National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer

Version 1.2023 — September 16, 2022

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue

NCCN Guidelines Version 1.2023
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

*Edward M. Schaeffer, MD, PhD/Chair ω
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

*Sandy Srinivas, MD/Vice-Chair † ω
Stanford Cancer Institute

Yi An, MD §
Yale Cancer Center/Smilow Cancer Hospital

Daniel Barocas, MD, MPH ω
Vanderbilt-Ingram Cancer Center

Rhonda Bitting, MD †
Duke Cancer Institute

Alan Bryce, MD †
Mayo Clinic Cancer Center

Brian Chapin, MD ω
The University of Texas MD Anderson Cancer Center

Heather H. Cheng, MD, PhD †
Fred Hutchinson Cancer Center

Anthony Victor D'Amico, MD, PhD §
Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center

Neil Desai, MD, MHS §
UT Southwestern Simmons Comprehensive Cancer Center

Tanya Dorff, MD †
City of Hope National Cancer Center

James A. Eastham, MD ω
Memorial Sloan Kettering Cancer Center

Thomas A. Farrington ¥
Prostate Health Education Network (PHEN)

Xin Gao, MD † Þ
Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center

Shilpa Gupta, MD †
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Thomas Guzzo, MD, MPH ω
Abramson Cancer Center at The University of Pennsylvania

Joseph E. Ippolito, MD, PhD ф
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Michael R. Kuettel, MD, MBA, PhD §
Roswell Park Comprehensive Cancer Center

Joshua M. Lang, MD, MS †
University of Wisconsin Carbone Cancer Center

Tamara Lotan, MD ≠
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Rana R. McKay, MD †
UC San Diego Moores Cancer Center

Todd Morgan, MD ω
University of Michigan Rogel Cancer Center

George Netto, MD ≠
O'Neal Comprehensive Cancer Center at UAB

Julio M. Pow-Sang, MD ω
Moffitt Cancer Center

Robert Reiter, MD, MBA ω
UCLA Jonsson Comprehensive Cancer Center

Mack Roach, III, MD §
UCSF Helen Diller Family Comprehensive Cancer Center

Tyler Robin, MD, PhD §
University of Colorado Cancer Center

Stan Rosenfeld ¥
University of California San Francisco
Patient Services Committee Chair

Ahmad Shabsigh, MD ω
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Daniel Spratt, MD §
Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Benjamin A. Teply, MD †
Fred & Pamela Buffett Cancer Center

Jonathan Tward, MD, PhD §
Huntsman Cancer Institute at the University of Utah

Richard Valicenti, MD §
UC Davis Comprehensive Cancer Center

Jessica Karen Wong, MD §
Fox Chase Cancer Center

ф Diagnostic/Interventional radiology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocate
§ Radiotherapy/Radiation oncology
ω Urology
* Discussion Section Writing Committee

Continue

NCCN
Ryan Berardi, MSc
Deborah Freedman-Cass, PhD
Dorothy A. Shead, MS

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Prostate Cancer

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.

Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-1

- Clinically localized prostate cancer, Workup:
  - 3rd bullet modified: Perform and/or collect prostate-specific antigen (PSA) and calculate PSA density ~~and PSA doubling time (PSADT)~~
  - 8th bullet added: Assess quality-of-life measures
- Regional prostate cancer and metastatic prostate cancer, Workup:
  - 7th bullet added: Assess quality-of-life measures
  - Footnote d added: See Principles of Quality-of-Life and Shared Decision-Making (PROS-B)

PROS-2

- Risk Group, Additional Evaluation:
  - Very low, modified: Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)~~Consider confirmatory mpMRI ± prostate biopsy if MRI not performed initially. All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy.~~
  - Low, modified: Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5) ~~Consider confirmatory mpMRI ± prostate biopsy and/or molecular tumor analysis if MRI not performed initially to establish candidacy for active surveillance. All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy.~~
  - Intermediate, modified: Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5) ~~Consider confirmatory mpMRI ± prostate biopsy and/or molecular tumor analysis if MRI not performed initially for those considering active surveillance. All patients should undergo a confirmatory prostate biopsy within 1-2 years of their diagnostic biopsy.~~

PROS-3

- Very-Low-Risk Group:
  - >20 y, Initial Therapy
    - ◊ Added: See Active Surveillance Program (PROS-F 2 of 5)
    - ◊ Removed the following bullets:
      - Consider confirmatory mpMRI +/- prostate biopsy if MRI not performed initially
      - All patients should undergo a confirmatory prostate biopsy within 1–2 years of their diagnostic biopsy
      - PSA no more often than every 6 mo unless clinically indicated
      - DRE no more often than every 12 mo unless clinically indicated
      - Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
      - Repeat mpMRI no more often than every 12 mo unless clinically indicated
  - 10–20 y, Initial Therapy:
    - ◊ Added: See Active Surveillance Program (PROS-F 2 of 5)
    - ◊ Removed the following bullets:
      - Consider confirmatory mpMRI +/- prostate biopsy if MRI not performed initially
      - All patients should undergo a confirmatory prostate biopsy within 1–2 years of their diagnostic biopsy
      - PSA no more often than every 6 mo unless clinically indicated
      - DRE no more often than every 12 mo unless clinically indicated
      - Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
      - Repeat mpMRI no more often than every 12 mo unless clinically indicated

Continued
UPDATES

Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-4
- Low-Risk Group:
  - ≥10 y, Initial Therapy:
    - ◊ Added: See Active Surveillance Program (PROS-F 2 of 5)
    - ◊ Removed the following bullets:
      - – Consider confirmatory mpMRI +/- prostate biopsy and/or molecular tumor analysis if MRI not performed initially
      - – All patients should undergo a confirmatory prostate biopsy within 1–2 years of their diagnostic biopsy
      - – PSA no more often than every 6 mo unless clinically indicated
      - – DRE no more often than every 12 mo unless clinically indicated
      - – Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
      - – Repeat mpMRI no more often than every 12 mo unless clinically indicated

PROS-5
- Favorable Intermediate-Risk Group:
  - >10 y, Initial Therapy:
    - ◊ Added: See Active Surveillance Program (PROS-F 2 of 5)
    - ◊ Removed the following bullets:
      - – Consider confirmatory mpMRI +/- prostate biopsy and/or molecular tumor analysis if MRI not performed initially
      - – All patients should undergo a confirmatory prostate biopsy within 1–2 years of their diagnostic biopsy
      - – PSA no more often than every 6 mo unless clinically indicated
      - – DRE no more often than every 12 mo unless clinically indicated
      - – Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
      - – Repeat mpMRI no more often than every 12 mo unless clinically indicated
    - ◊ Modified: RP ± pelvic lymph node dissection (PLND) ~~if predicted probability of lymph node metastasis ≥2%~~

PROS-6
- Unfavorable Intermediate Risk Group:
  - >10 y, Initial Therapy, modified: ~~RP ± PLND~~ *RP* + *PLND* ~~if predicted probability of lymph node metastasis ≥2%~~

PROS-7
- High- or Very-High-Risk Group:
  - >5 y or symptomatic, Initial Therapy, removed: EBRT + ADT (2 y) + docetaxel for 6 cycles (for very-high-risk only)
  - Footnote ff added: Patients in STAMPEDE had at least two of the following: cT3–4, Grade Group 4 or 5, and PSA >40 ng/mL. (Also on PROS-8A)

PROS-8
- Regional Risk Group (Any T, N1, M0)
  - >5 y or symptomatic, Initial Therapy:
    - ◊ Modified: EBRT + ADT + abiraterone *(preferred)*
    - ◊ Modified: EBRT + ADT ~~(preferred)~~
    - ◊ Modified: RP + PLND *in select patients*
- Footnote jj added: 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. (Also on PROS-8A)

Continued
UPDATES

Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-8A

- Footnote o modified: If higher grade and/or higher T stage is found *during confirmatory testing*, see PROS-2.
- Footnote t modified: Decipher molecular assay ~~is recommended~~ *should be considered* if not previously performed to inform adjuvant treatment if adverse features are found post-RP.
- Footnote removed: See Principles of Risk Stratification.
- Footnote removed: Repeat molecular tumor analysis is discouraged.
- Footnote z modified: PSA persistence/recurrence after RP is defined as 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.* (Also on PROS-9 and PROS-10)

PROS-9

- Monitoring, Initial definitive therapy, 2nd bullet modified: DRE *if suspicion of recurrence* ~~every year, but may be omitted if PSA undetectable.~~
- Recurrence, Biopsy of metastatic site, modified: See Systemic Therapy for Castration-~~Naive~~ *Sensitive* Disease

PROS-10

- The algorithm has been divided into two branches: *Life expectancy >5 y* and *Life expectancy ≤5 y*
  - Life expectancy >5 y
    - ◊ Modified:
      - – Studies negative for distant metastases *and pelvic recurrence*
      - – EBRT ± ADT *(preferred)* or ~~Observation~~ *Monitoring*
    - ◊ Added: Studies positive for pelvic recurrence
      - – Added: EBRT + ADT ± abiraterone
        - ▪ Added: Progression
  - Life expectancy ≤5 y
    - ◊ Added: Observation
      - – Added: Progression
- Modified: See Systemic Therapy for Castration ~~Naive~~ *Sensitive* Disease
- Footnote oo modified: *Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or 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. 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. Soft tissue imaging of 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.~~ (Also on PROS-11A)
- Footnote pp added: The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B).

PROS-11

- This page has been extensively revised.

Continued
UPDATES

Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-12

- Page heading has been modified: Systemic Therapy for Castration-~~Naive~~ *Sensitive* Prostate Cancer
- M1:
  - ADT with one of the following, removed: Docetaxel 75 mg/m^2 for 6 cycles (category 1)
  - Added: or ADT with docetaxel and one of the following:
    - ◊ Preferred regimens:
      - – Abiraterone (category 1)
      - – Darolutamide (category 1)
  - Modified: or ADT with EBRT to the primary tumor for low-~~volume~~ *metastatic burden* M1
- 3rd bullet modified: ~~Consider periodic imaging~~ *Conventional imaging every 3–6 mo* to monitor treatment response.

PROS-12A

- Footnote rr modified: The term "castration-~~naive~~ *sensitive"* 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-~~naïve~~ *sensitive*" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.
- Footnote zz modified: ~~Routine use of bone antiresorptive therapy is not recommended in the castration-naïve setting unless for elevated fracture risk~~ *Bone antiresorptive therapy is indicated for elevated fracture risk based upon FRAX in the castration-sensitive setting.* See PROS-I.
- Footnote removed: High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.
- Footnote aaa added: The panel encourages ADT with docetaxel and either darolutamide or abiraterone for patients with high-volume disease who are fit for chemotherapy. See Principles of Non-Hormonal Systemic Therapy (PROS-J).
- Footnote bbb added: EBRT to the primary tumor is associated with an overall survival 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-G).
- Footnote ccc added: 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.
- Footnote removed: See Principles of Non-Hormonal Systemic Therapy.
- Footnote ddd modified: Patients who were under monitoring for M0 disease should receive an appropriate therapy for castration-~~naive~~ *sensitive* disease.

PROS-13

- Footnote removed: 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.

PROS-14

- First-line and subsequent treatment options:
  - 1st bullet, 5th sub-bullet added: For additional options, See NCCN Guidelines for Small Cell Lung Cancer.
- Footnote removed: For additional small cell/NEPC therapy options, see NCCN Guidelines for Small Cell Lung Cancer

Continued
UPDATES

Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-15

- Prior novel hormonal therapy/no prior docetaxel:
  - Preferred regimens, removed: Sipuleucel-T
  - Useful in certain circumstances:
    - ◊ Removed: Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb
    - ◊ Added: Sipuleucel-T
- Prior docetaxel/no prior novel hormone therapy:
  - Useful in certain circumstances:
    - ◊ Removed: Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb
    - ◊ Added: Sipuleucel-T
  - Other recommended regimens, removed: Sipuleucel-T

PROS-15A

- Footnote mmm modified: Novel hormone therapies include abiraterone, enzalutamide, darolutamide, or apalutamide ~~received for metastatic castration-naïve sensitive disease, M0 CRPC, or previous lines of therapy for M1 CRPC.~~ *Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered prior novel hormonal therapy.*
- Footnote ttt modified: Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair 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.* ~~Patients with PPP2R2A mutations in the PROfound trial experienced an unfavorable risk-benefit profile. Therefore, olaparib is not recommended in patients with a PPP2R2A mutation.~~ There may be heterogeneity of response to olaparib for non-*BRCA* mutations based on ~~which gene has a~~ *the specific gene* mutation.

PROS-B

- A new section has been added to the guidelines: Principles of Quality-of-Life and Shared Decision-Making

PROS-C 1 of 3

- 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.

PROS-C 2 of 3

- By family history and/or ancestry,
  - 1st bullet, 3rd sub-bullet modified: male *(sex assigned at birth)* breast cancer at any age.
  - 2nd bullet modified: ≥1 first-degree relative (~~father~~ *parent* or ~~brother~~ *sibling*) with:

PROS-C 3 of 3

- Testing, 2nd sub-bullet modified: Tumor testing for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) is recommended in patients with metastatic castration-resistant prostate cancer and may be considered in patients with regional or castration-~~naïve~~ *sensitive* metastatic prostate cancer.
- Post-test Considerations, 1st sub-bullet modified: 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).

Continued
UPDATES

Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-D
- This section has been extensively revised.

PROS-E 3 of 3
- Positron Emission Tomography, 2nd bullet modified: 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.~~
- Positron Emission Tomography, 8th bullet added: PSMA imaging should be done before initiation of ADT because ADT may affect detection sensitivity.

PROS-F 1 of 5
- Candidacy for Active Surveillance, 2nd bullet modified: Active surveillance is preferred for most patients with low-risk prostate cancer (See 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)~~, and/or a known BRCA2 germline mutation~~…

PROS-F 2 of 5
- Active Surveillance Program, 1st bullet, 4th sub-bullet modified: *Consider* repeat mpMRI no more often than every 12 months unless clinically indicated.

PROS-F 3 of 5
- Observation, 3rd bullet modified: Observation ~~may be considered for~~ *is preferred for*: Asymptomatic patients with favorable and unfavorable intermediate-risk prostate cancer and a life expectancy between 5–10 years.

PROS-F 5 of 5
- Reference removed: Carter HB, Helfand B, Mamawala M, et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. Eur Urol 2019;75:743-749.

PROS-G 2 of 7
- Definitive Radiation Therapy by Risk Group
  - 6th bullet, 1st sub-bullet modified: Nodal radiation should be performed. Clinically positive nodes should be dose-escalated as dose-volume histogram parameters allow. ADT is required unless medically contraindicated, and the addition of abiraterone or fine-particle abiraterone (category 2B) to ADT ~~can be considered~~ *is preferred.*
  - 7th bullet modified: Low~~-volume~~ metastatic *burden*, castration-~~naive~~ *sensitive* disease
    - ◊ 1st sub-bullet modified: Radiation therapy to the prostate is an option in patients with low~~-volume~~ metastatic burden castration-~~naïve~~ sensitive metastatic disease, without contraindications to radiotherapy. ADT is required unless medically contraindicated.
  - 8th bullet and subsequent bullets added: Low metastatic burden is defined as either non-regional, lymph-node-only disease OR <4 bone metastases and without visceral/other metastasis.
    - ◊ Number and location of lesions is defined by conventional imaging.
    - ◊ At this time, metastases defined only by PET imaging should not be used to exclude a patient from treatment of the primary tumor.
  - 9th bullet modified: This recommendation is based on the STAMPEDE phase 3 randomized trial, 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, but not overall survival. The prespecified low-volume subset had a significant improvement in both failure-free survival and overall survival. *A meta-analysis with two other studies confirmed this benefit for primary RT to the primary tumor in lower volume disease.*

Continued
UPDATES

Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-G 3 of 7

- Principles of Radiation Therapy, 1st bullet added: STAMPEDE Arm H has now distinguished the CHAARTED definition of low metastatic disease to one that more granularly quantifies who benefits from treatment of the primary based on number of bone metastases. This is relevant because a patient can have 12 spine metastases and be classified as low volume by CHAARTED, but would not derive benefit in overall survival or failure-free survival when quantifying number of bone metastases. Thus, the number of bone metastases may be preferred to define candidacy for treatment of the primary tumor.
- Footnote a added: 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.
- References added:
  - Parker CC, James ND, Brawley CD, et al. Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353-2366.
  - Burdett S, Boevé LM, Ingleby FC, et al. Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis. Eur Urol 2019;76:115-124.
  - Ali A, Hoyle A, Haran ÁM, et al. Association of bone metastatic burden with survival benefit from prostate radiotherapy in patients with newly diagnosed metastatic prostate cancer: A secondary analysis of a randomized clinical trial. JAMA Oncol 2021;7:555-563.

PROS-G 4 of 7

- Table 1, Conventional Fractionation, Preferred Dose/Fractionation added: 2.2 Gy x 35 fx + micro-boost to MRI-dominant lesion to up to 95 Gy (fractions up to 2.7 Gy)
- Regimen, EBRT, added: SBRT
  - Preferred Dose/Fractionation added: 9.5 Gy x 4x

PROS-G 5 of 7

- Post-Prostatectomy Radiation Therapy:
  - Sub-bullet removed: The ongoing SPPORT trial (NCT00567580) of patients with PSA levels between 0.1 and 2.0 ng/mL at least 6 weeks after RP has reported preliminary results on clinicaltrials.gov. The primary outcome measure of percentage of participants free from progression 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 also received 4–6 months of ADT (LHRH agonist plus antiandrogen).
  - 1st bullet, 3rd sub-bullet added: The SPPORT 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 lymphs 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). Pollack A, Karrison TG, et al. Lancet 2022;399:1886-1901.

Continued
UPDATES

NCCN Guidelines Version 1.2023
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-G 7 of 7

- Palliative Radiotherapy, 3rd bullet modified: *20 Gy in 5 fractions*, 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)~~.

PROS-H 1 of 2

- Pelvic Lymph Node Dissection:
  - Bullet removed: A PLND can be excluded in patients with <2% predicated probability of nodal metastases by nomograms, although some patients with lymph node metastases will be missed.
  - 4th bullet added: While PLND at the time of RP has not been shown to improve oncologic outcomes, it can provide staging and prognostic information.
  - 5th bullet added: 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%.
  - 6th bullet added: 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%.Thus, basing the decision to perform PLND on a negative PSMA PET scan could result in missing 19% of patients with positive lymph nodes.
- Radical Prostatectomy:
  - 3rd bullet modified: 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*.

PROS-H 2 of 2

- References have been updated.

PROS-I 1 of 5

- ADT for Clinically Localized (N0,M0) Disease
  - 3rd bullet, 1st sub-bullet, 1st tertiary bullet modified: Goserelin, ~~histrelin~~, leuprolide, or triptorelin
  - 3rd bullet, sub-bullet removed: LHRH agonist, LHRH agonist plus first-generation antiandrogen, or degarelix with docetaxel (very high risk only)
- ADT for Regional (N1, M0) Disease:
  - 3rd bullet, 2nd sub-bullet, 1st tertiary bullet modified: Goserelin, ~~histrelin~~, leuprolide, or triptorelin

Continued
UPDATES

Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-I 2 of 5

- Heading modified: ADT for M0 PSA Persistence/Recurrence After RP or EBRT (ADT for M0 Castration-~~Naïve~~ *Sensitive* Disease)
- 7th bullet, 1st sub-bullet, 2nd tertiary bullet added: EBRT + LHRH agonist or degarelix with abiraterone (studies positive for pelvic recurrence only)
- 7th bullet, 2nd sub-bullet modified: M0 radiation therapy recurrence, ~~TRUS~~ biopsy negative or M0 PSA recurrence after progression on salvage EBRT
  - 7th bullet, 2nd sub-bullet, 2nd tertiary bullet, 1st quaternary bullet modified: Goserelin, ~~histrelin~~, leuprolide, or triptorelin
  - 8th bullet added: Abiraterone should be given with concurrent steroid [see ADT for Regional (N1,M0) Disease].
- Heading modified: ADT for Metastatic Castration-~~Naïve~~ *Sensitive* Disease
  - 2nd bullet modified: Treatment options for patients with M1 castration-~~naïve~~ *sensitive* disease are:
    - ◊ 1st sub-bullet, 2 subsequent bullets added:
      - LHRH agonists: Goserelin, leuprolide, or triptorelin
      - First-generation antiandrogens: Nilutamide, flutamide, or bicalutamide
    - ◊ The following sub-bullets have been removed:
      - Orchiectomy plus docetaxel
      - LHRH agonist alone plus docetaxel
        - Goserelin, histrelin, leuprolide, or triptorelin
        - 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
      - LHRH agonist (as above) plus first-generation antiandrogen plus docetaxel
        - Nilutamide, flutamide, or bicalutamide
      - Degarelix plus docetaxel
    - ◊ The following sub-bullets have been added:
      - Orchiectomy plus docetaxel and abiraterone or daralutamide
      - LHRH agonist (as above) plus docetaxel and abiraterone or daralutamide
      - Degarelix plus docetaxel and abiraterone or daralutamide

PROS-I 3 of 5

- 1st bullet modified: When EBRT to primary is given with ADT in low-~~volume~~ *metastatic burden* M1, the options are LHRH agonist, LHRH antagonist, and orchiectomy.
- 2nd bullet modified: Two randomized phase 3 clinical trials of abiraterone with prednisone plus ADT in patients with castration-~~naïve~~ *sensitive* metastatic prostate cancer...
- 3rd bullet modified: A double-blind randomized phase 3 clinical trial of apalutamide plus ADT in patients with castration-~~naïve~~ *sensitive* metastatic prostate cancer demonstrated improved overall survival over ADT alone...
- 4th bullet modified: An open-label randomized phase 3 clinical trial of enzalutamide plus ADT in patients with castration-~~naïve~~ *sensitive* metastatic prostate cancer demonstrated improved overall survival 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 overall survival benefit*. Adverse events associated with enzalutamide included fatigue, seizures, and hypertension.

PROS-I 4 of 5

- 3rd bullet modified: A phase 3 study of docetaxel-~~naïve~~ *sensitive* patients

Continued

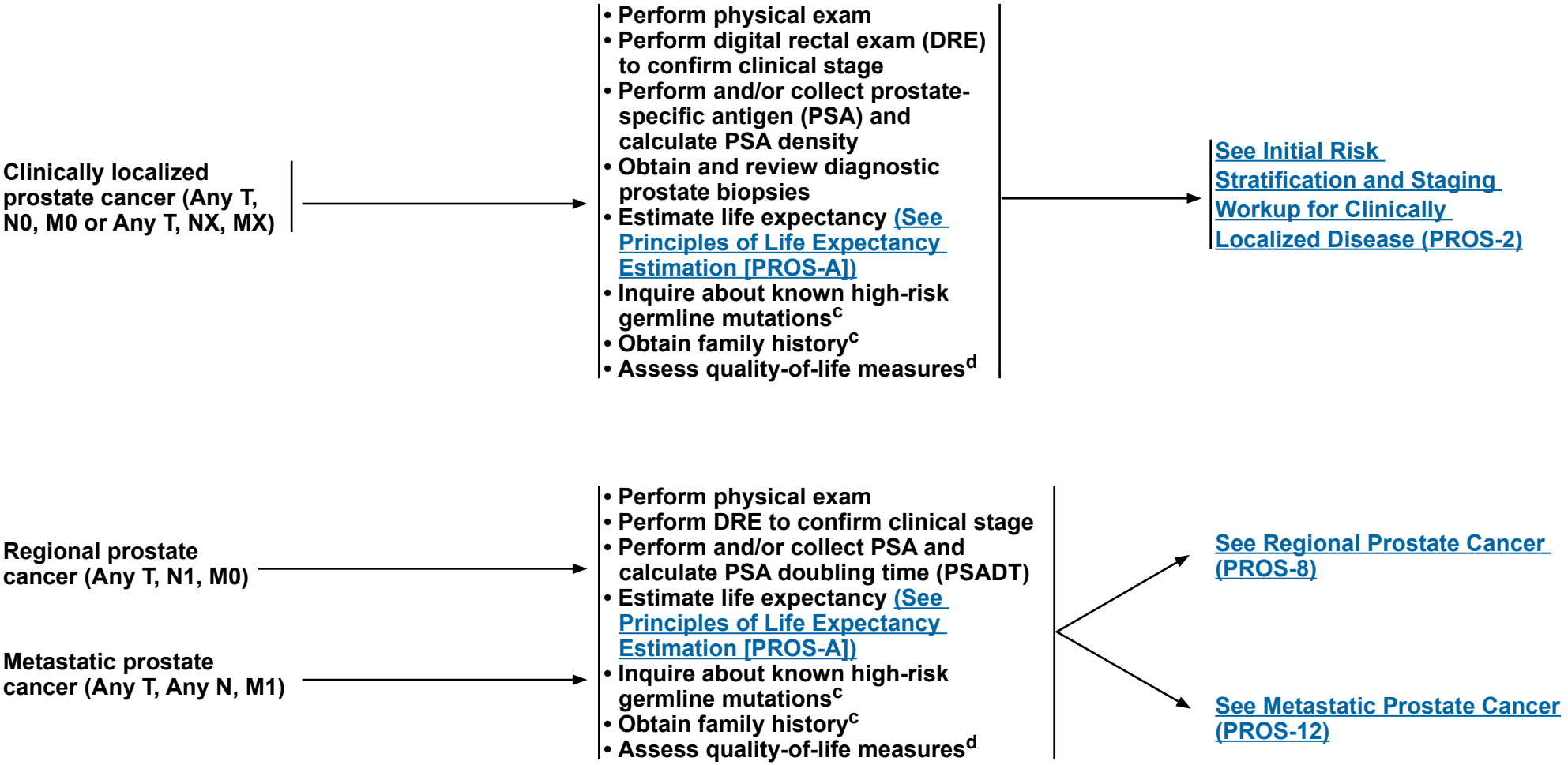
Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-J 1 of 3

- Heading has been removed: Non-Hormonal Systemic Therapy for Very-High-Risk Prostate Cancer
  - Bullet removed: Docetaxel can be added to EBRT and 2 years of ADT in patients with very-high-risk prostate cancer. In the STAMPEDE trial, the hazard ratio for OS in 96 randomized patients with nonmetastatic disease was 0.93 (95% CI, 0.60–1.43) with the addition of docetaxel to EBRT and ADT.
- Heading has been modified: Non-Hormonal Systemic Therapy for M1 Castration-~~Naïve~~ *Sensitive* Prostate Cancer
  - Bullet removed: Patients with high-volume, ADT-naïve, metastatic disease should be considered for ADT (See PROS-H) and docetaxel based on the results of the ECOG 3805 (CHAARTED) trial. In this study, 790 patients were randomized to 6 cycles of docetaxel at 75 mg/m2 every 3 weeks with dexamethasone with ADT vs. ADT alone. In the majority subset of patients with high-volume disease, defined as 4 or more bone metastases including one extra-axial bone lesion or visceral metastases, a 17-month improvement in overall survival was observed (HR, 0.60; *P* = .0006). Improvements in PSA response, time to clinical progression, and time to recurrence were observed with use of docetaxel. Toxicities of 6 cycles of docetaxel included fatigue, neuropathy, stomatitis, diarrhea, and neutropenia with or without fever.
- 1st bullet added: 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 daralutamide based on phase 3 studies:
  - 1st sub-bullet added: ADT plus docetaxel and abiraterone improved overall survival and ~~radiographic progression-free survival~~ rPFS in the open-label PEACE-1 study. A modest increase in toxicity was seen.
  - 2nd sub-bullet added: ADT plus docetaxel and darolutamide improved overall survival in the ARASENS trial. Adverse events were similar between arms.
  - 3rd sub-bullet modified: The use of myeloid growth factors should follow the NCCN Guidelines for Hematopoietic Growth Factors, based on risk of neutropenic fever. ~~Docetaxel should not be offered to patients with low-volume metastatic prostate cancer, since this subgroup was not shown to have improved survival in either the ECOG study or a similar European (GETUG-AFU 15) trial.~~
- Non-Hormonal Systemic Therapy for M1 CRPC Chemotherapy, 3rd bullet modified: Cabazitaxel/carboplatin with concurrent ~~prednisone~~ *steroid* ~~twice daily~~

PROS-J 2 of 3

- 1st bullet modified: Cabazitaxel at 25 mg/m² with concurrent steroid has been shown in a randomized phase 3 study (TROPIC) to prolong overall survival, PFS,~~ and~~ PS*A response*, and radiologic response~~s~~ when compared with mitoxantrone ~~with~~ *and* prednisone and is FDA approved in the post-docetaxel secondline setting.
- 4th bullet modified: Docetaxel retreatment can be attempted after progression on a novel hormone therapy in patients with metastatic CRPC *whose cancer has* ~~have~~ not demonstrated definitive evidence of progression on prior docetaxel therapy in the castration-~~naïve~~ *sensitive* setting.
- Targeted Therapy, 1st bullet modified: Consider inclusion of olaparib in patients who have an HRR mutation and ~~have~~ *whose cancer has* progressed on prior treatment with androgen receptor-directed therapy regardless of prior docetaxel therapy. *Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair 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 which gene has a the specific gene mutation.*
- Immunotherapy, 3rd bullet, 1st sub-bullet modified: Pembrolizumab is recommended only as subsequent systemic therapy for patients with metastatic CRPC ~~who have~~ *whose cancer* has progressed through prior docetaxel and~~/or~~ a novel hormone therapy.



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

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[e]

Risk Group	Clinical/Pathologic Features See Staging (ST-1)			Additional Evaluation[h,i]	Initial Therapy
Very low[f]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] • PSA density <0.15 ng/mL/g			• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See PROS-3
Low[f]	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 (See PROS-F 2 of 5)	See PROS-4
Intermediate[f]	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)[g]	• Confirmatory testing can be used to assess the appropriateness of active surveillance (See PROS-F 2 of 5)	See 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)[g]	Bone and soft tissue imaging[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See 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[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See 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[j,k] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7

See 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

[e] Tumor-based molecular assays and germline genetic testing are other tools that can assist with risk stratification. 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-D) to determine if a patient is an appropriate candidate for tumor-based molecular assays. to determine if a patient is an appropriate candidate for tumor-based molecular assays.

