escalation (75.6–90 Gy) resulted in a dose-dependent improvement in OS for patients with intermediate- or high-risk prostate cancer.[393] In light of these findings, the conventional 70 Gy dose is no longer considered adequate. A dose of 75.6 to 79.2 Gy in conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Patients Intermediate-risk and high-risk disease should receive doses of up to 81.0 Gy.[369,394,395]

Data suggested that EBRT and radical prostatectomy were effective for the treatment of localized prostate cancer.[396] 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 widely available 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.[397]

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.[397,398] The risk of late rectal complications following RT is related to the volume of the rectum receiving doses of radiation close to or exceeding the radiation dose required to control the primary tumor.

Biomaterials have been developed, tested, and FDA approved to serve as spacer materials when inserted between the rectum and prostate.[399,400] In a randomized phase 3 multicenter clinical trial of patients undergoing image-guided IMRT (IG-IMRT), where the risk of late (3-year) common terminology criteria for adverse events (CTCAE) was grade 2 or higher, physician-recorded rectal complications declined from 5.7% to 0% in the control versus hydrogel spacer group.[401] The hydrogel spacer group had a significant reduction in bowel QOL decline. No significant differences in

adverse events were noted in those receiving hydrogel placement versus controls. Results of a secondary analysis of this trial suggest that use of a perirectal spacer may decrease the sexual side effects of radiation.[402] Spacer implantation, however, is quite expensive and may be associated with rare complications such as rectum perforation and urethral damage.[403,404] Retrospective data also support its use in similar patients undergoing brachytherapy. Overall, the panel believes that biocompatible and biodegradable perirectal spacer materials may be implanted between the prostate and rectum in patients undergoing external radiotherapy with organ-confined prostate cancer in order to displace the rectum from high radiation dose regions. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.

If the cancer recurs, radical prostatectomy after RT is associated with a higher risk of complications than primary radical prostatectomy.[405] 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 PFS 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 (DFS) remained steady at 73% between 15 and 25 years of follow-up.[406] The panel lists several acceptable dosing schemas in the guidelines. The NRG Oncology/RTOG 0126 randomized clinical trial compared 79.2 Gy (44 fractions) and 70.2 Gy (39 fractions), both in 1.8 Gy fractions, in 1499 patients with intermediate-risk prostate cancer.[407] After a median follow-up of 8.4 years, the escalated dose reduced biochemical recurrences, but increased late toxicity and had no effect on OS.

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

EBRT has demonstrated efficacy in patients with high-risk and very-high-risk prostate cancer. One study randomized 415 patients to EBRT alone or EBRT plus 3-year ADT.[408] In another study (RTOG 8531), 977 patients with T3 disease treated with EBRT were randomized to adjuvant ADT or ADT at relapse.[409] Two other randomized phase 3 trials evaluated long-term ADT with or without radiation in a population of patients who mostly had T3 disease.[410-413] In all four studies, the combination group showed improved disease-specific survival and OS compared to single-modality treatment. Patients with a PSA nadir >0.5 ng/mL after radiation and 6 months of ADT have an adjusted HR for all-cause mortality of 1.72 (95% CI, 1.17–2.52; *P* = .01) compared with patients who received radiation only.[414]

Prophylactic nodal radiation should be considered in this population. [415-417] The randomized controlled phase 3 POP-RT trial showed that pelvic radiation can improve biochemical failure-free survival (FFS) and DFS compared with prostate-only radiation in patients with high- and very-high-risk prostate cancer.[418] The randomized phase 3 FLAME trial showed that a focal radiation boost to the mpMRI-visible lesion can improve biochemical DFS in this population.[419]

Some earlier data suggested that the use of docetaxel in combination with ADT and EBRT may benefit fit patients with high- and very-high-risk localized disease. The GETUG 12 trial randomized 413 patients with high- or very-high-risk prostate cancer to IMRT and ADT or ADT, docetaxel, and estramustine.[420] After a median follow-up of 8.8 years, 8-year relapse-free survival was 62% in the combination therapy arm and 50% in the ADT-only arm (adjusted HR, 0.71; 95% CI, 0.54–0.94; *P* = .017). The multicenter, phase 3 NRG Oncology RTOG 0521 trial randomized 563

patients with high- or very-high-risk prostate cancer ADT plus EBRT with or without docetaxel.[421] After a median follow-up of 5.7 years, 4-year OS was 89% (95% CI, 84%–92%) for ADT/EBRT and 93% (95% CI, 90%–96%) for ADT/EBRT/docetaxel (HR, 0.69; 90% CI, 0.49–0.97; one-sided *P* = .03). Improvements were also seen in DFS and the rate of distant metastasis. In the STAMPEDE trial, the addition of docetaxel to EBRT and ADT improved FFS in the non-metastatic group (HR, 0.60; 95% CI, 0.45–0.80; *P* < .01).[422] OS analysis did not show a significant difference, but was limited in power. Based on these data, the panel recommends the addition of docetaxel added to EBRT and 2 years of ADT as an option for patients with very-high-risk prostate cancer. The Panel recommends the addition of docetaxel to ADT plus EBRT as an option for patients with very-high-risk prostate cancer, but does not recommend it for patients with high-risk prostate cancer at this time.

The Panel recommends the addition of abiraterone to ADT plus EBRT as an option for patients with very-high-risk prostate cancer (fine-particle abiraterone can also be used, category 2B). This recommendation is based on data from the STAMPEDE trial. In STAMPEDE, the HRs for FFS in patients with non-metastatic disease treated with EBRT/ADT plus abiraterone compared with EBRT/ADT was 0.21 (95% CI, 0.15–0.31).[423]

A head-to-head comparison of ADT with either abiraterone or docetaxel in this setting and in patients with metastatic disease showed no difference in safety or in efficacy endpoints including OS.[424]

EBRT for Node-Positive Disease

EBRT with neoadjuvant, concurrent, and/or adjuvant ADT is the preferred option for patients with clinical N1 disease. Abiraterone can be added. In addition, ADT alone or with abiraterone are options. In each case, the use of the fine-particle formulation of abiraterone is a category 2B recommendation.

For adjuvant therapy for node-positive disease after radical prostatectomy, see *Adjuvant Therapy for pN1*, below.

EBRT to the Primary Tumor in Low-Volume M1 Disease

Patients with newly diagnosed, low-volume metastatic prostate cancer can be considered for ADT with EBRT to the primary tumor based on results from the randomized controlled phase 3 STAMPEDE trial.[333] In this multicenter, international study, 2061 patients were randomized to lifelong ADT with or without EBRT to the primary tumor (either 55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6 weekly fractions over 6 weeks). The primary outcome of OS by intention-to-treat (ITT) analysis was not met (HR, 0.92; 95% CI, 0.80–1.06; *P* = .266), but EBRT improved the secondary outcome of FFS (HR, 0.76; 95% CI, 0.68–0.84; *P* < .0001). In a pre-planned subset analysis, outcomes of patients with high metastatic burden (defined as visceral metastases; ≥4 bone metastases with ≥1 outside the vertebral bodies or pelvis; or both) and those with low metastatic burden (all others) were determined. EBRT improved OS (adjusted HR, 0.68; 95% CI, 0.52–0.90), prostate cancer-specific survival (adjusted HR, 0.65; 95% CI, 0.47–0.90), FFS (adjusted HR, 0.59; 95% CI, 0.49–0.72), and PFS (adjusted HR, 0.78; 95% CI, 0.63–0.98) in patients with low metastatic burden, but not in patients with high metastatic burden. Randomized clinical trials are ongoing to better test the value of removal or radiation of the primary tumor in patients with low metastatic burden who are beginning ADT.[425-429]

The Panel recommends against EBRT to the primary tumor in the case of high-volume M1 disease based on the HORRAD and STAMPEDE trials.[333,430] No improvement in OS was seen from the addition of EBRT to the primary when combined with standard systemic therapy in patients with high-volume M1 disease in either trial.

Stereotactic Body Radiation Therapy

The relatively slow proliferation rate of prostate cancer is reflected in a low α/β ratio,[431] most commonly reported between 1 and 4. These values are similar to that for the rectal mucosa. Because 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.

SBRT is a technique that delivers highly conformal, high-dose radiation in five or fewer treatment fractions, which are safe to administer only with precise, image-guided delivery.[432] Single-institution series with median follow-up as long as 6 years report excellent biochemical PFS and similar early toxicity (bladder, rectal, and QOL) compared to standard radiation techniques.[431-437] According to a pooled analysis of phase 2 trials, the 5-year biochemical relapse-free survival is 95%, 84%, and 81% for patients with low-, intermediate-, and high-risk disease, respectively.[438] A study of individual patient data from a cohort of 2142 patients with low- or intermediate-risk prostate cancer from 10 single-institution phase 2 trials and 2 multi-institutional phase 2 trials found that the 7-year cumulative rates of biochemical recurrence were 4.5%, 8.6%, and 14.9% for low-risk disease, favorable intermediate-risk disease, and unfavorable intermediate-risk disease, respectively.[439] Severe acute toxicity was rare, at 0.6% for grade 3 or higher genitourinary toxic events and 0.09% for grade 3 or higher gastrointestinal toxic events. Late (7-year cumulative incidence) toxicity rates were 2.4% and 0.4% for grade 3 or higher genitourinary toxic events and gastrointestinal toxic events, respectively.

SBRT may be associated with more toxicity than moderately fractionated IMRT. One retrospective study of 4005 patients reported higher genitourinary toxicity at 24 months after SBRT than IMRT (44% vs. 36%; *P* = .001).[440] Another phase 2 trial found increased toxicity with doses >47.5 Gy delivered in 5 fractions.[441] An analysis using the SEER database also reported that SBRT was more toxic than IMRT.[442] Overall, prospective evidence supports the use of SBRT in the setting of localized prostate cancer.[443]

Several phase 3 trials have been initiated comparing conventional regimens to SBRT.[444-446] Preliminary results show that the genitourinary and bowel toxicity is similar with the two techniques. In addition, the HYPO-RT-PC trial demonstrated non-inferiority of 42.7 Gy in seven fractions to 78.0 Gy in 39 fractions with respect to FFS in patients with intermediate-to-high-risk prostate cancer.[446]

SBRT/extremely hypofractionated IG-IMRT regimens (6.5 Gy per fraction or greater) can be considered 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 because late toxicity theoretically could be worse in hypofractionated regimens compared to conventional fractionation (1.8–2.0 Gy per fraction).

Brachytherapy

Brachytherapy involves placing radioactive sources into the prostate tissue. Brachytherapy has been used traditionally for low-risk cases because earlier studies found it less effective than EBRT for high-risk disease.[94,447] 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.[448,449]

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.[450] 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.[398] 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 recurrence compared with iodine-125 or palladium-103 permanent seed implants.[451,452] Current brachytherapy techniques attempt to improve the radioactive seed placement and radiation dose distribution.

There are currently two methods for prostate brachytherapy: low dose-rate (LDR) and high dose-rate (HDR). 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. Post-implant dosimetry should be performed to document the quality of an LDR implant.[453] HDR brachytherapy, which involves temporary insertion of a radiation source, is a newer approach.

Two groups have observed a lower risk of urinary frequency, urgency, and rectal pain with HDR brachytherapy compared with LDR brachytherapy (permanent seed implant).[454,455] Vargas and colleagues[456] reported that HDR brachytherapy results in a lower risk of erectile dysfunction than LDR brachytherapy. Commonly prescribed doses for LDR and HDR brachytherapy are listed in the guidelines.

For patients with very large or very small prostates, symptoms of bladder outlet obstruction (high International Prostate Symptom Score), or a previous TURP, seed implantation may be more difficult. These patients also have an increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, increased toxicity is expected from ADT, and prostate size may not decline in some patients. The potential toxicity of ADT must be weighed against the possible benefit of target reduction.

Ideally, the accuracy of brachytherapy treatment should be verified by daily prostate localization with techniques of IGRT: CT, ultrasound, implanted fiducials, or electromagnetic targeting/tracking. Endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials (discussed under *External Beam Radiation Therapy*, above) may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient-related factors (eg, medication usage, comorbid conditions). Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.

Brachytherapy Alone for Localized Disease

Brachytherapy alone is an option for patients with very low, low, or favorable intermediate-risk prostate cancer, depending on life expectancy. Patients with high-risk cancers are generally considered poor candidates for brachytherapy alone. Either LDR or HDR brachytherapy can be used in this setting.

Retrospective analyses show that LDR or HDR brachytherapy alone can be effective and well tolerated in this population.[457-461] A phase 2 trial in 300 patients with intermediate-risk prostate cancer also found LDR brachytherapy alone to be safe and effective.[462] However, randomized controlled trials comparing brachytherapy to radical prostatectomy or EBRT in this population are limited. In a single-center trial, 165 patients with low-risk prostate cancer were randomized to LDR brachytherapy with

iodine-125 seeds or radical prostatectomy. The 2-year biochemical FFS rates were similar between the groups at 96.1% after brachytherapy and 97.4% after radical prostatectomy (P = .35).[463] At 6-month follow-up, continence was better in the brachytherapy group whereas potency was better in the radical prostatectomy group.

Brachytherapy Boost

LDR or HDR brachytherapy can be added as a boost to EBRT plus ADT in patients with unfavorable intermediate-, high-, or very-high-risk prostate cancer being treated with curative intent. Combining EBRT and brachytherapy allows dose escalation while minimizing acute or late toxicity in patients with high-risk localized or locally advanced cancer.[464-467] This combination has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials, but with higher toxicity.[468-470] 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.[471]

The randomized ASCENDE-RT trial compared two methods of dose escalation in 398 patients with intermediate- or high-risk prostate cancer: dose-escalated EBRT boost to 78 Gy or LDR brachytherapy boost.[472] All patients were initially treated with 12 months of ADT and pelvic EBRT to 46 Gy. An ITT analysis found that the primary endpoint of biochemical PFS was 89% versus 84% at 5 years; 86% versus 75% at 7 years; and 83% versus 62% at 9 years for the LDR versus EBRT boost arms (log-rank P < .001). Toxicity was higher in the brachytherapy arm, with the cumulative incidence of grade 3 genitourinary events at 5 years of 18.4% for brachytherapy boost and 5.2% for EBRT boost (P < .001).[473] A trend for increased gastrointestinal toxicity with brachytherapy boost was also seen (cumulative incidence of grade 3 events at 5 years, 8.1% vs. 3.2%; P = .12). However, at 6-year follow-up, health-related QOL was similar between the groups in most domains, except that physical and urinary function scales were significantly lower in the LDR arm.[474] Whereas the toxicity is increased with the use of brachytherapy boost, this and other randomized controlled trials have not shown an improvement in OS or cancer-specific survival.[475]

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 PFS and disease-specific survival reaching 87% and 91%, respectively.[476,477] 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.[478] 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 recurrence rate when ADT was added to brachytherapy and EBRT.[479,480]

A large, multicenter, retrospective cohort analysis that included 1809 patients with Gleason score 9–10 prostate cancer found that multimodality therapy with EBRT, brachytherapy, and ADT was associated with improved prostate cancer-specific mortality and longer time to distant metastasis than either radical prostatectomy or EBRT with ADT.[481] In addition, an analysis of outcomes of almost 43,000 patients with high-risk prostate cancer in the National Cancer Database found that mortality was similar in patients treated with EBRT, brachytherapy, and ADT versus those treated with radical prostatectomy, but was worse in those treated with EBRT and ADT.[482]

To address historical trial data concerns for increased toxicity incidence associated with brachytherapy boost, careful patient selection and contemporary planning associated with lesser toxicity, such as use of

recognized organ at risk dose constraints, use of high-quality ultrasound and other imaging, and prescription of dose as close as possible to the target without excessive margins should be implemented.

Post-Recurrence Brachytherapy

Brachytherapy can be considered in patients with biochemical recurrence after EBRT. In a retrospective study of 24 patients who had EBRT as primary therapy and permanent brachytherapy after biochemical recurrence, the cancer-free and biochemical relapse-free survival rates were 96% and 88%, respectively, after a median follow-up of 30 months.[483] Results of a phase 2 study of post-recurrence 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.[484] Toxicities were mostly grade 1 and 2 and included gastrointestinal toxicity and urethral strictures, and one case of Grade 3 urinary incontinence. In another prospective phase 2 trial, the primary endpoint of grade ≥3 late treatment-related gastrointestinal and genitourinary adverse events at 9 to 24 months after post-recurrence brachytherapy was below the unacceptable threshold, at 14%.[485]

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 and are relatively resilient to radiation injury; therefore, 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.[486] 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 accurately predict 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 patients treated with proton therapy or EBRT report similar early toxicity rates.[487,488] A prospective QOL 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.[489] A Medicare analysis of 421 patients treated with proton therapy and a matched cohort of 842 patients treated with IMRT showed less genitourinary toxicity at 6 months for protons, although the difference disappeared after 1 year.[488] No other significant differences were seen between the groups. In contrast, a single-center report of prospectively collected QOL data revealed significant problems with incontinence, bowel dysfunction, and impotence at 3 months, 12 months, and greater than 2 years after treatment with proton therapy.[487] In that report, only 28% of patients 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.[490] With follow-up as mature as 80 months and using both propensity scoring and instrumental variable analysis, the authors concluded that patients 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.[488] The American Society for Radiation Oncology (ASTRO) evaluated proton therapy and created a model policy to support the society's position on payment coverage for proton beam therapy in 2014.[491] This model policy was updated in 2017 and recommends coverage of proton therapy for the treatment of non-metastatic prostate cancer if the patient is enrolled in either an institutional review board (IRB)-approved study or a multi-institutional registry that adheres to Medicare requirements for Coverage with Evidence Development (CED). The policy states: "In the treatment of prostate cancer, the use of [proton beam therapy] is evolving as the comparative efficacy evidence is still being developed. In order for an informed consensus on the role of [proton beam therapy] for prostate cancer to be reached, it is essential to collect further data, especially to understand how the effectiveness of proton therapy compares to other RT modalities such as IMRT and brachytherapy. There is a need for more well-designed registries and studies with sizable comparator cohorts to help accelerate data collection. Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry."

A prospective phase 2 clinical trial enrolled 184 patients with low- or intermediate-risk prostate cancer who received 70 Gy of hypofractionated proton therapy in 28 fractions.[492] The 4-year rate of biochemical-clinical FFS was 93.5% (95% CI, 89%–98%). Grade ≥2 acute GI and urologic toxicity rates were 3.8% and 12.5%, respectively. Late GI and urologic toxicity rates were 7.6% and 13.6%, respectively, at 4 years.

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

EBRT is an effective means of palliating isolated bone metastases from prostate cancer. Studies have confirmed the common practice in Canada

and Europe of managing prostate cancer with bone metastases with a short course of radiation to the bone. A short course of 8 Gy x 1 is as effective as, and less costly than, 30 Gy in 10 fractions.[493] 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 in 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).[494] 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.[495] The SCORAD randomized trial did not show non-inferiority for ambulatory status of single-fraction 8-Gy EBRT to 20 Gy in 5 fractions.[496]

The Panel notes that 8 Gy as a single dose is as effective for pain palliation at any bony site as longer courses of radiation, but re-treatment rates are higher. Other regimens (ie, 30 Gy in 10 fractions or 37.5 Gy in 15 fractions) may be used as alternative palliative dosing depending on clinical scenario (both category 2B).

Radiation to metastases has also been studied in the oligometastatic setting. The ORIOLE phase 2 randomized trial randomized 54 patients with recurrent castration-naïve prostate cancer and 1 to 3 metastases to receive SABR or observation at a 2:1 ratio.[497] The primary outcome measure was progression at 6 months by increasing PSA, progression detected by conventional imaging, symptomatic progression, initiation of ADT for any reason, or death. Progression at 6 months was lower in patients in the SABR arm than in the observation arm (19% vs. 61%; P = .005). The secondary endpoint of PFS was also improved in the patients who received SABR (not reached vs. 5.8 months; HR, 0.30; 95% CI, 0.11–0.81; P = .002). The SABR-COMET phase 2, international trial randomized 99 patients with controlled primary tumors and 1 to 5 metastatic lesions at 10 centers to standard of care or standard of care plus SABR.[498] Sixteen patients had prostate cancer. After a median follow-up of 51 months, the 5-year OS rate was higher in the SABR group (17.7% vs. 42.3%; stratified log-rank P = .006), as was the 5-year PFS rate (3.2% vs. 17.3%; P = .001). No differences were seen in adverse events or QOL.

The Panel believes that SBRT to metastases can be considered in the following circumstances:

- In patients with limited metastatic disease to the vertebra or paravertebral region when ablation is the goal (eg, concern for impending fracture or tumor encroachment on spinal nerves or vertebra).
- In patients with oligometastatic progression where PFS is the goal.
- In symptomatic patients where the lesion occurs in or immediately adjacent to a previously irradiated treatment field.

Comparison of Treatment Options for Localized Disease

Several large prospective, population/cohort-based studies have compared the outcomes of patients with localized prostate cancer treated with EBRT, brachytherapy, radical prostatectomy, observation, and/or active surveillance. Barocas et al compared radical prostatectomy, EBRT, and active surveillance in 2550 patients and found that, after 3 years, radical prostatectomy was associated with a greater decrease in urinary and sexual function than either EBRT or active surveillance.[499] Active surveillance, however, was associated with an increase in urinary irritative symptoms. Health-related QOL measures including bowel and hormonal function were similar among the groups, as was disease-specific survival.

Chen et al compared radical prostatectomy, EBRT, and brachytherapy against active surveillance in 1141 patients.[500] As in the Barocas study, radical prostatectomy was associated with greater declines in sexual and urinary function than other treatments at 3 months. In this study, EBRT

was associated with worse short-term bowel function, and both EBRT and brachytherapy were associated with worsened urinary obstructive and irritative symptoms. By 2 years, however, differences among the groups compared with active surveillance were insignificant. Results of a systematic review showed similar findings to these studies.[501]

Another study examined patient-reported outcomes in greater than 2000 patients with localized prostate cancer managed by radical prostatectomy, brachytherapy, EBRT with or without ADT, or active surveillance.[502] By 5 years, most functional differences were minimal between management approaches. However, radical prostatectomy was associated with worse incontinence in the full cohort and with worse sexual function in those with unfavorable intermediate-, high-, or very-high-risk disease than those treated with EBRT and ADT.

Other Local Therapies

Many therapies have been investigated for the treatment of localized prostate cancer in the initial disease and recurrent settings, with the goals of reducing side effects and matching the cancer control of other therapies. 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. At this time, the panel recommends only cryosurgery and high-intensity focused ultrasound (HIFU; category 2B) as local therapy options for RT recurrence in the absence of metastatic disease.

Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that damages tumor tissue through local freezing. In the initial disease setting, the reported 5-year biochemical disease-free rate after cryotherapy ranged from 65% to 92% in patients with low-risk disease using different definitions of biochemical recurrence.[503] A report suggests that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer.[504] A study by Donnelly and colleagues[505] randomly assigned 244 patients with T2 or T3 disease to either cryotherapy or EBRT. All patients received neoadjuvant ADT. There was no difference in 3-year OS or DFS. Patients who received cryotherapy reported poorer sexual function.[506] 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 survival and OS were similar.[507]

Cryosurgery has been assessed in patients with recurrent disease after RT.[508-510] In one registry-based study of 91 patients, the biochemical DFS rates at 1, 3, and 5 years were 95.3%, 72.4%, and 46.5%, respectively. Adverse events included urinary retention (6.6%), incontinence (5.5%), and rectourethral fistula (3.3%).[510]

HIFU has been studied for treatment of initial disease.[511,512] A prospective multi-institutional study used HIFU in 111 patients with localized prostate cancer.[511] The radical treatment-free survival rate was 89% at 2 years, and continence and erectile functions were preserved in 97% and 78% of patients, respectively, at 12 months. Morbidity was acceptable, with a grade III complication rate of 13%. In another prospective multi-institutional study, 625 patients with localized prostate cancer were treated with HIFU.[513] Eighty-four percent of the cohort had intermediate- or high-risk disease. The primary endpoint of FFS was 88% at 5 years (95% CI, 85%–91%). Pad-free urinary continence was reported by 98% of participants. Other case series studies have seen similar results.[514,515]

HIFU also has been studied for treatment of radiation recurrence.[516-522] Analysis of a prospective registry of patients treated with HIFU for radiation recurrence revealed median biochemical recurrence-free survival at 63 months, 5-year OS of 88%, and cancer-specific survival of 94%.[523] Morbidity was acceptable, with a grade III/IV complication rate of 3.6%.

Analysis of a separate prospective registry showed that 48% of those who received HIFU following radiotherapy recurrence were able to avoid ADT at a median follow-up of 64 months.[524]

Other emerging local therapies, such as focal laser ablation and vascular-targeted photodynamic (VTP) therapy have also been studied.[525,526] The multicenter, open-label, phase 3, randomized controlled CLIN1001 PCM301 trial compared VTP therapy (IV padeliporfin, optical fibers inserted into the prostate, and subsequent laser activation) to active surveillance in 413 patients with low-risk prostate cancer.[527] After a median follow-up of 24 months, 28% of participants in the VTP arm had disease progression compared with 58% in the active surveillance arm (adjusted HR, 0.34; 95% CI, 0.24–0.46; $P < .0001$). Negative prostate biopsy results were more prevalent in the VTP group (49% vs. 14%; adjusted RR, 3.67; 95% CI, 2.53–5.33; $P < .0001$). The most common serious adverse event in the VTP group was urinary retention (3 of 206 patients), which resolved within 2 months in all cases.

Disease Monitoring

Please refer to the NCCN Guidelines for Survivorship (available at www.NCCN.org) for recommendations regarding common consequences of cancer and cancer treatment (eg, cardiovascular disease risk assessment; anxiety, depression, trauma, and distress; hormone-related symptoms; sexual dysfunction) and on the promotion of physical activity, weight management, and proper immunizations in survivors.

Patients After Initial Definitive Therapy

For patients initially treated with intent to cure, serum PSA levels should be measured every 6 to 12 months for the first 5 years and then annually. PSA testing every 3 months may be better for patients 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.[528] 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 RT, the monitoring of serum PSA levels is recommended every 6 months for the first 5 years and then annually and a DRE is recommended annually. The clinician may opt to omit the DRE if PSA levels remain undetectable.

Patients with Castration-Naïve Disease on ADT

The intensity of clinical monitoring for patients on ADT for castration-naïve disease is determined by the response to initial ADT, EBRT, or both. Follow-up evaluation of these patients should include history and physical examination and PSA measurement every 3 to 6 months based on clinical judgment. Imaging can be considered periodically to monitor treatment response. The relative risk for bone metastasis or death increases as PSADT falls; a major inflection point appears at PSADT of 8 months. Bone imaging should be performed more frequently in these patients.[529]

Patients with Localized Disease Under Observation

Patients with localized disease on observation follow the same monitoring recommendations as patients with castration-naïve disease who are on ADT, except that the physical exam and PSA measurement should only be done every 6 months.

Workup for Progression

Castrate levels of testosterone should be documented if clinically indicated in patients with signs of progression, with adjustment of ADT as necessary. If serum testosterone levels are <50 ng/dL, the patient should undergo disease workup with bone and soft tissue imaging (see *Imaging Techniques* above for more details):

- Bone imaging can be achieved by conventional technetium-99m-MDP bone scan.
    - Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 PSMA-11, or F-18 PyL PSMA can be considered for equivocal results on initial bone imaging.
- Soft tissue imaging of pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI.
- Alternatively, Ga-68 PSMA-11 or F-18 PyL PSMA PET/CT or PET/MRI can be considered for bone and soft tissue (full body) imaging.
    - Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA-PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.

ASCO has published guidelines on the optimal imaging strategies for patients with advanced prostate cancer.[530] ASCO recommendations are generally consistent with those provided here.

Post-Radical Prostatectomy Treatment

Most patients who have undergone radical prostatectomy are cured of prostate cancer. However, some patients will have adverse pathologic features, positive lymph nodes, or biochemical persistence or recurrence. Some patients 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.[531,532] Serial PSA measurements can be helpful for stratifying patients at highest risk of progression and metastases.

Selecting patients appropriately for adjuvant radiation is difficult.

Adjuvant/Early Treatment for Adverse Features

Adjuvant radiation with or without ADT can be given to patients with PSA persistence (PSA does not fall to undetectable levels) or adverse pathologic features (ie, positive margins, seminal vesicle invasion, extracapsular extension) who do not have lymph node metastases. 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.[533] Monitoring after radical prostatectomy is also appropriate, with consideration of early EBRT for a detectable and rising PSA or PSA >0.1 ng/mL.

Decisions about when to initiate post-radical prostatectomy radiation and whether to include ADT are complex. The Panel recommends use of nomograms and consideration of age and comorbidities, clinical and pathologic information, PSA levels, PSADT, and Decipher molecular assay to individualize treatment discussion. Older trials conducted by SWOG and EORTC showed that post-prostatectomy adjuvant radiation improved biochemical PFS in patients with extraprostatic disease at radical prostatectomy.[534-536] More recent randomized trials that used modern surgical and radiation techniques provide high-level evidence that can be used to counsel patients and are discussed herein.

In the RADICALS-RT trial, 1396 patients with adverse features after radical prostatectomy were followed for a median 4.9 years and no differences were seen in 5-year biochemical PFS and freedom from non-protocol hormone therapy.[537] However, urinary incontinence and grade 3–4 urethral strictures were more frequent in the adjuvant therapy group. The

GETUG-AFU 17 trial and the TROG 08.03/ANZUP RAVES trial were both terminated early for unexpectedly low event rates, but similarly found no evidence of oncologic benefit with increased risk of genitourinary toxicity and erectile dysfunction when adjuvant therapy was used.[538,539] Another randomized trial, however, saw an improvement in 10-year survival for biochemical recurrence with the use of adjuvant therapy (HR, 0.26; 95% CI, 0.14–0.48; $P < .001$).[540]

Systematic reviews come to conflicting conclusions on the utility of immediate post-prostatectomy radiation in patients with adverse features.[541,542] A retrospective cohort analysis of more than 26,000 patients concluded that patients with adverse features after radical prostatectomy (ie, Gleason 8–10; pT3/4; pN1) should be candidates for adjuvant radiation because a reduction in all-cause mortality was observed in such patients.[543]

A limited amount of data inform the decision regarding the addition of ADT to EBRT in this setting. The ongoing SPPORT trial (NCT00567580) of patients with PSA levels between 0.1 and 2.0 ng/mL at least 6 weeks after radical prostatectomy has reported preliminary results on clinicaltrials.gov. The primary outcome measure of percentage of participants free from progression (FFP) at 5 years was 70.3 (95% CI, 66.2–74.3) for those who received EBRT to the prostate bed and 81.3 (95% CI, 77.9–84.6) for those who received EBRT with 4 to 6 months of ADT (luteinizing hormone-releasing hormone [LHRH] agonist plus antiandrogen). Results of a retrospective analysis of radical prostatectomy specimens from patients in RTOG 9601 suggest that those with low PSA and a low Decipher score derived less benefit (development of distant metastases, OS) from bicalutamide than those with a high Decipher score.[544] Patients with high Decipher genomic classifier scores (GC >0.6) should be strongly considered for EBRT and addition of ADT when the opportunity for early EBRT has been missed.

Overall, the Panel believes that adjuvant or early EBRT after recuperation from operation may be beneficial in patients with one or more adverse laboratory or pathologic features, which include positive surgical margin, seminal vesicle invasion, and/or extracapsular extension as noted in the guideline by the American Urological Association (AUA) and ASTRO.[545]

The value of whole pelvic irradiation in this setting is unclear due to a lack of benefit in PFS in two trials (RTOG 9413 and GETUG 01)[416,417,546,547]; whole pelvic radiation may be appropriate for selected patients.

Adjuvant Therapy for pN1

Adjuvant therapy can also be given to patients with positive lymph nodes found during or after radical prostatectomy. Several management options should be considered. ADT is a category 1 option, as discussed below (see *Neoadjuvant, Concurrent, and/or Adjuvant ADT with EBRT for Regional Disease*).[548] Retrospective data show that initial observation may be safe in some patients with N1 disease at radical prostatectomy, because 28% of a cohort of 369 patients remained free from biochemical recurrence at 10 years.[549] Therefore, another option is monitoring with consideration of early treatment for a detectable and rising PSA or PSA >0.1 ng/mL, based further on extrapolation of data from RADICALS-RT, GETUG-AFU 17, and TROG 08.03/ANZUP RAVES.[537-539] 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 Database 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.[550-553]

Biochemical Recurrence After Radical Prostatectomy

Patients who experience biochemical recurrence after radical prostatectomy fall into three groups: 1) those whose PSA level does not

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 two or more subsequent laboratory determinations (PSA recurrence); 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."[531] Group 3 does not require further evaluation until PSA increases, but the workup for 1 and 2 must include an evaluation for distant metastases.

Several retrospective studies have assessed the prognostic value of various combinations of pretreatment PSA levels, Gleason scores, PSADT, and the presence or absence of positive surgical margins.[554-558] A large retrospective review of 501 patients who received radiation for detectable and increasing PSA after radical prostatectomy[557] 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 PSADT ≤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 pathologic criteria.[559] Delivery of adjuvant or post-recurrence EBRT becomes both therapeutic and diagnostic—PSA response indicates local persistence/recurrence. Delayed biochemical recurrence requires restaging, and a nomogram[118,560] may prove useful to predict response, but it has not been validated.

The utility of imaging for patients with an early biochemical recurrence after radical prostatectomy depends on disease risk before operation and pathologic stage, Gleason grade, PSA, and PSADT 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.[561,562] In a series of 414 bone scans performed in 230 patients with biochemical recurrence after radical prostatectomy, the rate of a positive bone scan for patients with PSA >10 ng/mL was only 4%.[563]

The specific staging tests depend on the clinical history, but should include a calculation of PSADT to inform nomogram use and counseling. In addition, bone imaging; chest CT; abdominal/pelvic CT or abdominal/pelvic MRI; C-11 choline PET/CT or PET/MRI or F-18 fluciclovine PET/CT or PET/MRI; and prostate bed biopsy may be useful. The Decipher molecular assay can be considered for prognostication after radical prostatectomy (category 2B). A meta-analysis of five studies with 855 patients and median follow-up of 8 years found that the 10-year cumulative incidence metastases rates for patients classified as low, intermediate, and high risk by Decipher after radical prostatectomy were 5.5%, 15.0%, and 26.7%, respectively ($P < .001$).[564]

Bone imaging is 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.[565] A prostate bed biopsy may be helpful when imaging suggests local recurrence.

Patients with PSA recurrence (undetectable PSA that increases on two or more measurements) after radical prostatectomy may be observed or undergo primary EBRT with or without ADT if distant metastases are not detected.

Large retrospective cohort studies support the use of EBRT in the setting of biochemical recurrence, because it is associated with decreased all-cause mortality and increased prostate cancer-specific survival.[559,566] 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.[533] Treatment is most effective when pre-

treatment PSA level is below 0.5 ng/mL.[560] Paradoxically, post-recurrence EBRT was shown to be most beneficial when the PSADT time was less than 6 months in a cohort analysis of 635 patients,[559] although another study of 519 patients reported mortality reduction for both those with PSADT less than 6 months and those with PSADT greater than or equal to 6 months.[566] Most patients with prolonged PSADT may be observed safely.[567]

Six months of concurrent/adjuvant ADT can be coadministered with radiation in patients with rising PSA levels based on the results of GETUG-16.[568,569] However, a secondary analysis of RTOG 9601 found that patients with PSA ≤0.6 ng/mL had no OS improvement with the addition of bicalutamide to EBRT.[570] Two years instead of 6 months of ADT can be considered in addition to radiation for patients with persistent PSA after radical prostatectomy or for PSA levels that exceed 1.0 ng/mL at the time of initiation of therapy, based on results of RTOG 9601.[571] For 2 years of ADT, level 1 evidence supports 150 mg bicalutamide daily but an LHRH agonist could be considered as an alternative.[571]

ADT alone becomes the treatment when there is proven or high suspicion for distant metastases after PSA recurrence. Pelvic radiation is not recommended but may be given to the site of bone metastasis if in weight-bearing bones or if the patient is symptomatic. 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-Radiation Recurrence

The 2006 Phoenix definition was revised by ASTRO and the RTOG in Phoenix: 1) PSA rise by 2 ng/mL or more above the nadir PSA is the standard definition for biochemical recurrence after EBRT with or without hormonal therapy; 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 additional local therapy who are young and healthy.[572] 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 patients.