[f] For asymptomatic patients 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 and androgen deprivation therapy (ADT) should be given (See PROS-I).

[g] 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.

[h] See Principles of Imaging (PROS-E).

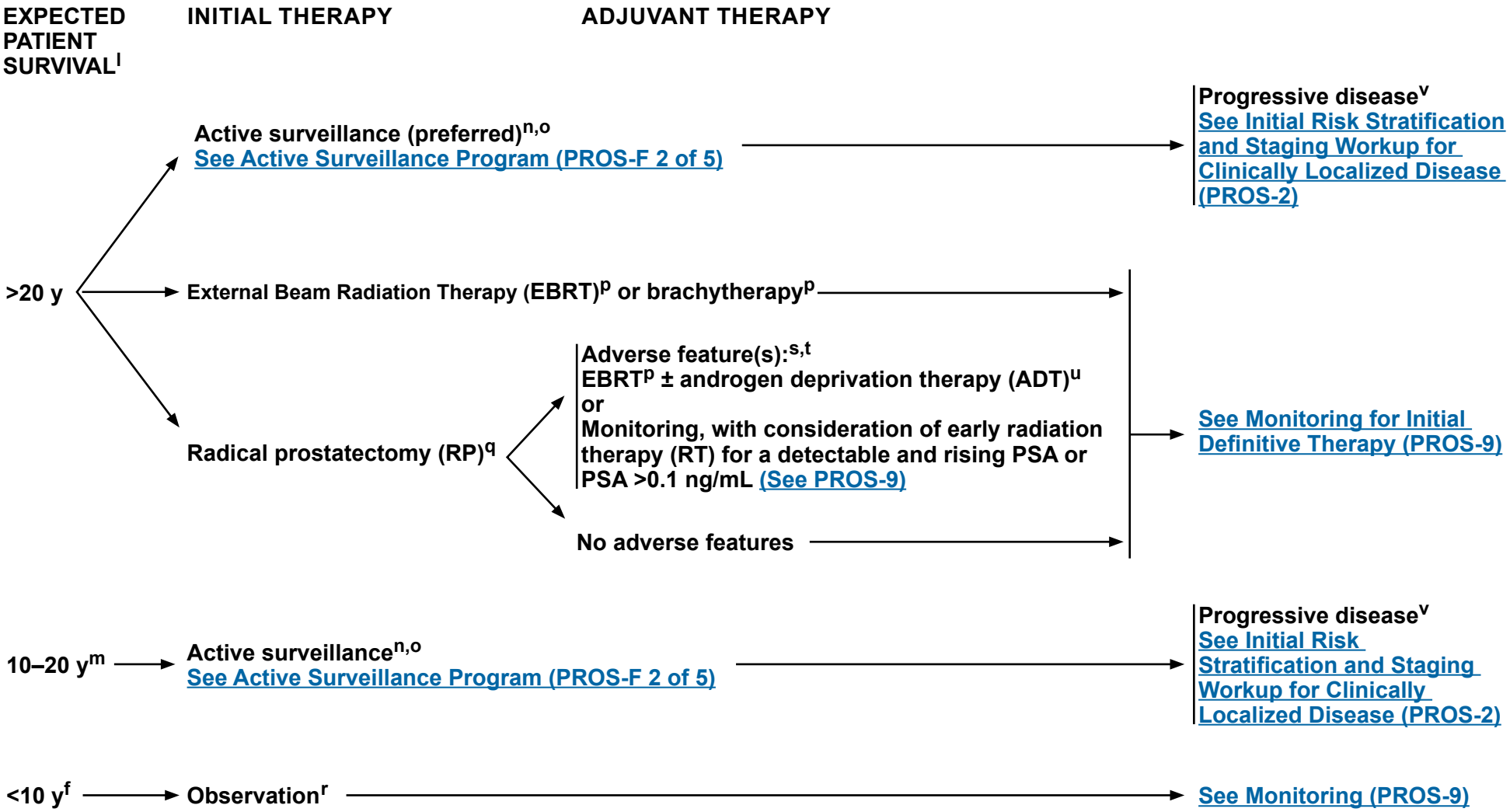
[i] Bone imaging should be performed for any patient with symptoms consistent with bone metastases.

[j] Bone imaging can be achieved by conventional technetium-99m-methylene diphosphonate (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. See Principles of Imaging (PROS-E).

[k] 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.

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.

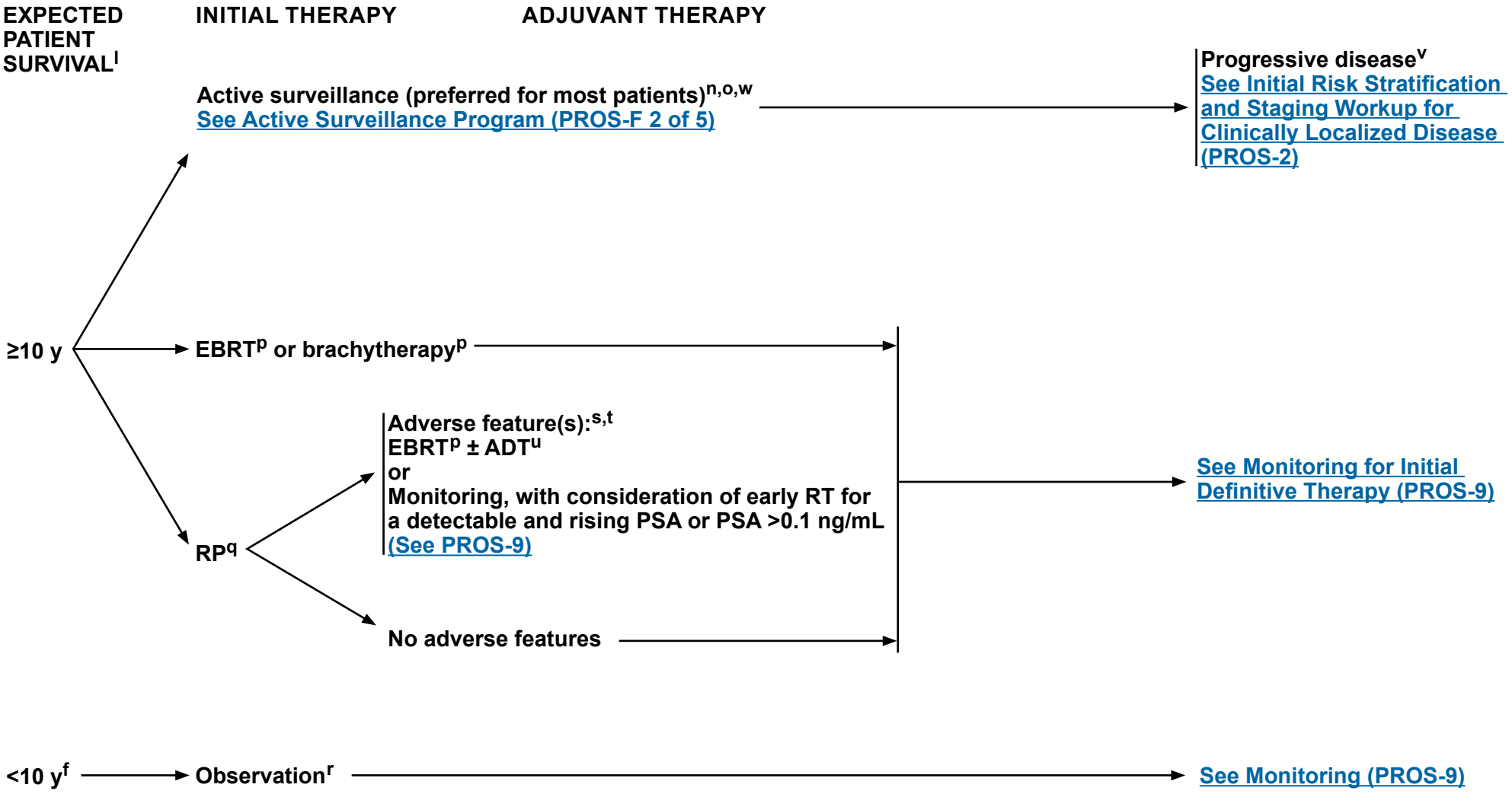
VERY-LOW-RISK GROUP



See 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

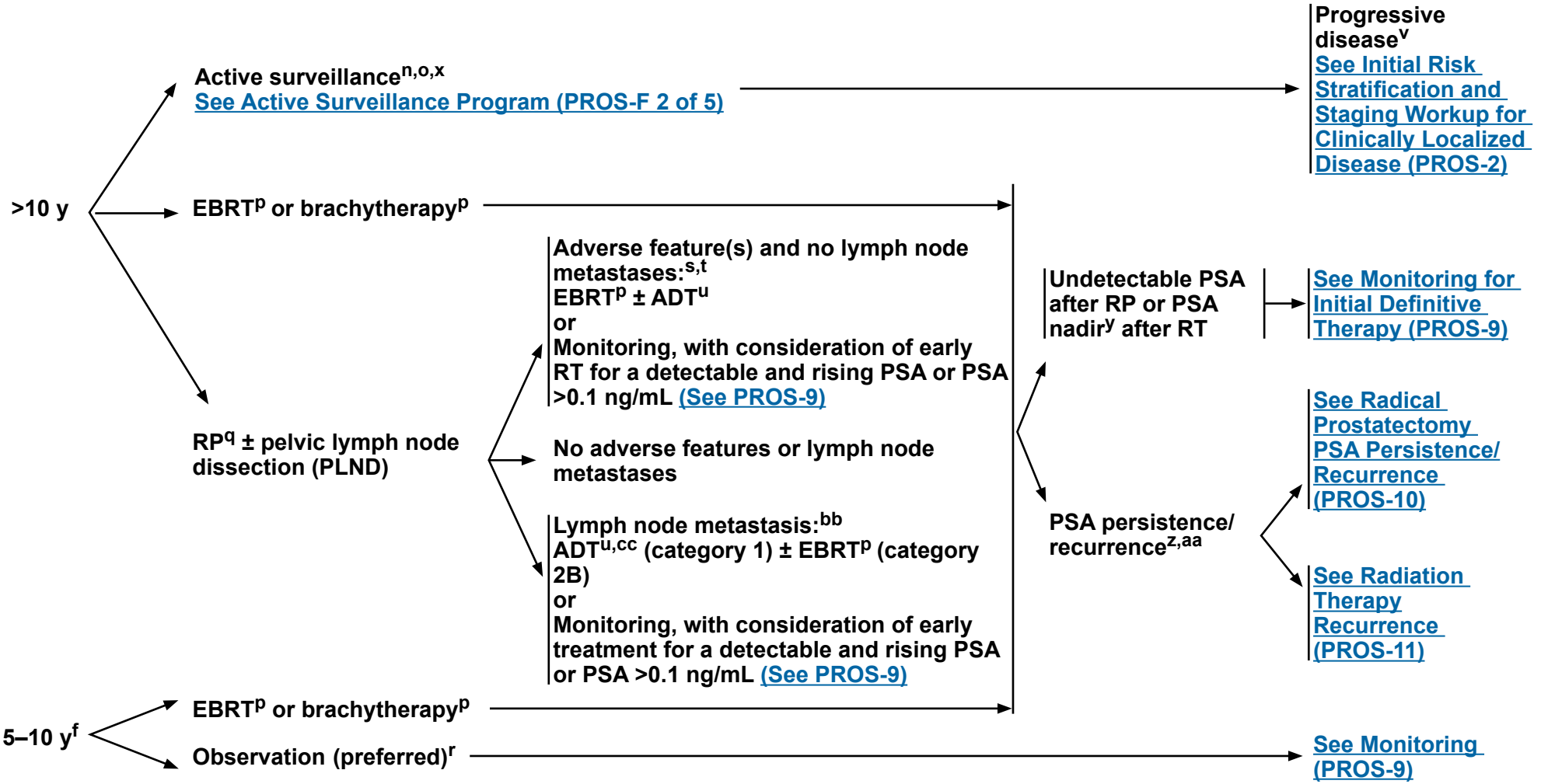


See Footnotes for Risk Groups (PROS-8A).

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

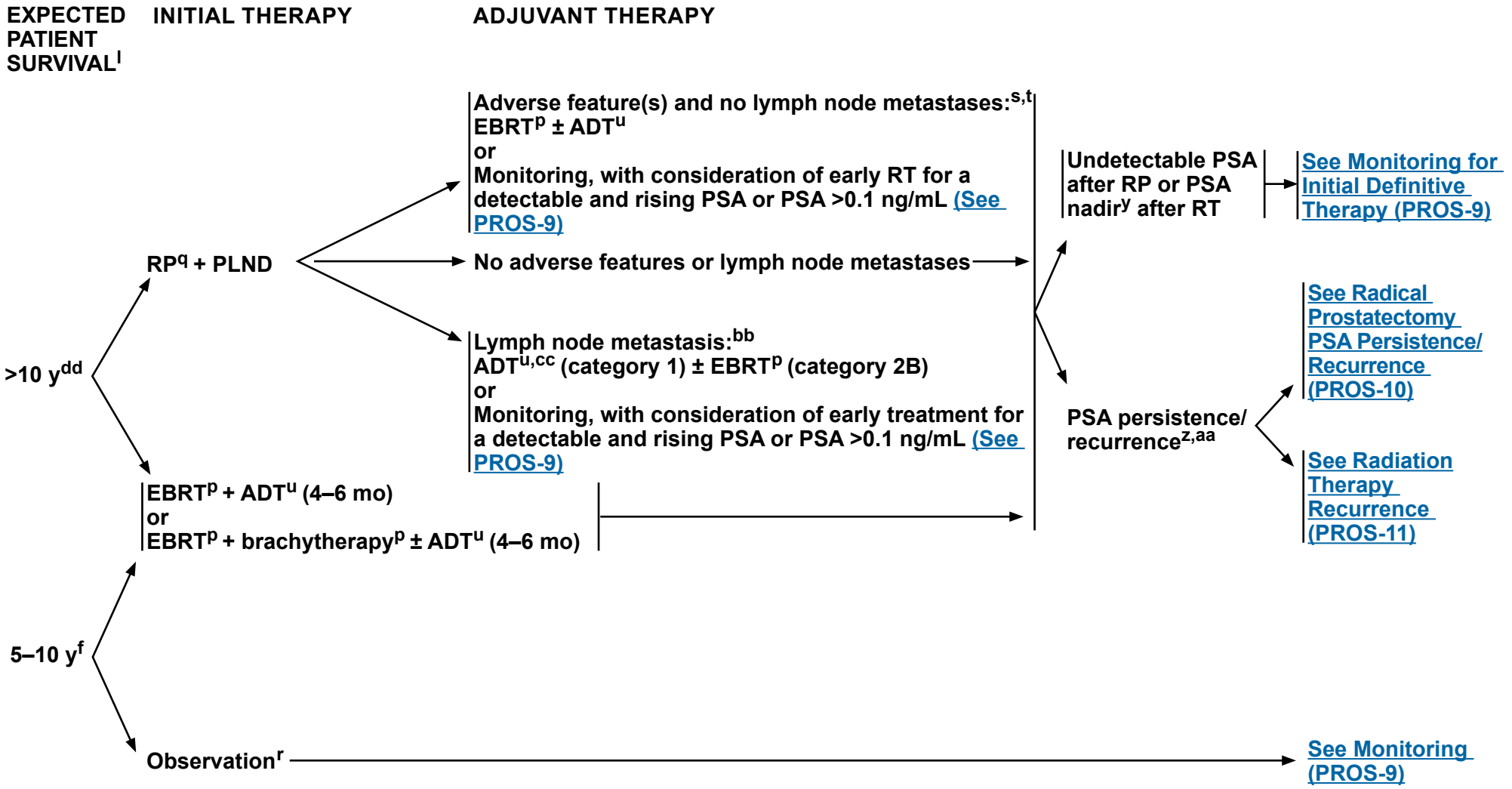
EXPECTED PATIENT SURVIVAL[l]	INITIAL THERAPY	ADJUVANT THERAPY



See 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.

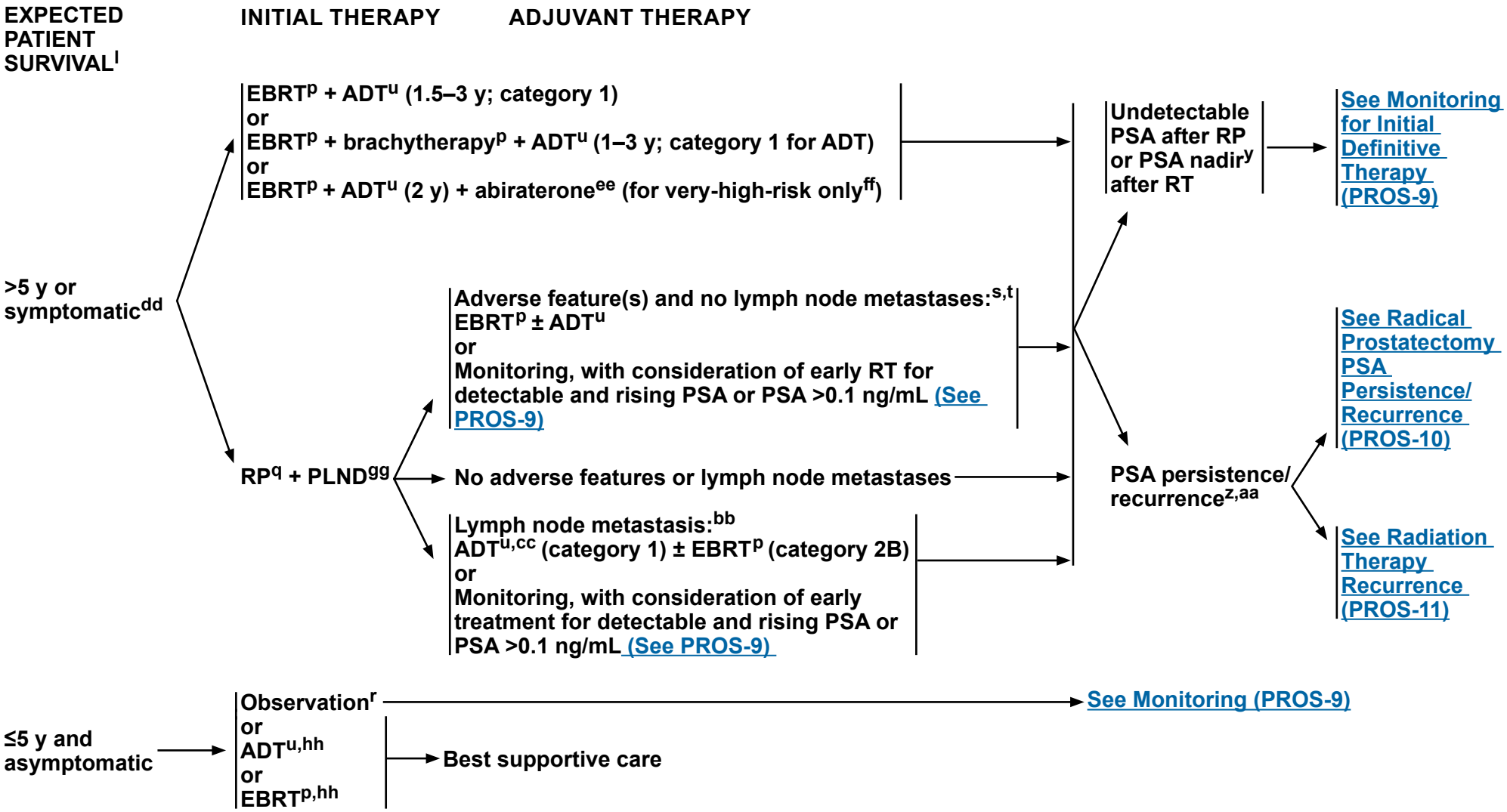
UNFAVORABLE INTERMEDIATE-RISK GROUP



See 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.

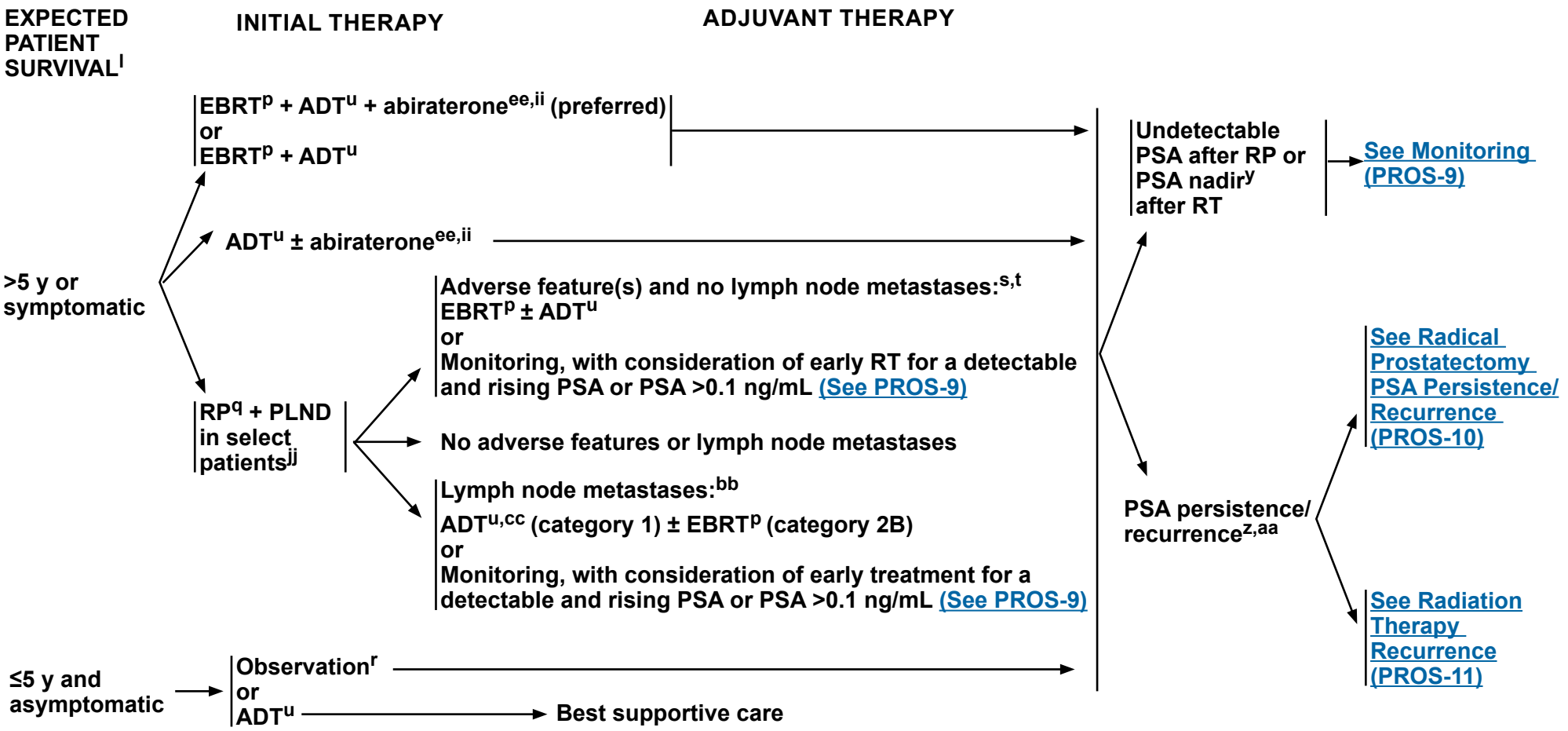
HIGH- OR VERY-HIGH-RISK GROUP



See 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)



See 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

[f] For asymptomatic patients 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 and ADT should be given (See PROS-I).

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

[m] 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.

[n] 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).

[o] If higher grade and/or higher T stage is found during confirmatory testing, see PROS-2.

[p] See Principles of Radiation Therapy (PROS-G).

[q] See Principles of Surgery (PROS-H).

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

[t] Decipher molecular assay should be considered if not previously performed to inform adjuvant treatment if adverse features are found post-RP.

[u] See Principles of Androgen Deprivation Therapy (PROS-I).

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

[w] 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 radical prostatectomy or prostate RT may be preferred based on shared decision-making with the patient. See Principles of Active Surveillance and Observation (PROS-F).

[x] 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).

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

[z] PSA persistence/recurrence after RP is defined as 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.

[aa] 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 HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier patients.

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

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

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

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

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

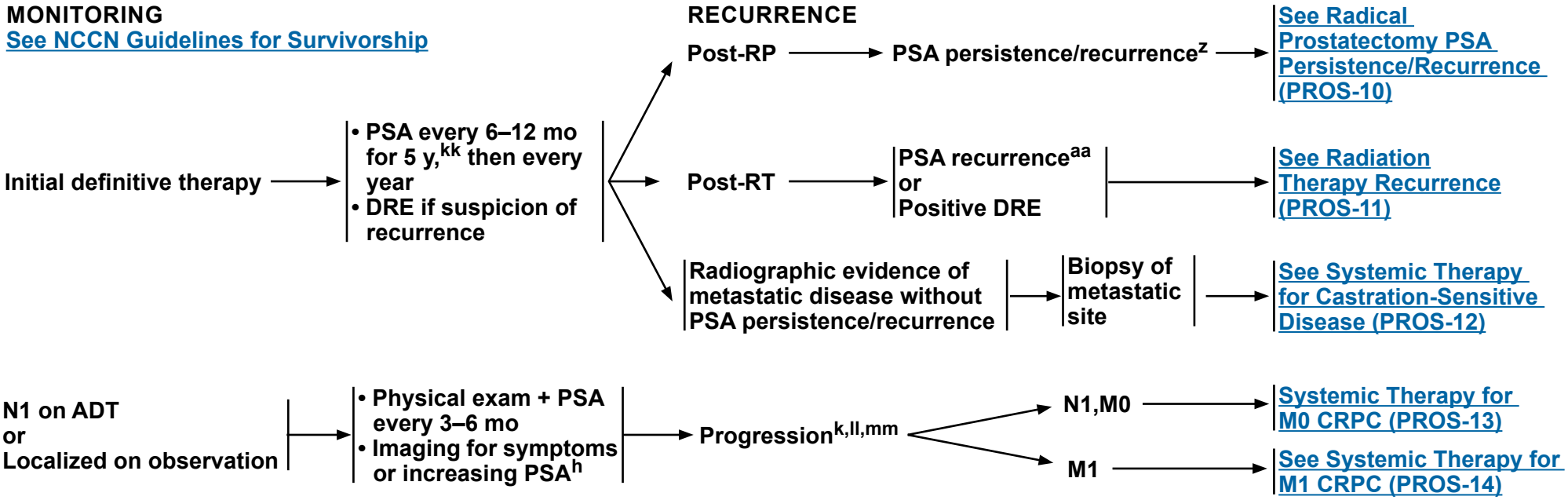
[gg] RP + PLND can be considered in younger, healthier patients without tumor fixation to the pelvic sidewall.

[hh] 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.

[ii] 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. (See PROS-I).

[jj] 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.



[h] See Principles of Imaging (PROS-E).

[k] 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.

[z] PSA persistence/recurrence after RP is defined as 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.

[aa] 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 HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier patients.

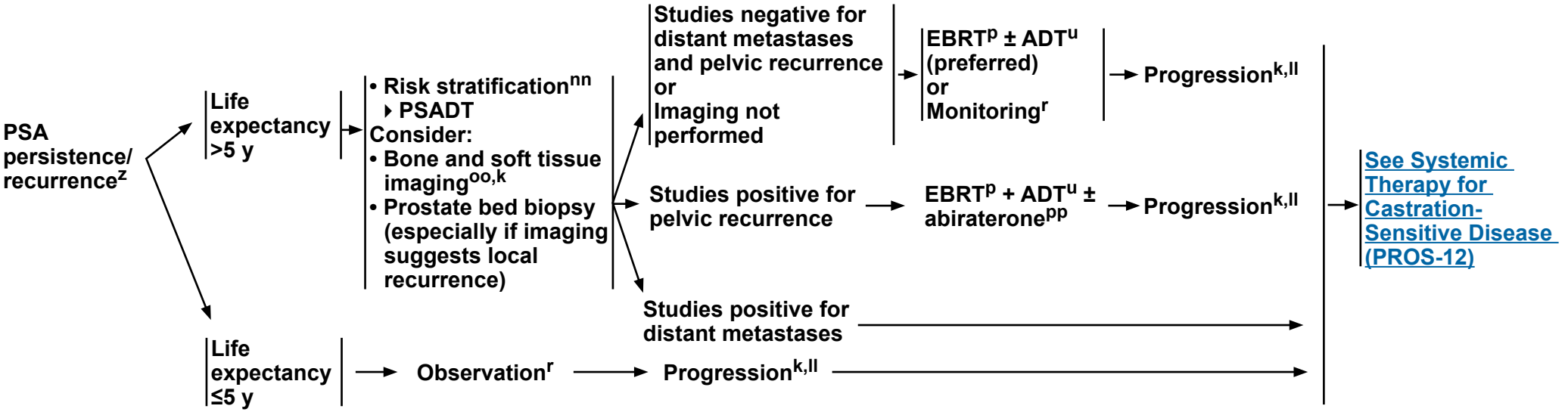
[kk] PSA as frequently as every 3 mo may be necessary to clarify disease status, especially in high-risk patients.

[ll] 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. 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. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. 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. See Principles of Imaging (PROS-E).

[mm] Treatment for patients whose cancer progressed on observation of localized disease is ADT. See Principles of Androgen Deprivation 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.

RADICAL PROSTATECTOMY PSA PERSISTENCE/RECURRENCE



[k] 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.

[p] See Principles of Radiation Therapy (PROS-G).

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

[z] PSA persistence/recurrence after RP is defined as 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.

[ll] 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. 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. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. 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. See Principles of Imaging (PROS-E).