Workup for RT recurrence typically includes PSADT calculation, bone imaging, TRUS biopsy, and prostate MRI; in addition, a chest CT, an abdominal/pelvic CT or abdominal/pelvic MRI, C-11 choline PET/CT or PET/MRI, or F-18 fluciclovine PET/CT or PET/MRI can be considered.

Local radiation recurrences are most responsive to additional therapy when PSA levels at the time of treatment are low (<5 ng/mL). Biopsy should be encouraged at the time of radiation biochemical recurrence 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 recurrence.

Options for therapy for those with positive biopsy but low suspicion of metastases to distant organs and a life expectancy greater than 10 years include observation or radical prostatectomy with PLND in selected cases by highly experienced surgeons. Radical prostatectomy after RT recurrence can result in long-term disease control, but is often associated with impotence and urinary incontinence.[573] Other options for localized interventions include cryotherapy,[574] HIFU (category 2B),[516-519,523,524] and brachytherapy (reviewed by Allen and colleagues[575] and discussed in *Post-Recurrence Brachytherapy*, above). Treatment, however, needs to be individualized based on the patient's risk of progression, the likelihood of success, and the risks involved with therapy. For those with a life

expectancy less than or equal to 10 years, positive biopsy, and no distant metastases, observation or ADT are appropriate options.

Negative TRUS biopsy after post-radiation biochemical recurrence poses clinical uncertainties. Therefore, mpMRI or full-body PET imaging can be considered (see *Imaging Techniques,* above). In the absence of detectable metastases with a negative biopsy, observation or ADT are options for patients with PSA recurrence after radiation.

Patients with radiographic evidence of distant metastases should proceed to ADT for castration-naïve disease.

Androgen Deprivation Therapy

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

In the community, ADT has been commonly used as primary therapy for early-stage, low-risk disease, especially in the patients who are older. This practice has been challenged by a large cohort study of 66,717 patients ≥66 years of age with T1–T2 tumors.[576] No 15-year survival benefit was found in patients receiving ADT compared to observation alone. Similarly, another cohort study of 15,170 patients 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.[577] Placing patients with early prostate cancer on ADT should not be routine practice.

Antiandrogen 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.[578,579]

Castrate levels of serum testosterone (<50 ng/dL; <1.7 nmol/L) should be achieved with ADT, because low nadir serum testosterone levels were shown to be associated with improved cause-specific survival in the PR-7 study.[580] Patients who do not achieve adequate suppression of serum testosterone (<50 ng/dL) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, LHRH antagonists, or steroids), although the clinical benefit remains uncertain. Monitoring testosterone levels 12 weeks after first dose of LHRH therapy and upon increase in PSA should be considered.

ADT for Clinically Localized (N0,M0) Disease

ADT should not be used as monotherapy in clinically localized prostate cancer unless there is a contraindication to definitive local therapy, such as life expectancy less than 5 years and comorbidities. Under those circumstances, ADT may be an acceptable alternative if the disease is high or very high risk (see *Palliative ADT*, below).

In the clinically localized setting, ADT using an LHRH agonist—alone or with a first-generation antiandrogen—or an LHRH antagonist can be used as a neoadjuvant, concurrent, and/or adjuvant to EBRT in patients with unfavorable intermediate-, high-, or very-high-risk prostate cancer, as described in more detail below.

ADT used as neoadjuvant treatment before radical prostatectomy is strongly discouraged outside of a clinical trial.

Neoadjuvant, Concurrent, and/or Adjuvant ADT with EBRT for Intermediate-Risk Disease

The addition of short-term ADT to radiation improved OS and cancer-specific survival in three randomized trials containing 20% to 60% of patients 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).[571,581-583] Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly patients with high-risk disease (RTOG 8610).[584] Results of the EORTC 22991 trial showed that the addition of 6 months of ADT significantly improved biochemical DFS compared with radiation alone in those with intermediate-risk (75% of study population) and high-risk disease.[585] A secondary analysis of the RTOG 9408 trial showed that the benefit of ADT given with EBRT in patients intermediate-risk prostate cancer was limited to those in the unfavorable subset.[586]

RTOG 9910 and RTOG 9902 reinforced two important principles concerning the optimal duration of ADT and use of systemic chemotherapy in conjunction with EBRT.[587,588] RTOG 9910 is a phase 3 randomized trial targeting patients with intermediate-risk prostate cancer that compared 4 months to 9 months of ADT. RTOG 9408 had previously shown that 4 months of ADT combined with EBRT improved survival in those with intermediate-risk disease compared to EBRT alone.[583] Consistent with earlier studies, RTOG 9910 demonstrated that there is no reason to extend ADT beyond 4 months when given in conjunction with EBRT in patients with intermediate-risk disease.

RTOG 9902 compared long-term ADT and EBRT with and without paclitaxel, estramustine, and etoposide (TEE) chemotherapy in patients with locally advanced, high-risk prostate cancer.[589] In the randomized cohort of 397 patients with a median follow-up of 9.2 years, results demonstrated no significant difference in ADT+EBRT versus ADT+EBRT+TEE in OS (65% vs. 63%; *P* = .81), biochemical recurrence (58% vs. 54%; *P* = .82), distant metastases (16% vs. 14%; *P* = .42), or DFS (22% vs. 26%; *P* = .61), but a substantial increase in toxicity (3.9% vs. 0% treatment-related deaths), which resulted in early closure of the trial.[589] Thus, the fact that 6 months of ADT improved survival compared to EBRT alone does not mean it is better than 4 months of ADT, and the fact that systemic chemotherapy is effective in one setting (high-volume metastatic disease or CRPC) should not lead to the assumption that it will be beneficial in other settings (eg, high-risk localized disease).[590,591]

At this time, the Panel recommends 4 to 6 months of ADT when EBRT is given to patients as initial treatment of unfavorable intermediate-risk prostate cancer. If brachytherapy is added to EBRT in this setting, then 4 to 6 months of ADT is optional.

Neoadjuvant, Concurrent, and/or Adjuvant ADT with EBRT for 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 above. Combination therapy was consistently associated with improved disease-specific survival and OS compared to single-modality treatment in randomized phase 3 studies.[408,409,411,412,592]

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.[593] 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 OS. A subgroup analysis of patients with a Gleason score of 8 to 10 found an advantage in OS for long-term ADT at 10 years (32% vs. 45%, *P* = .0061). At a median follow-up of 19.6 years, long-term ADT was superior for all endpoints including OS in the entire cohort (12% relative reduction; *P* = .03).[594]

The 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.[595] The DART01/05 GICOR trial also reported similar results in patients with high-risk disease.[596] In a

secondary analysis of RTOG 8531, which mandated lifelong ADT for patients with locally advanced prostate cancer treated with EBRT, those who adhered to the protocol had better survival than those who discontinued ADT within 5 years.[597] Two randomized phase 3 trials showed 1.5 years of ADT was not inferior to 3 years of ADT.[598,599]

A meta-analysis of data from 992 patients enrolled in 6 randomized controlled trials showed that a longer duration of ADT with EBRT benefited patients with Grade Group 4 or 5 prostate cancer.[600]

Neoadjuvant, Concurrent, and/or Adjuvant ADT with EBRT for Recurrent Disease

Patients who develop PSA recurrence after radical prostatectomy without evidence of metastases can receive pelvic EBRT with neoadjuvant/concurrent/adjuvant ADT (see *ADT for M0 Biochemical Recurrence*, below).

ADT for Regional Disease

Primary ADT for Lymph Node Metastases

Patients initially diagnosed with node-positive disease who have a life expectancy greater than 5 years can be treated with primary ADT. Primary ADT options are orchiectomy, an LHRH agonist, an LHRH agonist with a first-generation antiandrogen, or an LHRH antagonist (category 2B); or orchiectomy, LHRH agonist, or LHRH antagonist with abiraterone. Another option for these patients is EBRT with 2 to 3 years of neoadjuvant/concurrent/adjuvant ADT (category 1, see *Neoadjuvant, Concurrent, and/or Adjuvant ADT with EBRT for Regional Disease*, below). For those patients with N1 disease who are treated with radiation to the prostate and pelvic nodes, abiraterone acetate (abiraterone) with ADT should be considered for a total of 2 years. Abiraterone should not be coadministered with an antiandrogen (see *Abiraterone Acetate in Castration-Naïve Prostate Cancer*, below).

The EORTC 30846 trial randomized 234 treatment-naïve patients with node-positive prostate cancer to immediate versus delayed ADT.[601] At 13 years median follow-up, the authors reported similar survival between the two arms, although the study was not powered to show non-inferiority.

Neoadjuvant, Concurrent, and/or Adjuvant ADT with EBRT for Regional Disease

Patients initially diagnosed with pelvic lymph node-positive disease who have a life expectancy greater than 5 years can be treated with EBRT with 2 to 3 years of neoadjuvant/concurrent/adjuvant ADT (category 1) with or without abiraterone. Alternatively, they can receive primary ADT without EBRT with or without abiraterone (see *Primary ADT for Lymph Node Metastases*, above and *Abiraterone Acetate in Castration-Naïve Prostate Cancer*, below). Neoadjuvant/concurrent/adjuvant ADT options are an LHRH agonist, an LHRH agonist with a first-generation antiandrogen, or an LHRH antagonist. Abiraterone should not be coadministered with an antiandrogen.

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 98 patients who were found to have positive lymph nodes at the time of radical prostatectomy to immediate continuous ADT or observation.[548] In the immediate ADT arm of 47 patients, 30 remained alive, 29 of whom were prostate cancer recurrence-free and 26 of whom were PSA recurrence-free after a median follow-up of 11.9 years (range, 9.7–14.5 years for survivors).[548,602] Those receiving immediate ADT also had a significant improvement in OS (HR, 1.84; 95% CI, 1.01–3.35).

However, these results differ from a SEER Medicare, population-based test of ADT published subsequently.[603] The SEER Medicare-based study of patients who underwent radical prostatectomy and had positive lymph nodes used propensity matching to compare patients who received ADT

within 120 days to those who were observed. The groups had similar median and range of follow-up for survivors, but OS and prostate cancer-specific survival were similar. The Messing study occurred prior to the PSA era, but the studies are similar in almost all other respects. The Messing study showed almost unbelievable benefit, and the population-based study of 731 patients showed no benefit. Furthermore, a meta-analysis resulted in a recommendation against ADT for pathologic lymph node metastatic prostate cancer in the ASCO guidelines.[604] In addition, a cohort analysis of 731 patients with positive nodes did not demonstrate a survival benefit of ADT initiated within 4 months of radical prostatectomy compared to observation.[603] At this time, the Panel recommends that patients with lymph node metastases found at radical prostatectomy should be considered for immediate ADT (category 1) with or without EBRT (category 2B), but that observation is also an option for these patients.

Palliative ADT

Palliative ADT can be given to patients with a life expectancy of less than or equal to 5 years who have high-risk, very-high-risk, regional, or metastatic prostate cancer. Palliative ADT also can be given to patients with disease progression during observation, usually when symptoms develop or when changes in PSA levels suggest that symptoms are imminent. The options in this setting are orchiectomy, LHRH agonist, or LHRH antagonist (category 2B for LHRH antagonist).

ADT for Castration-Naive Disease

The term “castration-naive" is used to define patients who have not been treated with ADT and those 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, and/or adjuvant ADT as part of RT provided they have recovered testicular function. Options for patients with castration-naïve disease who require ADT depend on the presence of distant metastases, and can be found in full in the Guidelines algorithm above.

ADT for castration-naïve prostate cancer can be accomplished using bilateral orchiectomy, an LHRH agonist or antagonist, or an LHRH agonist plus a first-generation antiandrogen. As discussed below, abiraterone or docetaxel can be added to orchiectomy, LHRH agonist, or LHRH antagonist for M1 disease. For patients with M0 disease, observation is preferred over ADT.

LHRH agonists and LHRH antagonists appear equally effective in patients with advanced prostate cancer.[605]

Medical or surgical castration combined with an antiandrogen 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 antiandrogen.[604] Meta-analysis data suggest that bicalutamide may provide an incremental relative improvement in OS by 5% to 20% over LHRH agonist monotherapy.[606,607] However, others have concluded that more complete disruption of the androgen axis (with finasteride, dutasteride, or antiandrogen added to medical or surgical castration) provides little if any benefit over castration alone.[608,609] Combined androgen blockade therapy adds to cost and side effects, and prospective randomized evidence that combined androgen blockade is more efficacious than ADT is lacking.

Antiandrogen monotherapy appears to be less effective than medical or surgical castration and is not recommended for primary ADT. Furthermore, dutasteride plus bicalutamide showed no benefit over bicalutamide alone in patients with locally advanced or metastatic prostate cancer.[610]

Recent evidence suggests that orchiectomy may be safer than an LHRH agonist. Four hundred twenty-nine patients with metastatic prostate cancer

who underwent orchiectomy were compared to 2866 patients who received LHRH agonist between 1995 and 2009. Orchiectomy was associated with lower risk of fracture, peripheral arterial disease, and cardiac-related complications, although risk was similar for diabetes, deep vein thrombosis, pulmonary embolism, and cognitive disorders.[611] Post-hoc analysis of a randomized trial of LHRH antagonist versus LHRH agonist found lower risk of cardiac events in patients with existing cardiac disease treated with LHRH antagonist.[612] The heart and T lymphocytes have receptors for LHRH. Therefore, LHRH agonists may affect cardiac contractility, vascular plaque stability, and inflammation.[613]

A new LHRH antagonist, relugolix, has been studied as ADT in patients with advanced prostate cancer in the randomized phase 3 HERO trial.[614] In this study, 622 patients received relugolix (120 mg orally once daily) and 308 received leuprolide (injections every 3 months) for 48 weeks. The patients had recurrence after primary definitive therapy, newly diagnosed metastatic castration-naïve disease, or advanced localized disease deemed unlikely to be cured with definite therapy. The primary endpoint, sustained castrate levels of testosterone (<50 ng per deciliter) through 48 weeks, showed noninferiority and superiority of relugolix over leuprolide (96.7%; 95% CI, 94.9–97.9 vs. 88.8% [95% CI, 84.6–91.8]; $P < .001$ for superiority). The secondary endpoint of castrate levels of testosterone on day 4 was also improved in the relugolix arm (56% vs. 0%). However, relugolix did not achieve superiority in the key clinical secondary endpoint of castration resistance-free survival compared to leuprolide (74% vs. 75%; $P = .84$). The incidence of major adverse cardiovascular events was 2.9% in the relugolix arm and 6.2% in the leuprolide arm (HR, 0.46; 95% CI, 0.24–0.88). The Panel includes relugolix alone as an option for ADT in patients with castration-naïve disease. However, the Panel notes that data are limited on long-term adherence of oral relugolix and the potential effects non-adherence may have on optimal ADT. Ongoing monitoring for sustained suppression of testosterone (<50 ng/dL) can be considered, and relugolix may not be a preferred agent if adherence is uncertain.

It is important to note that the HERO trial did not include patients receiving curative intent therapy (ie, individuals getting definitive EBRT plus ADT). Furthermore, relugolix shows a shorter time to testosterone recovery, which might be associated with a higher risk of death from prostate cancer.[615] Therefore, although the Panel considers relugolix to be an acceptable option in the curative-intent setting, additional studies in this setting are needed.

Patients should be queried about adverse effects related to ADT. Intermittent ADT should be used for those who experience significant side effects of ADT (see *Intermittent Versus Continuous ADT,* below).

ADT for M0 Biochemical Recurrence

Controversy remains about the timing and duration of ADT when disease persists or recurs after local therapy. Many believe that early ADT is best, but cancer control must be balanced against side effects. Early ADT is associated with increased side effects and the potential development of the metabolic syndrome.

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 (PSADT), 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 multicenter phase 3

TROG 03.06/VCOG PR 01-03 [TOAD] trial randomized 293 patients with PSA relapse after operation or radiation (n = 261) or who were not considered for curative treatment (n = 32) to immediate ADT or ADT delayed by a recommended interval of greater than or equal to 2 years.[616] Five-year OS was improved in the immediate therapy arm compared with the delayed therapy arm (91.2% vs. 86.4%; log-rank *P* = .047). No significant differences were seen in the secondary endpoint of global health-related QOL at 2 years.[617] In addition, there were no differences over 5 years in global QOL, physical functioning, role or emotional functioning, insomnia, fatigue, dyspnea, or feeling less masculine. However, sexual activity was lower and the hormone treatment-related symptoms score was higher in the immediate ADT group compared with the delayed ADT group. Most clinical trials in this patient population require PSA level ≥0.5 mg/dL (after radical prostatectomy) or "nadir + 2" (after radiation) for enrollment.

The Panel believes that the benefit of early ADT is uncertain and must be balanced against the risk of ADT side effects. Patients with an elevated PSA and/or a shorter PSADT (rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier. Patients 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 PSADT or rapid PSA velocity and long life expectancy may be encouraged to consider early ADT. Patients with prolonged PSADTs who are older are excellent candidates for observation.