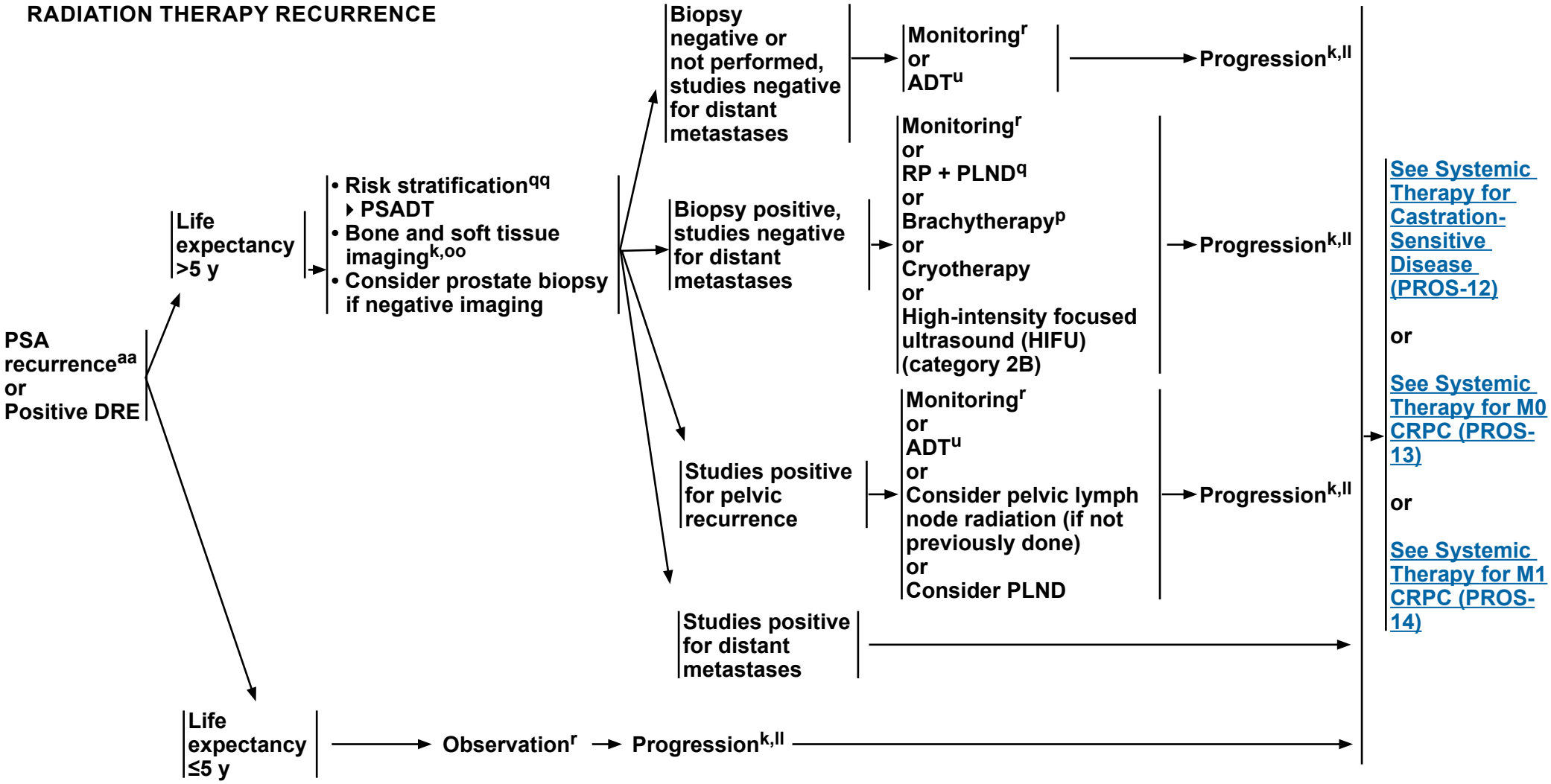
[nn] PSADT can be calculated to inform nomogram use and counseling and/or Decipher molecular assay (category 2B) can be considered to inform counseling.

[oo] Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or 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. 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. 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. See Principles of Imaging (PROS-E).

[pp] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B).

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



See 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.

FOOTNOTES

[k] 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.

[p] See Principles of Radiation Therapy (PROS-G).

[q] See Principles of Surgery (PROS-H).

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

[aa] 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 HT; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is not yet 2 ng/mL, especially in candidates for salvage local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in younger or healthier patients.

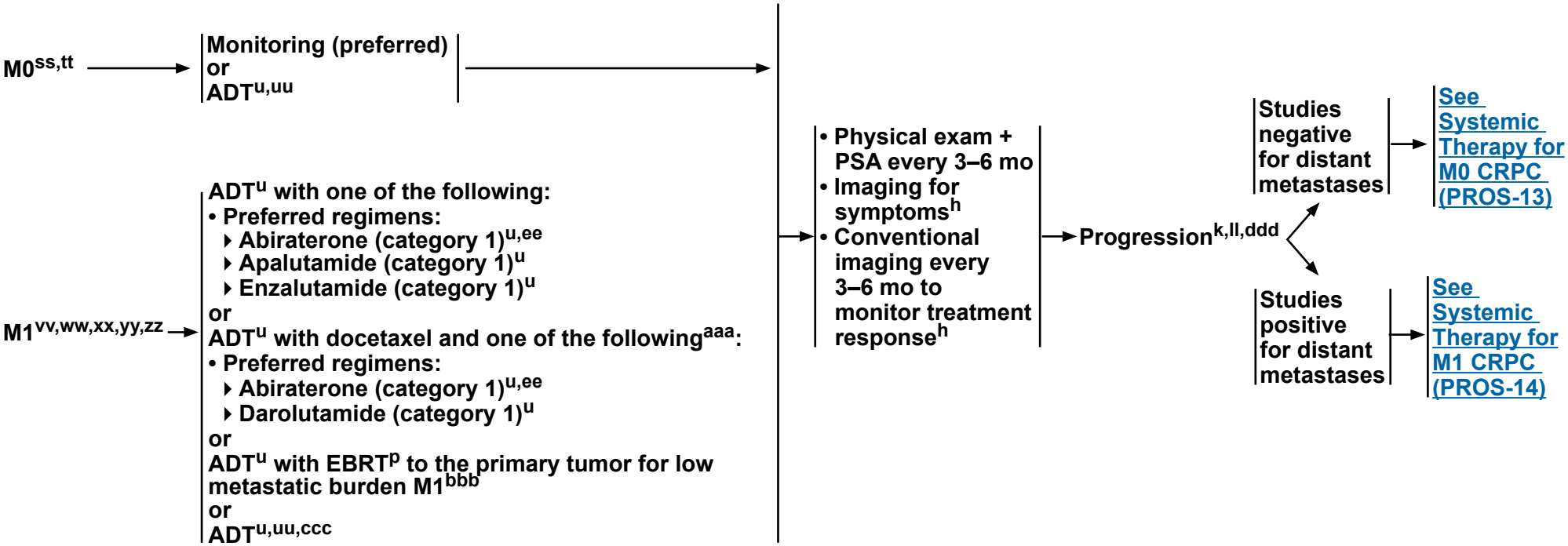
[ll] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. Bone imaging can be achieved by conventional technetium-99m-MDP bone scan. Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 sodium fluoride, C-11 choline, F-18 fluciclovine, Ga-68 PSMA-11, or F-18 piflufolastat PSMA can be considered for equivocal results on initial bone imaging. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. 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. See Principles of Imaging (PROS-E).

[oo] Ga-68 PSMA-11 or F-18 piflufolastat PSMA PET/CT or 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. 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. 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. See Principles of Imaging (PROS-E)..

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

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 CASTRATION-SENSITIVE PROSTATE CANCER[rr]



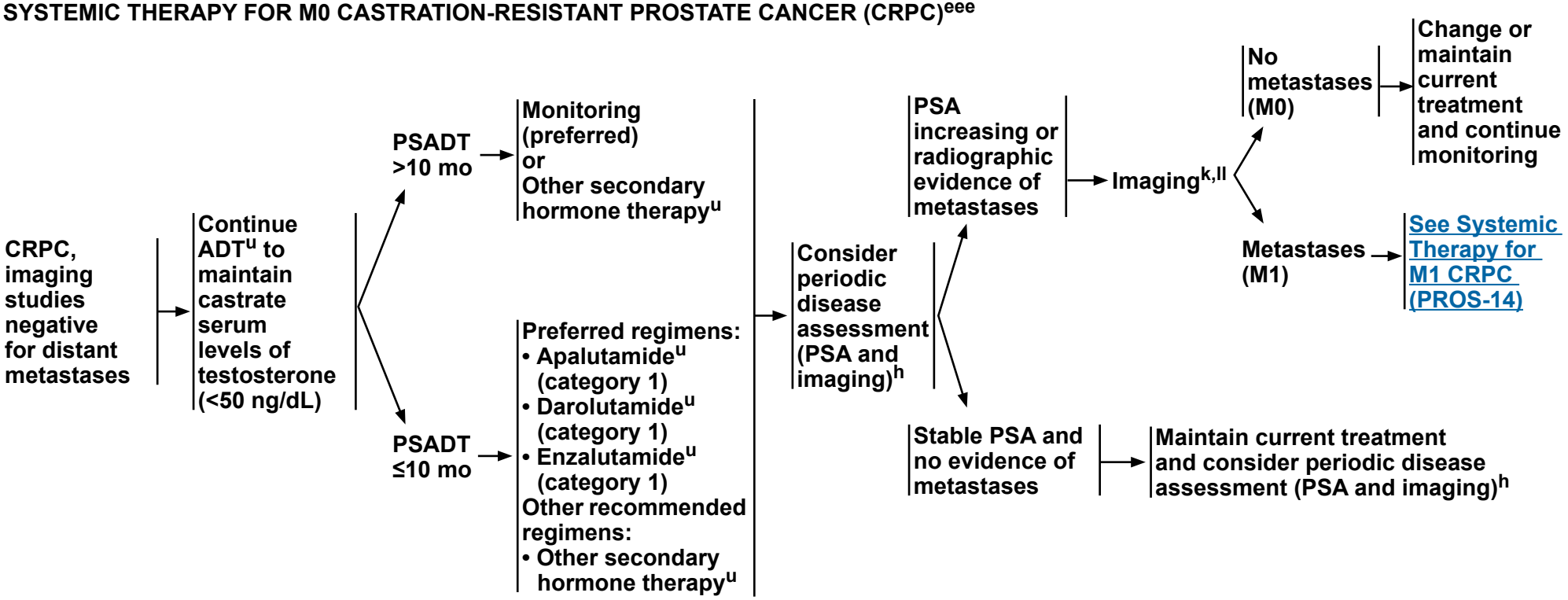
See footnotes on PROS-12A

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.

[h] See Principles of Imaging (PROS-E).
[k] 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.
[p] See Principles of Radiation Therapy (PROS-G).
[u] See Principles of Androgen Deprivation Therapy (PROS-I).
[ee] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended option).
[ll] 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. 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. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. 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. See Principles of Imaging (PROS-E).
[rr] The term "castration-sensitive" 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-sensitive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of RT provided they have recovered testicular function.
[ss] PSADT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease.
[tt] Patients with a life expectancy ≤5 years can consider observation. See Principles of Active Surveillance and Observation (PROS-F).
[uu] Intermittent ADT can be considered for patients with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-I).
[vv] EBRT to sites of bone metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.
[ww] ADT alone (see PROS-I) or observation are recommended for asymptomatic patients with metastatic disease and life expectancy ≤5 years.
[xx] 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).
[yy] Stereotactic body RT (SBRT) to metastases can be considered in patients with oligometastatic progression where progression-free survival (PFS) is the goal.
[zz] Bone antiresorptive therapy is indicated for elevated fracture risk based upon FRAX in the castration-sensitive setting. See PROS-I.
[aaa] The panel encourages ADT with docetaxel and either darolutamide or abiraterone for patients with high-volume disease who are fit for chemotherapy. See Principles of Non-Hormonal Systemic Therapy (PROS-J).
[bbb] EBRT to the primary tumor is associated with an overall survival 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-G).
[ccc] 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.
[ddd] Patients who were under monitoring for M0 disease should receive an appropriate therapy for castration-sensitive disease.

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)[eee]



[h] See Principles of Imaging (PROS-E).

[k] 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.

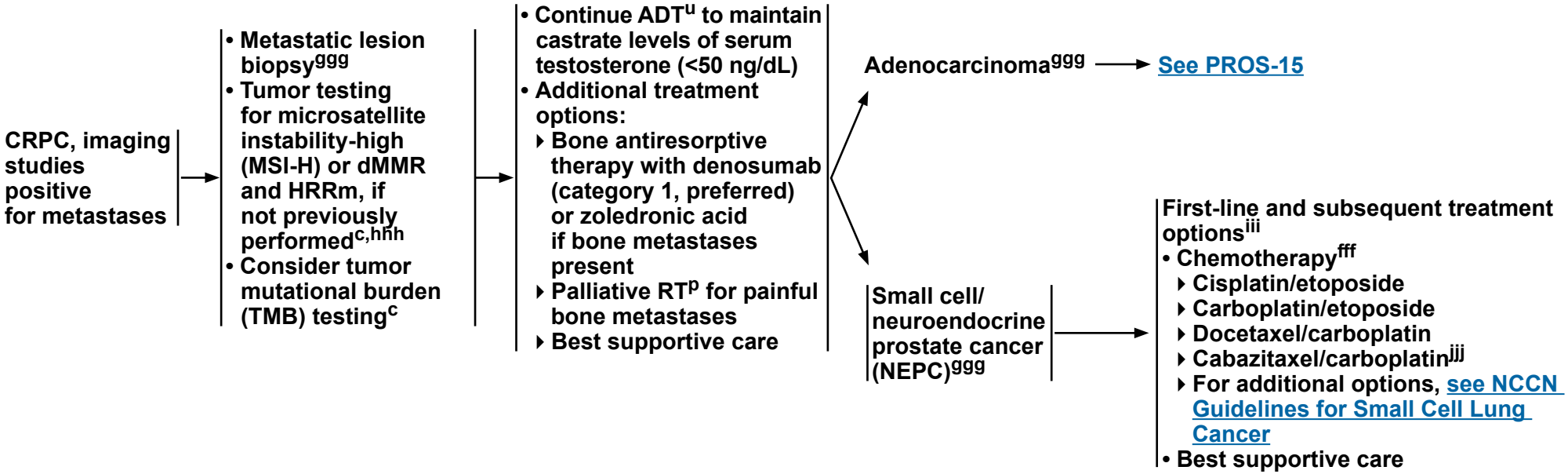
[u] See Principles of Androgen Deprivation Therapy (PROS-I).

[ll] 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. 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. Soft tissue imaging of the pelvis, abdomen, and chest can include chest CT and abdominal/pelvic CT or abdominal/pelvic MRI. 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. See Principles of Imaging (PROS-E).

[eee] 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.

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 M1 CRPC[eee]



[c] See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[p] See Principles of Radiation Therapy (PROS-G).
[u] See Principles of Androgen Deprivation Therapy (PROS-I).
[eee] 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.
[fff] See Principles of Non-Hormonal Systemic Therapy (PROS-J).
[ggg] 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.
[hhh] Germline testing for HRRm is recommended if not performed previously. See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[iii] 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.
[jjj] 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.

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 M1 CRPC: ADENOCARCINOMA[iii,kkk,lll]

No prior docetaxel/no prior novel hormone therapy[mmm]

- Preferred regimens
  - Abiraterone[u,nnn] (category 1[ooo])
  - Docetaxel[fff,ppp] (category 1)
  - Enzalutamide[u] (category 1)
- Useful in certain circumstances
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Sipuleucel-T[fff,qqq] (category 1)
- Other recommended regimens
  - Other secondary hormone therapy[u]

Prior novel hormone therapy/no prior docetaxel[mmm,sss]

- Preferred regimens
  - Docetaxel (category 1)[fff]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Olaparib for HRRm (category 1)[ttt]
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCA mutation[uuu]
  - Sipuleucel-T[fff,qqq]
- Other recommended regimens
  - Abiraterone[u,nnn]
  - Abiraterone + dexamethasone[nnn,vvv]
  - Enzalutamide[u]
  - Other secondary hormone therapy[u]

Prior docetaxel/no prior novel hormone therapy[mmm]

- Preferred regimens
  - Abiraterone[u,nnn] (category 1)
  - Cabazitaxel[fff]
  - Enzalutamide[u] (category 1)
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff]
  - Radium-223[rrr] for symptomatic bone metastases (category 1)
  - Sipuleucel-T[fff,qqq]
- Other recommended regimens
  - Other secondary hormone therapy[u]

Prior docetaxel and prior novel hormone therapy[mmm,sss]

- Useful in certain circumstances
  - Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases (category 1)[www]

(The following systemic therapies are category 2B if visceral metastases are present)

- Preferred regimens
  - Cabazitaxel[fff] (category 1[ooo])
  - Docetaxel rechallenge[fff]
- Useful in certain circumstances
  - Cabazitaxel/carboplatin[fff,jjj]
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff]
  - Olaparib for HRRm (category 1[ooo])[ttt]
  - Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff]
  - Radium-223[rrr] for symptomatic bone metastases (category 1[ooo])
  - Rucaparib for BRCA mutation[uuu]
- Other recommended regimens
  - Abiraterone[u,nnn]
  - Enzalutamide[u]
  - Other secondary hormone therapy[u]

See Footnotes for Systemic Therapy M1 CRPC (PROS-15A).

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

[u] See Principles of Androgen Deprivation Therapy (PROS-I).

[fff] See Principles of Non-Hormonal Systemic Therapy (PROS-J).

[iii] 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.

[jjj] 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 (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.

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

[lll] Patients can continue through all treatment options listed. Best supportive care is always an appropriate option.

[mmm] 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.

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

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

[ppp] 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.

[qqq] 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.

[rrr] 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-G).

[sss] Consider AR-V7 testing to help guide selection of therapy (See Discussion).

[ttt] Olaparib is a treatment option for patients with metastatic castration-resistant prostate cancer (mCRPC) and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair 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. (See Discussion).

[uuu] 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.

[vvv] 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.

[www] 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. The panel believes that both Ga-68 PSMA-11 or F-18 piflufolastat PSMA imaging can be used to determine eligibility. Sartor et al. N Engl J Med 2021; 385:1091-1103. See Principles of Radiation 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.

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**
- **Example 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.**

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

PRINCIPLES OF 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 management decision.[6]**

References

[1] Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008;358:1250-1261.
[2] Chen RC, Basak R, Meyer AM, et al. Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. JAMA 2017;317:1141-1150.
[3] Hoffman KE, Penson DF, Zhao Z, et al. Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer. JAMA 2020;323:149-163.
[4] Donovan JL, Hamdy FC, Lane JA, et al; ProtecT Study Group. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2016;375:1425-1437.
[5] Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology 2010;76:1245-1250.
[6] Makarov D, Fagerlin A, Finkelstein J et al. AUA White Paper on Implementation of Shared Decision Making into Urological Practice. American Urological Association 2022. Available at: https://www.auanet.org//guidelines-and-quality/guidelines/best-practice-statements-and-whitepapers/shared-decision-making

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

PRINCIPLES OF 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 PROS-C, 2 of 3) 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 (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.**
  - **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.**

- **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 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 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.**

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

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

Germline testing is recommended *in patients with a personal history of prostate cancer* in the following scenarios:

- **By prostate cancer stage or risk group (diagnosed at any age)**
  - **Metastatic, regional (node positive), very-high-risk localized, or high-risk localized prostate cancer**

- **By family history[a] and/or ancestry**
  - **≥1 first-, second-, or third-degree relative with:**
    - ◊ **breast cancer at age ≤50 y**
    - ◊ **colorectal or endometrial cancer at age ≤50 y**
    - ◊ **male (sex assigned at birth) breast cancer at any age**
    - ◊ **ovarian cancer at any age**
    - ◊ **exocrine pancreatic cancer at any age**
    - ◊ **metastatic, regional, very-high-risk, or high-risk prostate cancer at any age**
  - **≥1 first-degree relative (parent or sibling) with:**
    - ◊ **prostate cancer[b] at age ≤60 y**
  - **≥2 first-, second-, or third-degree relatives with:**
    - ◊ **breast cancer at any age**
    - ◊ **prostate cancer[b] at any age**
  - **≥3 first- or second-degree relatives with:**
    - ◊ **Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer**
  - **A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2,* and *EPCAM***
  - **Ashkenazi Jewish ancestry**
- **Personal history of breast cancer**

Germline testing may be considered *in patients with a personal history of prostate cancer* in the following scenarios:

- **By prostate cancer tumor characteristics (diagnosed at any age)**
  - ◊ **intermediate-risk prostate cancer with intraductal/cribriform histology[c]**
- **By prostate cancer[b] AND a prior personal history of any of the following cancers:**
  - ◊ **exocrine pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, and small intestinal**

[a] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. See Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

[b] Family history of prostate cancer should not include relatives with clinically localized Grade Group 1 disease.

[c] Acinar prostate adenocarcinoma with invasive cribriform pattern, intraductal carcinoma of prostate, or ductal adenocarcinoma component have increased genomic instability, and germline testing may be considered.

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

PRINCIPLES OF 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 see 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**
  - **Tumor testing for alterations in homologous recombination DNA repair genes, such as *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 metastatic castration-resistant prostate cancer and may be considered in patients with regional or castration-sensitive metastatic prostate cancer.**
  - **TMB testing may be considered in patients with metastatic castration-resistant prostate cancer.**
- **Tumor Specimen and Assay Considerations**
  - **The panel strongly recommends a metastatic biopsy for histologic and molecular evaluation. When unsafe or unfeasible, plasma ciculating 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 MMR are different assays measuring different biological effects caused by dMMR function. If MSI is used, testing using an 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.**

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

PRINCIPLES OF 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 that have been designed with superior performance, but have not been routinely reported in clinical trials. This limits the ability to provide evidence-based guideline treatment recommendations using these methods.
  - 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 have created this section to assist.
- Current treatment recommendations for localized through recurrent prostate cancer are based on prognosis, rather than use of predictive biomarkers. Prognosis is estimated through risk stratification.
  - The only identified exception to this, from a routine clinical or pathologic variable with randomized clinical trial validation, is pre-salvage radiotherapy PSA level, which has been shown to be both prognostic and predictive of benefit from hormone therapy with salvage radiotherapy in a phase III randomized trial.[1,2]
- Clinical trials that have established the benefit of various treatments in localized and recurrent prostate cancer often enroll patients across a spectrum of risk. Subgroup analyses, absolute benefit estimates, and expert opinion are used to provide simplified treatment recommendations for each NCCN risk group.
  - Given the moderate 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.
- Multivariable models should be used for risk stratification.
  - Multivariable risk stratification models, such as NCCN and STAR-CAP,[3] 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 risk classification models that have been shown to outperform NCCN risk groups.[3,4] There are also common histopathology variables that are prognostic (ie, cribriform, intraductal carcinoma, percent Gleason pattern 4); however, they have been rarely reported in the context of clinical trials.
- Imaging (ie, MRI and PET/CT) can also aid in risk stratification. See Principles of Imaging (PROS-E).

PRINCIPLES OF RISK STRATIFICATION

- There are advanced risk stratification tools (ie, gene expression biomarkers, AI digital pathology[5]) that independently improve risk stratification. See Table 1: Initial Risk Stratification for Clinically Localized Disease.
  - These tools are recommended to be used when they will have the potential ability to change management. These tools should not be ordered reflexively.
  - 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 randomized clinical trial data across multiple clinical trials.
  - These tools are not recommended for patients with very-low-risk prostate cancer.
  - Patients with NCCN low, favorable intermediate, unfavorable intermediate, or high-risk disease and life expectancy ≥10 y may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, and Prolaris.
  - AI digital pathology can be used for patients with localized prostate cancer with life expectancy ≥10 years if the results will impact management (category 2B).[5]
  - The data are limited and inconsistent regarding the prognostic impact of germline testing results for localized prostate cancer, and thus there is poor quality evidence to use this information to change treatment recommendations. The current evidence in localized prostate cancer is limited to small retrospective series with inconsistent results, and none has assessed the independent prognostic effect of germline mutation in complete multivariable clinical and pathologic models.[6-9] The prognostic impact of germline testing results should be viewed as distinct from the purposes for cascade testing, see PROS-C.

PRINCIPLES OF RISK STRATIFICATION

Table 1. Initial Risk Stratification for Clinically Localized Disease

Category	Tool	Predictive	Prognostic	Endpoint Trained For[a]	Level of Evidence for Validation[b]
Clinical	NCCN	No	Yes	See note[c]	1
	STAR-CAP[2]	No	Yes	PCSM	3
	CAPRA[11,d]	No	Yes	BCR	3
	MSKCC[12]	No	Yes	BCR and PCSM[f]	3
AI	ArteraAI Prostate (category 2B)[5,e]	No	Yes	BCR, DM, PCSM[g]	1
Gene Expression Testing	Decipher[13]	No	Yes	DM	1
	Prolaris[14]	No	Yes	See note[h]	3
	Oncotype[15]	No	Yes	Adverse pathology	3
Germline	HRR	No	Uncertain	See note[i]	4

BCR, biochemical recurrence; DM, distant metastases; PCSM, prostate cancer-specific mortality

[a] "Endpoint trained for" specifically relates to what the biomarker or model was designed and optimized to predict. This is distinct from endpoints for which the biomarker has been shown to be prognostic in validation.

[b] Levels of evidence for biomarkers in this section are based on modified Simon et al criteria:[10]
1: Validation in the context of multiple clinical trials with consistent results. Randomized trials are necessary for predictive biomarkers for validation.
2: Validation in multiple independent prospective registry/observational cohorts with consistent results.
3: Validation in multiple independent retrospective studies with consistent results.
4: Validation in a single retrospective study, or multiple independent retrospective studies with inconsistent results.

[c] NCCN risk groups were not trained for a specific endpoint. They were a modification of the original D'Amico risk groups trained for BCR. Subsequently, NCCN risk groups were subdivided into seven risk groups (very low, low, favorable intermediate, unfavorable intermediate, high, very high, and regional disease).

[d] CAPRA does not include cT3b–T4 or cN+ patients.

[e] ArteraAI Prostate, also known as a multi-modal AI biomarker, has trained and validated multiple AI-derived digital histopathology-based biomarkers from five phase III randomized radiation-based trials.[5]

[f] These are two separate models developed and trained for different endpoints.

[g] ArteraAI Prostate trained three distinct prognostic models, one for each endpoint (BCR, DM, and PCSM).

[h] Prolaris is a composite of CAPRA and cell cycle progression (CCP) score. The derivation of CCP was based on genes involved in the cell cycle that were highly correlated and provided highly reproducible measurements of cell proliferation. Like other biomarkers it has been validated for multiple endpoints, but the test was not specifically trained for an endpoint a priori.[16]

[i] Studies have inconsistent results in the setting of small biomarker-positive sample sizes. In addition, studies commonly do not adjust for standard clinical and pathologic factors and have variable follow-up and heterogeneous reporting quality.

See References on PROS-D 4 of 4.

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

PRINCIPLES OF RISK STRATIFICATION

[1] Dess RT, Sun Y, Jackson WC, et al. Association of presalvage radiotherapy PSA levels after prostatectomy with outcomes of long-term antiandrogen therapy in men with prostate cancer. JAMA Oncol 2020;6:735-743.
[2] Pollack A, Karrison TG, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet 2022;399:1886-1901.
[3] Dess RT, Suresh K, Zelefsky MJ, et al. Development and validation of a clinical prognostic stage group system for nonmetastatic prostate cancer using disease-specific mortality results from the international staging collaboration for cancer of the prostate. JAMA Oncol 2020;6:1912-1920.
[4] Zelic R, Garmo H, Zugna D, et al. Predicting prostate cancer death with different pretreatment risk stratification tools: A head-to-head comparison in a nationwide cohort study. Eur Urol 2020;77:180-188.
[5] Esteva A, Feng J, van der Wal D, et al. Prostate cancer therapy personalization via multi-modal deep learning on randomized phase III clinical trials. NPJ Digit Med 2022;5:71.
[6] Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748-1757.
[7] Berchuck JE, Zhang Z, Silver R, et al. Impact of pathogenic germline DNA damage repair alterations on response to intense neoadjuvant androgen deprivation therapy in high-risk localized prostate cancer. Eur Urol 2021;80:295-303.
[8] Halstuch D, Ber Y, Kedar D, Golan S, Baniel J, Margel D. Short-term outcomes of active surveillance for low risk prostate cancer among men with germline DNA repair gene mutations. J Urol 2020;204:707-713.
[9] Carter HB, Helfand B, Mamawala M, et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. Eur Urol 2019;75:743-749.
[10] Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst 2009;101:1446-1452.
[11] Cooperberg MR, Pasta DJ, Elkin EP, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol 2005;173:1938-1942.
[12] Graefen M, Karakiewicz PI, Cagiannos I, et al. International validation of a preoperative nomogram for prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2002;20:3206-3212.
[13] Jairath NK, Dal Pra A, Vince R Jr, et al. A systematic review of the evidence for the Decipher Genomic Classifier in prostate cancer. Eur Urol 2021;79:374-383.
[14] Sommariva S, Tarricone R, Lazzeri M, et al. Prognostic value of the cell cycle progression score in patients with prostate cancer: A systematic review and meta-analysis. Eur Urol 2016;69:107-115.
[15] Covas Moschovas M, Chew C, Bhat S, et al. Association between Oncotype DX Genomic Prostate Score and adverse tumor pathology after radical prostatectomy. Eur Urol Focus 2022;8:418-424.
[16] Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol 2011;12:245-255.

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

PRINCIPLES OF IMAGING

Goals of Imaging

- Imaging is performed for the detection and characterization of disease to select treatment or guide change in management.
- Imaging techniques can evaluate anatomic or functional parameters.
  - Anatomic imaging techniques include plain film radiographs, ultrasound, CT, and MRI.
  - Functional imaging techniques include radionuclide bone scan, PET/CT, and advanced MRI techniques, such as spectroscopy and 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 there is failure of PSA to fall to undetectable levels, or when there is undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more subsequent determinations.
- Bone 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.