Primary ADT for M1 Castration-Naïve Prostate Cancer

ADT with treatment intensification is preferred for most patients with metastatic prostate cancer. ADT alone is appropriate for some patients.[604] A PSA value ≤4 ng/mL after 7 months of ADT is associated with improved survival of patients newly diagnosed with metastatic prostate cancer.[618]

ADT options for M1 castration-naïve disease are:

- Orchiectomy ± docetaxel
- LHRH agonist alone ± docetaxel
- LHRH agonist plus first-generation antiandrogen ± docetaxel
- LHRH antagonist ± docetaxel
- Orchiectomy plus abiraterone, apalutamide, or enzalutamide
- LHRH agonist plus abiraterone, apalutamide, or enzalutamide
- LHRH antagonist plus abiraterone, apalutamide, or enzalutamide

In patients with overt metastases in weight-bearing bone who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone, antiandrogen therapy should precede or be coadministered with LHRH agonist for at least 7 days to diminish ligand binding to the androgen receptor.[619,620] 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 coadministration of antiandrogen is unnecessary.

The data supporting the addition of abiraterone, apalutamide, enzalutamide, or docetaxel to ADT in this setting are discussed below. These are all category 1, preferred options; the fine-particle formulation of abiraterone (discussed in *Abiraterone Acetate in M1 CRPC*, below) can be added to ADT as a category 2B option. ADT (LHRH agonist, LHRH antagonist, or orchiectomy) with EBRT to the primary tumor for low-volume metastatic disease is discussed in *EBRT to the Primary Tumor in Low-Volume M1 Disease*, above.

Abiraterone Acetate in Castration-Naïve Prostate Cancer

In February 2018, the FDA approved abiraterone in combination with prednisone for metastatic castration-naïve prostate cancer.[621,622] This approval was based on two randomized phase 3 clinical trials of

abiraterone and low-dose prednisone plus ADT that were reported in patients with newly diagnosed metastatic prostate cancer or high-risk or node-positive disease (STAMPEDE and LATITUDE) that demonstrated improved OS over ADT alone.[623] In LATITUDE, 1199 patients with high-risk, metastatic, castration-naïve prostate cancer were randomized to abiraterone with prednisone 5 mg once daily or matching placebos. High-risk disease was defined as at least two of the following: Gleason score 8–10, ≥3 bone metastases, and visceral metastases.[623] Efficacy was demonstrated at the first interim analysis, and the trial was unblinded. The primary endpoint of OS was met and favored abiraterone (HR, 0.62; 95% CI, 0.51–0.76; *P* < .0001). Estimated 3-year OS rates improved from 49% to 66% at 30 months follow-up. Secondary endpoints were improved and included delayed castration-resistant radiographic progression (from median 14.8–33.2 months), PSA progression (7.4–33.2 months), time to pain progression, and initiation of chemotherapy. After the first interim analysis, 72 patients crossed over from placebo to abiraterone. Final OS analysis of LATITUDE after a median follow-up of 51.8 months showed median OS was significantly longer in the abiraterone group than in the placebo group (53.3 months vs. 36.5 months; HR, 0.66; 95% CI, 0.56–0.78; *P* < .0001).[624]

Adverse events were higher with abiraterone and prednisone but were generally mild in nature and largely related to mineralocorticoid excess (ie, hypertension, hypokalemia, edema), hormonal effects (ie, fatigue, hot flushes), and liver toxicity.[623] Cardiac events, such as atrial fibrillation, were rare but slightly increased with abiraterone. The overall discontinuation rate due to side effects was 12%. Patient-reported outcomes were improved with the addition of abiraterone, with improvements in pain intensity progression, fatigue, functional decline, prostate cancer-related symptoms, and overall health-related QOL.[625] A limitation of this trial is that only 27% of placebo-treated patients received abiraterone or enzalutamide at progression, and only 52% of these patients received any life-prolonging therapy.[623]

A second randomized trial (STAMPEDE) of 1917 patients with castration-naïve prostate cancer demonstrated similar OS benefits.[423] However, unlike LATITUDE, STAMPEDE eligibility permitted patients with high-risk N0,M0 disease (2 of 3 high-risk factors: stage T3/4, PSA >40, or Gleason score 8–10; n = 509), or N1,M0 disease (pelvic nodal metastases; n = 369) in addition to M1 patients, who made up the majority of patients (n = 941). The majority of patients were newly diagnosed, while a minority had recurrent, high-risk, or metastatic disease after local therapy (n = 98). Thus, STAMPEDE was a heterogeneous mix of patients with high-risk, non-metastatic, node-positive, or M1 disease. In M1 patients, treatment with abiraterone plus prednisone was continued until progression. In patients with N1 or M0 disease, 2 years of abiraterone plus prednisolone was used if curative-intent EBRT was utilized. OS was improved in the overall population (HR, 0.63; 95% CI, 0.5–0.76; *P* < .0001) and in the M1 and N1 subsets, without any heterogeneity of treatment effect by metastatic status. The survival benefit of abiraterone was larger in patients <70 years of age than those ≥70 years (HR, 0.94 vs. HR, 0.51). Patients who were older also suffered increased toxicities, which suggests heterogeneity in clinical benefits by age and comorbidity. The secondary endpoint of FFS, which included PSA recurrence, was improved overall (HR, 0.29; *P* < .0001) and in all subgroups regardless of M1 (HR, 0.31), N1 (HR, 0.29), or M0 (HR, 0.21) status. No heterogeneity for FFS was observed based on subgroups or by age. In this trial, subsequent life-prolonging therapy was received by 58% of those in the control group, which included 22% who received abiraterone and 26% who received enzalutamide. Thus, these data reflect a survival advantage of initial abiraterone in newly diagnosed patients compared with deferring therapy to the CRPC setting.

Adverse events in STAMPEDE were similar to that reported in LATITUDE, but were increased in patients who were older, with higher incidences of grade 3–5 adverse events with abiraterone (47% vs. 33%) and 9 versus 3 treatment-related deaths. Severe hypertension or cardiac disorders were noted in 10% of patients and grade 3–5 liver toxicity in 7%, which illustrates the need for blood pressure and renal and hepatic function monitoring.

Taken together, these data led the NCCN Panel to recommend abiraterone with 5-mg once-daily prednisone as a treatment option with ADT for patients with newly diagnosed, M1, castration-naïve prostate cancer (category 1). Alternatively, the fine-particle formulation of abiraterone can be used (category 2B; see *Abiraterone Acetate in M1 CRPC*, below). For patients undergoing curative-intent treatment for N1 disease, abiraterone can be added to EBRT with 2 to 3 years of neoadjuvant/concurrent/adjuvant ADT or can be given with ADT for castration-naïve disease (without EBRT). The fine-particle formulation of abiraterone is an option (category 2B; see *Abiraterone Acetate in M1 CRPC*, below). However, there was insufficient survival, FFS data, and follow-up available to recommend abiraterone for patients with high-risk or very-high-risk N0 M0 prostate cancer. Further follow-up and dedicated ongoing clinical trials are needed in this curative-intent RT population.

Abiraterone can be given at 250 mg/day and administered following a low-fat breakfast, as an alternative to the dose of 1000 mg/day after an overnight fast (see *Abiraterone Acetate in M1 CRPC*, below).[626] The cost savings may reduce financial toxicity and improve adherence.

Apalutamide in Castration-Naïve Prostate Cancer

The double-blind phase 3 TITAN clinical trial randomized 1052 patients with metastatic, castration-naïve prostate cancer to ADT with apalutamide (240 mg/day) or placebo.[627] Participants were stratified by Gleason score at diagnosis, geographic region, and previous docetaxel treatment. The median follow-up was 22.7 months. Both primary endpoints were met: radiographic PFS (68.2% vs. 47.5% at 24 months; HR for radiographic progression or death, 0.48; 95% CI, 0.39–0.60; $P < .001$) and OS (82.4% vs. 73.5% at 24 months; HR for death, 0.67; 95% CI, 0.51–0.89; $P = .005$). Adverse events that were more common with apalutamide than with placebo included rash, hypothyroidism, and ischemic heart disease. Health-related QOL was maintained during treatment.[628] At final analysis of TITAN, median OS was improved with apalutamide plus ADT compared with ADT alone after a median follow-up of 44 months (NR vs. 52.2 months; HR, 0.65; 95% CI, 0.53–0.79; $P < .001$)[629]

Apalutamide is a category 1 option for patients with M1 castration-naïve prostate cancer. The FDA approved this indication in September of 2019.[630,631]

Enzalutamide in Castration-Naïve Prostate Cancer

The open-label randomized phase 3 ENZAMET clinical trial compared enzalutamide (160 mg/day) plus ADT (LHRH analog or surgical castration) with a first-generation antiandrogen (bicalutamide, nilutamide, or flutamide) plus ADT in 1125 patients with metastatic castration-naïve prostate cancer.[632] Stratification was by volume of disease, planned use of early docetaxel, planned use of bone anti-resorptive therapy, comorbidity score, and trial site. The primary endpoint of OS was met at the first interim analysis with median follow-up of 34 months (HR for death, 0.67; 95% CI, 0.52–0.86; $P = .002$). Enzalutamide also improved secondary endpoints, such as PFS using PSA levels and clinical PFS.

In the double-blind randomized phase 3 ARCHES clinical, 1150 patients with metastatic castration-naïve prostate cancer were randomized to receive ADT with either enzalutamide (160 mg/day) or placebo. Participants were stratified by disease volume and prior docetaxel use. The primary endpoint was radiographic PFS, which was improved in the

enzalutamide group after a median follow-up of 14.4 months (19.0 months vs. not reached; HR, 0.39; 95% CI, 0.30–0.50; *P* < .001).[633]

The safety of enzalutamide in these trials was similar to that seen in previous trials in the castration-resistant setting. Adverse events associated with enzalutamide in these trials included fatigue, seizures, and hypertension.[632,633]

Enzalutamide is a category 1 option for patients with M1 castration-naïve prostate cancer.

Intermittent Versus Continuous ADT

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 QOL.[634,635] Some patients 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.

Intermittent ADT in Non-Metastatic Disease

The Canadian-led PR.7 trial was a phase 3 trial of intermittent versus continuous ADT in patients with non-metastatic prostate cancer who experienced biochemical recurrence after primary or post-recurrence EBRT.[636] One thousand three hundred eighty-six patients with PSA >3 ng/mL 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 OS (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 in 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 patients with Gleason sum greater than 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).[636] In this situation, patients should be given the option to weigh the effects of ADT on QOL 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.[637]

The multinational European ICELAND trial randomized 702 participants with locally advanced or biochemically recurrent prostate cancer to continuous or intermittent ADT.[638] Clinical outcomes, which included time to PSA progression, PSA PFS, OS, mean PSA levels over time, QOL, and adverse events, were similar between the arms.

A 2015 meta-analysis identified 6 randomized controlled trials comparing continuous with intermittent ADT in patients with locally advanced prostate cancer and found no difference in mortality and progression and an advantage of the intermittent approach in terms of QOL and adverse effects.[639]

Intermittent ADT in Metastatic Disease

Hussain and colleagues[640] 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 HR for death with intermittent ADT was 1.10 with a 90% CI between 0.99 and 1.23, which exceeded the prespecified 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 prespecified time points. A secondary analysis of SWOG 9346 showed that intermittent ADT did not reduce endocrine, bone, or cognitive events, whereas it increased the incidence of ischemic and thrombotic events.[641]

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).[640] 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.

A population-based analysis that included 9772 patients with advanced prostate cancer aged greater than or equal to 66 years showed that intermittent ADT reduced the risks of total serious cardiovascular events by 36%, heart failure by 38%, and pathologic fracture by 48%, compared with continuous ADT.[642] Furthermore, several meta-analyses of randomized controlled trials reported no difference in survival between intermittent ADT and continuous ADT.[643-645] Another recent analysis concluded that the non-inferiority of intermittent to continuous ADT in terms of survival has not been clearly demonstrated.[646] Still, the intermittent approach leads to marked improvement in QOL compared to the continuous approach in most studies, and the Panel believes that intermittent ADT should be strongly considered.

A more personalized approach could be to 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[618]: 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 QOL, and therefore continuous ADT is reasonable because it is easier to administer.[637] However, for those patients with significant side effects impacting QOL, 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 initially present 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, loss of libido, erectile dysfunction, shrinkage of penis and testicles, loss of muscle mass and strength, fatigue, anemia, breast enlargement and tenderness/soreness, depression and mood swings, hair

loss, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes, acute kidney injury, and cardiovascular disease.[647-649] The intensity and spectrum of these side effects vary greatly. In general, the side effects of continuous ADT increase with the duration of treatment. In addition, some forms of ADT may result in lower risk than others. For example, relugolix was associated with a lower risk of major adverse cardiovascular events than leuprolide in the phase 3 HERO study (also see *ADT for Castration-Naïve Disease,* above), although the FDA considered these results in HERO to be exploratory and therefore did not allow for these data to be included in the prescribing information for relugolix.[614] Overall, very limited prospective head-to-head studies to date have evaluated the cardiovascular toxicity of LHRH agonists versus LHRH antagonists as the primary endpoint.

Recent evidence suggests that a link between ADT and cognitive decline, dementia, or future Alzheimer's disease may exist, although data are inconsistent, the risk is low, and the link remains to be proven.[650-657]

Patients and their medical providers should be advised about these risks prior to treatment. Many side effects of ADT are reversible or can be avoided or mitigated. For example, physical activity can counter many of these symptoms and should be recommended (see NCCN Guidelines for Survivorship, available at www.NCCN.org). Use of statins also should be considered.

Bone Health During ADT

Medical or surgical ADT is associated with greater risk for osteoporosis and clinical fractures. In large population-based studies, for example, ADT was associated with a 21% to 54% relative increase in fracture risk.[658-660] Longer treatment duration conferred greater fracture risk. Age and comorbidity also were associated with higher fracture incidence. In a population-based cohort of 3295 patients, surgical castration was associated with a significantly lower risk of fractures than medical castration using an LHRH agonist (HR, 0.77; 95% CI, 0.62–0.94; $P = .01$).[613] ADT increases bone turnover and decreases bone mineral density,[661-664] 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,[665] and treatment-related sarcopenia appears to contribute to frailty and increased risk of falls in patients who are older.

The NCCN Guidelines Panel recommends screening and treatment for osteoporosis according to guidelines for the general population from the National Osteoporosis Foundation.[666] A baseline bone mineral density study should be considered for the patients on ADT. The National Osteoporosis Foundation guidelines include: 1) calcium (1000–1200 mg daily from food and supplements) and vitamin D3 (400–1000 IU daily); and 2) additional treatment for males aged greater than or equal to 50 years with low bone mass (T-score between -1.0 and -2.5, osteopenia) at the femoral neck, total hip, or lumbar spine by dual-energy x-ray absorptiometry (DEXA) scan and a 10-year probability of hip fracture greater than or equal to 3% or a 10-year probability of a major osteoporosis-related fracture greater than or equal to 20%. Fracture risk can be assessed using the algorithm FRAX®, recently released by WHO.[667] 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.[668-670] 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 3 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.[671] Denosumab also was approved for prevention of SREs in patients with bone metastasis (see *Chemotherapy, Immunotherapy, and Targeted Therapy*).

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 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.[672] After controlling for other variables, which included age and comorbidity, ADT with an LHRH 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.[584,672-679] 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.[680] Other population-based studies resulted in similar findings.[613,681] However, a Taiwan National Health Insurance Research Database analysis found no difference in ischemic events with LHRH agonist therapy or orchiectomy.[682] A French database study showed the cardiovascular risk to be similar in patients taking LHRH agonists and antagonists.[683] However, some data suggest that LHRH antagonists might be associated with a lower risk of cardiac events within 1 year in patients with preexisting cardiovascular disease (history of myocardial ischemia, coronary artery disease, myocardial infarction, cerebrovascular accident, angina pectoris, or coronary artery bypass) compared with agonists.[612] Patients with a recent history of cardiovascular disease appear to have higher risk,[684] and increased physical activity may decrease the symptoms and cardiovascular side effects of patients treated with ADT.[685]

Several mechanisms may contribute to greater risk for diabetes and cardiovascular disease during ADT. ADT increases fat mass and decreases lean body mass.[665,686,687] ADT with an LHRH agonist increases fasting plasma insulin levels[688,689] and decreases insulin sensitivity.[690] ADT also increases serum levels of cholesterol and triglycerides.[688,691]

ADT may also prolong the QT/QTc interval. Providers should consider whether the benefits of ADT outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, and frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected, and periodic monitoring of electrocardiograms and electrolytes should be considered.

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 patients receiving ADT. Whether strategies for screening, prevention, and treatment of diabetes and cardiovascular

disease in patients receiving ADT should differ from those of the general population remains uncertain.

Management of Metastatic Castration-Sensitive Prostate Cancer

ADT with treatment intensification is strongly recommended for patients with metastatic castration-sensitive prostate cancer. The use of ADT monotherapy in this setting is discouraged unless there are clear contraindications to combination therapy. Treatment intensification options include doublet therapy of ADT with abiraterone, apalutamide, or enzalutamide; triplet therapy of ADT with docetaxel and abiraterone or darolutamide; or ADT with EBRT to the primary tumor for low-metastatic burden. The data supporting doublet or triplet therapy in this setting are discussed below. The doublet and triplet therapies are all category 1, preferred options; the fine-particle formulation of abiraterone (discussed in *Abiraterone Acetate in M1 CRPC*, below) can be added to ADT as a category 2B, other recommended option. ADT with EBRT to the primary tumor for patients with low metastatic burden is discussed in *EBRT to the Primary Tumor in Low-Metastatic-Burden M1 Disease*, above.

Doublet Therapies for Castration-Sensitive Prostate Cancer

Abiraterone Acetate in Castration-Sensitive Prostate Cancer

In February 2018, the FDA approved abiraterone in combination with prednisone for metastatic castration-sensitive prostate cancer. This approval was based on two randomized phase 3 clinical trials of abiraterone and low-dose prednisone plus ADT in patients with newly diagnosed metastatic prostate cancer or high-risk or node-positive disease (STAMPEDE and LATITUDE) that demonstrated improved OS over ADT alone.[623]

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Taken together, these data led the NCCN Panel to recommend abiraterone with 5-mg once-daily prednisone as a treatment option with ADT for patients with newly diagnosed, M1, castration-sensitive prostate cancer (category 1). Alternatively, the fine-particle formulation of abiraterone can be used (category 2B; see *Abiraterone Acetate in M1 CRPC*, below).