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

PRINCIPLES OF 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 pre-treatment baseline scan, may not indicate disease progression.
- New lesions in the setting of a falling PSA or soft tissue response and in the absence of pain progression at that site may indicate bone scan flare or an osteoblastic healing reaction. For this reason, a confirmatory bone scan 8–12 weeks later is warranted to determine true progression from flare reaction. Additional new lesions favor progression. Stable scans make continuation of treatment reasonable. Bone scan flare is common, particularly on initiation of new hormonal therapy, and may be observed in nearly half of patients treated with the newer agents, enzalutamide and abiraterone. Similar flare 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
  - Plain films, CT, MRI, PET/CT, or PET/MRI with F-18 piflufolastat PSMA, Ga-68 PSMA-11, 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 or F-18 piflufolastat 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 (see PROS-2) and as part of workup for recurrence or progression (see PROS-11 through PROS-15).

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 (see PROS-2) and as part of workup for recurrence or progression (see PROS-11 through PROS-15).
- MRI may be considered in patients after RP when PSA fails to fall to undetectable levels or when an undetectable PSA becomes detectable and increases on 2 or more subsequent determinations, or after RT for 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.
- 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.

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 (also known as F-18 DCFPyL) and Ga-68 PSMA-11. See Table 2 in the Discussion section for more detail.
- 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.
- 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 F-18 piflufolastat PSMA or Ga-68 PSMA-11 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 (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.
- 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 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 overall survival of M1 disease is improved, whereas progression-free but not overall survival 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 overall survival 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.
- F-18 fluorodeoxyglucose (FDG) PET/CT should not be used routinely for staging prostate cancer since data are limited in patients with prostate cancer.

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

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **The NCCN Prostate Cancer Panel and the NCCN Prostate Cancer Early Detection Panel (See NCCN Guidelines for Prostate Cancer Early Detection) remain concerned about 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 (See 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 (see Principles of Life Expectancy Estimation, PROS-A).**

- **Candidacy for Active Surveillance:**
  - **Active surveillance is preferred for patients with very-low-risk prostate cancer (See 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 (See 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] In some of these cases, upfront treatment with RP or prostate RT may be preferred based on shared decision-making with the patient.**
  - **Patients with favorable intermediate-risk prostate cancer (See 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) below for a summary of major active surveillance cohorts, including their inclusion criteria.**

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

PRINCIPLES OF 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-D).**
  - **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 on an individual basis, most patients should have prostate biopsies incorporated 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.**

- **Considerations for Treatment of Patients on Active Surveillance:**
  - **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, and patient anxiety.**
  - **Considerations for a change in management strategy should be made in the context of the patient's life expectancy.**

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

PRINCIPLES OF 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 life expectancy ≤5 years.**
- **Life expectancy can be challenging to estimate for individual patients (see Principles of Life Expectancy Estimation, PROS-A). Consider incorporating a validated metric of comorbidity (see *Life Expectancy*, above).**
- **If patients under observation become symptomatic, an assessment of disease burden can be performed, and treatment or palliation can be considered (see PROS-12).**

- **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.**

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

PRINCIPLES OF 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).

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

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

REFERENCES

[1] Ganz PA, Barry JM, Burke W, et al. NIH State-of-the-Science Conference Statement: Role of active surveillance in the management of men with localized prostate cancer. NIH Consens State Sci Statements 2011;28:1-27.
[2] Ng SP, Duchesne G, Tai KH, et al. Support for the use of objective comorbidity indices in the assessment of noncancer death risk in prostate cancer patients. Prostate Int 2017;5:8-12.
[3] Cooperberg MR, Zheng Y, Faino AV, et al. Tailoring intensity of active surveillance for low-risk prostate cancer based on individualized prediction of risk stability. JAMA Oncol 2020;6:e203187.
[4] Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol 2015;33:3379-3385.
[5] Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 2015;33:272-277.
[6] Cooley LF, Emeka AA, Meyers TJ, et al. Factors associated with time to conversion from active surveillance to treatment for prostate cancer in a multi-institutional cohort. J Urol 2021;206:1147-1156.
[7] Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2010;28:126-131.
[8] Yamamoto T, Musunuru HB, Vesprini D, et al. Metastatic prostate cancer in men initially treated with active surveillance. J Urol 2016;195:1409-1414.
[9] Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol 2007;178:2359-2364; discussion 2364-2365.
[10] Sheridan TB, Carter HB, Wang W, et al. Change in prostate cancer grade over time in men followed expectantly for stage T1c disease. J Urol 2008;179:901-904; discussion 904-905.
[11] Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 2011;29:2185-2190.
[12] Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. Cancer 2008;112:2664-2670.
[13] Welty CJ, Cowan JE, Nguyen H, et al. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. J Urol 2015;193:807-811.
[14] Newcomb LF, Thompson IM, Jr., Boyer HD, et al. Outcomes of active surveillance for the management of clinically localized prostate cancer in the prospective, multi-institutional Canary PASS cohort. J Urol 2015;195:313-320.
[15] Bokhorst LP, Valdagni R, Rannikko A, et al. A decade of active surveillance in the PRIAS Study: An update and evaluation of the criteria used to recommend a switch to active treatment. Eur Urol 2016;70:954-960.

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

PRINCIPLES OF RADIATION THERAPY

Definitive Radiation Therapy General Principles

- Highly conformal RT techniques should be used to treat localized prostate cancer.
- Photon or proton EBRT are both effective at achieving highly conformal radiotherapy with acceptable and similar biochemical control and long-term side effect profiles (See Discussion).
- Ideally, the accuracy of treatment should be verified by daily prostate localization, with any of the following: techniques of image-guided RT (IGRT) using CT, ultrasound, implanted fiducials, or electromagnetic targeting/tracking. Endorectal balloons may be used to improve prostate immobilization. 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. A randomized phase III trial demonstrated reduced rectal bleeding in patients undergoing the procedure compared to controls. Retrospective data also support its use in similar patients undergoing brachytherapy. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.
- Various fractionation and dose regimens can be considered depending on the clinical scenario (See Table 1 on PROS-G 4 of 7). Dose escalation has been proven to achieve the best biochemical control in patients with intermediate- and high-risk disease.
- Stereotactic body RT (SBRT) is acceptable in practices with appropriate technology, physics, and clinical expertise. SBRT for metastases can be considered in the following circumstances:
  - In a patient 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 a patient with oligometastatic progression where progression-free survival is the goal
  - In a symptomatic patient where the lesion occurs in or immediately adjacent to a previously irradiated treatment field.
- Biologically effective dose (BED) modeling with the linear-quadratic equation may not be accurate for extremely hypofractionated (SBRT/stereotactic ablative radiotherapy [SABR]) 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 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.

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.

Continued

PRINCIPLES OF RADIATION THERAPY

Definitive Radiation Therapy by Risk Group

- Very low risk
  - Patients with NCCN very-low-risk prostate cancer are encouraged to pursue active surveillance.
- Low risk
  - Patients with NCCN low-risk prostate cancer are encouraged to pursue active surveillance.
  - Prophylactic lymph node radiation should NOT be performed routinely. ADT or antiandrogen therapy should NOT be used routinely.
- Favorable intermediate risk[a]
  - Prophylactic lymph node radiation is not performed routinely, and ADT or antiandrogen therapy is not used routinely. Prophylactic lymph node radiation and/or ADT use is reasonable if additional risk assessments suggest aggressive tumor behavior.
- Unfavorable intermediate risk[a]
  - Prophylactic nodal radiation can be considered if additional risk assessments suggest aggressive tumor behavior. ADT should be used unless additional risk assessments suggest less-aggressive tumor behavior or if medically contraindicated. The duration of ADT can be reduced when combined with EBRT and brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT can be considered if delivering longer courses of EBRT would present medical or social hardship.
- High and very high risk[a]
  - Prophylactic nodal radiation should be considered. ADT is required unless medically contraindicated. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT, can be considered if delivering longer courses of EBRT would present a medical or social hardship.
- Regional disease
  - Nodal radiation should be performed. Clinically positive nodes should be dose-escalated as dose-volume histogram parameters allow. ADT is required unless medically contraindicated, and the addition of abiraterone or fine-particle abiraterone (category 2B) to ADT is preferred.
- Low metastatic burden, castration-sensitive disease
  - RT to the prostate is an option in patients with low metastatic burden castration-sensitive metastatic disease, without contraindications to radiotherapy. ADT is required unless medically contraindicated.
- Low metastatic burden is defined as either non-regional, lymph-node-only disease OR <4 bone metastases and without visceral/other metastasis.
  - ◊ Number and location of lesions is defined by conventional imaging.
  - ◊ At this time, metastases defined only by 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, 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, but not overall survival. The prespecified low-volume subset had a significant improvement in both failure-free survival and overall survival.[1] A meta-analysis with two other studies confirmed this benefit for primary RT to the primary tumor in lower volume disease.[2]

See References (PROS-G 3 of 7)

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.

Continued

PRINCIPLES OF RADIATION THERAPY

- **STAMPEDE Arm H has now distinguished the CHAARTED definition of low metastatic disease to one that more granularly quantifies who benefits from treatment of the primary based on number of bone metastases. This is relevant because a patient can have 12 spine metastases and be classified as low volume by CHAARTED, but would not derive benefit in overall survival or failure-free survival when quantifying number of bone metastases. Thus, the number of bone metastases may be preferred to define candidacy for treatment of the primary tumor.[3]**
- **Minimizing toxicity is paramount when delivering RT to the primary in patients with metastatic disease.**
- **It remains uncertain whether treatment of regional nodes in addition to the primary improves outcomes; nodal treatment should be performed in the context of a clinical trial.**
- **Dose escalation beyond BED equivalents of the two-dose prescriptions used in STAMPEDE (55 Gy in 20 fractions or 6 Gy x 6 fractions) is not recommended given the known increase in toxicity from dose intensification without overall survival improvement in localized disease.**
- **Brachytherapy is not recommended outside of a clinical trial, as safety and efficacy have not been established in this patient population.**

- **High-volume metastatic disease**
  - **RT to the prostate should NOT be performed 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 overall survival from the addition of radiotherapy to the primary when combined with standard systemic therapy.**

[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.

References

[1] Parker CC, James ND, Brawley CD, et al. Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353-2366.
[2] Burdett S, Boevé LM, Ingleby FC, et al. Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis. Eur Urol 2019;76:115-124.
[3] Ali A, Hoyle A, Haran ÁM, et al. Association of bone metastatic burden with survival benefit from prostate radiotherapy in patients with newly diagnosed metastatic prostate cancer: A secondary analysis of a randomized clinical trial. JAMA Oncol 2021;7:555-563.

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.

Continued

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-12, 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	Low Volume M1[a]
EBRT							
Moderate Hypofractionation (Preferred)	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	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓	✓	
	2.2 Gy x 35 fx + micro-boost to MRI-dominant lesion to up to 95 Gy (fractions up to 2.7 Gy)		✓	✓	✓		
SBRT	9.5 Gy x 4 fx	✓	✓	✓	✓		
Ultra-Hypofractionation	7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	✓	✓	✓	✓		
	6 Gy x 6 fx						✓
Brachytherapy Monotherapy							
LDR Iodine 125 Palladium 103 Cesium 131	145 Gy 125 Gy 115 Gy	✓	✓				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓				
EBRT and Brachytherapy (combined with 45–50.4 Gy x 25–28 fx or 37.5 Gy x 15 fx)							
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			✓	✓		
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			✓	✓		

[a] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.

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.

Continued

PRINCIPLES OF RADIATION THERAPY

Salvage Brachytherapy

- Permanent LDR or temporary HDR brachytherapy is a treatment option for pathologically confirmed local recurrence after EBRT or brachytherapy. Subjects should have restaging imaging according to the NCCN high-risk stratification group to rule out regional nodal or metastatic disease. Patients should be counseled that salvage brachytherapy significantly increases the probability of urologic, sexual, and bowel toxicity compared to primary brachytherapy.

Post-Prostatectomy Radiation Therapy

- 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. 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.
  - EBRT with 2 years of 150 mg/day of bicalutamide demonstrated improved overall and metastasis-free survival on a prospective randomized trial (RTOG 9601) versus radiation alone in the salvage setting. A secondary analysis of RTOG 9601 found that patients with PSA ≤0.6 ng/mL had no overall survival 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 Decipher score derived less benefit (development of distant metastases, overall survival) from bicalutamide than those with a high Decipher score.
  - EBRT with 6 months of ADT (luteinizing hormone-releasing hormone [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.
  - The SPPORT 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). Pollack A, Karrison TG, et al. Lancet 2022;399:1886-1901.
- The panel recommends consultation with the American Society for Radiation Oncology (ASTRO)/American Urological Association (AUA) Guidelines. Evidence supports offering adjuvant/salvage RT in most patients with adverse pathologic features or detectable PSA and no evidence of disseminated disease.
- Indications for adjuvant RT include pT3a disease, positive margin(s), or seminal vesicle involvement. Adjuvant RT is usually given within 1 year after RP and after operative side effects have improved/stabilized. Patients with positive surgical margins may benefit the most.
- Indications for salvage RT include an undetectable PSA that becomes subsequently detectable and increases on 2 measurements or a PSA that remains persistently detectable after RP. Treatment is more effective when pre-treatment PSA is low and PSADT is long.
- The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64–72 Gy in standard fractionation. Biopsy-proven gross recurrence may require higher doses.
- Nuclear medicine advanced imaging techniques can be useful for localizing disease with PSA levels as low as 0.5 ng/mL (see Discussion).
- Nomograms, and tumor-based molecular assays, can be used to prognosticate risk of metastasis and prostate cancer-specific mortality in patients with adverse risk features after RP.
- Target volumes include the prostate bed and may include the whole pelvis according to physician discretion.

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.

Continued

PRINCIPLES OF RADIATION THERAPY

Radiopharmaceutical Therapy

- 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 differs from beta-emitting agents, such as samarium-153 and strontium-89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3–4 hematologic toxicity (ie, 2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at low frequency.
- Radium-223 is administered IV once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or RT departments.
- Prior to the initial dose, patients must have absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, and hemoglobin ≥10 g/dL.
- Prior to subsequent doses, patients must have ANC ≥1 x 10^9/L and platelet count ≥50 x 10^9/L (per label). Radium-223 should be discontinued if a delay of 6–8 weeks does not result in the return of blood counts to these levels.
- Non-hematologic side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms may occur because radium-223 is eliminated predominantly by fecal excretion.
- Radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression, except in a clinical trial.
- Radium-223 may increase fracture risk when given concomitantly with abiraterone.
- Radium-223 is not recommended for use in combination with docetaxel or any other systemic therapy except ADT.
- Concomitant use of denosumab or zoledronic acid is recommended; it does not interfere with the beneficial effects of radium-223 on survival.
- Lu-177–PSMA-617
  - 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 overall survival in patients with progressive mCRPC previously treated with androgen receptor inhibitors and taxane chemotherapy. Sartor O, et al. N Engl J Med 2021;385:1091-1103.
  - 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 can also be used in the same space due to multiple reports describing the equivalency of the two imaging agents in:
    - ◊ PSMA molecular recognition motifs,
    - ◊ normal organ biodistribution, and
    - ◊ detection accuracy of prostate cancer lesions.

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.

Continued

PRINCIPLES OF RADIATION THERAPY

Palliative Radiotherapy

- **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.**
- **Widespread bone metastases can be palliated using strontium-89 or samarium-153 with or without focal EBRT.**
- **20 Gy in 5 fractions, 30 Gy in 10 fractions, or 37.5 Gy in 15 fractions may be used as alternative palliative dosing depending on clinical scenario.**

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

PRINCIPLES OF SURGERY

Pelvic Lymph Node Dissection

- 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.

Salvage Radical Prostatectomy

- Salvage RP is an option for highly selected patients with local recurrence after EBRT, brachytherapy, or cryotherapy in the absence of metastases, but the morbidity (ie, incontinence, loss of erection, anastomotic stricture) is high and the operation should be performed by surgeons who are experienced with salvage RP.

See References (PROS-H 2 of 2)

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

PRINCIPLES OF SURGERY
References

[1] Fossati N, Willemse PPM, Van den Broeck T, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: A systematic review. Eur Urol 2017;72:84-109.
[2] Cagiannos I, Karakiewicz P, Eastham JA, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol 2003;170:1798-803.
[3] Briganti A, Larcher A, Abdollah F, et al. Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. Eur Urol 2012;61:480-487.
[4] Gandaglia G, Ploussard G, Valerio M, et al. A novel nomogram to identify candidates for extended pelvic lymph node dissection among patients with clinically localized prostate cancer diagnosed with magnetic resonance imaging-targeted and systematic biopsies. Eur Urol 2019;75:506-514.
[5] Gandaglia G, Martini A, Ploussard G, et al; EAU-YAU Prostate Cancer Working Group. External validation of the 2019 Briganti nomogram for the identification of Pprostate cancer patients who should be considered for an extended pelvic lymph node dissection. Eur Urol 2020;78:138-142.
[6] Hope TA, Eiber M, Armstrong WR, et al. Diagnostic accuracy of 68Ga-PSMA-11 PET for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: A multicenter prospective phase 3 imaging trial. JAMA Oncol 2021;7:1635-1642.
[7] Pienta KJ, Gorin MA, Rowe SP, et al. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with 18F-DCFPyL in prostate cancer patients (OSPREY). J Urol 2021;206:52-61.

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

PRINCIPLES OF 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-I, 4 of 5)].
- Giving ADT before, during, and/or after radiation (neoadjuvant, concurrent, and/or adjuvant ADT) prolongs survival in selected radiation-managed patients. Options are:
  - 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 degarelix with abiraterone (very high risk only)
- 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 overall survival with the addition of abiraterone to EBRT and ADT in patients with node-negative disease was 0.69 (95% CI, 0.49–0.96).
  - 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 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 degarelix 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
  - Degarelix plus abiraterone
  - Patients with regional disease and life expectancy <5 years who chose ADT can receive LHRH agonist, LHRH antagonist, or orchiectomy.

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 overall survival 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.

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.

Continued

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for M0 PSA Persistence/Recurrence After RP or EBRT (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 salvage 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 overall survival 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]
    - ◊ EBRT + LHRH agonist or degarelix with abiraterone (studies positive for pelvic recurrence only)
  - M0 RT recurrence, biopsy negative or M0 PSA recurrence after progression on salvage EBRT:
    - ◊ 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
  - Abiraterone should be given with concurrent steroid [see ADT for Regional (N1,M0) Disease].

ADT for Metastatic Castration-Sensitive Disease

- ADT with treatment intensification is preferred for most patients with metastatic prostate cancer. ADT alone is appropriate for some patients.
- 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
  - Degarelix plus abiraterone, enzalutamide, or apalutamide
  - Degarelix plus docetaxel and abiraterone or darolutamide
- Abiraterone should be given with concurrent steroid [see ADT for Regional (N1,M0) Disease].
- When EBRT to primary is given with ADT in low metastatic burden M1, the options are LHRH agonist, LHRH antagonist, and orchiectomy.
- Two randomized phase 3 clinical trials of abiraterone with prednisone plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved overall survival 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.

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.

Continued

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

- A double-blind randomized phase 3 clinical trial of apalutamide plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved overall survival 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 overall survival 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 overall survival 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 failed to show a difference in survival between intermittent and continuous ADT.
- Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.

<u>Secondary Hormone Therapy for M0 or M1 CRPC</u>

- 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 degarelix 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.
- Administration of secondary hormonal therapy can include:
  - Second-generation antiandrogen
    - ◊ Apalutamide (for M0 and PSADT ≤10 months)
    - ◊ Darolutamide (for M0 and PSADT ≤10 months)
    - ◊ Enzalutamide (for M0 and PSADT ≤10 months or M1)
  - Androgen metabolism inhibitor
    - ◊ Abiraterone + prednisone (for M1 only)
    - ◊ Fine-particle abiraterone + methylprednisolone (for M1 only)
  - Other secondary hormone therapy (for M0 or M1)
    - ◊ First-generation antiandrogen (nilutamide, flutamide, or bicalutamide)
    - ◊ Corticosteroids (hydrocortisone, prednisone, or dexamethasone)
    - ◊ Antiandrogen withdrawal
    - ◊ Ketoconazole plus hydrocortisone
- 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 metastasis-free survival over placebo (40.5 months vs. 16.2 months). After a median follow-up of 52 months, final overall survival analysis showed an improved median overall survival 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 metastasis-free survival over placebo (36.6 months vs. 14.7 months). Median overall survival 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.

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.

Continued

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

- 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 metastasis-free survival over placebo (40.4 months vs. 18.4 months). Overall survival 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 overall survival was demonstrated. Use of abiraterone and prednisone in this setting is a category 1 recommendation. The side effects of abiraterone that require ongoing monitoring include hypertension, hypokalemia, peripheral edema, atrial fibrillation, congestive heart failure, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.
- A phase 3 study of docetaxel-sensitive patients with M1 CRPC showed that enzalutamide (160 mg daily) resulted in significant improvement in rPFS and overall survival. The use of enzalutamide in this setting is category 1. The side effects of enzalutamide that require long-term monitoring include fatigue, diarrhea, hot flashes, headache, and seizures (reported in 0.9% of patients on enzalutamide).
- For symptomatic patients with M1 CRPC, all secondary hormone options listed above are allowed, but initial use of docetaxel may be preferred. Both randomized trials of abiraterone and enzalutamide in the pre-docetaxel setting were conducted in patients who had no or minimal symptoms due to M1 CRPC. How these agents compare to docetaxel for pain palliation in this population of patients is not clear. Both drugs have palliative effects in the post-docetaxel setting. Both abiraterone and enzalutamide are approved in this pre-docetaxel setting and have category 1 recommendations. Both drugs are suitable options for patients who are not good candidates to receive docetaxel.
- 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 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.
- Evidence-based guidance on the sequencing of agents in either pre- or post-docetaxel remains limited.

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.
- Relugolix has not been adequately studied in combination with potent

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.

Continued

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

androgen receptor inhibitors such as enzalutamide, apalutamide, darolutamide, or abiraterone acetate, nor has it been studied in combination with docetaxel or cabazitaxel chemotherapy. Potential drug interactions include induction of cytochrome P450 enzymes and reduced concentration and efficacy of relugolix with enzalutamide or apalutamide and cardiac QTc interactions with abiraterone. Further studies of relugolix dosing and drug interactions with commonly used agents in advanced prostate cancer are needed to ensure patient safety and proper dosing.

- Data are limited on long-term compliance of 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 patient compliance 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 (see 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.
- Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation (www.nof.org). The National Osteoporosis Foundation guidelines include recommendations for: 1) calcium (1000–1200 mg daily from food and supplements) and vitamin D3 (400–1000 IU daily); and 2) additional treatment for males aged ≥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 ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20%. Fracture risk can be assessed using FRAX, the algorithm released by WHO. ADT should be considered "secondary osteoporosis" when using the FRAX algorithm. Treatment options to increase bone density, a surrogate for fracture risk in patients without metastases, include denosumab (60 mg SQ every 6 months), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly).
- A baseline DEXA scan should be obtained before starting therapy in patients at increased risk for fracture based on FRAX screening. A follow-up DEXA scan after 1 year of therapy is recommended by the International Society for Clinical Densitometry, although there is no consensus on the optimal approach to monitoring the effectiveness of drug therapy. Use of biochemical markers of bone turnover to monitor response to therapy is not recommended. The serum level of 25-hydroxy vitamin D and average daily dietary intake of vitamin D will assist the nutritionist in making a patient-specific recommendation for vitamin D supplementation. There are currently no guidelines on how often to monitor vitamin D levels. However, for those who require monitoring with DEXA scans, it makes sense to check the serum vitamin D level at the same time.
- Denosumab (60 mg SQ every 6 months), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly) increase bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either denosumab, zoledronic acid, or alendronate sodium is recommended when the absolute fracture risk warrants drug therapy.
- Screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended in patients receiving ADT. These medical conditions are common in older individuals and it remains uncertain whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in patients receiving ADT should differ from the general population.

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

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 plus docetaxel and abiraterone improved overall survival and rPFS in the open-label PEACE-1 study. A modest increase in toxicity was seen.
  - ADT plus docetaxel and darolutamide improved overall survival in the ARASENS trial. Adverse events were similar between arms.
  - 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 steroids may include: dexamethasone on the day of chemotherapy or daily prednisone.
- Cabazitaxel with concurrent steroid
  - Concurrent steroids may include: dexamethasone on the day of chemotherapy or daily prednisone.
- Cabazitaxel/carboplatin with concurrent steroid
  - Concurrent steroids may include: dexamethasone on the day of chemotherapy or daily prednisone.
- Mitoxantrone with prednisone
- 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. Radium-223 has been studied in symptomatic patients who are not candidates for docetaxel-based regimens and resulted in improved overall survival. Abiraterone and enzalutamide have been shown to extend survival in patients whose cancer progressed on docetaxel. (See PROS-I). Mitoxantrone with prednisone may provide palliation but has not been shown to extend survival.
- Only regimens utilizing docetaxel on an every-3-week schedule demonstrated beneficial impact on survival. The duration of therapy should be based on the assessment of benefit and toxicities. In the pivotal trials establishing survival advantage of docetaxel-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted.
- Patients who are not candidates for docetaxel or who are intolerant of docetaxel should be considered for cabazitaxel with concurrent steroid, based on recent results that suggest clinical activity of cabazitaxel in mCRPC. Cabazitaxel was associated with lower rates of peripheral neuropathy than docetaxel, particularly at 20 mg/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.
- Increasing PSA should not be used as the sole criteria for progression. Assessment of response should incorporate clinical and radiographic criteria.
- Cabazitaxel at 25 mg/m² with concurrent steroid has been shown in a randomized phase 3 study (TROPIC) to prolong overall survival, 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 overall survival (13.4 months vs. 14.5 months) compared to 25 mg/m². 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 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.
- 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*). Corn PG, et al. Lancet Oncol 2019;20:1432-1443.

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.

Continued

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

- Docetaxel retreatment can be attempted after progression on a novel hormone therapy in patients with metastatic CRPC whose cancer has not demonstrated definitive evidence of progression on prior docetaxel therapy in the castration-sensitive setting.
- No chemotherapy regimen to date has demonstrated improved survival or quality of life after cabazitaxel, and trial participation should be encouraged.
- Treatment decisions around off-label chemotherapy use in the treatment-refractory CRPC should be individualized based on comorbidities and functional status and after informed consent.
- No benefits of combination approaches over sequential single-agent therapies have been demonstrated, and toxicity is higher with combination regimens. See NCCN Guidelines for Hematopoietic Growth Factors for recommendations on growth factor support.

Targeted Therapy

- Consider inclusion of olaparib in patients who have an *HRR* mutation and whose cancer has progressed on prior treatment with androgen receptor-directed therapy regardless of prior docetaxel therapy. Olaparib is a treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in a homologous recombination repair 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 which gene has a the specific gene mutation.
- Consider inclusion of rucaparib 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.

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 (for MSI-H, dMMR, or TMB ≥10 mut/Mb)
  - Pembrolizumab is recommended only as subsequent systemic therapy for patients with metastatic CRPC whose cancer has progressed through prior docetaxel and a novel hormone therapy.

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.

Continued

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

Prevention of Skeletal-Related Events

- 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 skeletal-related events.
- A phase 3 clinical trial that assessed a role for zoledronic acid in patients beginning ADT for bone metastases was negative.
- Choice of agent may depend on underlying comorbidities, whether the patient has been treated with zoledronic acid previously, logistics, and/or cost considerations.
  - Denosumab (preferred) is given SQ every 4 weeks. Although renal monitoring is not required, denosumab is not recommended in patients with creatinine clearance <30 mL/min. When creatinine clearance is <60 mL/min, the risk for severe hypocalcemia increases. Even in patients with normal renal function, hypocalcemia is seen twice as often with denosumab than zoledronic acid and all patients on denosumab should be treated with vitamin D and calcium with periodic monitoring of serum calcium levels.
  - Zoledronic acid is given IV every 3 to 4 weeks or every 12 weeks. The dose is based on the serum creatinine obtained just prior to each dose and must be adjusted for impaired renal function. Zoledronic acid is not recommended for creatinine clearance <30 mL/min.
- Osteonecrosis of the jaw (ONJ) is seen with both agents; risk is increased in patients who have tooth extractions, poor dental hygiene, or a dental appliance. Patients should be referred for dental evaluation before starting either zoledronic acid or denosumab. If invasive dental procedures are required, bone-targeted therapy should be withheld until the dentist indicates that the patient has healed completely from all dental procedure(s).
- The optimal duration of therapy for either denosumab or zoledronic acid remains uncertain.
- The toxicity profile of denosumab when denosumab is used in patients who have been treated with zoledronic acid remains uncertain.

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.

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.

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

ABBREVIATIONS

ADT	androgen deprivation therapy
AI	artificial intelligence
AUC	area under the curve
BCR	biochemical recurrence
BED	biologically effective dose
CCP	cell cycle progression
CEA	carcinoembryonic antigen
CRPC	castration-resistant prostate cancer
ctDNA	circulating tumor DNA
DM	distant metastases
dMMR	mismatch repair deficient
DRE	digital rectal exam
DWI	diffusion-weighted imaging
EBRT	external beam radiation therapy
HDR	high dose-rate
HR	high risk
HRRm	homologous recombination repair gene mutations
IGRT	image-guided radiation therapy
IR	intermediate risk
IRF	intermediate risk factor
LDH	lactate dehydrogenase
LDR	low dose-rate
LHRH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
MDP	methylene diphosphonate
mpMRI	multiparametric MRI
MSI	microsatellite instability
MSI-H	microsatellite instability-high
NEPC	neuroendocrine prostate cancer
OAR	organ at risk
OS	overall survival
PCSM	prostate cancer-specific mortality
PFS	progression-free survival
PLND	pelvic lymph node dissection
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PSMA	prostate-specific membrane antigen
RP	radical prostatectomy
rPFS	radiographic progression-free survival
RT	radiation therapy
SBRT	stereotactic body radiation therapy
TMB	tumor mutational burden

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.

NCCN Guidelines Version 1.2023
Prostate Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Prostate Cancer. Last updated: May 10, 2022.

Table of Contents

Overview

An estimated 248,530 new cases of prostate cancer will be diagnosed in the United States in 2021, accounting for almost 26% of new cancer cases in males.[1] Researchers further estimate that prostate cancer will account for 10.7% of male cancer deaths in the United States in 2021, with an estimated 34,130 deaths.[1] Over the past several years, the incidence of prostate cancer has declined, likely in part as a result of decreased detection attributed to decreased rates of prostate-specific antigen (PSA) screening.[2-4] The age-adjusted death rate from prostate cancer declined by 52% from 1993 to 2017, but the death rate has become stable in recent years.[1] For all stages combined, the 5-year relative survival rate for prostate cancer is 98%.[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.