Abiraterone can be given at 250 mg/day and administered following a low-fat breakfast as an alternative to the dose of 1000 mg/day after an overnight fast (see *Abiraterone Acetate in M1 CRPC*, below).[626] The cost savings may reduce financial toxicity and improve adherence.

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Enzalutamide in Castration-Sensitive Prostate Cancer

The open-label randomized phase 3 ENZAMET clinical trial compared enzalutamide (160 mg/day) plus ADT (LHRH analog or surgical castration) with a first-generation antiandrogen (bicalutamide, nilutamide, or flutamide) plus ADT in 1125 patients with metastatic castration-sensitive prostate cancer.[632] Stratification was by volume of disease, planned use of early docetaxel, planned use of bone antiresorptive therapy, comorbidity score, and trial site. The primary endpoint of OS was met at the first interim analysis with median follow-up of 34 months (HR for death, 0.67; 95% CI, 0.52–0.86; *P* = .002). Enzalutamide also improved secondary endpoints, such as PFS using PSA levels and clinical PFS. An additional analysis was triggered at 470 deaths.[692] After a median follow-up of 68 months, the 5-year OS rate was again lower in the first-generation antiandrogen group than in the enzalutamide group (HR, 0.70; 95% CI, 0.58–0.84; *P* < .0001). The median OS was not reached.

In the double-blind randomized phase 3 ARCHES clinical, 1150 patients with metastatic castration-sensitive prostate cancer were randomized to receive ADT with either enzalutamide (160 mg/day) or placebo. Participants were stratified by disease volume and prior docetaxel use. The primary endpoint was radiographic PFS, which was improved in the enzalutamide group after a median follow-up of 14.4 months (19.0 months vs. not reached; HR, 0.39; 95% CI, 0.30–0.50; *P* < .001).[633] At the final, prespecified OS analysis, median OS was not met in either group, but a 34% reduction in the risk of death was observed in those receiving enzalutamide versus placebo (HR, 0.66; 95% CI, 0.53–0.81; *P* < .001).[693] This result could be an underestimate of the effect of enzalutamide, since approximately 32% of the patients assigned placebo crossed over to enzalutamide after unblinding.

The safety of enzalutamide in these trials was similar to that seen in previous trials in the castration-resistant setting. Adverse events associated with enzalutamide in these trials included fatigue, seizures, and hypertension.[632,633]

Enzalutamide is a category 1 option for patients with M1 castration-sensitive prostate cancer. The FDA approved this indication in December 2019.

Docetaxel in Castration-Sensitive Prostate Cancer

Docetaxel has been studied as an upfront option for patients with castration-sensitive prostate cancer and distant metastases based on results from two phase 3 trials (ECOG 3805/CHAARTED and STAMPEDE).[422,694] CHAARTED randomized 790 patients with metastatic, castration-sensitive prostate cancer to docetaxel (75 mg/m^2 IV q3 weeks x 6 doses) plus ADT or ADT alone.[694] After a median follow-up of 53.7 months, the patients in the combination arm experienced a longer OS than those in the ADT arm (57.6 months vs. 47.2 months; HR, 0.72; 95% CI, 0.59–0.89; *P* = .002).[695] Subgroup analysis showed that the survival benefit was more pronounced in the 65% of participants with high-volume disease (HR, 0.63; 95% CI, 0.50–0.79; *P* < .001). Patients with low metastatic burden in CHAARTED did not derive a survival benefit from the inclusion of docetaxel (HR, 1.04; 95% CI, 0.70–1.55; *P* = .86).

The STAMPEDE trial, a multi-arm, multi-stage phase 3 trial, included patients with both M0 and M1 castration-sensitive prostate cancer.[422] The results in the M1 population confirmed the survival advantage of adding docetaxel (75 mg/m^2 IV q3 weeks x 6 doses) to ADT seen in the CHAARTED trial. In STAMPEDE, extent of disease was not evaluated in the 1087 patients 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).

Patients with low metastatic burden did not have definitively improved survival outcomes in the ECOG CHAARTED study or a similar European trial (GETUG-AFU 15).[694,696,697] Furthermore, the triplet options of ADT with docetaxel and either abiraterone or darolutamide showed improved OS over ADT with docetaxel (see below). The panel therefore does not include docetaxel with ADT as an option for patients with metastatic castration-sensitive prostate cancer. Rather, patients with high-volume castration-sensitive metastatic prostate cancer who are fit for chemotherapy should be considered for triplet therapy.

Triplet Therapies for Castration-Sensitive Prostate Cancer

Data from the PEACE-1 and ARASENS trials indicate that triplet therapies of ADT with docetaxel and a novel hormone therapy—either abiraterone or darolutamide—improve OS over ADT with docetaxel.[698,699] These trials are discussed below. Both of these combinations are included as category 1, preferred options for patients with metastatic castration-sensitive prostate cancer, and their use is encouraged for patients with high-volume de novo disease who are fit for chemotherapy.

Docetaxel Plus Abiraterone in Castration-Sensitive Prostate Cancer

PEACE-1 was an international, open-label, randomized, phase 3 study conducted in seven European countries.[698] Using a 2 × 2 factorial design, 1173 patients with de novo metastatic prostate cancer were randomized at a 1:1:1:1 ratio to standard of care (ADT alone or with docetaxel), standard of care with RT, standard of care with abiraterone, or standard of care with radiation and abiraterone. The two primary endpoints of the trial were radiographic PFS and OS. Adjusted Cox regression modelling showed no interaction between abiraterone and RT, so data were pooled for the analysis of abiraterone efficacy. Consistent with results of older studies, radiographic PFS was longer in patients who received abiraterone than in those that did not (HR, 0.54; 99.9% CI, 0.41–0.71; $P < .0001$) as was OS (HR, 082; 95.1% CI, 0.69–0.98; $P = .030$).

As part of the analysis, the efficacy of abiraterone was assessed in the population that received docetaxel. As in the overall population, radiographic PFS (HR, 0.50; 99.9% CI, 0.34–0.71; $P < .0001$) and OS (HR, 0.75; 95.1% CI, 0.59–0.95; $P = .017$) were longer in those receiving all three therapies compared with those only receiving ADT and docetaxel. The populations receiving the triplet and doublet therapies experienced similar rates neutropenia, febrile neutropenia, fatigue, and neuropathy, although grade ≥3 adverse events occurred in 63% of patients who received the triplet combination compared with 52% of those receiving ADT and docetaxel.

Docetaxel Plus Darolutamide in Castration-Sensitive Prostate Cancer

The international, phase 3 trial ARASENS trial, the second phase 3 trial evaluating a triplet therapy, randomized 1306 patients with metastatic castration-sensitive prostate cancer to receive ADT and docetaxel with either darolutamide or matching placebo.[699] The primary endpoint, OS, was improved in the darolutamide group at 4 years (62.7%; 95% CI, 58.7–66.7) compared with the placebo group (50.4%; 95% CI, 46.3–54.6). The risk of death was lower in the darolutamide group by about 32% (HR, 0.68; 95% CI, 0.57–0.80; $P < .001$). The addition of darolutamide also showed significant benefits over placebo for secondary efficacy endpoints, including time to CRPC (HR, 0.36; 95% CI, 0.30–0.42; $P < .001$), skeletal event–free survival (HR, 0.61; 95% CI, 0.52–0.72; $P < .001$), and time to initiation of subsequent systemic antineoplastic therapy (HR, 0.39; 95% CI, 0.33–0.46; $P < .001$).

Adverse events of any grade, grade 3 to 5 adverse events, and serious adverse events occurred at similar incidence levels between the two arms. Many of these were known effects of docetaxel. The most frequent adverse events were alopecia (40.5% of patients in the darolutamide arm vs. 40.6% with placebo), neutropenia (39.3% vs. 38.8%), fatigue (33.1% vs. 32.9%), and anemia (27.8% vs 25.1%). Exceptions were rash (16.6%

vs. 13.5%) and hypertension (13.7% vs. 9.2%), which are known effects of androgen receptor pathway inhibitors and were more frequent in the darolutamide group.

The FDA approved this indication in August 2022.

Progression to and Management of CRPC

Most advanced disease eventually stops responding to traditional ADT and is categorized as castration-resistant (also known as castration-recurrent). CRPC is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL).[700] Patients whose disease progresses to CRPC during primary ADT should receive a laboratory assessment to assure a castrate level of testosterone (<50 ng/dL; <1.7 nmol/L). 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.

For patients who develop CRPC, ADT with an LHRH agonist or antagonist should be continued to maintain castrate serum levels of testosterone (<50 ng/dL).

Patients with CRPC and no signs of distant metastasis on conventional imaging studies (M0) can consider monitoring with continued ADT if PSADT is greater than 10 months (preferred), because these patients will have a relatively indolent disease history.[701] Secondary hormone therapy with continued ADT is an option mainly for patients with shorter PSADT (≤10 months) as described below.

For patients who develop metastatic CRPC, metastatic lesion biopsy is recommended, as is MSI/MMR testing, if not previously performed. If MSI-H or dMMR is found, referral to genetic counseling should be made to assess for the possibility of Lynch syndrome. These patients should also have germline and tumor testing to check for mutations in homologous recombination repair (HRR) genes (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA, RAD51D, CHEK2, CDK12*) if not done previously.[702] This information may be used for genetic counseling, early use of platinum chemotherapy, or understanding eligibility for biomarker-directed treatments or clinical trials. TMB testing should also be considered for patients with metastatic CRPC to inform possible use of pembrolizumab in later lines of therapy (see *Pembrolizumab,* below).

ADT is continued in patients with metastatic CRPC while additional therapies, including secondary hormone therapies, chemotherapies, immunotherapies, radiopharmaceuticals, and/or targeted therapies, are sequentially applied, as discussed in the sections that follow; all patients should receive best supportive care. The Panel defined treatment options for patients with metastatic CRPC based on previous exposure to docetaxel and to a novel hormone therapy. Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior novel hormonal therapy.

The decision to initiate therapy in the CRPC setting after disease progression on one or more treatments 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 therapeutic agents should be considered. Data to inform the optimal sequence for delivery of these agents in patients with metastatic CRPC is limited (see *Sequencing of Therapy in CRPC*, below). 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 being treated for CRPC be closely monitored with radiologic imaging (ie, CT, bone imaging), PSA tests, and

clinical exams for evidence of progression. Therapy should be continued until clinical progression or intolerability, with consideration of the fact that even in cases where PSA remains undetectable, bone imaging may reveal progression.[703,704] The sequential use of these agents is reasonable in a patient who remains a candidate for further systemic therapy. Clinical trial and best supportive care are additional options.

Secondary Hormone Therapy for CRPC

Research has shown enhancement of autocrine and/or paracrine androgen synthesis in the tumor microenvironment of patients receiving ADT.[705,706] Androgen signaling consequent to non-gonadal sources of androgen in CRPC refutes earlier beliefs that CRPC was resistant to further hormone therapies. The development of novel hormonal agents demonstrating efficacy in the non-metastatic and metastatic CRPC setting dramatically changed the paradigm of CRPC treatment.

Abiraterone Acetate in M1 CRPC

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

FDA approval in the post-docetaxel, metastatic CRPC setting was based on the results of a phase 3, randomized, placebo-controlled trial (COU-AA-301) in patients with metastatic CRPC previously treated with docetaxel-containing regimens.[707,708] 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, median survival was 15.8 versus 11.2 months in the abiraterone and placebo arm, respectively (HR, 0.74; 95% CI, 0.64–0.86; $P < .0001$).[708] Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone.[708,709]

FDA approval in the pre-docetaxel setting occurred in December 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 patients with asymptomatic or minimally symptomatic, metastatic CRPC.[710] Most participants 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 PFS was improved by treatment from 8.3 to 16.5 months (HR, 0.53; $P < .001$). OS 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; $P = .003$).[711] Key secondary endpoints of time to symptomatic deterioration, time to chemotherapy initiation, time to pain progression, and PSA PFS improved significantly with abiraterone treatment; 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%).

In May 2018, the FDA approved a novel, fine-particle formulation of abiraterone, in combination with methylprednisolone, for the treatment of patients with metastatic CRPC. In studies of healthy males, this formulation at 500 mg was shown to be bioequivalent to 1000 mg of the originator formulation.[712,713] In a phase 2 therapeutic equivalence study, 53

patients with metastatic CRPC who were not treated previously with abiraterone, enzalutamide, radium-223, or chemotherapy (docetaxel for metastatic CRPC completed ≥1 year prior to enrollment was allowed) were randomized to 500 mg daily of the new, fine-particle formulation plus 4 mg methylprednisolone orally twice daily or to 1000 mg of the originator formulation daily plus 5 mg prednisone orally twice daily.[714] Bioequivalence of these doses was confirmed based on serum testosterone levels, PSA response, and abiraterone pharmacokinetics. The rates of total and grade 3/4 adverse events were similar between the arms, with musculoskeletal and connective tissue disorders occurring more frequently in the originator-treated patients (37.9% vs. 12.5%). The Panel believes that the fine-particle formulation of abiraterone can be used instead of the original formulation of abiraterone in the treatment of patients with metastatic CRPC (category 2A).

Based on the studies described here, abiraterone is a category 1, preferred option for metastatic CRPC without prior novel hormone therapy. For patients with metastatic CRPC and prior novel hormone therapy, abiraterone is included in the *other recommended regimens* category. The fine-particle formulation of abiraterone is included under other recommended options in all metastatic CRPC settings.

Abiraterone should be given with concurrent steroid (either oral prednisone 5 mg twice daily or oral methylprednisolone 4 mg twice daily, depending on which formulation is given) to abrogate signs of mineralocorticoid excess that can result from treatment. These signs include hypertension, hypokalemia, and peripheral edema. Thus, monitoring of liver function, potassium and phosphate levels, and blood pressure readings on a monthly basis is warranted during abiraterone therapy. Symptom-directed assessment for cardiac disease also is warranted, particularly in patients with pre-existing cardiovascular disease.

A randomized phase 2 non-inferiority study of 75 patients with M1 CRPC compared 1000 mg/day abiraterone after an overnight fast with 250 mg/day after a low-fat breakfast.[626] The primary endpoint was log change in PSA, with secondary endpoints of PSA response (≥50%) and PFS. The primary endpoint favored the low-dose arm (log change in PSA, -1.59 vs. -1.19), as did the PSA response rate (58% vs. 50%), with an equal PFS of 9 months in both arms. Noninferiority of the low dose was established according to the predefined criteria. Therefore, abiraterone can be given at 250 mg/day administered following a low-fat breakfast, as an alternative to the dose of 1000 mg/day after an overnight fast in patients who will not take or cannot afford the standard dose. The cost savings may reduce financial toxicity and improve adherence. Food impacts absorption unpredictably; side effects should be monitored and standard dosing (1000 mg on empty stomach) utilized if excess toxicity is observed on modified dosing (250 mg with food).

Abiraterone with Dexamethasone in M1 CRPC

Switching from prednisone to dexamethasone 1 mg/day can be considered for patients with M1 CRPC with disease progression on either formulation of abiraterone. Trials show improved PSA responses and PFS and acceptable safety using this strategy.

The SWITCH study was a single-arm, open-label, phase 2 study of this approach with 26 enrolled patients.[715] The primary endpoint, the proportion of patients with a PSA decline ≥30% in 6 weeks, was 46.2%. No significant toxicities were observed, and two radiologic responses were seen. In another study, 48 consecutive patients with metastatic CRPC, with disease progression on abiraterone with prednisone, were switched to abiraterone with 0.5 mg/day dexamethasone.[716] The primary endpoint of median PFS was 10.35 months, and PSA levels decreased or stabilized in 56% of patients after switching to dexamethasone.

Enzalutamide in M0 and M1 CRPC

In August 2012, the FDA approved enzalutamide, a next-generation antiandrogen, for treatment of patients with metastatic CRPC who had received prior docetaxel chemotherapy. Approval was based on the results of the randomized, phase 3, placebo-controlled AFFIRM trial.[717,718] AFFIRM randomized 1199 patients to enzalutamide or placebo in a 2:1 ratio and the primary endpoint was OS. 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 patients with >50% PSA decline (54% vs. 2%), radiographic response (29% vs. 4%), radiographic PFS (8.3 vs. 2.9 months), and time to first SRE (16.7 vs. 13.3 months). QOL 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 LHRH 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.[717,719]

Another phase 3 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.[720,721] The study was stopped early due to benefits shown in the treatment arm. Compared to the placebo group, the enzalutamide group showed improved median PFS (20.0 months vs. 5.4 months) and median OS (35.3 months vs. 31.3 months). Improvements in all secondary endpoints were also observed (eg, the time until chemotherapy initiation or first SRE).

Two randomized clinical trials have reported that enzalutamide may be superior to bicalutamide for cancer control in metastatic CRPC. The TERRAIN study randomized 375 patients with treatment-naïve, metastatic CRPC to 160 mg/day enzalutamide or 50 mg/day bicalutamide in a 1:1 manner.[722] The enzalutamide group had significantly better PFS (defined as PSA progression, soft tissue progression, or development of additional bony metastases) compared to the bicalutamide group (median time to progression, 15.7 vs. 5.8 months; HR, 0.44; 95% CI, 0.34–0.57).

The STRIVE trial randomized 396 patients with M0 or M1 treatment-naïve CRPC to 160 mg/day enzalutamide or 50 mg/day bicalutamide in a 1:1 manner.[723] The primary endpoint in this study was PFS, defined as either PSA progression, radiographic progression of disease, or death from any cause. Enzalutamide reduced the risk of progression or death by 76% compared to bicalutamide (HR, 0.24; 95% CI, 0.18–0.32). These studies demonstrated that enzalutamide extended PFS better than bicalutamide in patients choosing an antiandrogen for secondary hormonal therapy treatment of CRPC. Bicalutamide can still be considered in some patients, given the different side-effect profiles of the agents and the increased cost of enzalutamide.