Early detection can lead to overtreatment of prostate cancers that do not threaten life expectancy, which results in unnecessary side effects that impair quality of life (QOL) and increase health care expenditures. The U.S. Preventive Services Task Force (USPSTF) recommended against PSA testing in 2012.[5] The incidence of metastatic disease has increased since that time.[4,6,7] The rate of prostate cancer mortality, which had been in decline for 2 decades, has stabilized.[1,4] Prostate cancer incidence and deaths have increased in the past few years for the first time in recent history, with prostate cancer deaths increasing from an estimated 26,730 in 2017 to 34,130 in 2021.[1,8] Increases in the incidence of metastases at presentation and prostate cancer deaths may be influenced by declines in the rates of prostate cancer early detection, biopsies, diagnosis of localized prostate cancers, and radical prostatectomy that followed the 2012 USPSTF recommendations.[9-19] The USPSTF released updated recommendations in 2018 that include individualized, informed decision-making regarding prostate cancer screening in males aged 55 to 69 years.[20] These updated recommendations may allow for a more balanced approach to prostate cancer early detection. 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 (see the NCCN Guidelines for Prostate Cancer Early Detection, available at www.NCCN.org) should decrease the risk of overdetection. This reduced overdetection along with the use of active surveillance in appropriate patients should reduce overtreatment AND preserve the decrease in prostate cancer mortality.

Literature Search Criteria and Guidelines Update Methodology

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.[21]

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

The 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.

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

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.[22] 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.[23]

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,[24] the WHO's Life Tables by Country,[25] or the Memorial Sloan Kettering Male Life Expectancy tool[26] 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.[27] 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.[28-31] 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).[31-36] In fact, approximately 11% of patients with prostate cancer and at least 1 additional primary cancer carry germline mutations associated with increased cancer risk.[37] Therefore, the panel recommends a thorough review of personal and family history for all patients with prostate cancer.[38,39]

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).[40-42] 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.[43] 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*.[43,44] 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.[43] In localized prostate cancer, that number was 60%.[44]

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%).[43,45-51] 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*.[50]

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).[47] 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).[52] 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*.[53]

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.[54] 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.[55]

Germline *BRCA1* or *BRCA2* mutations have been associated with an increased risk for prostate cancer in numerous reports.[35,36,55-65] 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.[35,36,55,57,59,64,66,67] In addition, limited data suggest that germline mutations in *ATM, PALB2,* and *CHEK2* increase the risk of prostate cancer.[68-71] Furthermore, prostate cancer in individuals with germline *BRCA* mutations appears to occur earlier, has a more aggressive phenotype, and is associated with significantly reduced survival times than in non-carrier patients.[41,42,66,72-76]

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 older patients with germline *MSH2* mutations.[77,78]

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).[32] 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).[79] 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*.[53]

Effect of Intraductal/Cribriform or Ductal Histology

Ductal prostate carcinomas are rare, accounting for approximately 1.3% of prostate carcinomas.[80] Intraductal prostate cancer may be more common, especially in higher risk groups, and may be associated with a poor prognosis.[81] 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.[82-85] In particular, tumors with these histologies may be more likely to harbor somatic MMR gene alterations than those with adenocarcinoma histology.[85-87] In addition, limited data suggest that germline homologous DNA repair gene mutations may be more common in prostate tumors of ductal or intraductal origin[88,89] and that intraductal histology is common in germline *BRCA2* mutation carriers with prostate cancer.[90] 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[38,39]:

- 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.[91,92]

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.[93]

If MSI testing is performed, testing using an NGS assay validated for prostate cancer is preferred.[94-96] 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.[43] 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,[97,98] 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.[99] Risk group stratification has been published widely and validated, and provides a better basis for treatment recommendations than clinical stage alone.[100,101]

A new prostate cancer grading system was developed during the 2014 International Society of Urological Pathology (ISUP) Consensus Conference.[102] 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.[103,104] 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.[105] Additional studies have supported the validity of this new system.[106-111] 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).[112] 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.[113,114] Evidence also shows heterogeneity in the low-risk group, with PSA levels and percent positive cores affecting pathologic findings after radical prostatectomy.[115,116]

In a retrospective study, 1024 patients with intermediate-risk prostate cancer were treated with radiation with or without neoadjuvant and concurrent ADT.[117] 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.[118-121] 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,[122-124] radical prostatectomy,[125-128] neurovascular bundle preservation[129-131] or omission of pelvic lymph node dissection (PLND) during radical prostatectomy,[132-135] brachytherapy,[125,136-138] or external beam RT (EBRT).[125,139] Biochemical progression-free survival (PFS) can be reassessed postoperatively using age, diagnostic serum PSA, and pathologic grade and stage.[125,140-142] Potential success of adjuvant or post-recurrence RT after unsuccessful radical prostatectomy can be assessed using a nomogram.[125,143]

None of the current models predicts with perfect accuracy, and only some of these models predict metastasis[124,125,140,144,145] and cancer-specific death.[126,128,146-148] 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.[149] 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.[150-162] 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.[163]

Clinical utility studies on the tissue-based molecular assays have also been performed.[164-166] 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.[164] 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).[165] 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 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.[167] 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).[168] 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.[169]

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.[170] 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.[171] 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.[169] ***First,*** mpMRI helps detect larger and/or more poorly differentiated cancers (ie, Grade Group ≥2).[172] 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.[173-175] In fact, a recently published clinical study identified that MRI-targeted biopsy synergized with conventional systematic biopsy to identify more clinically significant cancers.[176] ***Second,*** mpMRI aids in better assessment of extracapsular extension (T staging), with high negative predictive values (NPVs) in low-risk patients.[177] mpMRI results may inform decision-making regarding nerve-sparing operation.[178] ***Third,*** mpMRI is equivalent to CT scan for staging of pelvic lymph nodes.[179,180] 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).[181]

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.[169] 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.[182-184]

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.[185-187] 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.[188-193] The reported sensitivity and specificity for PSMA-11 PET/CT in the detection of nodal involvement in primary staging of intermediate-, high-, and very-high-risk patients is 40% and 95%, respectively.[194] The patient-level positive predictive value (PPV) in detection of lesions in patients with BCR is 92%.[195] Similarly, the reported sensitivity and specificity for piflufolastat PET/CT in the detection of nodal involvement in primary staging of unfavorable intermediate-, high-, and very-high-risk patients is 31% to 42% and 96% to 99%, respectively.[196,197] The patient-level correct localization rate (CLR; patient-level PPV validated by anatomic lesion co-localization) for piflufolastat PET/CT is 85% to 87%.[198] 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.[199,200] 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.[201-210] The reported sensitivity and specificity of F-18 fluciclovine PET/CT ranges from 37% to 90% and from 40% to 100%, respectively.[207,211,212] A prospective study compared F-18 fluciclovine and C-11 choline PET/CT scans in 89 patients, and agreement was 85%.[207] 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 management for 64%.[213] In addition, the LOCATE trial demonstrated that fluciclovine frequently changed management plans in patients with biochemical recurrence.[214] 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 management in over half of a

prospective cohort of 635 patients with BCR.[215,216] 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.[217] 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.[218]

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. [219-222]

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.[223,224] Moreover, although PET imaging may change treatment,[214] 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.[225] 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.[226] 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).[227] 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 from failure to detect a tumor or tumor recurrence (ie, false negative), but harm to the patient and added expense to the medical system also can result from false-positive scans. 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 management of patients with malignancy. However, as with any medical procedure, imaging is not without risks to patients. Inappropriate use of imaging also has been identified as a significant contributor to health care costs in the United States and worldwide. Therefore, imaging should be performed only when medically appropriate, and in a manner that reduces risk (eg, minimizing radiation dose). An algorithmic approach to the use of imaging, such as by NCCN and the Appropriateness Criteria developed by the American College of Radiology,[228] 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 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 elderly or frail patients with comorbidity that will likely out-compete prostate cancer for cause of death. Johansson and colleagues[229] 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.[230-232] For example, in one study, 55% of the population remained untreated at 15 years.[231] 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.[230-240] 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.[241]

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.[242] 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.[242,243] 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.[244] 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.[244-249]

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 younger than 65 years and from 3% to 41% of those 65 years or older.[250] 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.[251] 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.[252]

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.[237] 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[253]; the high frequency of positive prostate biopsies in individuals with normal DREs and serum PSA values[254]; 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[255,256] or 100 patients with low-risk prostate cancer[257] to prevent one death from the disease. The controversy regarding overtreatment of prostate cancer and the value of prostate cancer early detection[255-261] has been further informed by publication of the Goteborg study, a subset of the European Randomized Study of Screening for Prostate Cancer (ERSPC).[262,263] 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%).[262] Most impressively, 40% of the patients were initially managed using 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.[264] 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.[265]

The best models of prostate cancer detection and progression estimate that 23% to 42% of all U.S. screen-detected cancers were overtreated[266] and that PSA detection was responsible for up to 12.3 years of lead-time bias.[267] 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[268] 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.[269,270] A new nomogram may be better.[271] Although many variations upon this definition have been proposed (reviewed by Bastian and colleagues[272]), 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.[267]

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.[273-275] 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.[276] 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.[277] 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).[278] 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[279] 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.[231,234,235] 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%).[280]

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.[281-284] 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.[285] 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.[286] In one study, the increase in prostate-cancer-specific mortality in African American patients was limited to those with grade group 1.[287] 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.[288,289] However, other studies have not seen different rates of upstaging or upgrading.[290,291] 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.[290]

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.[292-295] African Americans in the low- to intermediate-risk categories also appear to suffer from an increased risk of biochemical recurrence after treatment.[296] 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.[297]

Reasons for these clinical disparities are under investigation, but treatment disparities and access to health care may play a significant role.[298,299] In fact, results of some studies suggest that racial disparities in prostate cancer outcomes are minimized when health care access is equal.[300-303] 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.[304]

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 men 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.[305] Patients with PI-RADS 4 or 5 on mpMRI have an increased risk of biopsy progression during active surveillance.[306]

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.[163] 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.[307] 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.[308] 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.[309] Another study found the NPV of mpMRI to be 80%.[310]

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.[311] 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,[259] and those who develop urinary tract

infection are often fluoroquinolone-resistant.[312] Radical prostatectomy may become technically challenging after multiple sets of biopsies, especially as it pertains to potency preservation.[313] 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.[314]

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.[315-317] 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.[318-320]

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.[321] 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.[230,231,236-239,322-325] Reclassification criteria were met by 23% of patients with a median follow-up of 7 years in the Toronto experience,[323] 36% of patients with a median follow-up of 5 years in the Johns Hopkins experience,[230] and 16% of patients with a median follow-up of 3.5 years in the University of California, San Francisco (UCSF) experience[239] (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.[326] 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.[327] 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.[230] 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.[323] 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%.[323] 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.[231] 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.[328] 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%).[329] 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.[325] 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.[230] Several studies have shown that delayed radical prostatectomy does not increase the rates of adverse pathology.[237,330-332]

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[128] 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).[333,334] 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.[333] The reduction in mortality was confirmed at 18 years of follow-up, with an absolute difference of 11%.[334] Overall, 8 patients needed to be treated to avert one death; that number fell to 4 for patients younger than 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.[335] 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.[336] 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.[337-339] 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.[340]

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.[341,342] Overall and cancer-specific 10-year survival ranged from 54% to 89% and 70% to 83%, respectively.[341] 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.[343,344] Laparoscopic and robot-assisted radical prostatectomy are commonly used and are considered comparable to conventional approaches in experienced hands.[345-347] 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.[348] 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.[349] Oncologic outcome of a robotic versus open approach was similar when assessed by use of additional therapies[348] or rate of positive surgical margins,[350] 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.[350] 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[351] and potency recovery.[352] 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.[353,354] 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.[353]

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.[355] 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.[356]

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.[357] 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.[358,359] Replacement of resected nerves with nerve grafts does not appear to be effective for patients undergoing wide resection of the neurovascular bundles.[360] The ability of mpMRI to detect extracapsular extension can aid in decision-making in nerve-sparing surgery.[178]

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.[133] 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.[361] 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.[133]

PLND should be performed using an extended technique.[362,363] 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.[364-366] A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to elimination of microscopic metastases,[365,367-369] although definitive proof of oncologic benefit is lacking.[370] 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.[371]

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.[144,372-374] The second-generation 3D technique, IMRT, has been used increasingly in practice.[375] 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.[376-379]

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.[380-389] Toxicity was similar between moderately hypofractionated and conventional regimens in some[380,384,387,388] but not all of the trials.[382,385,386] 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.[390] 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.[391] 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.[392]

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.[393-398] Kuban and colleagues[396] 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.[399] 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.[400] In light of these findings, the conventional 70 Gy dose is no longer considered adequate. A dose of 75.6 to 79.2 Gy in conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Intermediate-risk and high-risk patients should receive doses of up to 81.0 Gy.[376,401,402]

Data suggested that EBRT and radical prostatectomy were effective for the treatment of localized prostate cancer.[403] 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.[404]

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.[404,405] 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.[406,407] 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.[408] 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.[409] Spacer implantation, however, is quite expensive and may be associated with rare complications such as rectum perforation and urethral damage.[410,411] 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.[412] 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.[413] 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.[414] 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.[415] In another study (RTOG 8531), 977 patients with T3 disease treated with EBRT were randomized to adjuvant ADT or ADT at relapse.[416] Two other randomized phase 3 trials evaluated long-term ADT with or without radiation in a population of patients who mostly had T3 disease.[417-420] 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.[421]

Prophylactic nodal radiation should be considered in this population. [422-424] 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.[425] The randomized phase 3 FLAME trial showed that a focal radiation boost to the mpMRI-visible lesion can improve biochemical DFS in this population.[426]

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.[427] 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.[428] 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).[429] 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).[430]

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.[431]

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.[340] 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 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.[432-436]

The Panel recommends against EBRT to the primary tumor in the case of high-volume M1 disease based on the HORRAD and STAMPEDE trials.[340,437] 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,[438] 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.[439] 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.[438-444] 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.[445] 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.[446] 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).[447] Another phase 2 trial found increased toxicity with doses >47.5 Gy delivered in 5 fractions.[448] An analysis using the SEER database also reported that SBRT was more toxic than IMRT.[449] Overall, prospective evidence supports the use of SBRT in the setting of localized prostate cancer.[450]

Several phase 3 trials have been initiated comparing conventional regimens to SBRT.[451-453] 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.[453]

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.[101,454] 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.[455,456]

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.[457] 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.[405] 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.[458,459] 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.[460] 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).[461,462] Vargas and colleagues[463] 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.[464-468] A phase 2 trial in 300 patients with intermediate-risk prostate cancer also found LDR brachytherapy alone to be safe and effective.[469] 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).[470] 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.[471-474] This combination has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials, but with higher toxicity.[475-477] 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.[478]

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.[479] All patients were initially treated with 12 months of ADT and pelvic EBRT to 46 Gy. An intention-to-treat 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).[480] 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.[481] Whereas the toxicity is increased with the use of brachytherapy boost, this and other randomized controlled trials have failed to show an improvement in OS or cancer-specific survival.[482]

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.[483,484] 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.[485] 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.[486,487]

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.[488] 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.[489]

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.[490] 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.[491] 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%.[492]

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.[493] 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.[494,495] 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.[496] 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.[495] 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.[494] 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.[497] 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.[495] 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.[498] 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.[499] 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.[500] 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).[501] 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.[502] The SCORAD randomized trial failed to show non-inferiority for ambulatory status of single-fraction 8-Gy EBRT to 20 Gy in 5 fractions.[503]

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.[504] 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.[505] 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.

Lutetium Lu 177 vipivotide tetraxetan

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.[506] The active moiety is a radionuclide which delivers radiation to PSMA-expressing and surrounding cells, inducing DNA damage which leads to cell death.[506] 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 were previously treated with at least one androgen receptor-directed therapy and one or two taxane-based chemotherapy regimens. Patients had at least one PSMA-positive metastatic lesion and no PSMA-negative lesions determined by gallium-68 (Ga-68) labeled PSMA-11 PET/CT imaging. Patients were randomized in a 2:1 ratio to receive standard of care (abiraterone, enzalutamide, bisphosphonates, radiation therapy, 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. [507]

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. [507]

The NCCN Panel recommends Lu-177-PSMA-617 as a category 1, useful in certain circumstances 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. 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. The NCCN Panel believes that both Ga-68 PSMA-11 or F-18 piflufolastat PSMA imaging can be used to determine eligibility.

Radium-223 and Other Radiopharmaceuticals

In May 2013, the U.S. Food and Drug Administration (FDA) approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This first-in-class radiopharmaceutical was approved for treatment of metastatic 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.[508] 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 skeletal-related event (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.[509] Intention-to-treat analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic SREs.[510] Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), likely due to the short range of radioactivity.[508] 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.[511]

The multicenter, international, double-blind, placebo-controlled, phase 3 ERA 223 trial randomized bone-metastatic patients with chemotherapy-naïve CRPC to abiraterone with or without radium-223.[512] The patients were asymptomatic or mildly symptomatic. The primary endpoint of symptomatic skeletal event-free survival in the intention-to-treat 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 Panel therefore does not recommend this combination.

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.[513] Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial has the potential for additive myelosuppression.[513] 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, and it should be given with concomitant denosumab or zoledronic acid.

Beta-emitting radiopharmaceuticals are an effective and appropriate option for patients with widespread metastatic disease, particularly if they are no longer candidates for effective chemotherapy.[514] Because many patients have multifocal bone pain, systemic targeted treatment of skeletal metastases offers the potential of pain relief with minimal side effects. Unlike the alpha-emitting agent radium-223, beta emitters confer no survival advantage and are palliative. Beta-emitting radiopharmaceuticals developed for the treatment of painful bone metastases most commonly used for prostate cancer include strontium-89 (89Sr) or samarium-153 (153Sm).[515,516] The risk of bone marrow suppression, which might influence the ability to provide additional systemic chemotherapy, should be considered before this therapy is initiated.

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.[517] 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.[518] 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.[519]

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.[520] 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 managed 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.[521] A report suggests that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer.[522] A study by Donnelly and colleagues[523] 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.[524] 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.[525]

Cryosurgery has been assessed in patients with recurrent disease after RT.[526-528] 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%).[528]

HIFU has been studied for treatment of initial disease.[529,530] A prospective multi-institutional study used HIFU in 111 patients with localized prostate cancer.[529] 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.[531] 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.[532,533]

HIFU also has been studied for treatment of radiation recurrence.[534-540] 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%.[541] 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 failure were able to avoid ADT at a median follow-up of 64 months.[542]

Other emerging local therapies, such as focal laser ablation and vascular-targeted photodynamic (VTP) therapy have also been studied.[543,544] 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.[545] 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.[546] 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.[547]

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.[548] 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.[549,550] 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 (failure of PSA to 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.[551] 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.[552-554] 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.[555] 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.[556,557] 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).[558]

Systematic reviews come to conflicting conclusions on the utility of immediate post-prostatectomy radiation in patients with adverse features.[559,560] 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.[561]

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.[562] 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.[563]

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)[423,424,564,565]; 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*).[566] 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.[567] 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.[555-557] 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.[568-571]

Biochemical Recurrence After Radical Prostatectomy

Patients who experience biochemical recurrence after radical prostatectomy fall into three groups: 1) those whose PSA level fails to fall

to undetectable levels after radical prostatectomy (persistent disease); 2) those who achieve an undetectable PSA after radical prostatectomy with a subsequent detectable PSA level that increases on 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."[549] 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.[572-576] A large retrospective review of 501 patients who received radiation for detectable and increasing PSA after radical prostatectomy[575] 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.[577] 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[125,578] 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.[579,580] 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%.[581]

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 ($P < .001$).[582]

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.[583] 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.[577,584] 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.[551] Treatment is most effective when pre-

treatment PSA level is below 0.5 ng/mL.[578] 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,[577] 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.[584] Most patients with prolonged PSADT may be observed safely.[585]

Six months of concurrent/adjuvant ADT can be coadministered with radiation in patients with rising PSA levels based on the results of GETUG-16.[586,587] 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.[588] 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.[589] For 2 years of ADT, level 1 evidence supports 150 mg bicalutamide daily but an LHRH agonist could be considered as an alternative.[589]

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.[590] 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.[591] Other options for localized interventions include cryotherapy,[592] HIFU (category 2B),[534-537,541,542] and brachytherapy (reviewed by Allen and colleagues[593] 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 elderly. This practice has been challenged by a large cohort study of 66,717 elderly patients with T1–T2 tumors.[594] 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.[595] 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.[596,597]

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.[598] 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).[589,599-601] Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly high-risk patients (RTOG 8610).[602] Results of the EORTC 22991 trial showed that the addition of 6 months of ADT significantly improved biochemical DFS compared with radiation alone in intermediate-risk (75% of study population) and high-risk patients.[603] 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.[604]

RTOG 9910 and RTOG 9902 reinforced two important principles concerning the optimal duration of ADT and use of systemic chemotherapy in conjunction with EBRT.[605,606] 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.[601] 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.[607] 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.[607] 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).[608,609]

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.[415,416,418,419,610]

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.[611] 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).[612]

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.[613] The DART01/05 GICOR trial also reported similar results in patients with high-risk disease.[614] 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.[615] Two randomized phase 3 trials showed 1.5 years of ADT was not inferior to 3 years of ADT.[616,617]

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.[618]

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.[619] 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.[566] 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).[566,620] 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.[621] 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.[622] In addition, a cohort analysis of 731 patients with positive nodes failed to demonstrate a survival benefit of ADT initiated within 4 months of radical prostatectomy compared to observation.[621] 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.[623]

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.[622] Meta-analysis data suggest that bicalutamide may provide an incremental relative improvement in OS by 5% to 20% over LHRH agonist monotherapy.[624,625] 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.[626,627] 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.[628]

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.[629] 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.[630] The heart and T lymphocytes have receptors for LHRH. Therefore, LHRH agonists may affect cardiac contractility, vascular plaque stability, and inflammation.[631]

A new LHRH antagonist, relugolix, has been studied as ADT in patients with advanced prostate cancer in the randomized phase 3 HERO trial.[632] 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 compliance of oral relugolix and the potential effects non-compliance 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 patient compliance 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.[633] 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 local therapy has failed. 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.[634] 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.[635] 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.[622] A PSA value ≤4 ng/mL after 7 months of ADT is associated with improved survival of patients newly diagnosed with metastatic prostate cancer.[636]

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.[637,638] 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.[639,640] 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.[641] 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.[641] 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).[642]

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.[641] 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.[643] 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.[641]

A second randomized trial (STAMPEDE) of 1917 patients with castration-naïve prostate cancer demonstrated similar OS benefits.[430] 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 less than 70 years of age than in older patients (HR, 0.94 vs. HR, 0.51). Older patients 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 older patients, 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).[644] The cost savings may reduce financial toxicity and improve compliance.

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.[645] 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.[646] 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; $P < .001$)[647]

Apalutamide is a category 1 option for patients with M1 castration-naïve prostate cancer. The FDA approved this indication in September of 2019.[648,649]

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.[650] 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; $P < .001$).[651]

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.[650,651]

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.[652,653] 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.[654] 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).[654] 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.[655]

The multinational European ICELAND trial randomized 702 participants with locally advanced or biochemically recurrent prostate cancer to continuous or intermittent ADT.[656] 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.[657]

Intermittent ADT in Metastatic Disease

Hussain and colleagues[658] 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.[659]

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).[658] 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.[660] Furthermore, several meta-analyses of randomized controlled trials reported no difference in survival between intermittent ADT and continuous ADT.[661-663] Another recent analysis concluded that the non-inferiority of intermittent to continuous ADT in terms of survival has not been clearly demonstrated.[664] 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[636]: 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.[655] 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.[665-667] 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.[632] 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.[668-675]

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.[676-678] 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; $P = .01$).[631] ADT increases bone turnover and decreases bone mineral density,[679-682] 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,[683] and treatment-related sarcopenia appears to contribute to frailty and increased risk of falls in older patients.

The NCCN Guidelines Panel recommends screening and treatment for osteoporosis according to guidelines for the general population from the National Osteoporosis Foundation.[684] 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.[685] 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.[686-688] 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.[689] 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.[690] 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.[602,690-697] 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.[698] Other population-based studies resulted in similar findings.[631,699] However, a Taiwan National Health Insurance Research Database analysis found no difference in ischemic events with LHRH agonist therapy or orchiectomy.[700] A French database study showed the cardiovascular risk to be similar in patients taking LHRH agonists and antagonists.[701] 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.[630] Patients with a recent history of cardiovascular disease appear to have higher risk,[702] and increased physical activity may decrease the symptoms and cardiovascular side effects of patients treated with ADT.[703]

Several mechanisms may contribute to greater risk for diabetes and cardiovascular disease during ADT. ADT increases fat mass and decreases lean body mass.[683,704,705] ADT with an LHRH agonist increases fasting plasma insulin levels[706,707] and decreases insulin sensitivity.[708] ADT also increases serum levels of cholesterol and triglycerides.[706,709]

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.

Progression to and Management of CRPC

Most patients with advanced disease eventually stop responding to traditional ADT and are 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).[710] 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 observation with continued ADT if PSADT is greater than 10 months (preferred), because these patients will have a relatively indolent disease history.[711] Secondary hormone therapy with continued ADT is an option mainly for patients with shorter PSADT (≤10 months) as described below, because the androgen receptor may remain active.

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 genes (ie, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*) if not done previously.[712] This information may be used for genetic counseling, early use of platinum chemotherapy, use of PARP inhibitors, or eligibility for 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 received for metastatic castration-naïve disease, M0 CRPC, or previous lines of therapy for M1 CRPC.

The Panel notes that relugolix has not been adequately studied in combination with potent androgen receptor inhibitors such as enzalutamide, apalutamide, darolutamide, or abiraterone acetate, nor has it been studied in combination with docetaxel or cabazitaxel chemotherapy. Potential drug interactions include induction of cytochrome P450 enzymes and reduced concentration and efficacy of relugolix with enzalutamide or apalutamide and cardiac QTc interactions with abiraterone. Further studies of relugolix dosing and drug interactions with commonly used agents in advanced prostate cancer are needed to ensure patient safety and proper dosing. Therefore, relugolix is not recommended in combination with other therapies at this time.

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. There are not much data to inform the optimal sequence for delivery of these agents in patients with metastatic CRPC (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 in cases where PSA or bone imaging changes may indicate flare rather than true clinical progression.[713,714] 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.[715,716] 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.[717,718] 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; $P < .0001$).[718] Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone.[718,719]

FDA approval in the pre-docetaxel setting occurred on December 10, 2012, and was based on the randomized phase 3 COU-AA-302 trial of abiraterone and prednisone (n = 546) versus prednisone alone (n = 542) in patients with asymptomatic or minimally symptomatic, metastatic CRPC.[720] 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; $P = .003$).[721] Key secondary endpoints of time to symptomatic deterioration, time to chemotherapy initiation, time to pain progression, and PSA PFS improved significantly with abiraterone treatment, and PSA declines (62% vs. 24% with >50% decline) and radiographic responses (36% vs. 16% RECIST responses) were more common.

The most common adverse reactions with abiraterone/prednisone (>5%) were fatigue (39%); back or joint discomfort (28%–32%); peripheral edema (28%); diarrhea, nausea, or constipation (22%); hypokalemia (17%); hypophosphatemia (24%); atrial fibrillation (4%); muscle discomfort (14%); hot flushes (22%); urinary tract infection; cough; hypertension

(22%, severe hypertension in 4%); urinary frequency and nocturia; dyspepsia; or upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase (11%–12%), or cardiac disorders (19%, serious in 6%).

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.[722,723] In studies of healthy males, this formulation at 500 mg was shown to be bioequivalent to 1000 mg of the originator formulation.[724,725] 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.[726] 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.[644] 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 compliance. 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.[727] 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 mCRPC, with disease progression on abiraterone with prednisone, were switched to abiraterone with 0.5 mg/day dexamethasone.[728] 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

On August 31, 2012, the FDA approved enzalutamide, a next-generation antiandrogen, for treatment of patients with metastatic CRPC who had received prior docetaxel chemotherapy.[729,730] Approval was based on the results of the randomized, phase 3, placebo-controlled trial (AFFIRM).[731,732] 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.[729,731]

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.[733,734] 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.[735] 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.[736] 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.[737] 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; $P = 0.001$).[738] 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.[739]

The FDA expanded approval for enzalutamide to include patients with non-metastatic CRPC on July 13, 2018,[729,730] 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).

Patients receiving enzalutamide have no restrictions for food intake and concurrent prednisone is permitted but not required.[731]

Apalutamide in M0 CRPC

The FDA approved apalutamide for treatment of patients with non-metastatic CRPC on February 14, 2018.[648] 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.[740] 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%). Patients with M0 CRPC can be offered apalutamide, if PSADT is less than or equal to 10 months (category 1). In a prespecified exploratory analysis of SPARTAN, health-related QOL was maintained in both the apalutamide and placebo groups.[741]

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; $P = .016$).[742] 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 on July 30, 2019.[743,744] 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.[745] 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).[746] 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%).[745]

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.[747-749] 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.[750] 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 in Metastatic Prostate Cancer

Recent research has expanded the therapeutic options for patients with metastatic CRPC depending on the presence or absence of symptoms, the location of metastases, and the presence of certain biomarkers.

Docetaxel

Two randomized phase 3 studies evaluated docetaxel-based regimens in symptomatic or rapidly progressive CRPC (TAX 327 and SWOG 9916).[609,751,752] TAX 327 compared docetaxel (every 3 weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1006 patients.[751] 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.[752] The SWOG 9916 study also showed improved survival with docetaxel when combined with estramustine compared to mitoxantrone plus prednisone.[609]

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.[753] 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.

Docetaxel is the traditional mainstay of treatment for symptomatic metastatic CRPC. Docetaxel is not commonly used for asymptomatic patients in this setting, but may be considered when the patient shows signs of rapid progression or visceral metastases despite lack of symptoms. 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-naïve and CRPC settings.[754] Retrospective analysis from the GETUG-AFU 15 trial suggests that docetaxel only benefits some patients with CRPC who received docetaxel in the castration-naïve setting.[755]

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-naive setting.

Docetaxel is also included as an upfront option for patients with castration-naïve prostate cancer and distant metastases based on results from two phase 3 trials (ECOG 3805/CHAARTED and STAMPEDE).[429,756] CHAARTED randomized 790 patients with metastatic, castration-naïve prostate cancer to docetaxel (75 mg/m^2 IV q3 weeks x 6 doses) plus ADT or ADT alone.[756] 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).[757] 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-volume disease 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-naïve prostate cancer.[429] The results in the M1 population essentially 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). The results of the STAMPEDE trial seem to confirm the results of the CHAARTED trial.

Patients with low-volume metastatic disease can be offered early treatment with docetaxel combined with ADT; however, they have less certain benefit from treatment than patients with higher-volume disease, as this subgroup did not have definitively improved survival outcomes in the ECOG CHAARTED study or a similar European trial (GETUG-AFU 15).[756,758,759] Meta-analyses of randomized controlled trials also concluded that docetaxel provides a significant OS benefit in this setting, with no evidence that the benefit was dependent on the volume of disease.[760-762]

The direct randomized comparison of docetaxel with ADT and abiraterone with ADT in STAMPEDE showed that the two treatment options resulted in similar efficacy and safety outcomes in patients with metastatic castration-naïve prostate cancer.[431]

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.[763] 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.[764] 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.[765]

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.[766] 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. Cabazitaxel at 20 mg/m^2 every 3 weeks, with or without growth factor support, is now recommended for fit patients. Cabazitaxel at 25 mg/m^2 may be considered for healthy patients who wish to be more aggressive.

Recent results from the phase 3 FIRSTANA study suggested that cabazitaxel has clinical activity in patients with chemotherapy-naïve mCRPC.[767] 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%). Therefore, patients who are not candidates for docetaxel, who are intolerant of docetaxel, or who have pre-existing mild peripheral neuropathy should be considered for cabazitaxel.[767]

The NCCN Guidelines Panel included cabazitaxel as an option after progression on docetaxel for patients with symptomatic metastatic CRPC. This recommendation is category 1 in patients who also had prior treatment with a novel hormone therapy based on randomized phase 3 study data (see *Cabazitaxel*, above).[763,767] 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-naïve setting.

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.[768] 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.[769] Therefore, 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 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 pre-treated, high-risk population. In addition, supportive care should include antiemetics (prophylactic antihistamines, H2 antagonists, and corticosteroids prophylaxis) and symptom-directed antidiarrheal agents. Cabazitaxel was tested in patients with hepatic dysfunction in a small, phase I, dose-escalation study.[770] 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, 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.[771] 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 intention-to-treat 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).[772] 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.[773] 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/neuroendocrine prostate cancer. The Panel prefers that sipuleucel-T be used as initial 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 subsequent to 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 on May 23, 2017.[774] The indication has since been expanded to include several cancer types, but not prostate cancer specifically.[775] The recommended adult doses of pembrolizumab for this indication are 200 mg every 3 weeks or 400 mg every 6 weeks administered intravenously.

FDA-accelerated 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).[774] 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.

A growing number of additional patients with metastatic CRPC treated with pembrolizumab have been reported.[79,776-780] 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.[776] Some of the patients also had experienced disease progression on additional therapies (docetaxel for castration-naïve 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 from two PSA responders and two PSA non-responders revealed that one responder had an MSI-H tumor, whereas the other responder and the non-responders 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.[778] 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.[781] 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 ORR in cohorts 1 and 2 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 at least one line of systemic therapy for M1 CRPC. The prevalence of MMR deficiency in metastatic CPRC is estimated at 2% to 5%,[43,777] 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.[775] Results from prospective biomarker analysis of the multicohort, non-randomized, open-label, phase 2 KEYNOTE-158 trial support this approval.[782] This trial included 233 evaluable patients with unresectable or metastatic solid tumors, 6 of whom had prostate cancer.[780] The prospective TMB study included patients with anal, biliary, cervical, endometrial, mesothelioma, neuroendocrine, salivary, small-cell lung, thyroid, and vulvar cancer. Objective responses to pembrolizumab were seen in 30 of 102 patients in the TMB-high group (29%; 95% CI, 21%–39%) and 43 of 688 patients in the non–TMB-high group (6%; 95% CI, 5%–8%). Safety was as expected based on other studies of pembrolizumab. Therefore, the Panel includes pembrolizumab as an option for patients with metastatic CRPC, prior docetaxel and/or novel hormone therapy, and TMB >10 mut/Mb.

Mitoxantrone

Two randomized trials assessed the role of mitoxantrone in patients with metastatic CRPC.[783,784] 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 homologous recombination repair (HRR) genes (eg, *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*) may be predictive of the clinical benefit of poly-ADP ribose polymerase (PARP) inhibitors.[785-787] PARP inhibitors are oral agents that exert their activity through the concept of synthetic lethality.[788] At present, two PARP inhibitors are approved by the FDA for use in prostate cancer (see *Olaparib* and see *Rucaparib*, below).[789,790]

DNA repair defects have also been reported to be predictive for sensitivity to platinum agents in CRPC and other cancers.[791-795] Platinum agents have shown some activity in patients with CRPC without molecular selection.[796] Studies of platinum agents in patients with CRPC that have DNA repair gene mutations are needed.

In addition, a recent 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.[51] 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.[797,798]

Patients with *CDK12* mutations tend to have aggressive disease with high rates of metastases and short OS. They also do 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 responded to PD-1 inhibitors (ie, nivolumab, pembrolizumab), some with durable responses.[799,800] 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.[786,787,801] 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 mCRPC and progression on at least one novel hormonal agent (abiraterone or enzalutamide) and up to one prior taxane agent (permitted but not required).[802] Patients had 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.[803]

The Panel notes that there may be heterogeneity of response to olaparib based on which gene has a mutation. For example, patients with *BRCA2* mutations 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).[803] 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.[802]

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 mCRPC 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.[804] *PPP2R2A* was excluded due to preliminary evidence of inferior activity of olaparib in this subset.

Since prior taxane therapy was not mandated in the PROfound study, olaparib use might be reasonable in mCRPC patients both 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.[802]

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*. Patients with *PPP2R2A* mutations in the PROfound trial experienced an unfavorable risk-benefit profile; therefore, olaparib is not recommended in patients with *PPP2R2A* mutations.

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 a second PARP inhibitor approved for use in patients with mCRPC.[790] 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 mCRPC 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.[805] 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).[805] The FDA indication for rucaparib (600 mg twice daily) is for use in patients with mCRPC and deleterious or suspected deleterious germline or somatic *BRCA1* or *BRCA2* mutations, and who had previously received treatment with both a novel hormonal agent (enzalutamide or abiraterone) as well as one taxane-containing chemotherapy. Based on this information, the Panel does not generally recommend the use of rucaparib in *BRCA1/2*-mutated mCRPC patients who have not previously received a taxane agent unless the patient is not fit for chemotherapy. Furthermore, rucaparib should not be used in patients with HRR gene mutations other than *BRCA1/2*.[806] 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.[805,806] Full FDA approval of rucaparib is contingent upon a favorable efficacy and safety profile of this drug in the phase 3 TRITON3 study (NCT02975934), a randomized trial of rucaparib versus physician's choice of therapy (abiraterone, enzalutamide, or docetaxel) in patients with mCRPC and a germline or somatic *BRCA1/2* or *ATM* mutation who have previously received a novel hormonal agent but no chemotherapy for mCRPC. The results of this trial are awaited.

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. If the patient is not fit for chemotherapy, rucaparib can be considered even if taxane-based therapy has not been given.

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.

Small Cell/Neuroendocrine Prostate Cancer

De novo small cell carcinoma in untreated prostate cancers occurs rarely and is very aggressive.[807] Treatment-associated small cell/neuroendocrine prostate cancer that occurs in patients with metastatic CRPC is more common.[808] 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%.[808] 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 who no longer respond to ADT and test positive for metastases. These relatively rare tumors are associated with low PSA levels despite large metastatic burden and visceral disease.[809] Those with initial Grade Group 5 are especially at risk. Biopsy of accessible metastatic lesions should be considered to identify patients with small cell/neuroendocrine histomorphologic features in patients with visceral metastases.[810]

These cases may be managed by cytotoxic chemotherapy (ie, cisplatin/etoposide, carboplatin/etoposide, docetaxel/carboplatin, cabazitaxel/carboplatin).[771,811,812] Physicians should consult the NCCN Guidelines for Small Cell Lung Cancer (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.

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.[813] 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).[814] 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-naïve 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.[815]

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.[816] 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.[817] 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.[818]

Therefore, denosumab every 4 weeks (category 1) 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.[819] 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.[820] 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.[821] 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.[822] 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, and the use of palliative, systemic radiation with either 89Sr or 153Sm (see *Radium-223 and Other Radiopharmaceuticals*, above).

Clinical research continues on the prevention or delay of disease spread to bone. 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.[823] OS was not improved, and the FDA did not approve this indication for denosumab.

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 less 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 all systemic therapies are given a category 2B recommendation.

Sequencing of Therapy in CRPC

No chemotherapy regimen has demonstrated improved survival or QOL after cabazitaxel, although several systemic agents other than

mitoxantrone have shown palliative and radiographic response benefits in clinical trials (ie, carboplatin, cyclophosphamide, doxorubicin, vinorelbine, carboplatin/etoposide, docetaxel/carboplatin, gemcitabine/oxaliplatin, paclitaxel/carboplatin[824-833]). Prednisone or dexamethasone at low doses may provide palliative benefits in the chemotherapy-refractory setting.[834] No survival benefit for combination regimens over sequential single-agent regimens has been demonstrated, and toxicity is higher with combination regimens. Treatment with these agents could be considered after an informed discussion between the physician and an individual patient about treatment goals and risks/side effects and alternatives, which must include best supportive care. Participation in a clinical trial is encouraged.

No randomized trials that compare taxane chemotherapies versus novel hormonal therapies in patients who previously had abiraterone or enzalutamide have been reported, and some data suggest cross-resistance between abiraterone and enzalutamide.[835-838] One molecular biomarker that may aid appropriate selection of therapy after progression on abiraterone or enzalutamide is the presence of AR-V7 in CTCs (See *AR-V7 Testing*, below).[839] 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.[840]

AR-V7 Testing

Cross resistance between novel androgen receptor pathway inhibitors is common with sequential therapy. This lack of response of patients with metastatic CRPC to abiraterone and enzalutamide, particularly after failure of enzalutamide or abiraterone, is associated with detection of AR-V7 mRNA in CTCs using an RNA-based polymerase chain reaction (PCR) assay.[841] AR-V7 presence did not preclude clinical benefit from taxane chemotherapies (docetaxel and cabazitaxel).[842] While other mechanisms of cross-resistance clearly exist, patients with AR-V7–positive CTCs exhibited superior PFS with taxanes compared to novel hormonal therapies (abiraterone and enzalutamide); the two classes of agents resulted in comparable PFS in patients with AR-V7–negative CTCs. A confirmatory study used a different CTC assay that detected nuclear-localized AR-V7 protein using immunofluorescence. Patients with AR-V7–positive CTCs had superior OS with taxanes versus abiraterone or enzalutamide, whereas OS was not different between the two classes of agents among patients with AR-V7–negative CTCs.[843]

A blinded, correlative study at three cancer centers assessed the correlation between AR-V7 results before second-line treatment and OS in patients with metastatic CRPC.[844] Approximately half of the validation cohort received taxane therapy in first line, whereas half received an androgen receptor signaling inhibitor. In a high-risk subset of this cohort, patients negative for AR-V7 had superior OS if they were treated with an androgen receptor signaling inhibitor than if they were treated with a taxane (median OS, 19.8 vs. 12.8 months; HR, 1.67; 95% CI, 1.00–2.81; $P = .05$).

PROPHECY was a prospective multicenter validation study, which enrolled 118 patients with metastatic CRPC who were starting abiraterone or enzalutamide.[845] The primary endpoint was to validate the prognostic significance of baseline AR-V7 in CTCs on radiographic or clinical PFS. Secondary endpoints included OS. Prior exposure to enzalutamide or abiraterone was permitted if the alternative hormonal therapy was planned. After adjusting for CTC number and clinical prognostic factors, the detection of AR-V7 was associated with a shorter PFS (HR, 1.9 [$P = .032$] or 2.4 [$P = .020$], depending on the test used) and OS (HR, 4.2 [95% CI, 2.1–8.5] or 3.5 [95% CI, 1.6–8.1], depending on the test used) regardless of first- or second-line AR inhibitor use. In the updated final analyses, CTC AR-V7 was confirmed to be independently a poor prognostic factor for AR therapy, but was not significantly predictive of the

benefits of docetaxel nor cabazitaxel, where outcomes were similar regardless of AR-V7 status.[846]

These clinical experiences suggest that AR-V7 assays may be a useful predictor of abiraterone and enzalutamide resistance in patients with metastatic CRPC particularly following progression on prior enzalutamide or abiraterone. The prevalence of AR-V7 positivity is only 3% in patients prior to treatment with enzalutamide, abiraterone, and taxanes,[843] so the Panel believes AR-V7 detection would not be useful to inform treatment decisions before these treatments are given. On the other hand, the prevalence of AR-V7 positivity is higher after progression on abiraterone or enzalutamide (19%–39%[841]), but data have already shown that abiraterone/enzalutamide crossover therapy is rarely effective long-term, and taxanes are more effective in this setting. The Panel recommends that use of AR-V7 tests can be considered to help guide selection of therapy in the post-abiraterone/enzalutamide metastatic CRPC setting.

Summary

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

Table 1. Available Tissue-Based Tests for Prostate Cancer 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)	155,158,159,582,847-860	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	861-864	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	157,865,866	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	150-153,867-869	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	870-874	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)[195,875]	68	Generator or Cyclotron (Regional)	Binds extracellular epitope of PSMA	Renal	40% sensitivity and 95% specificity to detect nodal involvement in primary staging of intermediate-, high-, and very-high-risk patients 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)[198,876]	110	Cyclotron (Regional)	Binds extracellular epitope of PSMA	Renal	31%–42% sensitivity and 96%99% specificity to detect nodal involvement in primary staging of unfavorable intermediate-risk, high-risk, and very-high-risk patients 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 for more details)
C-11 choline[877]	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)[878]	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[217]	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 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.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33433946.

2. Herget KA, Patel DP, Hanson HA, et al. Recent decline in prostate cancer incidence in the United States, by age, stage, and Gleason score. Cancer Med 2015;5:136-141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26628287.

3. Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst 2015;107:djv048. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25825511.

4. Negoita S, Feuer EJ, Mariotto A, et al. Annual Report to the Nation on the Status of Cancer, part II: Recent changes in prostate cancer trends and disease characteristics. Cancer 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29786851.

5. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine 2012;157:120-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22801674.

6. Kelly SP, Anderson WF, Rosenberg PS, Cook MB. Past, current, and future incidence rates and burden of metastatic prostate cancer in the United States. Eur Urol Focus 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29162421.

7. Jemal A, Culp MB, Ma J, et al. Prostate Cancer Incidence 5 Years After US Preventive Services Task Force Recommendations Against Screening. J Natl Cancer Inst 2021;113:64-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32432713.

8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28055103.

9. Barocas DA, Mallin K, Graves AJ, et al. Effect of the USPSTF grade D recommendation against screening for prostate cancer on incident prostate cancer diagnoses in the United States. J Urol 2015;194:1587-1593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26087383.

10. Drazer MW, Huo D, Eggener SE. National prostate cancer screening rates after the 2012 US Preventive Services Task Force recommendation discouraging prostate-specific antigen-based screening. J Clin Oncol 2015;33:2416-2423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26056181.

11. Etzioni R, Gulati R. Recent trends in PSA testing and prostate cancer incidence: A look at context. JAMA Oncol 2016;2:955-956. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27010657.

12. Fedewa SA, Ward EM, Brawley O, Jemal A. Recent patterns of prostate-specific antigen testing for prostate cancer screening in the United States. JAMA Intern Med 2017;177:1040-1042. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28437537.

13. Halpern JA, Shoag JE, Artis AS, et al. National trends in prostate biopsy and radical prostatectomy volumes following the US Preventive Services Task Force guidelines against prostate-specific antigen screening. JAMA Surg 2017;152:192-198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27806151.

14. Houston KA, King J, Li J, Jemal A. Trends in prostate cancer incidence rates and prevalence of prostate-specific antigen screening by socioeconomic status and regions in the US, 2004-2013. J Urol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28965781.

15. Kearns JT, Holt SK, Wright JL, et al. PSA screening, prostate biopsy, and treatment of prostate cancer in the years surrounding the USPSTF recommendation against prostate cancer screening. Cancer 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29781117.

16. Jemal A, Fedewa SA, Ma J, et al. Prostate cancer incidence and PSA testing patterns in relation to USPSTF screening recommendations. JAMA 2015;314:2054-2061. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26575061.

17. Maurice MJ, Kim SP, Abouassaly R. Current status of prostate cancer diagnosis and management in the United States. JAMA Oncol 2016;2:1505-1507. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27356204.

18. Sammon JD, Abdollah F, Choueiri TK, et al. Prostate-specific antigen screening after 2012 US Preventive Services Task Force recommendations. JAMA 2015;314:2077-2079. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26575066.

19. Zavaski ME, Meyer CP, Sammon JD, et al. Differences in prostate-specific antigen testing among urologists and primary care physicians following the 2012 USPSTF recommendations. JAMA Intern Med 2016;176:546-547. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26857148.

20. Prostate cancer: Screening. The US Preventive Services Task Force (USPSTF); 2018. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/prostate-cancer-screening. Accessed November 14, 2021.

21. PubMed Overview. National Institutes of Health; Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed November 14, 2021.

22. Amin MB, Greene FL, Edge S, et al., eds. AJCC Cancer Staging Manual (ed 8th Edition). New York: Springer; 2017.

23. Protocol for the Examination of Radical Prostatectomy Specimens From Patients With Carcinoma of the Prostate Gland. College of American Pathologists; 2020. Available at: https://documents.cap.org/protocols/cp-malegenital-prostate-radicalprostatectomy-20-4101.pdf. Accessed November 14, 2021.

24. Social Security Administration. Period Life Table. 2017. Available at: https://www.ssa.gov/OACT/STATS/table4c6.html. Accessed November 14, 2021.

25. Life Tables By Country. World Health Organization; Available at: http://apps.who.int/gho/data/view.main.60000?lang=en. Accessed November 14, 2021.

26. Male Life Expectancy Survey. Memorial Sloan Kettering Cancer Center; Available at: https://webcore.mskcc.org/survey/surveyform.aspx?preview=true&excelsurveylistid=4. Accessed November 14, 2021.

27. Howard DH. Life expectancy and the value of early detection. J Health Econ 2005;24:891-906. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16129128.

28. Albright F, Stephenson RA, Agarwal N, et al. Prostate cancer risk prediction based on complete prostate cancer family history. Prostate 2015;75:390-398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25408531.

29. Bratt O, Drevin L, Akre O, et al. Family history and probability of postate cancer, differentiated by risk category: a nationwide population-based study. J Natl Cancer Inst 2016;108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27400876.

30. Jansson F, Drevin L, Frisell T, et al. Concordance of non-low-risk disease among pairs of brothers with prostate cancer. J Clin Oncol 2018:JCO2017766907. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29652556.

31. Beebe-Dimmer JL, Kapron AL, Fraser AM, et al. Risk of prostate cancer associated with familial and hereditary cancer syndromes. J Clin Oncol 2020;38:1807-1813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32208047.

32. Latham A, Srinivasan P, Kemel Y, et al. Microsatellite instability is associated with the presence of Lynch syndrome pan-cancer. J Clin Oncol

2018:JCO1800283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30376427.

33. Haraldsdottir S, Hampel H, Wei L, et al. Prostate cancer incidence in males with Lynch syndrome. Genet Med 2014;16:553-557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24434690.

34. Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:437-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24425144.

35. Moran A, O'Hara C, Khan S, et al. Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Fam Cancer 2012;11:235-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22187320.

36. Mersch J, Jackson MA, Park M, et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer 2015;121:269-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25224030.

37. Pilie PG, Johnson AM, Hanson KL, et al. Germline genetic variants in men with prostate cancer and one or more additional cancers. Cancer 2017;123:3925-3932. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28657667.

38. Cheng HH, Sokolova AO, Schaeffer EM, et al. Germline and somatic mutations in prostate cancer for the clinician. J Natl Compr Canc Netw 2019;17:515-521. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31085765.

39. Giri VN, Knudsen KE, Kelly WK, et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 2020;38:2798-2811. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32516092.

40. Castro E, Goh C, Leongamornlert D, et al. Effect of BRCA mutations on metastatic relapse and cause-specific survival after radical treatment for localised prostate cancer. Eur Urol 2015;68:186-193. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25454609.

41. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748-1757. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23569316.

42. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 2016;71:740-747. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27989354.

43. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215-1228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26000489.

44. Cancer Genome Atlas Research N. The molecular taxonomy of primary prostate cancer. Cell 2015;163:1011-1025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26544944.

45. Carter HB, Helfand B, Mamawala M, et al. Germline mutations in ATM and BRCA1/2 are associated with grade reclassification in men on active surveillance for prostate cancer. Eur Urol 2019;75:743-749. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30309687.

46. Wu Y, Yu H, Li S, et al. Rare germline pathogenic mutations of DNA repair genes are most strongly associated with grade group 5 prostate cancer. Eur Urol Oncol 2020;3:224-230. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31948886.

47. Giri VN, Obeid E, Gross L, et al. Inherited mutations in men undergoing multigene panel testing for prostate cancer: Emerging implications for personalized prostate cancer genetic evaluation. JCO Precision Oncol 2017;published online May 4, 2017. Available at: http://ascopubs.org/doi/full/10.1200/PO.16.00039.

48. Yadav S, Hart SN, Hu C, et al. Contribution of inherited DNA-repair gene mutations to hormone-sensitive and castrate-resistant metastatic

prostate cancer and implications for clinical outcome. JCO Precis Oncol 2019;3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32923857.

49. Boyle JL, Hahn AW, Kapron AL, et al. Pathogenic germline DNA repair gene and HOXB13 mutations in men with metastatic prostate cancer. JCO Precis Oncol 2020;4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32923906.

50. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443-453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27433846.

51. Castro E, Romero-Laorden N, Del Pozo A, et al. PROREPAIR-B: A prospective cohort study of the impact of germline DNA repair mutations on the outcomes of patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2019;37:490-503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30625039.

52. Giri VN, Hegarty SE, Hyatt C, et al. Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing. Prostate 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30450585.

53. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30730552.

54. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336:1401-1408. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9145676.

55. Kirchhoff T, Kauff ND, Mitra N, et al. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clin Cancer Res 2004;10:2918-2921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15131025.

56. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. J Natl Cancer Inst 1999;91:1310-1316. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10433620.

57. Agalliu I, Gern R, Leanza S, Burk RD. Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. Clin Cancer Res 2009;15:1112-1120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188187.

58. Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 1994;343:692-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7907678.

59. Gallagher DJ, Gaudet MM, Pal P, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 2010;16:2115-2121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20215531.

60. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer 2012;106:1697-1701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22516946.

61. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol 2004;22:735-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14966099.

62. Thompson D, Easton DF. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002;94:1358-1365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12237281.

63. Tulinius H, Olafsdottir GH, Sigvaldason H, et al. The effect of a single BRCA2 mutation on cancer in Iceland. J Med Genet 2002;39:457-462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12114473.

64. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med

Genet 2005;42:711-719. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16141007.

65. Lecarpentier J, Silvestri V, Kuchenbaecker KB, et al. Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. J Clin Oncol 2017;35:2240-2250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28448241.

66. Page EC, Bancroft EK, Brook MN, et al. Interim results from the IMPACT study: Evidence for prostate-specific antigen screening in BRCA2 mutation carriers. Eur Urol 2019;76:831-842. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31537406.

67. Mano R, Tamir S, Kedar I, et al. Malignant abnormalities in male BRCA mutation carriers: Results from a prospectively screened cohort. JAMA Oncol 2018;4:872-874. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29710070.

68. Helgason H, Rafnar T, Olafsdottir HS, et al. Loss-of-function variants in ATM confer risk of gastric cancer. Nat Genet 2015;47:906-910. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26098866.

69. Erkko H, Xia B, Nikkila J, et al. A recurrent mutation in PALB2 in Finnish cancer families. Nature 2007;446:316-319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17287723.

70. Naslund-Koch C, Nordestgaard BG, Bojesen SE. Increased risk for other cancers in addition to breast cancer for CHEK2*1100delC heterozygotes estimated from the Copenhagen General Population Study. J Clin Oncol 2016;34:1208-1216. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26884562.

71. Wu Y, Yu H, Zheng SL, et al. A comprehensive evaluation of CHEK2 germline mutations in men with prostate cancer. Prostate 2018;78:607-615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29520813.

72. Mitra A, Fisher C, Foster CS, et al. Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. Br J Cancer 2008;98:502-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182994.

73. Narod SA, Neuhausen S, Vichodez G, et al. Rapid progression of prostate cancer in men with a BRCA2 mutation. Br J Cancer 2008;99:371-374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18577985.

74. Thorne H, Willems AJ, Niedermayr E, et al. Decreased prostate cancer-specific survival of men with BRCA2 mutations from multiple breast cancer families. Cancer Prev Res (Phila) 2011;4:1002-1010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21733824.

75. Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst 2007;99:929-935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17565157.

76. Wei Y, Wu J, Gu W, et al. Prognostic value of germline DNA repair gene mutations in de novo metastatic and castration-sensitive prostate cancer. Oncologist 2020;25:e1042-e1050. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32190957.

77. Dominguez-Valentin M, Sampson JR, Seppala TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med 2020;22:15-25. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31337882.

78. Moller P, Seppala TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut 2018;67:1306-1316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28754778.

79. Abida W, Cheng ML, Armenia J, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30589920.

80. Zhou M. High-grade prostatic intraepithelial neoplasia, PIN-like carcinoma, ductal carcinoma, and intraductal carcinoma of the prostate. Mod Pathol 2018;31:S71-79. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29297491.

81. Porter LH, Lawrence MG, Ilic D, et al. Systematic review links the prevalence of intraductal carcinoma of the prostate to prostate cancer risk categories. Eur Urol 2017;72:492-495. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28342640.

82. Chua MLK, Lo W, Pintilie M, et al. A prostate cancer "nimbosus": Genomic instability and SChLAP1 dysregulation underpin aggression of intraductal and cribriform subpathologies. Eur Urol 2017;72:665-674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28511883.

83. Seipel AH, Whitington T, Delahunt B, et al. Genetic profile of ductal adenocarcinoma of the prostate. Hum Pathol 2017;69:1-7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28457729.

84. Bottcher R, Kweldam CF, Livingstone J, et al. Cribriform and intraductal prostate cancer are associated with increased genomic instability and distinct genomic alterations. BMC Cancer 2018;18:8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29295717.

85. Schweizer MT, Antonarakis ES, Bismar TA, et al. Genomic characterization of prostatic ductal adenocarcinoma identifies a high prevalence of DNA repair gene mutations. JCO Precis Oncol 2019;3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31123724.

86. Antonarakis ES, Shaukat F, Isaacsson Velho P, et al. Clinical features and therapeutic outcomes in men with advanced prostate cancer and DNA mismatch repair gene mutations. Eur Urol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30337059.

87. Antonarakis ES, Shaukat F, Isaacsson Velho P, et al. Clinical features and therapeutic outcomes in men with advanced prostate cancer and DNA mismatch repair gene mutations. Eur Urol 2019;75:378-382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30337059.

88. Isaacsson Velho P, Silberstein JL, Markowski MC, et al. Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer. Prostate 2018;78:401-407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29368341.

89. Taylor RA, Fraser M, Livingstone J, et al. Germline BRCA2 mutations drive prostate cancers with distinct evolutionary trajectories. Nat Commun 2017;8:13671. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28067867.

90. Risbridger GP, Taylor RA, Clouston D, et al. Patient-derived xenografts reveal that intraductal carcinoma of the prostate is a prominent pathology in BRCA2 mutation carriers with prostate cancer and correlates with poor prognosis. Eur Urol 2015;67:496-503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25154392.

91. Ewing CM, Ray AM, Lange EM, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med 2012;366:141-149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22236224.

92. Kote-Jarai Z, Mikropoulos C, Leongamornlert DA, et al. Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. Ann Oncol 2015;26:756-761. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25595936.

93. Jensen K, Konnick EQ, Schweizer MT, et al. Association of Clonal Hematopoiesis in DNA Repair Genes With Prostate Cancer Plasma Cell-free DNA Testing Interference. JAMA Oncol 2021;7:107-110. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33151258.

94. Middha S, Zhang L, Nafa K, et al. Reliable pan-cancer microsatellite instability assessment by using targeted next-generation sequencing data. JCO Precis Oncol 2017;2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30211344.

95. Guedes LB, Antonarakis ES, Schweizer MT, et al. MSH2 loss in primary prostate cancer. Clin Cancer Res 2017;23:6863-6874. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28790115.

96. Hempelmann JA, Lockwood CM, Konnick EQ, et al. Microsatellite instability in prostate cancer by PCR or next-generation sequencing. J Immunother Cancer 2018;6:29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29665853.

97. Dess RT, Suresh K, Zelefsky MJ, et al. Development and validation of a clinical prognostic stage group system for nonmetastatic prostate cancer using disease-specific mortality results from the international staging collaboration for cancer of the prostate. JAMA Oncol 2020;6:1912-1920. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33090219.

98. Zelic R, Garmo H, Zugna D, et al. Predicting prostate cancer death with different pretreatment risk stratification tools: A head-to-head comparison in a nationwide cohort study. Eur Urol 2020;77:180-188. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31606332.

99. D'Amico AV, Whittington R, Malkowicz SB, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. J Clin Oncol 1999;17:168-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10458230.

100. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localized prostate carcinoma in the prostate specific antigen era. Cancer 2002;95:281-286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12124827.

101. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969-974. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9749478.

102. Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol 2016;40:244-252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26492179.

103. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. Eur Urol 2016;69:428-435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26166626.

104. Loeb S, Folkvaljon Y, Robinson D, et al. Evaluation of the 2015 Gleason grade groups in a nationwide population-based cohort. Eur Urol 2016;69:1135-1141. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26707871.

105. Ham WS, Chalfin HJ, Feng Z, et al. New prostate cancer grading system predicts long-term survival following surgery for Gleason score 8-10 prostate cancer. Eur Urol 2016;71:907-912. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27876305.

106. Delahunt B, Egevad L, Srigley JR, et al. Validation of International Society of Urological Pathology (ISUP) grading for prostatic adenocarcinoma in thin core biopsies using TROG 03.04 'RADAR' trial clinical data. Pathology 2015;47:520-525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26325671.

107. Mathieu R, Moschini M, Beyer B, et al. Prognostic value of the new grade groups in prostate cancer: a multi-institutional European validation study. Prostate Cancer Prostatic Dis 2017;20:197-202. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28071673.

108. Leapman MS, Cowan JE, Simko J, et al. Application of a prognostic Gleason grade grouping system to assess distant prostate cancer outcomes. Eur Urol 2016;71:750-759. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27940155.

109. He J, Albertsen PC, Moore D, et al. Validation of a contemporary five-tiered Gleason grade grouping using population-based data. Eur Urol

2017;71:760-763. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27939073.

110. Pompe RS, Davis-Bondarenko H, Zaffuto E, et al. Population-based validation of the 2014 ISUP Gleason grade groups in patients treated with radical prostatectomy, brachytherapy, external beam radiation, or no local treatment. Prostate 2017;77:686-693. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28156003.

111. Kirmiz S, Qi J, Babitz SK, et al. Grade Groups provide improved predictions of pathological and early oncologic outcomes compared with Gleason score risk groups. J Urol 2019;201:278-283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30195846.

112. Reese AC, Pierorazio PM, Han M, Partin AW. Contemporary evaluation of the National Comprehensive Cancer Network prostate cancer risk classification system. Urology 2012;80:1075-1079. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22995570.

113. Muralidhar V, Chen MH, Reznor G, et al. Definition and validation of "favorable high-risk prostate cancer": implications for personalizing treatment of radiation-managed patients. Int J Radiat Oncol Biol Phys 2015;93:828-835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26530751.

114. Gandaglia G, Karnes RJ, Sivaraman A, et al. Are all grade group 4 prostate cancers created equal? Implications for the applicability of the novel grade grouping. Urol Oncol 2017;35:461 e467-461 e414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28359746.

115. Dinh KT, Muralidhar V, Mahal BA, et al. Occult high-risk disease in clinically low-risk prostate cancer with >/=50% positive biopsy cores: should national guidelines stop calling them low-risk? Urology 2015;87:125-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26391387.

116. Dinh KT, Mahal BA, Ziehr DR, et al. Incidence and predictors of upgrading and up staging among 10,000 contemporary patients with low risk prostate cancer. J Urol 2015;194:343-349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25681290.

117. Zumsteg ZS, Spratt DE, Pei I, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. Eur Urol 2013;64:895-902. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23541457.

118. Johns Hopkins Medicine. The Partin Tables. Available at: https://www.hopkinsmedicine.org/brady-urology-institute/specialties/conditions-and-treatments/prostate-cancer/fighting-prostate-cancer/partin-table.html. Accessed November 14, 2021.

119. Makarov DV, Trock BJ, Humphreys EB, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. Urology 2007;69:1095-1101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17572194.

120. Borque A, Rubio-Briones J, Esteban LM, et al. Implementing the use of nomograms by choosing threshold points in predictive models: 2012 updated Partin Tables vs a European predictive nomogram for organ-confined disease in prostate cancer. BJU Int 2014;113:878-886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24529282.

121. Tosoian JJ, Chappidi M, Feng Z, et al. Prediction of pathological stage based on clinical stage, serum prostate-specific antigen, and biopsy Gleason score: Partin Tables in the contemporary era. BJU Int 2017;119:676-683. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27367645.

122. Kattan MW, Eastham JA, Wheeler TM, et al. Counseling men with prostate cancer: a nomogram for predicting the presence of small, moderately differentiated, confined tumors. J Urol 2003;170:1792-1797. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14532778.

123. Leyh-Bannurah SR, Dell'Oglio P, Tian Z, et al. A proposal of a new nomogram for predicting upstaging in contemporary D'Amico low-risk

prostate cancer patients. World J Urol 2017;35:189-197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27289238.

124. Wong LM, Neal DE, Finelli A, et al. Evaluation of models predicting insignificant prostate cancer to select men for active surveillance of prostate cancer. Prostate Cancer Prostatic Dis 2015;18:137-143. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25667108.

125. Memorial Sloan-Kettering Cancer Center. Prostate Cancer Nomograms. Available at: http://www.mskcc.org/mskcc/html/10088.cfm. Accessed November 14, 2021.

126. Punnen S, Freedland SJ, Presti JC, Jr., et al. Multi-institutional validation of the CAPRA-S score to predict disease recurrence and mortality after radical prostatectomy. Eur Urol 2014;65:1171-1177. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23587869.

127. Stephenson AJ, Scardino PT, Eastham JA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 2006;98:715-717. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16705126.

128. Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol 2009;27:4300-4305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19636023.

129. Graefen M, Haese A, Pichlmeier U, et al. A validated strategy for side specific prediction of organ confined prostate cancer: a tool to select for nerve sparing radical prostatectomy. J Urol 2001;165:857-863. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11176486.

130. Ohori M, Kattan MW, Koh H, et al. Predicting the presence and side of extracapsular extension: a nomogram for staging prostate cancer. J Urol 2004;171:1844-1849; discussion 1849. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15076291.

131. Steuber T, Graefen M, Haese A, et al. Validation of a nomogram for prediction of side specific extracapsular extension at radical prostatectomy. J Urol 2006;175:939-944; discussion 944. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16469587.

132. Briganti A, Chun FK, Salonia A, et al. A nomogram for staging of exclusive nonobturator lymph node metastases in men with localized prostate cancer. Eur Urol 2007;51:112-119; discussion 119-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16806662.

133. Cagiannos I, Karakiewicz P, Eastham JA, et al. A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol 2003;170:1798-1803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14532779.

134. Gandaglia G, Fossati N, Zaffuto E, et al. Development and internal validation of a novel model to identify the candidates for extended pelvic lymph node dissection in prostate cancer. Eur Urol 2017;72:632-640. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28412062.

135. Gandaglia G, Ploussard G, Valerio M, et al. A novel nomogram to identify candidates for extended pelvic lymph node dissection among patients with clinically localized prostate cancer diagnosed with magnetic resonance imaging-targeted and systematic biopsies. Eur Urol 2019;75:506-514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30342844.

136. Kattan MW, Potters L, Blasko JC, et al. Pretreatment nomogram for predicting freedom from recurrence after permanent prostate brachytherapy in prostate cancer. Urology 2001;58:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11549487.

137. Potters L, Morgenstern C, Calugaru E, et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. J Urol 2008;179:S20-24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18405743.

138. Potters L, Roach M, 3rd, Davis BJ, et al. Postoperative nomogram predicting the 9-year probability of prostate cancer recurrence after permanent prostate brachytherapy using radiation dose as a prognostic

variable. Int J Radiat Oncol Biol Phys 2010;76:1061-1065. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19540064.

139. Zelefsky MJ, Kattan MW, Fearn P, et al. Pretreatment nomogram predicting ten-year biochemical outcome of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for prostate cancer. Urology 2007;70:283-287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17826490.

140. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006;295:801-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16478903.

141. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. J Clin Oncol 1999;17:1499-1507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10334537.

142. Ondracek RP, Kattan MW, Murekeyisoni C, et al. Validation of the Kattan nomogram for prostate cancer recurrence after radical prostatectomy. J Natl Compr Canc Netw 2016;14:1395-1401. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27799510.

143. Tendulkar RD, Agrawal S, Gao T, et al. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. J Clin Oncol 2016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27528718.

144. Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet 1999;353:267-272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9929018.

145. Khoo VS. Radiotherapeutic techniques for prostate cancer, dose escalation and brachytherapy. Clin Oncol (R Coll Radiol) 2005;17:560-571. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16238144.

146. D'Amico AV, Cote K, Loffredo M, et al. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. J Clin Oncol 2002;20:4567-4573. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12454114.

147. Dell'Oglio P, Suardi N, Boorjian SA, et al. Predicting survival of men with recurrent prostate cancer after radical prostatectomy. Eur J Cancer 2016;54:27-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26707594.

148. Abdollah F, Karnes RJ, Suardi N, et al. Predicting survival of patients with node-positive prostate cancer following multimodal treatment. Eur Urol 2014;65:554-562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24094576.

149. D'Amico AV, Moul JW, Carroll PR, et al. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. J Natl Cancer Inst 2003;95:1376-1383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13130113.

150. Bishoff JT, Freedland SJ, Gerber L, et al. Prognostic utility of the cell cycle progression score generated from biopsy in men treated with prostatectomy. J Urol 2014;192:409-414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24508632.

151. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol 2011;12:245-255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21310658.

152. Cuzick J, Berney DM, Fisher G, et al. Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort. Br J Cancer 2012;106:1095-1099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22361632.

153. Freedland SJ, Gerber L, Reid J, et al. Prognostic utility of cell cycle progression score in men with prostate cancer after primary external beam radiation therapy. Int J Radiat Oncol Biol Phys 2013;86:848-853. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23755923.

154. Klein EA, Cooperberg MR, Carroll PR. Reply to Yuri Tolkach, Markus Kuczyk, Florian Imkamp's Letter to the Editor re: Eric A. Klein, Matthew R. Cooperberg, Cristina Magi-Galluzzi, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol 2014;66:550-60. Eur Urol 2014;66:e117-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25150174.

155. Zhao SG, Chang SL, Spratt DE, et al. Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. Lancet Oncol 2016;17:1612-1620. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27743920.

156. Sinnott JA, Peisch SF, Tyekucheva S, et al. Prognostic utility of a new mRNA expression signature of Gleason score. Clin Cancer Res 2017;23:81-87. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27663590.

157. Van Den Eeden SK, Lu R, Zhang N, et al. A biopsy-based 17-gene genomic prostate score as a predictor of metastases and prostate cancer death in surgically treated men with clinically localized disease. Eur Urol 2018;73:129-138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28988753.

158. Kim HL, Li P, Huang HC, et al. Validation of the Decipher Test for predicting adverse pathology in candidates for prostate cancer active surveillance. Prostate Cancer Prostatic Dis 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30542054.

159. Spratt DE, Zhang J, Santiago-Jimenez M, et al. Development and validation of a novel integrated clinical-genomic risk group classification for localized prostate cancer. J Clin Oncol 2018;36:581-590. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29185869.

160. Berlin A, Murgic J, Hosni A, et al. Genomic classifier for guiding treatment of intermediate-risk prostate cancers to dose-escalated image guided radiation therapy without hormone therapy. Int J Radiat Oncol Biol Phys 2019;103:84-91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30170099.

161. Kornberg Z, Cooperberg MR, Cowan JE, et al. A 17-gene genomic prostate score as a predictor of adverse pathology in men on active surveillance. J Urol 2019;202:702-709. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31026214.

162. Herlemann A, Huang HC, Alam R, et al. Decipher identifies men with otherwise clinically favorable-intermediate risk disease who may not be good candidates for active surveillance. Prostate Cancer Prostatic Dis 2020;23:136-143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31455846.

163. Lin DW, Zheng Y, McKenney JK, et al. 17-gene genomic prostate score test results in the canary prostate active surveillance study (PASS) cohort. Journal of Clinical Oncology 2020;38:1549-1557. Available at:

164. Hu JC, Tosoian JJ, Qi J, et al. Clinical utility of gene expression classifiers in men with newly diagnosed prostate cancer JCO Precis Oncol 2018;published online, October 19, 2018 Available at: http://ascopubs.org/doi/abs/10.1200/PO.18.00163.

165. Marascio J, Spratt DE, Zhang J, et al. Prospective study to define the clinical utility and benefit of Decipher testing in men following prostatectomy. Prostate Cancer Prostatic Dis 2020;23:295-302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31719663.

166. Vince RA, Jr., Jiang R, Qi J, et al. Impact of Decipher Biopsy testing on clinical outcomes in localized prostate cancer in a prospective statewide collaborative. Prostate Cancer Prostatic Dis 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34285350.

167. Merdan S, Womble PR, Miller DC, et al. Toward better use of bone scans among men with early-stage prostate cancer. Urology 2014;84:793-798. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25096341.

168. Risko R, Merdan S, Womble PR, et al. Clinical predictors and recommendations for staging computed tomography scan among men with prostate cancer. Urology 2014;84:1329-1334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25288575.

169. Mason BR, Eastham JA, Davis BJ, et al. Current status of MRI and PET in the NCCN Guidelines for Prostate Cancer. J Natl Compr Canc Netw 2019;17:506-513. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31085758.

170. Schoots IG, Barentsz JO, Bittencourt LK, et al. PI-RADS Committee position on MRI without contrast medium in biopsy-naive men with suspected prostate cancer: Narrative review. AJR Am J Roentgenol 2021;216:3-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32812795.

171. de Rooij M, Hamoen EH, Witjes JA, et al. Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. Eur Urol 2016;70:233-245. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26215604.

172. Turkbey B, Mani H, Shah V, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. J Urol 2011;186:1818-1824. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21944089.

173. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol 2013;64:713-719. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23787357.

174. Rastinehad AR, Turkbey B, Salami SS, et al. Improving detection of clinically significant prostate cancer: magnetic resonance imaging/transrectal ultrasound fusion guided prostate biopsy. J Urol 2013;191:1749-1754. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24333515.

175. Wysock JS, Rosenkrantz AB, Huang WC, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. Eur Urol 2014;66:343-351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24262102.

176. Ahdoot M, Wilbur AR, Reese SE, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. N Engl J Med 2020;382:917-928. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32130814.

177. Somford DM, Hamoen EH, Futterer JJ, et al. The predictive value of endorectal 3 Tesla multiparametric magnetic resonance imaging for extraprostatic extension in patients with low, intermediate and high risk prostate cancer. J Urol 2013;190:1728-1734. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23680307.

178. Park BH, Jeon HG, Jeong BC, et al. Influence of magnetic resonance imaging in the decision to preserve or resect neurovascular bundles at robotic assisted laparoscopic radical prostatectomy. J Urol 2014;192:82-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24440235.

179. Pasoglou V, Larbi A, Collette L, et al. One-step TNM staging of high-risk prostate cancer using magnetic resonance imaging (MRI): toward an upfront simplified "all-in-one" imaging approach? Prostate 2014;74:469-477. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24375774.

180. Heck MM, Souvatzoglou M, Retz M, et al. Prospective comparison of computed tomography, diffusion-weighted magnetic resonance imaging and [11C]choline positron emission tomography/computed tomography for preoperative lymph node staging in prostate cancer patients. Eur J Nucl Med Mol Imaging 2014;41:694-701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24297503.

181. Lecouvet FE, El Mouedden J, Collette L, et al. Can whole-body magnetic resonance imaging with diffusion-weighted imaging replace Tc 99m bone scanning and computed tomography for single-step detection of metastases in patients with high-risk prostate cancer? Eur Urol 2012;62:68-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22366187.

182. Jadvar H, Desai B, Ji L, et al. Prospective evaluation of 18F-NaF and 18F-FDG PET/CT in detection of occult metastatic disease in biochemical recurrence of prostate cancer. Clin Nucl Med 2012;37:637-643. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22691503.

183. Richter JA, Rodriguez M, Rioja J, et al. Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment. Mol Imaging Biol 2010;12:210-217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19543774.

184. Schoder H, Herrmann K, Gonen M, et al. 2-[18F]fluoro-2-deoxyglucose positron emission tomography for the detection of disease in patients with prostate-specific antigen relapse after radical prostatectomy. Clin Cancer Res 2005;11:4761-4769. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16000572.

185. Rosar F, Dewes S, Ries M, et al. New insights in the paradigm of upregulation of tumoral PSMA expression by androgen receptor blockade: Enzalutamide induces PSMA upregulation in castration-resistant prostate cancer even in patients having previously progressed on enzalutamide. Eur J Nucl Med Mol Imaging 2020;47:687-694. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31901103.

186. Staniszewska M, Fragoso Costa P, Eiber M, et al. Enzalutamide enhances PSMA expression of PSMA-low prostate cancer. Int J Mol Sci 2021;22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34299051.

187. Emmett L, Yin C, Crumbaker M, et al. Rapid modulation of PSMA expression by androgen deprivation: serial (68)Ga-PSMA-11 PET in men with hormone-sensitive and castrate-resistant prostate cancer commencing androgen blockade. J Nucl Med 2019;60:950-954. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30552200.

188. Calais J, Ceci F, Eiber M, et al. (18)F-fluciclovine PET-CT and (68)Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 2019;20:1286-1294. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31375469.

189. Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015;42:197-209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25411132.

190. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid (68)Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med 2015;56:668-674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25791990.

191. Hoffmann MA, Buchholz HG, Wieler HJ, et al. PSA and PSA kinetics thresholds for the presence of (68)Ga-PSMA-11 PET/CT-detectable lesions in patients with biochemical recurrent prostate cancer. Cancers (Basel) 2020;12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32046318.

192. Dietlein F, Kobe C, Neubauer S, et al. PSA-stratified performance of (18)F- and (68)Ga-PSMA PET in patients with biochemical recurrence of prostate cancer. J Nucl Med 2017;58:947-952. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27908968.

193. Tan N, Oyoyo U, Bavadian N, et al. PSMA-targeted radiotracers versus (18)FfFluciclovine for the detection of prostate cancer biochemical recurrence after definitive therapy: A systematic review and meta-analysis. Radiology 2020;296:44-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32396045.

194. Hope TA, Eiber M, Armstrong WR, et al. Diagnostic accuracy of 68Ga-PSMA-11 PET for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection: A multicenter prospective phase 3 imaging trial. JAMA Oncol 2021;7:1635-1642. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34529005.

195. Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: A prospective single-arm clinical trial. JAMA Oncol 2019;5:856-863. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30920593.

196. Pienta KJ, Gorin MA, Rowe SP, et al. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with (18)F-DCFPyL in prostate cancer patients (OSPREY). J Urol 2021;206:52-61. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33634707.

197. Jansen BHE, Bodar YJL, Zwezerijnen GJC, et al. Pelvic lymph-node staging with (18)F-DCFPyL PET/CT prior to extended pelvic lymph-node dissection in primary prostate cancer - the SALT trial. Eur J Nucl Med Mol Imaging 2021;48:509-520. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32789599.

198. Morris MJ, Rowe SP, Gorin MA, et al. Diagnostic Performance of (18)F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study. Clin Cancer Res 2021;27:3674-3682. Available at:

199. Fuccio C, Castellucci P, Schiavina R, et al. Role of 11C-choline PET/CT in the re-staging of prostate cancer patients with biochemical relapse and negative results at bone scintigraphy. Eur J Radiol 2012;81:e893-896. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22621862.

200. Nanni C, Schiavina R, Brunocilla E, et al. 18F-fluciclovine PET/CT for the detection of prostate cancer relapse: a comparison to 11C-choline PET/CT. Clin Nucl Med 2015;40:e386-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26053708.

201. Evangelista L, Zattoni F, Guttilla A, et al. Choline PET or PET/CT and biochemical relapse of prostate cancer: a systematic review and meta-analysis. Clin Nucl Med 2013;38:305-314. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23486334.

202. Fanti S, Minozzi S, Castellucci P, et al. PET/CT with C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data. Eur J Nucl Med Mol Imaging 2015;43:55-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26450693.

203. Fanti S, Minozzi S, Castellucci P, et al. PET/CT with (11)C-choline for evaluation of prostate cancer patients with biochemical recurrence: meta-analysis and critical review of available data. Eur J Nucl Med Mol Imaging 2016;43:55-69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26450693.

204. Giovacchini G, Picchio M, Coradeschi E, et al. Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy. Eur J Nucl Med Mol Imaging 2010;37:301-309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19756592.

205. Kitajima K, Murphy RC, Nathan MA, et al. Detection of recurrent prostate cancer after radical prostatectomy: comparison of 11C-choline PET/CT with pelvic multiparametric MR imaging with endorectal coil. J Nucl Med 2014;55:223-232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24434294.

206. Mitchell CR, Lowe VJ, Rangel LJ, et al. Operational characteristics of (11)c-choline positron emission tomography/computerized tomography for prostate cancer with biochemical recurrence after initial treatment. J Urol 2013;189:1308-1313. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23123372.

207. Nanni C, Zanoni L, Pultrone C, et al. (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging 2016;43:1601-1610. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26960562.

208. Reske SN, Blumstein NM, Glatting G. [11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. Eur J Nucl Med Mol Imaging 2008;35:9-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17828534.

209. Scattoni V, Picchio M, Suardi N, et al. Detection of lymph-node metastases with integrated [11C]choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. Eur Urol 2007;52:423-429. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17397992.

210. Umbehr MH, Muntener M, Hany T, et al. The role of 11C-choline and 18F-fluorocholine positron emission tomography (PET) and PET/CT in prostate cancer: a systematic review and meta-analysis. Eur Urol 2013;64:106-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23628493.

211. Odewole OA, Tade FI, Nieh PT, et al. Recurrent prostate cancer detection with anti-3-[(18)F]FACBC PET/CT: comparison with CT. Eur J Nucl Med Mol Imaging 2016;43:1773-1783. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27091135.

212. Schuster DM, Nieh PT, Jani AB, et al. Anti-3-[(18)F]FACBC positron emission tomography-computerized tomography and (111)In-capromab pendetide single photon emission computerized tomography-computerized tomography for recurrent prostate carcinoma: results of a prospective clinical trial. J Urol 2014;191:1446-1453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24144687.

213. Scarsbrook AF, Bottomley D, Teoh EJ, et al. Effect of (18)F-fluciclovine positron emission tomography on the management of patients with recurrence of prostate cancer: Results from the FALCON trial. Int J Radiat Oncol Biol Phys 2020;107:316-324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32068113.

214. Andriole GL, Kostakoglu L, Chau A, et al. The impact of positron emission tomography with (18)F-fluciclovine on the management of patients with biochemical recurrence of prostate cancer: Results from the LOCATE trial. J Urol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30179618.

215. Wu SY, Boreta L, Shinohara K, et al. Impact of staging (68)Ga-PSMA-11 PET scans on radiation treatment plans in patients with prostate cancer. Urology 2019;125:154-162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30580002.

216. Fendler WP, Ferdinandus J, Czernin J, et al. Impact of (68)Ga-PSMA-11 PET on the management of recurrent prostate cancer in a prospective single-arm clinical trial. J Nucl Med 2020;61:1793-1799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32358094.

217. Zacho HD, Fonager RF, Nielsen JB, et al. Observer agreement and accuracy of (18)F-sodium fluoride PET/CT in the diagnosis of bone metastases in prostate cancer. J Nucl Med 2020;61:344-349. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31481577.

218. Rowe SP, Li X, Trock BJ, et al. Prospective comparison of PET imaging with PSMA-targeted (18)F-DCFPyL versus Na(18)F for bone lesion detection in patients with metastatic prostate cancer. J Nucl Med 2020;61:183-188. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31451492.

219. Even-Sapir E, Metser U, Mishani E, et al. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. J Nucl Med 2006;47:287-297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16455635.

220. Langsteger W, Balogova S, Huchet V, et al. Fluorocholine (18F) and sodium fluoride (18F) PET/CT in the detection of prostate cancer: prospective comparison of diagnostic performance determined by masked reading. Q J Nucl Med Mol Imaging 2011;55:448-457. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21738117.

221. Rohren EM, Etchebehere EC, Araujo JC, et al. Determination of skeletal tumor burden on 18F-fluoride PET/CT. J Nucl Med 2015;56:1507-1512. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26135112.

222. Wondergem M, van der Zant FM, van der Ploeg T, Knol RJ. A literature review of 18F-fluoride PET/CT and 18F-choline or 11C-choline PET/CT for detection of bone metastases in patients with prostate cancer. Nucl Med Commun 2013;34:935-945. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23903557.

223. Rowe SP, Pienta KJ, Pomper MG, Gorin MA. PSMA-RADS version 1.0: A step towards standardizing the interpretation and reporting of PSMA-targeted PET imaging studies. Eur Urol 2018;73:485-487. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29132714.

224. Toriihara A, Nobashi T, Baratto L, et al. Comparison of 3 interpretation criteria for (68)Ga-PSMA11 PET based on inter- and intrareader agreement. J Nucl Med 2020;61:533-539. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31562226.

225. Walsh L, Shore R, Auvinen A, et al. Risks from CT scans--what do recent studies tell us? J Radiol Prot 2014;34:E1-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24594968.

226. American College of Radiology. ACR Manual on Contrast Media. 2020. Available at: https://www.acr.org/Quality-Safety/Resources/Contrast-Manual. Accessed November 14, 2021.

227. American College of Radiology. ACR Manual on Contrast Media. 2021. Available at: https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed November 23, 2021.

228. American College of Radiology. ACR Appropriateness Criteria. Available at: http://www.acr.org/quality-safety/appropriateness-criteria. Accessed November 14, 2021.

229. Johansson JE, Holmberg L, Johansson S, et al. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. JAMA 1997;277:467-471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9020270.

230. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. J Clin Oncol 2015;33:3379-3385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26324359.

231. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 2015;33:272-277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25512465.

232. Cooley LF, Emeka AA, Meyers TJ, et al. Factors Associated with Time to Conversion from Active Surveillance to Treatment for Prostate Cancer in a Multi-Institutional Cohort. J Urol 2021;206:1147-1156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34503355.

233. Loeb S, Folkvaljon Y, Makarov DV, et al. Five-year nationwide follow-up study of active surveillance for prostate cancer. Eur Urol 2015;67:233-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24993868.

234. Roemeling S, Roobol MJ, de Vries SH, et al. Active surveillance for prostate cancers detected in three subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. Eur Urol 2007;51:1244-1250; discussion 1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17161520.

235. van As NJ, Norman AR, Thomas K, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol 2008;54:1297-1305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18342430.

236. Bokhorst LP, Valdagni R, Rannikko A, et al. A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. Eur Urol 2016;70:954-960. Available at:

237. Newcomb LF, Thompson IM, Jr., Boyer HD, et al. Outcomes of active surveillance for the management of clinically localized prostate cancer in the prospective, multi-institutional Canary PASS cohort. J Urol 2015;195:313-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26327354.

238. Welty CJ, Cowan JE, Nguyen H, et al. Extended followup and risk factors for disease reclassification in a large active surveillance cohort for localized prostate cancer. J Urol 2015;193:807-811. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25261803.

239. Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. Cancer 2008;112:2664-2670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18433013.

240. Maggi M, Cowan JE, Fasulo V, et al. The long-term risks of metastases in men on active surveillance for early stage prostate cCancer. J Urol 2020;204:1222-1228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33157570.

241. Simpkin AJ, Tilling K, Martin RM, et al. Systematic review and meta-analysis of factors determining change to radical treatment in active

surveillance for localized prostate cancer. Eur Urol 2015;67:993-1005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25616709.

242. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415-1424. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27626136.

243. Neal DE, Metcalfe C, Donovan JL, et al. Ten-year mortality, disease progression, and treatment-related side effects in men with localised prostate cancer from the ProtecT randomised controlled trial according to treatment received. Eur Urol 2020;77:320-330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31771797.

244. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2016;375:1425-1437. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27626365.

245. Carter G, Clover K, Britton B, et al. Wellbeing during Active Surveillance for localised prostate cancer: a systematic review of psychological morbidity and quality of life. Cancer Treat Rev 2015;41:46-60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25467109.

246. Jeldres C, Cullen J, Hurwitz LM, et al. Prospective quality-of-life outcomes for low-risk prostate cancer: Active surveillance versus radical prostatectomy. Cancer 2015;121:2465-2473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25845467.

247. Parker PA, Davis JW, Latini DM, et al. Relationship between illness uncertainty, anxiety, fear of progression and quality of life in men with favourable-risk prostate cancer undergoing active surveillance. BJU Int 2015;117:469-477. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25714186.

248. van den Bergh RC, Essink-Bot ML, Roobol MJ, et al. Anxiety and distress during active surveillance for early prostate cancer. Cancer 2009;115:3868-3878. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19637245.

249. Pham KN, Cullen J, Hurwitz LM, et al. Prospective quality of life in men choosing active surveillance compared to those biopsied but not diagnosed with prostate cancer. J Urol 2016;196:392-398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26976206.

250. Loeb S, Byrne N, Makarov DV, et al. Use of conservative management for low-risk prostate cancer in the Veterans Affairs Integrated Health Care System from 2005-2015. JAMA 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29800017.

251. Mahal BA, Butler S, Franco I, et al. Use of active surveillance or watchful waiting for low-risk prostate cancer and management trends across risk groups in the United States, 2010-2015. JAMA 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30743264.

252. Loppenberg B, Friedlander DF, Krasnova A, et al. Variation in the use of active surveillance for low-risk prostate cancer. Cancer 2018;124:55-64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28902401.

253. Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. In Vivo 1994;8:439-443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7803731.

254. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med 2004;350:2239-2246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15163773.

255. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981-990. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22417251.

256. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-1328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19297566.

257. Klotz L. Active surveillance for prostate cancer: for whom? J Clin Oncol 2005;23:8165-8169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16278468.

258. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360:1310-1319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19297565.

259. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010;362:1192-1202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20357281.

260. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012;104:125-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22228146.

261. Sandblom G, Varenhorst E, Rosell J, et al. Randomised prostate cancer screening trial: 20 year follow-up. BMJ 2011;342:d1539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21454449.

262. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010;11:725-732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20598634.

263. Godtman RA, Holmberg E, Khatami A, et al. Long-term results of active surveillance in the Goteborg randomized, population-based prostate cancer screening trial. Eur Urol 2016;70:760-766. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27090975.