Thus, enzalutamide represents a category 1, preferred treatment option for patients without prior novel hormone therapy in the metastatic CRPC setting. For patients with metastatic CRPC and prior novel hormone therapy, enzalutamide is included in the *other recommended regimens* group of options.

The randomized, double-blind, placebo-controlled phase 3 PROSPER trial assessed the use of enzalutamide in 1401 patients with non-metastatic CRPC.[724] Patients with PSADT less than or equal to 10 months were stratified according to PSADT (<6 months vs. ≥6 months) and use of bone-sparing agents and randomized 2:1 to enzalutamide (160 mg/day) plus ADT or placebo plus ADT. Enzalutamide improved the primary endpoint of

metastasis-free survival over placebo (36.6 months vs. 14.7 months; HR for metastasis or death, 0.29; 95% CI, 0.24–0.35; *P* < .0001). Median OS was longer in the enzalutamide group than in the placebo group (67.0 months vs. 56.3 months; HR for death, 0.73; 95% CI, 0.61–0.89; *P* = 0.001).[725] Adverse events included fatigue (33% vs. 14%), hypertension (12% vs. 5%), major adverse cardiovascular events (5% vs. 3%), and mental impairment disorders (5% vs. 2%). Patient-reported outcomes from PROSPER indicate that enzalutamide delayed pain progression, symptom worsening, and decrease in functional status, compared with placebo.[726]

The FDA expanded approval for enzalutamide to include patients with non-metastatic CRPC in July 2018, and the Panel believes that patients with M0 CRPC can be offered enzalutamide, if PSADT is less than or equal to 10 months (category 1, preferred option).

Patients receiving enzalutamide have no restrictions for food intake and concurrent prednisone is permitted but not required.[717]

Apalutamide in M0 CRPC

The FDA approved apalutamide for treatment of patients with non-metastatic CRPC in February 2018. This approval was based on the phase 3 SPARTAN trial of 1207 patients with M0 CRPC and PSADT less than or equal to 10 months.[727] Participants were stratified according to PSADT (>6 months vs. ≤6 months), use of bone-sparing agents, and the presence of metastatic pelvic lymph nodes (N0 vs. N1). After a median follow-up of 20.3 months, apalutamide at 240 mg/day with ADT improved the primary endpoint of metastasis-free survival over placebo with ADT (40.5 months vs. 16.2 months; HR for metastasis or death, 0.28; 95% CI, 0.23–0.35; *P* < .001). Adverse events included rash (24% vs. 5.5%), fracture (11% vs. 6.5%), and hypothyroidism (8% vs. 2%). In a prespecified exploratory analysis of SPARTAN, health-related QOL was maintained in both the apalutamide and placebo groups.[728]

After a median follow-up of 52 months, final OS analysis showed that participants in SPARTAN experienced an improved median OS with apalutamide versus placebo (73.9 months vs. 59.9 months; HR, 0.78; 95% CI, 0.64–0.96; *P* = .016).[729] This longer OS reached prespecified statistical significance, even though 19% of participants crossed over from placebo to apalutamide.

Apalutamide is a category 1, preferred option for patients with M0 CRPC if PSADT is less than or equal to 10 months.

Darolutamide in M0 CRPC

The FDA approved darolutamide for treatment of patients with non-metastatic CRPC in July 2019. The phase 3 ARAMIS study randomized 1509 patients with M0 CRPC and PSADT less than or equal to 10 months 2:1 to darolutamide (600 mg twice daily) or placebo.[730] Participants were stratified according to PSADT (>6 months vs. ≤6 months) and the use of osteoclast-targeted agents. The median follow-up time was 17.9 months. Darolutamide improved the primary endpoint of metastasis-free survival compared to placebo (40.4 months vs. 18.4 months; HR for metastasis or death, 0.41; 95% CI, 0.34–0.50; *P* < .001).

Patients in the placebo group of ARAMIS crossed over to darolutamide (n = 170) or received other life-prolonging therapy (n = 137). Final analysis occurred after a median follow-up time of 29.0 months. The risk of death was 31% lower in the darolutamide group than in the placebo group (HR for death, 0.69; 95% CI, 0.53–0.88; *P* = .003).[731] OS at 3 years was 83% (95% CI, 80–86) in the darolutamide group compared with 77% (95% CI, 72–81) in the placebo group. Adverse events that occurred more frequently in the treatment arm included fatigue (12.1% vs. 8.7%), pain in an extremity (5.8% vs. 3.2%), and rash (2.9% vs. 0.9%). The incidence of fractures was similar between darolutamide and placebo (4.2% vs. 3.6%).[730]

Darolutamide is a category 1, preferred option for patients with M0 CRPC if PSADT is less than or equal to 10 months.

Other Secondary Hormone Therapies

Other options for secondary hormone therapy include a first-generation antiandrogen, antiandrogen withdrawal, corticosteroid, or ketoconazole (adrenal enzyme inhibitor) with hydrocortisone.[732-734] However, none of these strategies has yet been shown to prolong survival in randomized clinical trials.

A randomized phase 2 trial, TRANSFORMER, compared the effect of bipolar androgen therapy (BAT) with that of enzalutamide on PFS in 195 patients with asymptomatic, metastatic CRPC with prior progression on abiraterone.[735] BAT involves rapid cycling between high and low serum testosterone to disrupt the adaptive upregulation of the androgen receptor that occurs with low testosterone levels. Patients in the BAT arm received testosterone cypionate 400 mg intramuscularly once every 28 days. The PFS was 5.7 months in both arms (HR, 1.14; 95% CI, 0.83–1.55; *P* = .42). Crossover was allowed after disease progression, and OS was similar between the groups. BAT resulted in more favorable patient-reported QOL. The Panel awaits more data on this approach.

Chemotherapy, Immunotherapy, and Targeted Therapy for Metastatic CRPC

Research has expanded the therapeutic options for patients with metastatic CRPC. In addition to the hormonal and radiopharmaceutical therapies described in other sections, options include chemotherapy, immunotherapy, and targeted therapy. As noted above, selection of therapy depends on patient preferences, prior treatment exposures, the presence or absence of symptoms, the location of metastases, the presence of certain biomarkers, and consideration of potential side effects.

Docetaxel

Two randomized phase 3 studies evaluated docetaxel-based regimens in symptomatic or rapidly progressive CRPC (TAX 327 and SWOG 9916).[591,736,737] TAX 327 compared docetaxel (every 3 weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1006 patients.[736] Every-3-week docetaxel resulted in higher median OS than mitoxantrone (18.9 vs. 16.5 months; *P* = .009). This survival benefit was maintained at extended follow-up.[737] The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared to mitoxantrone plus prednisone.[591]

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 patients with metastatic CRPC randomized to either every-2-week docetaxel or every-3-week docetaxel, each with maintenance of ADT and prednisone.[738] Patients 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 QOL were similar.

Treatment with greater than or equal to 8 cycles of docetaxel may be associated with better OS than fewer cycles in the metastatic CRPC setting, but prospective trials are necessary to test 6 versus 10 cycles of docetaxel in the metastatic castration-sensitive and CRPC settings.[739] Retrospective analysis from the GETUG-AFU 15 trial suggests that docetaxel only benefits some patients with CRPC who received docetaxel in the castration-sensitive setting.[740]

Thus, docetaxel is a category 1 preferred option for treatment of docetaxel-naïve metastatic CRPC. The Panel believes that docetaxel can be given as a rechallenge after progression on a novel hormone in the metastatic CRPC setting if given in the castration-sensitive setting.

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. Docetaxel rechallenge can be considered in patients who received docetaxel with ADT in the metastatic castration-sensitive setting.

Cabazitaxel

In June 2010, the FDA approved cabazitaxel, a semi-synthetic taxane derivative, for patients with metastatic CRPC previously treated with a docetaxel-containing regimen. An international randomized phase 3 trial (TROPIC) randomized 755 patients with progressive metastatic CRPC to receive cabazitaxel 25 mg/m^2 or mitoxantrone 12 mg/m^2, each with daily prednisone.[741] A 2.4-month improvement in OS 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 patients versus 1.3% of mitoxantrone-treated patients. The incidences of severe diarrhea (6%), fatigue (5%), nausea/vomiting (2%), anemia (11%), and thrombocytopenia (4%) also were higher in cabazitaxel-treated patients, which indicated the need for vigilance and treatment or prophylaxis in this setting to prevent febrile neutropenia. The survival benefit was sustained at an updated analysis with a median follow-up of 25.5 months.[742] Furthermore, results of a post-hoc analysis of this trial suggested that the occurrence of grade ≥3 neutropenia after cabazitaxel treatment was associated with improvements in both PFS and OS.[743]

The multicenter CARD study was a randomized, open-label clinical trial that compared cabazitaxel with either abiraterone or enzalutamide in 255 patients with metastatic CRPC who had previously received docetaxel and either abiraterone or enzalutamide.[744] Cabazitaxel at 25 mg/m^2 with concurrent steroid improved the primary endpoint of radiographic PFS (8.0 vs. 3.7 months; HR, 0.54; $P < .0001$) and reduced the risk of death (13.6 vs. 11.0 months; HR, 0.64; $P = .008$) compared with abiraterone or enzalutamide in these patients. Cabazitaxel was also associated with an increased rate of pain response and delayed time to pain progression and SREs.[745]

The phase 3 open-label, multinational, non-inferiority PROSELICA study compared 20 mg/m^2 cabazitaxel with 25 mg/m^2 cabazitaxel in 1200 patients with metastatic CRPC who progressed on docetaxel.[746] The lower dose was found to be noninferior to the higher dose for median OS (13.4 months [95% CI, 12.19–14.88] vs. 14.5 months [95% CI, 13.47–15.28]), and grade 3/4 adverse events were decreased (39.7% vs. 54.5%). In particular, grade ≥3 neutropenia rates were 41.8% and 73.3% for the lower and higher dose groups, respectively.

Results from the phase 3 FIRSTANA study suggested that cabazitaxel has clinical activity in patients with chemotherapy-naïve mCRPC.[747] Median OS, the primary endpoint, was similar between 20 mg/m^2 cabazitaxel, 25 mg/m^2 cabazitaxel, and 75 mg/m^2 docetaxel (24.5 months, 25.2 months, and 24.3 months, respectively). Cabazitaxel was associated with lower rates of peripheral sensory neuropathy than docetaxel, particularly at 20 mg/m^2 (12% vs. 25%). However, the Panel does not currently recommend cabazitaxel in docetaxel-naïve patients.

Based on these data, cabazitaxel is included in these Guidelines as a preferred option after progression occurs on docetaxel in patients with metastatic CRPC (category 1 after progression on docetaxel and a novel hormone therapy). Cabazitaxel at 20 mg/m^2 every 3 weeks, with or without growth factor support, is the recommended dose for fit patients. Cabazitaxel at 25 mg/m^2 may be considered for healthy patients who wish to be more aggressive.

Cabazitaxel should be given with concurrent steroids (daily prednisone or dexamethasone on the day of chemotherapy). Physicians should follow current guidelines for prophylactic white blood cell growth factor use, particularly in this heavily pretreated, high-risk population. In addition, supportive care should include antiemetics (prophylactic antihistamines, H2 antagonists, and corticosteroids prophylaxis) and symptom-directed antidiarrheal agents. Cabazitaxel was tested in patients with hepatic dysfunction in a small, phase I, dose-escalation study.[748] Cabazitaxel was tolerated in patients with mild to moderate hepatic impairment. However, cabazitaxel should not be used in patients with severe hepatic dysfunction. Cabazitaxel should be stopped upon clinical disease progression or intolerance.

Cabazitaxel/Carboplatin

Cabazitaxel 20 mg/m² plus carboplatin AUC 4 mg/mL per minute with growth factor support can be considered for fit patients with aggressive variant metastatic CRPC (visceral metastases, low PSA and bulky disease, high lactate dehydrogenase [LDH], high carcinoembryonic antigen [CEA], lytic bone metastases, and neuroendocrine prostate cancer [NEPC] histology) or unfavorable genomics (defects in at least 2 of *PTEN*, *TP53*, and *RB1*). This recommendation is based on a phase 1–2, open label, randomized study.[749] In the phase 2 portion, 160 patients were randomized to receive cabazitaxel alone or with carboplatin, and the primary endpoint was investigator-assessed PFS. In the ITT population, median PFS was 4.5 months in the cabazitaxel arm versus 7.3 months in the cabazitaxel/carboplatin arm (HR, 0.69; 95% CI, 0.50–0.95; *P* = .018). The most common grade 3–5 adverse events (fatigue, anemia, neutropenia, and thrombocytopenia) were all more common in the combination arm. Post-hoc analyses showed that patients with aggressive variant disease had a longer median PFS in the combination arm than the cabazitaxel arm (7.5 vs. 1.7 months; *P* = .017). Patients without aggressive variant tumors, on the other hand, had similar median PFS regardless of treatment (6.5 vs. 6.3 months; *P* = .38).

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 3, multicenter, randomized, double-blind trial (D9902B).[750] Five hundred twelve patients with minimally symptomatic or asymptomatic metastatic CRPC were randomized 2:1 to receive sipuleucel-T or placebo. Eighteen-point two percent of patients had received prior chemotherapy, which included docetaxel; eligibility requirements included no chemotherapy for 3 months and no steroids for 1 month prior to enrollment. Median survival in the vaccine arm was 25.8 months compared to 21.7 months in the control arm. In a subset analysis, both those who did and those who did not receive prior chemotherapy benefited from sipuleucel-T treatment. Sipuleucel-T treatment resulted in a 22% reduction in mortality risk (HR, 0.78; 95% CI, 0.61–0.98; *P* = .03). Common complications included mild to moderate chills (54.1%), pyrexia (29.3%), and headache (16.0%), which usually were transient.

A prospective registry of patients with metastatic CRPC, PROCEED, enrolled 1976 patients from 2011 to 2017, who were followed for a median of 46.6 months.[751] The safety and tolerability of sipuleucel-T were consistent with previous findings, and the median OS was 30.7 months (95% CI, 28.6–32.2 months).

Sipuleucel-T is a category 1 option for certain patients with metastatic CRPC who have not had previous treatment with docetaxel or with a novel hormone therapy. Benefit of sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. Sipuleucel-T is also not recommended for patients with small cell prostate cancer/NEPC. The Panel prefers that sipuleucel-T be used as a therapy for asymptomatic or minimally symptomatic patients with metastatic CRPC, so that disease burden is lower and immune function is potentially more intact. However, it is also an option for patients with metastatic CRPC who have had prior treatment with docetaxel or a novel hormone therapy, but not for patients who have already received both. Patients should have good performance level (ECOG 0-1), estimated life expectancy greater than 6 months, and no liver 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 seen. Therefore, benefit to the individual patient cannot be ascertained using currently available testing.

Treatment after sipuleucel-T treatment should proceed as clinically indicated, particularly if symptoms develop.

Pembrolizumab

The FDA approved the use of pembrolizumab, an anti-PD1 antibody, for treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors who have progressed on prior treatment and who have no satisfactory alternative treatment options in May 2017. This approval was based on the treatment of 149 patients across five clinical studies involving MSI-H or dMMR colorectal (n = 90) or non-colorectal (n = 59) cancer for an objective response rate of 40% (59/149).[719] All patients received greater than or equal to 1 prior regimen. Among the non-colorectal cohorts, two patients had metastatic CRPC: one achieved a partial objective response, and the other achieved stable disease for greater than 9 months.

Outcomes of additional patients with metastatic CRPC treated with pembrolizumab have been reported.[72,752-756] In an early study, 10 patients with CRPC and non-visceral metastases (bone = 7; lymph nodes = 2; bone and liver = 1) who had disease progression on enzalutamide were treated with pembrolizumab and enzalutamide.[752] Some of the patients also had experienced disease progression on additional therapies (docetaxel for castration-sensitive disease, abiraterone, and/or sipuleucel-T). Three of the 10 patients showed a near complete PSA response. Two of these three patients had radiographically measurable disease and achieved a partial radiographic response (including a response in liver metastases). Of the remaining patients, three showed stable disease, and four displayed no evidence of clinical benefit. Genetic analysis of biopsy tissue revealed that one patient whose disease showed PSA response had an MSI-H tumor, whereas the other patient with responsive disease and two with non-responsive disease did not. The nonrandomized phase Ib KEYNOTE-028 trial included 23 patients with advanced, progressive prostate cancer, of whom 74% had received greater than or equal to two previous therapies for metastatic disease.[754] The objective response rate by investigator review was 17.4% (95% CI, 5.0%–38.8%), with four confirmed partial responses. Eight patients (34.8%) had stable disease. Treatment-related adverse events occurred in 61% of patients after a median follow-up of 7.9 months; 17% of the cohort experienced grade 3/4 events (ie, grade 4 lipase increase, grade 3 peripheral neuropathy, grade 3 asthenia, grade 3 fatigue).

KEYNOTE-199 was a multi-cohort, open-label phase II study in 258 patients with metastatic CRPC and prior treatment with docetaxel and at least one novel hormonal therapy that assessed pembrolizumab in patients regardless of MSI status.[757] Cohorts 1 and 2 included patients with PD-L1–positive (n = 133) and PD-L1–negative (n = 66) prostate cancer, respectively. Cohort 3 included those with bone-predominant disease with positive or negative PD-L1 expression (n = 59). The primary endpoint of overall response rate (ORR) was 5% (95% CI, 2%–11%) in cohort 1 and 3% (95% CI, <1%–11%) in cohort 2. Responses were durable (range, 1.9 – ≥21.8 months).

The most common adverse events from pembrolizumab are fatigue, pruritus, diarrhea, anorexia, constipation, nausea, rash, fever, cough, dyspnea, and musculoskeletal pain. Pembrolizumab also may be associated with immune-mediated side effects, which include colitis, hepatitis, endocrinopathies, pneumonitis, or nephritis.

Based on the available data, the Panel supports the use of pembrolizumab in patients with MSI-H or dMMR metastatic CRPC whose disease has progressed through docetaxel and a novel hormone therapy. The prevalence of MMR deficiency in metastatic CPRC is estimated at 2% to 5%,[36,753] and testing for MSI-H or dMMR can be performed using DNA testing or immunohistochemistry. If tumor MSI-H or dMMR is identified, the Panel recommends referral to genetic counseling for consideration of germline testing for Lynch syndrome.

In June 2020, the FDA granted accelerated approval for pembrolizumab's use in patients with unresectable or metastatic TMB-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Results from prospective biomarker analysis of the multicohort, non-randomized, open-label, phase 2 KEYNOTE-158 trial support this approval.[758] The prospective TMB study included an efficacy population of 790 patients with anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small cell lung, thyroid, or vulvar cancer who were evaluable for TMB. Of these, 102 patients (13%) had TMB-H status. Objective responses to pembrolizumab were seen in 30 of 102 patients in the TMB-H group (29%; 95% CI, 21%–39%) and 43 of 688 patients in the non–TMB-H group (6%; 95% CI, 5%–8%). Safety was as expected based on other studies of pembrolizumab. Even though there were no patients with prostate cancer in the TMB pembrolizumab study, the Panel includes pembrolizumab as an option for patients with metastatic CRPC, prior docetaxel and novel hormone therapy, and TMB ≥10 mut/Mb based on extrapolation from other tumor types.

Mitoxantrone

Two randomized trials assessed the role of mitoxantrone in patients with metastatic CRPC.[759,760] Although there was no improvement in OS, palliative responses and improvements in QOL were seen with mitoxantrone.

Mitoxantrone can be used for palliation in symptomatic patients with metastatic CRPC who cannot tolerate other therapies after disease progression on prior docetaxel.

Treatment Options for Patients with DNA Repair Gene Mutations

Early studies suggest germline and somatic mutations in HRR genes (eg, *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*) may be predictive of the clinical benefit of poly-ADP ribose polymerase (PARP) inhibitors.[761-763] PARP inhibitors are oral agents that exert their activity through the concept of synthetic lethality.[764] PARP inhibitor therapy options are discussed below.

DNA repair defects have also been reported to be predictive for sensitivity to platinum agents in CRPC and other cancers.[765-769] Platinum agents have

shown some activity in patients with CRPC without molecular selection.[770] Studies of platinum agents in patients with CRPC that have DNA repair gene mutations are needed.

In addition, results of one study suggested that patients with metastatic CRPC and germline mutations in DNA repair genes may have better outcomes if treated with abiraterone or enzalutamide than with taxanes.[44] However, it should be noted that the response of patients with metastatic CRPC and HRR gene mutations to standard therapies is similar to the response of patients without mutations.[771,772]

Patients with *CDK12* mutations tend to have aggressive disease, with high rates of metastases and short OS. Their disease also does not respond well to hormonal therapy, PARP inhibitors, or taxanes. Two large, multi-institutional, retrospective studies have shown that 11% to 33% of patients with metastatic CRPC and *CDK12* mutations experienced disease response to PD-1 inhibitors (ie, nivolumab, pembrolizumab), some with durable responses.[773,774] The Panel awaits more data on the use of PD-1 inhibition in patients with *CDK12* mutations.

Olaparib

Preliminary clinical data using olaparib suggested favorable activity of this agent in patients with HRR gene mutations, but not in those without HRR mutations.[762,763,775] The phase 3 PROfound study was a randomized trial evaluating olaparib 300 mg twice daily versus physician's choice of abiraterone or enzalutamide in patients with metastatic CRPC and progression on at least one novel hormonal agent (abiraterone or enzalutamide) and up to one prior taxane agent (permitted but not required).[776] Patients were required to have a somatic or germline HRR gene mutation, and were allocated to one of two cohorts: cohort A comprised patients with *BRCA1/2* or *ATM* mutations, and cohort B comprised patients with a mutation in at least one of 12 other HRR genes (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, or *RAD54L*). The primary endpoint of improving radiographic PFS with olaparib versus abiraterone/enzalutamide was met in cohort A (HR, 0.34; 95% CI, 0.25–0.47; $P < .001$), and radiographic PFS was also superior in the entire study population encompassing cohorts A+B (HR, 0.49; 95% CI, 0.38–0.63; $P < .001$).

In addition, final OS analysis of PROfound showed that OS was improved with olaparib versus abiraterone/enzalutamide in cohort A (HR, 0.69; 95% CI, 0.50–0.97; $P = .02$), despite the fact that 86 of 131 patients (66%) crossed over to olaparib after disease progression in the control arm.[777]

The Panel notes that there may be heterogeneity of response to olaparib based on which gene has a mutation. Efficacy in PROfound appears to be driven by the cohort of patients with at least one alteration in *BRCA2*, *BRCA1*, or *ATM*, and in particular by patients with *BRCA2* or *BRCA1* mutations based on exploratory gene-by-gene analysis.[777] Patients with *BRCA2* mutations in PROfound experienced an OS benefit with olaparib (HR, 0.59; 95% CI, 0.37–0.95), whereas the HR for OS in patients with *ATM* mutations was 0.93 (95% CI, 0.53–1.75).[777] Furthermore, there were few patients in PROfound with mutations in some of the genes. For example, only 4 patients had *BRIP1* mutations (2 in olaparib arm and 2 in control arm), 2 patients had *RAD51D* mutations (both in olaparib arm), and no patients had *RAD51C* mutations.[776] Patients with *PPP2R2A* mutations in PROfound experienced an unfavorable risk-benefit profile.

As a result of the favorable efficacy data from the PROfound trial, the FDA approved olaparib (300 mg twice daily) in May 2020 for use in patients with metastatic CRPC and deleterious or suspected deleterious germline or somatic HRR gene mutations in at least one of 14 genes (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D*, or *RAD54L*) and who had previously received treatment with enzalutamide or abiraterone.

Since prior taxane therapy was not mandated in the PROfound study, olaparib use might be reasonable in metastatic CRPC patients before or after docetaxel treatment. Adverse events that may occur with olaparib treatment include anemia (including that requiring transfusion), fatigue, nausea or vomiting, anorexia, weight loss, diarrhea, thrombocytopenia, creatinine elevation, cough, and dyspnea. Rare but serious side effects may include thromboembolic events (including pulmonary emboli), drug-induced pneumonitis, and a theoretical risk of myelodysplasia or acute myeloid leukemia.[776]

The Panel recommends olaparib as an option for patients with metastatic CRPC, previous androgen receptor-directed therapy, and an HRRm regardless of prior docetaxel therapy (category 1). The HRR genes to be considered for use of olaparib are *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D* and *RAD54L*.

Any commercially available analytically and clinically validated somatic tumor and ctDNA assays and germline assays can be used to identify patients for treatment. Careful monitoring of complete blood counts and hepatic and renal function, along with type and screens and potential transfusion support and/or dose reductions as needed for severe anemia or intolerance are recommended during olaparib therapy.

Rucaparib

Rucaparib is another PARP inhibitor approved for use in patients with metastatic CRPC. This agent received accelerated FDA approval in May 2020 based on the preliminary favorable data from the TRITON2 clinical trial. In that open-label, single-arm, phase 2 trial, patients with metastatic CRPC harboring a deleterious or suspected deleterious germline or somatic *BRCA1* or *BRCA2* mutation, who had previously received therapy with a novel hormonal agent plus one taxane chemotherapy, were treated with rucaparib 600 mg twice daily.[778] The primary endpoint of TRITON2 was the objective response rate in patients with measurable disease, and was 43.5% (95% CI, 31.0%–56.7%) in this *BRCA1/2*-mutated population. Median radiographic PFS, a key secondary endpoint, was 9.0 months (95% CI, 8.3–13.5 months). The most common adverse events were asthenia/fatigue, nausea, and anemia/decreased hemoglobin, with grade ≥3 anemia/decreased hemoglobin in 25.2% of participants. Final analysis of TRITON2 confirmed results of the earlier analysis.[779]

In the randomized phase 3 TRITON3 study, patients with metastatic CRPC and a germline or somatic *BRCA1/2* or *ATM* mutation who have previously received a novel hormonal agent but no chemotherapy for mCRPC were randomized 2:1 to rucaparib versus physician's choice of therapy (abiraterone, enzalutamide, or docetaxel).[780] The primary endpoint of TRITON3, the median duration of imaging-based PFS, was significantly longer at 62 months in the group of 270 participants assigned to receive rucaparib than in the 135 participants who received a control medication (10.2 months vs. 6.4 months; HR, 0.61; 95% CI, 0.47–0.80; $P < .001$). This effect was also seen in the 201 patients and 101 patients in each group with a *BRCA*m (11.2 months vs. 6.4 months; HR, 0.50; 95% CI, 0.36–0.69). For those with *ATM* mutations, an exploratory analysis suggested a possible improvement as well (8.1 months vs. 6.8 months; HR, 0.95; 95% CI, 0.59–1.52). As in TRITON2, the most frequent adverse events with rucaparib were fatigue and nausea.

The Panel recommends rucaparib as an option for patients with metastatic CRPC, prior treatment with a novel hormone therapy, and a *BRCA1* or *BRCA2* mutation. Rucaparib should not be used in patients with HRR gene mutations other than *BRCA1/2*.[781] Adverse events that may occur with rucaparib include anemia (including that requiring transfusion), fatigue, asthenia, nausea or vomiting, anorexia, weight loss, diarrhea or constipation, thrombocytopenia, increased creatinine, increased liver transaminases, and rash. Rare but serious side effects of rucaparib

include a theoretical risk of myelodysplasia or acute myeloid leukemia, as well as fetal teratogenicity.[778,781]

The preferred method of selecting patients for rucaparib treatment is somatic analysis of *BRCA1* and *BRCA2* using a circulating tumor DNA sample. As with olaparib, careful monitoring of complete blood counts and hepatic and renal function, along with type and screens and potential transfusion support and/or dose reductions as needed for severe anemia or intolerance are recommended during treatment with rucaparib.

Olaparib Plus Abiraterone

Pre-clinical data suggest that PARP-1 promotes androgen receptor activity.[782] Additional pre-clinical data show that androgen receptor inhibitors can down-regulate DNA repair genes, creating a situation similar to that of HRR mutation.[783,784] These results suggest that the combination of PARP inhibition with androgen receptor inhibition may have an enhanced antitumor effect and that this effect may not be limited to patients with HRR mutations. In fact, a randomized phase 2 trial showed that the combination of abiraterone with olaparib increased radiographic PFS over abiraterone and placebo in patients with metastatic CRPC regardless of HRR status (ITT population: HR, 0.65; 95% CI, 0.44–0.97; $P = .034$).[763]

The PROpel trial was an international, double-blind, phase 3 trial comparing abiraterone and olaparib with abiraterone and placebo in 796 patients with metastatic CRPC regardless of HRR mutation status.[785] Prior docetaxel in the localized or metastatic castration-sensitive setting was allowed, but patients were untreated for CRPC. The primary endpoint, imaging-based PFS by investigator assessment in the ITT population, was significantly longer in the abiraterone/olaparib group than in the abiraterone/placebo group (24.8 vs. 16.6 months; HR, 0.66; 95% CI, 0.54–0.81; $P < .001$). HRR mutations were identified in tumors of 226 patients; 552 patients did not have HRR tumor mutations. The HR for the primary endpoint in those with HRR mutations was 0.50 (95% CI, 0.34–0.73). The safety profile of the olaparib/abiraterone combination was as expected based on the known safety profiles of the individual drugs, with the most common adverse events being anemia, fatigue/asthenia, and nausea.

OS data from PROpel were presented at the 2023 ASCO Genitourinary Cancers Symposium.[786] A trend towards an OS benefit with the abiraterone/olaparib combination was seen in the ITT population and in the HRRm, non-HRRm, BRCAm, and non-BRCAm subgroups. However, crossover was not allowed, so patients with HRRm in the control arm were unable to receive olaparib, likely contributing to the inferior survival in the control group.

In May 2023, the FDA approved the combination of olaparib with abiraterone for the treatment of adult patients with BRCAm metastatic CRPC. Based on the results of PROpel, olaparib/abiraterone is included in the NCCN Guidelines as an option in first-line metastatic CRPC for patients with a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received a novel hormone therapy or docetaxel (category 1) and for those who received prior docetaxel in the castration-sensitive setting (category 2A).

Talazoparib Plus Enzalutamide

Talazoparib is another PARP inhibitor; it has had an FDA indication in breast cancer. The open-label, international phase 2 TALAPRO-1 trial included 127 patients with an HRR mutation and progressive, metastatic CRPC, all of whom received at least one dose of talazoparib.[787] The objective response rate after a median follow-up of 16.4 months was 29.8% (95% CI, 21.2–39.6). The most common grade 3–4 treatment-emergent adverse events were anemia (31%), thrombocytopenia (9%), and neutropenia (8%).

As noted above (see *Olaparib Plus Abiraterone*), pre-clinical data suggest that the PARP inhibition combined with androgen receptor inhibition may have an enhanced antitumor effect that may not be limited to those with HRR mutations. The randomized, double-blind, phase 3 TALAPRO-2 study compared enzalutamide plus talazoparib with enzalutamide plus placebo in 805 patients with untreated metastatic CRPC.[788] HRR gene alteration status and treatment with docetaxel and/or abiraterone in the castration-sensitive setting were used to stratify the randomization. The primary endpoint was radiographic PFS in the ITT population. At the planned primary analysis, median radiographic PFS was not reached (95% CI, 27.5 months–not reached) for the talazoparib group and was 21.9 months (95% CI, 16.6–25.1) for the control group (HR, 0.63; 95% CI, 0.51–0.78; *P* < .0001).

HRR mutations were present in 21% of TALAPRO-2 participants, with *BRCA* alterations being the most common.[788] The HR for radiographic PFS in the HRR-deficient subgroup was more strongly in favor of the talazoparib combination than in the HRR-proficient/unknown population (0.46 [95% CI, 0.30–0.70; *P* = .0003] vs. 0.70 [95% CI, 0.54–0.89; *P* = .0039]). Among HRR mutations, talazoparib conferred a 77% lower risk of radiographic progression or death in those with tumor mutations in *BRCA1* or *BRCA2* (HR, 0.23; 95% CI, 0.10–0.53; *P* = .0002), whereas the corresponding reduction was 34% (HR, 0.66; 95% CI, 0.39–1.12; *P* = .12) in those with non-*BRCA* HRR alterations.

Prior therapy also affected the radiographic PFS outcomes in this trial.[788] In the 179 participants in TALAPRO-2 who had received docetaxel in earlier disease settings, the HR for radiographic PFS was 0.51 (95% CI, 0.32–0.81; *P* = .0034). In the small population of 50 participants in the ITT population who had received prior novel hormonal therapy, the corresponding HR was non-significant at 0.57 (95% CI, 0.28–1.16; *P* = .12).

The safety profile of enzalutamide plus talazoparib was consistent with the known safety profiles of the individual drugs, with the most common adverse events in those who received talazoparib being anemia, neutropenia, and fatigue. However, hematologic adverse events were of higher grades and occurred more frequently than would be expected with talazoparib alone. Overall, the combination had significant toxicity, with dose interruption due to adverse events in 75% of participants in the talazoparib group compared with 23% in the placebo group. Dose reductions due to adverse events occurred in 56% and 7% of the talazoparib and placebo groups, respectively.

Based on these results, the FDA approved talazoparib plus enzalutamide for HRRm metastatic CRPC in June 2023. The Panel includes talazoparib plus enzalutamide as a treatment option for patients with metastatic CRPC and a pathogenic mutation (germline and/or somatic) in one of certain HRR and other DNA repair genes (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2*, or *RAD51C*) who have not yet had treatment in the setting of CRPC. This is a category 1 recommendation for those without prior docetaxel or prior novel hormone therapy. It is a category 2A recommendation for those with prior docetaxel in the castration-sensitive setting and no prior novel hormone therapy. Use of talazoparib/enzalutamide for those who have received prior novel hormone therapy without prior docetaxel is controversial (category 2B) because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.

Niraparib Plus Abiraterone

Another PARP inhibitor, niraparib, has also been studied in combination with androgen inhibition in the setting of metastatic CRPC. The randomized, double-blinded phase 3 MAGNITUDE trial compared niraparib plus abiraterone to placebo plus abiraterone in 423 patients with metastatic CRPC and HRR mutations and an additional 247 patients

without HRR mutations.[789] Prior chemotherapy and novel hormonal therapy were allowed in the metastatic castration-sensitive or M0 CRPC settings, and were received by 3.1% and 20.1% of the total HRRm cohort, respectively.

The primary endpoint of MAGNITUDE was radiographic PFS. After a median follow-up of 18.6 months, radiographic PFS was improved for those receiving niraparib in the HRRm group overall (16.5 months vs. 13.7 months; HR, 0.73; 95% CI, 0.56–0.96; *P* = .022) as well as in the BRCAm subgroup (16.6 months vs. 10.9 months; HR, 0.53; 95% CI, 0.36–0.79; *P* = .001). However, radiographic PFS was not improved in the subgroup of patients with non-*BRCA* HRR mutations (HR, 0.99; 95% CI, 0.68–1.44). For the cohort without HRR mutations, futility was declared based on prespecified criteria. The secondary endpoints of time to symptomatic progression and time to initiation of cytotoxic chemotherapy were improved with the combination therapy in the HRRm and BRCAm cohorts.

A second interim analysis of MAGNITUDE included a prespecified, inverse probability censoring weighting analysis of OS, which was designed to account for the receipt of subsequent therapies, including PARP inhibitors.[790] Results of this analysis suggest that there may be an OS benefit for the combination therapy (HR, 0.54; 95% CI, 0.33–0.90; nominal *P* = .0181).

The incidence of grade 3/4 adverse events was higher with the combination of niraparib plus abiraterone compared with placebo and abiraterone (67.0% vs. 46.4%).[789] Anemia (28.3% vs. 7.6%) and hypertension (14.6% vs. 12.3%) were the most reported grade ≥3 adverse events. Overall, the combination was tolerable and QOL was maintained.

Based on these results, the FDA approved niraparib plus abiraterone for the treatment of patients with BRCAm metastatic CRPC in August 2023. The Panel includes niraparib plus abiraterone as a treatment option for patients with metastatic CRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet had treatment in the setting of metastatic CRPC. This is a category 1 recommendation for those without prior docetaxel or prior novel hormone therapy. It is a category 2A recommendation for those with prior docetaxel and no prior novel hormone therapy. Use of niraparib/abiraterone for those who have received prior novel hormone therapy without prior docetaxel is controversial (category 2B) because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.

Radiopharmaceuticals for Metastatic CRPC

Lutetium Lu 177 vipivotide tetraxetan

Lu-177-PSMA-617 is a radiopharmaceutical that is administered intravenously and is indicated for PSMA-positive M1 CRPC that has been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. The active moiety is a radionuclide that delivers radiation to PSMA-expressing and surrounding cells, which induces DNA damage and leads to cell death. The approval of Lu-177-PSMA-617 was based on the international, open-label phase III VISION trial of 831 patients with M1 CRPC and PSMA-positive metastatic lesions. Patients in VISION were previously treated with at least one androgen receptor-directed therapy and one or two taxane-based chemotherapy regimens.[791] Patients had at least one PSMA-positive metastatic lesion and no PSMA-negative lesions determined by Ga-68 labeled PSMA-11 PET/CT imaging. Patients were randomized in a 2:1 ratio to receive standard of care (abiraterone, enzalutamide, bisphosphonates, RT, denosumab, and/or glucocorticoids) and Lu-177-PSMA-617 (7.4 GBq or 200 mCi every 6 weeks for 4–6 cycles) or standard of care alone.

The median OS was improved in the Lu-177-PSMA-617 group compared to the control group (15.3 months vs. 11.3 months; HR, 0.62; 95% CI,

0.52–0.74; *P* < .001). Similarly, the median PFS was improved in the Lu-177-PSMA-617 group compared to the control group (8.7 months vs. 3.4 months; HR, 0.40; 99.2% CI, 0.29–0.57; *P* < .001). The incidence of grade ≥3 adverse events (particularly anemia, thrombocytopenia, lymphopenia, and fatigue) was significantly higher in the Lu-177-PSMA-617 group compared to the control group. [791]

The NCCN Panel recommends Lu-177-PSMA-617 as a category 1, useful in certain circumstances treatment option for patients with one or more PSMA-positive lesion and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with androgen receptor-directed therapy and a taxane-based chemotherapy. PSMA-negative lesions are defined as metastatic disease that lacks PSMA uptake including bone with soft tissue components ≥1.0 cm, lymph nodes ≥2.5 cm in short axis, and solid organ metastases ≥1.0 cm in size. Although the FDA has approved Ga-68 PSMA-11 for use with Lu-177–PSMA-617, the panel believes that F-18 piflufolastat PSMA and F-18 flotufolastat PSMA can also be used in the same space due to multiple reports describing the equivalency of these imaging agents.

Radium-223

In May 2013, the FDA approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This first-in-class radiopharmaceutical was approved for treatment of metastatic CRPC in patients with symptomatic bone metastases and no known visceral metastatic disease. Approval was based on clinical data from a multicenter, phase 3, randomized trial (ALSYMPCA) that included 921 patients with symptomatic CRPC, two or more bone metastases, and no known visceral disease.[792] 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 OS (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.[793] ITT analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic SREs.[794] Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), likely due to the short range of radioactivity.[792] Fecal elimination of the agent led to generally mild non-hematologic side effects, which included nausea, diarrhea, and vomiting. Radium-223 was associated with improved or slower decline of QOL in ALSYMPCA.[795]

The multicenter, international, double-blind, placebo-controlled, phase 3 ERA 223 trial randomized patients with bone-metastatic chemotherapy-naïve CRPC to abiraterone with or without radium-223.[796] The patients were asymptomatic or mildly symptomatic. The primary endpoint of symptomatic skeletal event-free survival in the ITT population was not met. In fact, the addition of radium-223 to abiraterone was associated with an increased frequency of bone fractures compared with placebo. The PEACE III trial (NCT02194842) is also comparing radium-223 in combination with a secondary hormonal therapy to secondary hormone therapy alone in patients with mildly symptomatic metastatic CRPC. In this trial, the use of bone-protecting agents (denosumab or zoledronic acid) was made mandatory following results from ERA 223. The cumulative incidence of fractures at 1.5 years in patients who received a bone-protecting agent was 2.8% in participants receiving radium-223 plus enzalutamide and 3.9% in those receiving enzalutamide alone.[797] In the absence of bone agents, these numbers were 45.9% and 22.3%, respectively. This result suggests that radium-223 combined with a secondary hormone therapy may be safe if preventive administration of a bone agent is used. The Panel awaits further efficacy data before

recommending radium-223 in combination with a secondary hormonal therapy.

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.[719] Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial has the potential for additive myelosuppression.[719] It is not recommended for use in combination with docetaxel or any other systemic therapy except ADT. It should not be used in patients with visceral metastases. Based on the PEACE III results described above, all patients receiving radium-223 should be given concomitant denosumab or zoledronic acid.

Small Cell/Neuroendocrine Prostate Cancer

De novo small cell carcinoma in untreated prostate cancer occurs rarely and is very aggressive.[798] Treatment-associated small cell prostate cancer/NEPC that occurs in patients with metastatic CRPC is more common.[799] In a multi-institution prospective series of 202 consecutive patients with metastatic CRPC, all of whom underwent metastatic biopsies, small cell/neuroendocrine histology was present in 17% of patients.[799] Patients with small cell/neuroendocrine tumors and prior abiraterone and/or enzalutamide had a shorter OS when compared with those with adenocarcinoma and prior abiraterone and/or enzalutamide (HR, 2.02; 95% CI, 1.07–3.82). Genomic analysis showed that DNA repair mutations and small cell/neuroendocrine histology were almost mutually exclusive.

Small cell/neuroendocrine carcinoma of the prostate should be considered in patients with disease that no longer responds to ADT and who test positive for metastases. These relatively rare tumors are associated with low PSA levels despite large metastatic burden and visceral disease.[800] Those with initial Grade Group 5 are especially at risk. Biopsy of accessible metastatic lesions to identify patients with small cell/neuroendocrine histomorphologic features is recommended in patients with metastatic CRPC.

These patients may be treated with cytotoxic chemotherapy (ie, cisplatin/etoposide, carboplatin/etoposide, docetaxel/carboplatin, cabazitaxel/carboplatin).[749,801,802] Physicians should consult the NCCN Guidelines for Small Cell Lung Cancer for additional options in the first and subsequent lines of therapy (available at www.NCCN.org), because the behavior of small cell/neuroendocrine carcinoma of the prostate is similar to that of small cell carcinoma of the lung.

Additional Treatment Options for Bone Metastases

In a multicenter study, 643 patients with CRPC and asymptomatic or minimally symptomatic bone metastases were randomized to intravenous zoledronic acid every 3 weeks or placebo.[803] At 15 months, fewer patients in the zoledronic acid 4-mg group than patients 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).[804] No significant differences were found in OS. Other bisphosphonates have not been shown to be effective for prevention of disease-related skeletal complications. Earlier use of zoledronic acid in patients with castration-sensitive prostate cancer and bone metastases is not associated with lower risk for SREs, and in general should not be used for SRE prevention until the development of metastatic CRPC.[805]

The randomized TRAPEZE trial used a 2 X 2 factorial design to compare clinical PFS (pain progression, SREs, or death) as the primary outcome in 757 patients with bone metastatic CRPC treated with docetaxel alone or with zoledronic acid, 89Sr, or both.[806] The bone-directed therapies had no statistically significant effect on the primary outcome or on OS in

unadjusted analysis. However, adjusted analysis revealed a small effect for 89Sr on clinical PFS (HR, 0.85; 95% CI, 0.73–0.99; *P* = .03). For secondary outcomes, zoledronic acid improved the SRE-free interval (HR, 0.78; 95% CI, 0.65–0.95; *P* = .01) and decreased the total SREs (424 vs. 605) compared with docetaxel alone.

Denosumab was compared to zoledronic acid in a randomized, double-blind, placebo-controlled study in patients with CRPC.[807] The absolute incidence of SREs was similar in the two groups; however, the median time to first SRE was delayed by 3.6 months by denosumab compared to zoledronic acid (20.7 vs. 17.1 months; *P* = .0002 for non-inferiority, *P* = .008 for superiority). The rates of important SREs with denosumab were similar to zoledronic acid and included spinal cord compression (3% vs. 4%), need for radiation (19% vs. 21%), and pathologic fracture (14% vs. 15%).

Treatment-related toxicities reported for zoledronic acid and denosumab were similar and included hypocalcemia (more common with denosumab 13% vs. 6%), arthralgias, and osteonecrosis of the jaw (ONJ, 1%–2% incidence). Most, but not all, patients who develop ONJ have preexisting dental problems.[808]

Therefore, denosumab every 4 weeks (category 1, preferred) or zoledronic acid every 3 to 4 weeks is recommended for patients with CRPC and bone metastases to prevent or delay disease-associated SREs. SREs include pathologic fractures, spinal cord compression, operation, or EBRT to bone. The optimal duration of zoledronic acid or denosumab in patients with CRPC and bone metastases remains unclear. A multi-institutional, open-label, randomized trial in 1822 patients with bone-metastatic prostate cancer, breast cancer, or multiple myeloma found that zoledronic acid every 12 weeks was non-inferior to zoledronic acid every 4 weeks.[809] In the every-12-weeks and every-4-weeks arms, 28.6% and 29.5% experienced at least 1 SRE within 2 years of randomization, respectively.

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.[810] 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 patients with impaired renal function (estimated creatinine clearance 30–60 mL/min) and held for creatinine clearance <30 mL/min. Denosumab may be administered to patients with impaired renal function or even patients 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.[719] Hypocalcemia should be corrected before starting denosumab, and serum calcium monitoring is required for denosumab and recommended for zoledronic acid, with repletion as needed.

Radium-223 is a category 1 option to treat symptomatic bone metastases without visceral metastases. The use of palliative, systemic radiation with either 89Sr or 153Sm with or without focal EBRT remains an option, though they are seldom used these days with other available options (see *Radium-223*, above). EBRT alone is also an option.

Clinical research on the prevention or delay of disease spread to bone continues. A phase 3 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.[811] OS was not improved, and the FDA did not approve denosumab for the prevention of bone metastases.

Considerations for Visceral Metastases

The panel defines visceral metastases as those occurring in the liver, lung, adrenal gland, peritoneum, or brain. Soft tissue/lymph node sites are not considered visceral metastases. In general, there are fewer data on treatment of patients with CRPC and visceral metastases than for those without visceral metastases. This is especially true in patients who have already received docetaxel and a novel hormone therapy, where most systemic therapies are given a category 2B recommendation.

Sequencing of Therapy in CRPC

The number of treatment options for patients with CRPC has expanded rapidly over the past several years. Although the optimal sequence of therapies remains undefined, some data are emerging that can help with treatment selection in some cases.

After abiraterone or enzalutamide, data suggest that giving the alternate novel hormone therapy may not be the optimal strategy considering the availability of other treatment options, including chemotherapy. The CARD trial, for instance, showed that treatment with cabazitaxel significantly improved clinical outcomes over enzalutamide or abiraterone in patients with metastatic CRPC who had been previously treated with docetaxel and the alternate hormonal therapy (abiraterone or enzalutamide).[744] Furthermore, data suggest cross-resistance between abiraterone and enzalutamide.[812-815] Results of a randomized, open-label, phase 2, crossover trial suggest that the sequence of abiraterone followed by enzalutamide is more efficacious than the reverse.[816]

Some data inform the sequencing of therapies in patients with actionable biomarkers. The multicenter, unblinded, randomized phase 2 TheraP trial compared PSA response after Lu-177-PSMA-617 vs. cabazitaxel in 200 patients with PSMA-positive metastatic CRPC who previously received docetaxel.[817] Prior androgen receptor-directed therapy was permitted. Among the ITT population, the PSA response rate was 66% in the Lu-177-PSMA-617 arm compared with 37% in the cabazitaxel arm (difference 29%; 95% CI, 16–42; $P < .0001$). These numbers were 66% and 44%, respectively, in those who received treatment (difference 23%; 95% CI, 9–37; $P = .0016$). Furthermore, grade 3–4 adverse events were less frequent in the Lu-177-PSMA-617 arm than in the cabazitaxel arm (33% vs. 53%). Results from the phase 3 PSMAfore trial (NCT04689828), which may inform the choice between Lu-177-PSMA-617 and switching to a different androgen receptor-directed therapy in docetaxel-naïve patients, are awaited. Data for patients with HRRm metastatic CRPC are more limited, but comparative effectiveness research suggests that olaparib may result in superior radiographic PFS than cabazitaxel in patients with *BRCA1* or *BRCA2* mutations and prior treatment with docetaxel.[818]

No chemotherapy regimen has demonstrated improved survival or QOL after cabazitaxel or cabazitaxel/carboplatin, 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[819-828]). No survival benefit for these combination regimens over sequential single-agent regimens has been demonstrated, and toxicity is higher. Treatment with these regimens 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. Prednisone or dexamethasone at low doses may provide palliative benefits in the chemotherapy-refractory setting.[829] Participation in a clinical trial is encouraged.

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 some of the 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 Risk Stratification/Prognosis

Test	Platform	Populations Studied	Outcome(s) Reported (Test independently predicts)	Selected References	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (46,050 genes and noncoding RNA) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	• Metastasis • Prostate cancer-specific mortality • Postoperative radiation sensitivity (PORTOS)	148,151,152,564,830-843	Cover post-biopsy for NCCN very-low-, low-risk, favorable intermediate-, and unfavorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy Cover post-RP for 1) pT2 with positive margins; 2) any pT3 disease; 3) rising PSA (above nadir)
		Post RP, biochemical recurrence/PSA persistence	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Post RP, adjuvant, or post-recurrence radiation	• Metastasis • Prostate cancer-specific mortality • PORTOS		
		Biopsy, localized prostate cancer post RP or EBRT	• Non-organ confined (pT3) or grade group 3 disease at RP • Lymph node metastasis • Biochemical failure/recurrence • Metastasis • Prostate cancer-specific mortality • Grade Group ≥4 disease at RP		
		M0 CRPC	• Metastasis-free survival		
Ki-67	IHC	Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality	844-847	Not recommended
		Biopsy, low- to intermediate-risk treated with RP	• Non-organ-confined pT3 or Grade Group ≥4 disease on RP		
Oncotype DX Prostate	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, very-low- to high-risk treated with RP	• Non-organ-confined pT3 or Grade Group 4 disease on RP • Biochemical recurrence • Metastases • Prostate cancer-specific mortality	150,848,849	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality	143-146,850-852	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
		Biopsy, localized prostate cancer	• Biochemical recurrence • Metastasis		
		Biopsy, intermediate-risk treated with EBRT	• Biochemical recurrence		
		RP, node-negative localized prostate cancer	• Biochemical recurrence		
		Biopsy, Gleason grade 3+3 or 3+4	• Non–organ-confined pT3 or Grade Group ≥3 on RP		
PTEN	Fluorescence in situ hybridization or IHC	Biopsy, Grade Group 1	• Upgrading to Grade Group ≥3 on RP	853-857	Not recommended
		RP, high-risk localized disease	• Biochemical recurrence		

Table 2. Summary of FDA-Cleared PET Imaging Tracers Studied in Prostate Cancer

Tracer	Half-life (min)	Production	Mechanism of Action	Excretion	Detection Rates*	Panel Recommendation
Ga-68 PSMA-11 (PSMA-HBED-CC)[188,858]	68	Generator or Cyclotron (Regional)	Binds extracellular epitope of PSMA	Renal	40% sensitivity and 95% specificity to detect nodal involvement in primary staging of patients with intermediate-, high-, and very-high-risk disease 92% patient-level PPV in BCR	May be used for detection of disease at initial staging, biochemical recurrence, and progression of disease in bone and soft tissues (see NCCN Guidelines algorithm for more details)
F-18 piflufolastat (DCFPyL)[191,859]	110	Cyclotron (Regional)	Binds extracellular epitope of PSMA	Renal	31%–42% sensitivity and 96%–99% specificity to detect nodal involvement in primary staging of patients with unfavorable intermediate-risk, high-risk, and very-high-risk disease 85%–87% patient-level CLR** in BCR	May be used for detection of disease at initial staging, biochemical recurrence, and progression of disease in bone and soft tissues (see NCCN Guidelines algorithm for more details)
C-11 choline[860]	20	Cyclotron (Onsite)	Cellular uptake and incorporation into cell membrane/lipid synthesis	Hepatic and renal	53%–96% PPV in BCR	May be used for detection of disease at biochemical recurrence and progression of disease in bone and soft tissues (see NCCN Guidelines algorithm for more details)
F-18 fluciclovine (FACBC)[861]	110	Cyclotron (Regional)	Cellular uptake by amino acid transporters ASCT2, LAT1, and SNAT2	Renal	87%–91% CLR** in BCR	May be used for detection of disease at biochemical recurrence and progression of disease in bone and soft tissues (see NCCN Guidelines algorithm for more details)
F-18 NaF[210]	110	Cyclotron (Regional)	Adsorption to bone matrix by osteoblasts	Renal	77%–94% sensitivity, 92%–99% specificity, and 82%–97% PPV for bone metastases	May be used as an alternative to bone scintigraphy

* Interpret with caution. Wherever possible, studies were included that used histopathologic confirmation, but not all studies used confirmatory histology as the gold standard. Values may vary depending upon the site of the lesion and phase of the disease process.

** CLR: Correct localization rate. Patient-level positive predictive value + anatomic lesion co-localization. Preferred over sensitivity and specificity in analyses of patients with BCR.

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