264. Hugosson J, Godtman RA, Carlsson SV, et al. Eighteen-year follow-up of the Goteborg Randomized Population-based Prostate Cancer Screening Trial: effect of sociodemographic variables on participation, prostate cancer incidence and mortality. Scand J Urol 2018;52:27-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29254399.

265. Miller DC, Gruber SB, Hollenbeck BK, et al. Incidence of initial local therapy among men with lower-risk prostate cancer in the United States. J Natl Cancer Inst 2006;98:1134-1141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16912266.

266. Draisma G, Etzioni R, Tsodikov A, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst 2009;101:374-383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19276453.

267. Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003;95:868-878. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12813170.

268. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994;271:368-374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7506797.

269. Bastian PJ, Mangold LA, Epstein JI, Partin AW. Characteristics of insignificant clinical T1c prostate tumors. A contemporary analysis. Cancer 2004;101:2001-2005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15372478.

270. Jeldres C, Suardi N, Walz J, et al. Validation of the contemporary Epstein criteria for insignificant prostate cancer in European men. Eur Urol 2008;54:1306-1313. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18083294.

271. Chun FK, Haese A, Ahyai SA, et al. Critical assessment of tools to predict clinically insignificant prostate cancer at radical prostatectomy in contemporary men. Cancer 2008;113:701-709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18553365.

272. Bastian PJ, Carter BH, Bjartell A, et al. Insignificant prostate cancer and active surveillance: from definition to clinical implications. Eur Urol

2009;55:1321-1330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19286302.

273. Ng SP, Duchesne G, Tai KH, et al. Support for the use of objective comorbidity indices in the assessment of noncancer death risk in prostate cancer patients. Prostate Int 2017;5:8-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28352617.

274. Cooperberg MR, Zheng Y, Faino AV, et al. Tailoring Intensity of Active Surveillance for Low-Risk Prostate Cancer Based on Individualized Prediction of Risk Stability. JAMA Oncol 2020;6:e203187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32852532.

275. Lonergan PE, Washington SL, 3rd, Cowan JE, et al. Risk factors for biopsy reclassification over time in men on active surveillance for early stage prostate cancer. J Urol 2020;204:1216-1221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32519915.

276. Cooperberg MR, Cowan JE, Hilton JF, et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. J Clin Oncol 2011;29:228-234. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21115873.

277. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-213. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22808955.

278. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 2017;377:132-142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28700844.

279. Dalela D, Karabon P, Sammon J, et al. Generalizability of the prostate cancer intervention versus observation trial (pivot) results to contemporary north american men with prostate cancer. Eur Urol 2017;71:511-514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27638094.

280. Musunuru HB, Yamamoto T, Klotz L, et al. Active surveillance for intermediate risk prostate cancer: Survival outcomes in the Sunnybrook experience. J Urol 2016;196:1651-1658. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27569437.

281. Patel HD, Tosoian JJ, Carter HB, Epstein JI. Adverse pathologic findings for men electing immediate radical prostatectomy: Defining a favorable intermediate-risk group. JAMA Oncol 2018;4:89-92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28715578.

282. Gearman DJ, Morlacco A, Cheville JC, et al. Comparison of pathological and oncologic outcomes of favorable risk Gleason score 3 + 4 and low risk Gleason score 6 prostate cancer: Considerations for active surveillance. J Urol 2018;199:1188-1195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29225057.

283. Aghazadeh MA, Frankel J, Belanger M, et al. National Comprehensive Cancer Network(R) favorable intermediate risk prostate cancer-Is active surveillance appropriate? J Urol 2018;199:1196-1201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29288120.

284. Loeb S, Folkvaljon Y, Bratt O, et al. Defining intermediate-risk prostate cancer suitable for active surveillance. J Urol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30240688.

285. Siegel DA, O'Neil ME, Richards TB, et al. Prostate cancer incidence and survival, by stage and race/ethnicity - United States, 2001-2017. MMWR Morb Mortal Wkly Rep 2020;69:1473-1480. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33056955.

286. DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for African Americans, 2016: progress and opportunities in reducing racial disparities. CA Cancer J Clin 2016;66:290-308. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26910411.

287. Mahal BA, Berman RA, Taplin ME, Huang FW. Prostate cancer-specific mortality across Gleason scores in black vs nonblack men. JAMA 2018;320:2479-2481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30561471.

288. Sundi D, Ross AE, Humphreys EB, et al. African American men With very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? J Clin Oncol 2013;31:2991-2997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23775960.

289. Vora A, Large T, Aronica J, et al. Predictors of Gleason score upgrading in a large African-American population. Int Urol Nephrol 2013;45:1257-1262. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23864415.

290. Leapman MS, Freedland SJ, Aronson WJ, et al. Pathological and biochemical outcomes among African-American and caucasian men with low risk prostate cancer in the SEARCH Database: implications for active surveillance candidacy. J Urol 2016;196:1408-1414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27352635.

291. Qi R, Moul J. African American men with low-risk prostate cancer are candidates for active surveillance: The Will-Rogers effect? Am J Mens Health 2017;11:1765-1771. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28830287.

292. Abern MR, Bassett MR, Tsivian M, et al. Race is associated with discontinuation of active surveillance of low-risk prostate cancer: results from the Duke Prostate Center. Prostate Cancer Prostatic Dis 2013;16:85-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23069729.

293. Iremashvili V, Soloway MS, Rosenberg DL, Manoharan M. Clinical and demographic characteristics associated with prostate cancer progression in patients on active surveillance. J Urol 2012;187:1594-1599. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22425088.

294. Sundi D, Faisal FA, Trock BJ, et al. Reclassification rates are higher among African American men than Caucasians on active surveillance. Urology 2015;85:155-160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25440814.

295. Deka R, Courtney PT, Parsons JK, et al. Association between African American race and clinical outcomes in men treated for low-risk prostate cancer with active surveillance. JAMA 2020;324:1747-1754. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33141207.

296. Faisal FA, Sundi D, Cooper JL, et al. Racial disparities in oncologic outcomes after radical prostatectomy: long-term follow-up. Urology 2014;84:1434-1441. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25432835.

297. Kovtun KA, Chen MH, Braccioforte MH, et al. Race and mortality risk after radiation therapy in men treated with or without androgen-suppression therapy for favorable-risk prostate cancer. Cancer 2016;122:3608-3614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27490845.

298. Bickell NA, Lin JJ, Abramson SR, et al. Racial disparities in clinically significant prostate cancer treatment: The potential health information technology offers. J Oncol Pract 2018;14:e23-e33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29194001.

299. Friedlander DF, Trinh QD, Krasnova A, et al. Racial disparity in delivering definitive therapy for intermediate/high-risk localized prostate cancer: The impact of facility features and socioeconomic characteristics. Eur Urol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28778619.

300. Dess RT, Hartman HE, Mahal BA, et al. Association of black race with prostate cancer-specific and other-cause mortality. JAMA Oncol 2019;5:975-983. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31120534.

301. Alexander M, Zhu K, Cullen J, et al. Race and overall survival in men diagnosed with prostate cancer in the Department of Defense Military Health System, 1990-2010. Cancer Causes Control 2019;30:627-635. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30997591.

302. Halabi S, Dutta S, Tangen CM, et al. Clinical outcomes in men of diverse ethnic backgrounds with metastatic castration-resistant prostate cancer. Ann Oncol 2020;31:930-941. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32289380.

303. Riviere P, Luterstein E, Kumar A, et al. Survival of African American and non-Hispanic white men with prostate cancer in an equal-access health care system. Cancer 2020;126:1683-1690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31984482.

304. Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA 2015;313:390-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25626035.

305. Ginsburg KB, Jacobs JC, Qi J, et al. Impact of early confirmatory tests on upgrading and conversion to treatment in prostate cancer patients on active surveillance. Urology 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32946908.

306. Kornberg Z, Cowan JE, Westphalen AC, et al. Genomic prostate score, PI-RADS version 2 and progression in men with prostate cancer on active surveillance. J Urol 2019;201:300-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30179620.

307. Gallagher KM, Christopher E, Cameron AJ, et al. Four-year outcomes from a multiparametric magnetic resonance imaging (MRI)-based active surveillance programme: PSA dynamics and serial MRI scans allow omission of protocol biopsies. BJU Int 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30113755.

308. Cantiello F, Russo GI, Kaufmann S, et al. Role of multiparametric magnetic resonance imaging for patients under active surveillance for prostate cancer: a systematic review with diagnostic meta-analysis. Prostate Cancer Prostatic Dis 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30487646.

309. Liss MA, Newcomb LF, Zheng Y, et al. Magnetic resonance imaging for the detection of high grade cancer in the Canary Prostate Active Surveillance Study. J Urol 2020;204:701-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32343189.

310. Chu CE, Lonergan PE, Washington SL, et al. Multiparametric magnetic resonance imaging alone is insufficient to detect grade reclassification in active surveillance for prostate cancer. Eur Urol 2020;78:515-517. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32631744.

311. Klotz L. Point: active surveillance for favorable risk prostate cancer. J Natl Compr Canc Netw 2007;5:693-698. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17692173.

312. Feliciano J, Teper E, Ferrandino M, et al. The incidence of fluoroquinolone resistant infections after prostate biopsy--are fluoroquinolones still effective prophylaxis? J Urol 2008;179:952-955; discussion 955. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18207185.

313. Fujita K, Landis P, McNeil BK, Pavlovich CP. Serial prostate biopsies are associated with an increased risk of erectile dysfunction in men with prostate cancer on active surveillance. J Urol 2009;182:2664-2669. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19836757.

314. Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol 2011;59:477-494. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21195536.

315. Bonekamp D, Bonekamp S, Mullins JK, et al. Multiparametric magnetic resonance imaging characterization of prostate lesions in the active surveillance population: incremental value of magnetic resonance imaging for prediction of disease reclassification. J Comput Assist Tomogr 2013;37:948-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24270118.

316. Mullins JK, Bonekamp D, Landis P, et al. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. BJU Int 2013;111:1037-1045. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23464904.

317. Nassiri N, Margolis DJ, Natarajan S, et al. Targeted biopsy to detect Gleason score upgrading during active surveillance for men with low

versus intermediate risk prostate cancer. J Urol 2016;197:632-639. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27639713.

318. Ma TM, Tosoian JJ, Schaeffer EM, et al. The role of multiparametric magnetic resonance imaging/ultrasound fusion biopsy in active surveillance. Eur Urol 2017;71:174-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27236496.

319. Recabal P, Assel M, Sjoberg DD, et al. The efficacy of multiparametric magnetic resonance imaging and magnetic resonance imaging targeted biopsy in risk classification for patients with prostate cancer on active surveillance. J Urol 2016;196:374-381. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26920465.

320. Tran GN, Leapman MS, Nguyen HG, et al. Magnetic resonance imaging-ultrasound fusion biopsy during prostate cancer active surveillance. Eur Urol 2016;72:275-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27595378.

321. Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol 2012;62:976-983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22698574

http://www.europeanurology.com/article/S0302-2838(12)00691-4/pdf/active-surveillance-for-prostate-cancer-a-systematic-review-of-the-literature.

322. Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. J Urol 2007;178:2359-2364; discussion 2364-2355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17936806.

323. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2010;28:126-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19917860.

324. Sheridan TB, Carter HB, Wang W, et al. Change in prostate cancer grade over time in men followed expectantly for stage T1c disease. J Urol 2008;179:901-904; discussion 904-905. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18207195.

325. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 2011;29:2185-2190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21464416.

326. Loblaw A, Zhang L, Lam A, et al. Comparing prostate specific antigen triggers for intervention in men with stable prostate cancer on active surveillance. J Urol 2010;184:1942-1946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20846681.

327. Ross AE, Loeb S, Landis P, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Clin Oncol 2010;28:2810-2816. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20439642.

328. Jain S, Loblaw A, Vesprini D, et al. Gleason upgrading with time in a large prostate cancer active surveillance cohort. J Urol 2015;194:79-84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25660208.

329. Yamamoto T, Musunuru B, Vesprini D, et al. Metastatic prostate cancer in men initially treated with active surveillance. J Urol 2016;195:1409-1414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26707510.

330. Tosoian JJ, Sundi D, Trock BJ, et al. Pathologic outcomes in favorable-risk prostate cancer: comparative analysis of men electing active surveillance and immediate surgery. Eur Urol 2015;69:576-581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26456680.

331. Dall'Era MA, Cowan JE, Simko J, et al. Surgical management after active surveillance for low-risk prostate cancer: pathological outcomes compared with men undergoing immediate treatment. BJU Int 2011;107:1232-1237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20804478.

332. Filippou P, Welty CJ, Cowan JE, et al. Immediate versus delayed radical prostatectomy: updated outcomes following active surveillance of prostate cancer. Eur Urol 2015;68:458-463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26138041.

333. Bill-Axelson A, Holmberg L, Filen F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. J Natl Cancer Inst 2008;100:1144-1154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18695132.

334. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014;370:932-942. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24597866.

335. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in prostate cancer - 29-year follow-up. N Engl J Med 2018;379:2319-2329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30575473.

336. Pierorazio PM, Ross AE, Lin BM, et al. Preoperative characteristics of high-Gleason disease predictive of favourable pathological and clinical outcomes at radical prostatectomy. BJU Int 2012;110:1122-1128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22373045.

337. Moschini M, Briganti A, Murphy CR, et al. Outcomes for Patients with Clinical Lymphadenopathy Treated with Radical Prostatectomy. Eur Urol 2016;69:193-196. Available at:

338. Seisen T, Vetterlein MW, Karabon P, et al. Efficacy of Local Treatment in Prostate Cancer Patients with Clinically Pelvic Lymph Node-positive Disease at Initial Diagnosis. Eur Urol 2018;73:452-461. Available at:

339. Jang TL, Patel N, Faiena I, et al. Comparative effectiveness of radical prostatectomy with adjuvant radiotherapy versus radiotherapy plus androgen deprivation therapy for men with advanced prostate cancer. Cancer 2018;124:4010-4022. Available at:

340. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30355464.

341. Chade DC, Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol 2012;61:961-971. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22280856.

342. Shekarriz B, Upadhyay J, Pontes JE. Salvage radical prostatectomy. Urol Clin North Am 2001;28:545-553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11590813.

343. Klein EA, Bianco FJ, Serio AM, et al. Surgeon experience is strongly associated with biochemical recurrence after radical prostatectomy for all preoperative risk categories. J Urol 2008;179:2212-2216; discussion 2216-2217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18423716.

344. Begg CB, Riedel ER, Bach PB, et al. Variations in morbidity after radical prostatectomy. N Engl J Med 2002;346:1138-1144. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11948274.

345. Herrell SD, Smith JA, Jr. Robotic-assisted laparoscopic prostatectomy: what is the learning curve? Urology 2005;66:105-107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16194715.

346. Smith JA, Jr., Herrell SD. Robotic-assisted laparoscopic prostatectomy: do minimally invasive approaches offer significant advantages? J Clin Oncol 2005;23:8170-8175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16278469.

347. Ilic D, Evans SM, Allan CA, et al. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. Cochrane Database Syst Rev 2017;9:CD009625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28895658.

348. Hu JC, Gu X, Lipsitz SR, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. JAMA 2009;302:1557-1564. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19826025.

349. Gandaglia G, Sammon JD, Chang SL, et al. Comparative effectiveness of robot-assisted and open radical prostatectomy in the postdissemination era. J Clin Oncol 2014;32:1419-1426. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24733797.

350. Parsons JK, Bennett JL. Outcomes of retropubic, laparoscopic, and robotic-assisted prostatectomy. Urology 2008;72:412-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18267330.

351. Ficarra V, Novara G, Rosen RC, et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2012;62:405-417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22749852.

352. Ficarra V, Novara G, Ahlering TE, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol 2012;62:418-430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22749850.

353. Coughlin GD, Yaxley JW, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. Lancet Oncol 2018;19:1051-1060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30017351.

354. Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet 2016;388:1057-1066. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27474375.

355. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 2013;368:436-445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23363497.

356. Nam RK, Cheung P, Herschorn S, et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. Lancet Oncol 2014;15:223-231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24440474.

357. Freire MP, Weinberg AC, Lei Y, et al. Anatomic bladder neck preservation during robotic-assisted laparoscopic radical prostatectomy: description of technique and outcomes. Eur Urol 2009;56:972-980. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19781848.

358. Abel EJ, Masterson TA, Warner JN, et al. Nerve-sparing prostatectomy and urinary function: a prospective analysis using validated quality-of-life measures. Urology 2009;73:1336-1340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19362347.

359. Avulova S, Zhao Z, Lee D, et al. The effect of nerve sparing status on sexual and urinary function: 3-year results from the CEASAR study. J Urol 2018;199:1202-1209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29253578.

360. Davis JW, Chang DW, Chevray P, et al. Randomized phase II trial evaluation of erectile function after attempted unilateral cavernous nerve-sparing retropubic radical prostatectomy with versus without unilateral sural nerve grafting for clinically localized prostate cancer. Eur Urol 2009;55:1135-1143. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18783876.

361. Leyh-Bannurah SR, Budaus L, Pompe R, et al. North American population-based validation of the National Comprehensive Cancer Network practice guideline recommendation of pelvic lymphadenectomy in contemporary prostate cancer. Prostate 2017;77:542-548. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28093788.

362. Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. Eur Urol 2009;55:1251-1265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19297079.

363. Heidenreich A, Ohlmann CH, Polyakov S. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. Eur Urol 2007;52:29-37. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17448592.

364. Masterson TA, Bianco FJ, Jr., Vickers AJ, et al. The association between total and positive lymph node counts, and disease progression in clinically localized prostate cancer. J Urol 2006;175:1320-1324; discussion 1324-1325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16515989.

365. Joslyn SA, Konety BR. Impact of extent of lymphadenectomy on survival after radical prostatectomy for prostate cancer. Urology 2006;68:121-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16806432.

366. Allaf ME, Palapattu GS, Trock BJ, et al. Anatomical extent of lymph node dissection: impact on men with clinically localized prostate cancer. J Urol 2004;172:1840-1844. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15540734.

367. Bader P, Burkhard FC, Markwalder R, Studer UE. Disease progression and survival of patients with positive lymph nodes after radical prostatectomy. Is there a chance of cure? J Urol 2003;169:849-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12576797.

368. Daneshmand S, Quek ML, Stein JP, et al. Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. J Urol 2004;172:2252-2255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15538242.

369. Wagner M, Sokoloff M, Daneshmand S. The role of pelvic lymphadenectomy for prostate cancer--therapeutic? J Urol 2008;179:408-413. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18076938.

370. Fossati N, Willemse PM, van den Bergh RC, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. Eur Urol 2017;72:84-109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28126351.

371. Pan HY, Jiang J, Hoffman KE, et al. Comparative toxicities and cost of intensity-modulated radiotherapy, proton radiation, and stereotactic body radiotherapy among younger men with prostate cancer. J Clin Oncol 2018:JCO2017755371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29561693.

372. Hanlon AL, Watkins Bruner D, Peter R, Hanks GE. Quality of life study in prostate cancer patients treated with three-dimensional conformal radiation therapy: comparing late bowel and bladder quality of life symptoms to that of the normal population. Int J Radiat Oncol Biol Phys 2001;49:51-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11163497.

373. Koper PC, Stroom JC, van Putten WL, et al. Acute morbidity reduction using 3DCRT for prostate carcinoma: a randomized study. Int J Radiat Oncol Biol Phys 1999;43:727-734. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10098427.

374. Michalski JM, Bae K, Roach M, et al. Long-term toxicity following 3D conformal radiation therapy for prostate cancer from the RTOG 9406 phase I/II dose escalation study. Int J Radiat Oncol Biol Phys 2010;76:14-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19577865.

375. Jacobs BL, Zhang Y, Schroeck FR, et al. Use of advanced treatment technologies among men at low risk of dying from prostate cancer. JAMA 2013;309:2587-2595. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23800935.

376. Zelefsky MJ, Levin EJ, Hunt M, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1124-1129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18313526.

377. Jani AB, Su A, Correa D, Gratzle J. Comparison of late gastrointestinal and genitourinary toxicity of prostate cancer patients undergoing intensity-modulated versus conventional radiotherapy using localized fields. Prostate Cancer Prostatic Dis 2007;10:82-86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16983394.

378. Jacobs BL, Zhang Y, Skolarus TA, et al. Comparative effectiveness of external-beam radiation approaches for prostate cancer. Eur Urol 2014;65:162-168. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22790288.

379. Goldin GH, Sheets NC, Meyer AM, et al. Comparative effectiveness of intensity-modulated radiotherapy and conventional conformal radiotherapy in the treatment of prostate cancer after radical prostatectomy. JAMA Intern Med 2013;173:1136-1143. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23689844.

380. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. J Clin Oncol 2013;31:3860-3868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24101042.

381. Arcangeli S, Strigari L, Gomellini S, et al. Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2012;84:1172-1178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22537541.

382. Arcangeli G, Saracino B, Arcangeli S, et al. Moderate Hypofractionation In High-Risk, Organ-Confined Prostate Cancer: Final Results Of A Phase III randomized trial. J Clin Oncol 2017;35:1891-1897. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28355113.

383. Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2016;17:1061-1069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27339116.

384. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17:1047-1060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27339115.

385. Aluwini S, Pos F, Schimmel E, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. Lancet Oncol 2015;16:274-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25656287.

386. Lee WR, Dignam JJ, Amin MB, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol 2016;34:2325-2332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27044935.

387. Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol 2017;35:1884-1890. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28296582.

388. Hoffman KE, Voong KR, Levy LB, et al. Randomized trial of hypofractionated, dose-escalated, intensity-modulated radiation therapy (IMRT) versus conventionally fractionated IMRT for localized prostate cancer. J Clin Oncol 2018;36:2943-2949. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30106637.

389. Bruner DW, Pugh SL, Lee WR, et al. Quality of life in patients with low-risk prostate cancer treated with hypofractionated vs conventional radiotherapy: A phase 3 randomized clinical trial. JAMA Oncol 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30763425.

390. Yu JB. Hypofractionated radiotherapy for prostate cancer: Further evidence to tip the scales. J Clin Oncol 2017;35:1867-1869. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28355114.

391. Nossiter J, Sujenthiran A, Cowling TE, et al. Patient-reported functional outcomes after hypofractionated or conventionally fractionated radiation for prostate cancer: A national cohort study in England. J Clin Oncol 2020;38:744-752. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31895608.

392. Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated radiation therapy for localized prostate cancer: An ASTRO, ASCO, and AUA

evidence-based guideline. J Clin Oncol 2018:JCO1801097. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30307776.

393. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol 2006;24:1990-1996. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648499.

394. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 2002;53:1097-1105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12128107.

395. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005;294:1233-1239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16160131.

396. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:67-74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17765406.

397. Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol 2014;15:464-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24581940.

398. Denham JW, Steigler A, Joseph D, et al. Radiation dose escalation or longer androgen suppression for locally advanced prostate cancer? Data from the TROG 03.04 RADAR trial. Radiother Oncol 2015;115:301-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26072289.

399. Pasalic D, Kuban DA, Allen PK, et al. Dose Escalation for Prostate Adenocarcinoma: A Long-Term Update on the Outcomes of a Phase 3, Single Institution Randomized Clinical Trial. Int J Radiat Oncol Biol Phys 2019;104:790-797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30836166.

400. Kalbasi A, Li J, Berman A, et al. Dose-escalated irradiation and overall survival in men with nonmetastatic prostate cancer. JAMA Oncol 2015;1:897-906. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26181727.

401. Xu N, Rossi PJ, Jani AB. Toxicity analysis of dose escalation from 75.6 gy to 81.0 gy in prostate cancer. Am J Clin Oncol 2011;34:11-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20101167.

402. Eade TN, Hanlon AL, Horwitz EM, et al. What dose of external-beam radiation is high enough for prostate cancer? Int J Radiat Oncol Biol Phys 2007;68:682-689. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17398026.

403. Wolff RF, Ryder S, Bossi A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. Eur J Cancer 2015;51:2345-2367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26254809.

404. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst 2004;96:1358-1367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15367568.

405. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008;358:1250-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18354103.

406. Mariados N, Sylvester J, Shah D, et al. Hydrogel spacer prospective multicenter randomized controlled pivotal trial: dosimetric and clinical effects of perirectal spacer application in men undergoing prostate image guided intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 2015;92:971-977. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26054865.

407. Miller LE, Efstathiou JA, Bhattacharyya SK, et al. Association of the placement of a perirectal hydrogel spacer with the clinical outcomes of men receiving radiotherapy for prostate cancer: A systematic review and meta-analysis. JAMA Netw Open 2020;3:e208221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32585020.

408. Hamstra DA, Mariados N, Sylvester J, et al. Continued benefit to rectal separation for prostate radiation therapy: final results of a phase III trial. Int J Radiat Oncol Biol Phys 2017;97:976-985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28209443.

409. Hamstra DA, Mariados N, Sylvester J, et al. Sexual quality of life following prostate intensity modulated radiation therapy (IMRT) with a rectal/prostate spacer: Secondary analysis of a phase 3 trial. Pract Radiat Oncol 2018;8:e7-e15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28951089.

410. Schorghofer A, Drerup M, Kunit T, et al. Rectum-spacer related acute toxicity - endoscopy results of 403 prostate cancer patients after implantation of gel or balloon spacers. Radiat Oncol 2019;14:47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30876433.

411. Levy JF, Khairnar R, Louie AV, et al. Evaluating the cost-effectiveness of hydrogel rectal spacer in prostate cancer radiation therapy. Pract Radiat Oncol 2019;9:e172-e179. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30342180.

412. Nguyen PL, D'Amico AV, Lee AK, Suh WW. Patient selection, cancer control, and complications after salvage local therapy for postradiation prostate-specific antigen failure: a systematic review of the literature. Cancer 2007;110:1417-1428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17694553.

413. Critz FA, Benton JB, Shrake P, Merlin ML. 25-Year disease-free survival rate after irradiation for prostate cancer calculated with the prostate specific antigen definition of recurrence used for radical prostatectomy. J Urol 2013;189:878-883. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23103235.

414. Michalski JM, Moughan J, Purdy J, et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: The NRG Oncology RTOG 0126 randomized clinical trial. JAMA Oncol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29543933.

415. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11:1066-1073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20933466.

416. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys 2005;61:1285-1290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15817329.

417. Mason MD, Parulekar WR, Sydes MR, et al. Final report of the Intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. J Clin Oncol 2015;33:2143-2150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25691677.

418. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 2011;378:2104-2111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22056152.

419. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 2009;373:301-308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19091394.

420. Fossa SD, Wiklund F, Klepp O, et al. Ten- and 15-yr prostate cancer-specific mortality in patients with nonmetastatic locally advanced or aggressive intermediate prostate cancer, randomized to lifelong endocrine treatment alone or combined with radiotherapy: final results of the Scandinavian Prostate Cancer Group-7. Eur Urol 2016;70:684-691. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27025586.

421. Royce TJ, Chen MH, Wu J, et al. Surrogate end points for all-cause mortality in men with localized unfavorable-risk prostate cancer treated with radiation therapy vs radiation therapy plus androgen deprivation therapy: a secondary analysis of a randomized clinical trial. JAMA Oncol 2017;3:652-658. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28097317.

422. Parry MG, Sujenthiran A, Cowling TE, et al. Treatment-related toxicity using prostate-only versus prostate and pelvic lymph node intensity-modulated radiation therapy: A national population-based study. J Clin Oncol 2019;37:1828-1835. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31163009.

423. Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. Lancet Oncol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30316827.

424. Lawton CA, DeSilvio M, Roach M, 3rd, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys 2007;69:646-655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17531401.

425. Murthy V, Maitre P, Kannan S, et al. Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. J Clin Oncol 2021;39:1234-1242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33497252.

426. Kerkmeijer LGW, Groen VH, Pos FJ, et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial. J Clin Oncol 2021;39:787-796. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33471548.

427. Fizazi K, Faivre L, Lesaunier F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. Lancet Oncol 2015;16:787-794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26028518.

428. Rosenthal SA, Hu C, Sartor O, et al. Effect of chemotherapy with docetaxel with androgen suppression and radiotherapy for localized high-risk prostate cancer: The randomized phase III NRG Oncology RTOG 0521 trial. J Clin Oncol 2019:JCO1802158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30860948.

429. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163-1177. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26719232.

430. James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338-351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28578639

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5533216/pdf/emss-73080.pdf.

431. Sydes MR, Spears MR, Mason MD, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. Ann Oncol 2018;29:1235-1248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29529169.

432. Rexer H. [Metastatic, hormone-naive prostate cancer interventional study : Multicenter, prospective, randomized study to evaluate the effect of standard drug therapy with or without radical prostatectomy in patients with limited bone metastasized prostate cancer (G-RAMPP - the AUO AP 75/13 study)]. Urologe A 2015;54:1613-1616. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26573673.

433. A Phase III Study for Patients With Metastatic Hormone-naïve Prostate Cancer (PEACE1). ClinicalTrials.gov; 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT01957436. Accessed November 14, 2021.

434. Sooriakumaran P. Testing radical prostatectomy in men with prostate cancer and oligometastases to the bone: a randomized controlled feasibility trial. BJU Int 2017;120:E8-E20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28581205.

435. A Prospective, Multi-Institutional, Randomized, Phase II Trial of Best Systemic Therapy or Best Systemic Therapy (BST) Plus Definitive Treatment (Radiation or Surgery) of the Primary Tumor in Metastatic (M1) Prostate Cancer (PC). ClinicalTrials.gov; 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT01751438. Accessed November 15, 2021.

436. Standard systemic therapy with or without definitive treatment in treating participants with metastatic prostate cancer. ClinicalTrials.gov; 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03678025. Accessed November 15, 2021.

437. Boeve LMS, Hulshof M, Vis AN, et al. Effect on survival of androgen deprivation therapy alone compared to androgen deprivation therapy combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomised clinical trial: Data from the HORRAD trial. Eur Urol 2019;75:410-418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30266309.

438. Dasu A. Is the alpha/beta value for prostate tumours low enough to be safely used in clinical trials? Clin Oncol (R Coll Radiol) 2007;19:289-301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17517328.

439. Buyyounouski MK, Price RA, Jr., Harris EE, et al. Stereotactic body radiotherapy for primary management of early-stage, low- to intermediate-risk prostate cancer: report of the American Society for Therapeutic Radiology and Oncology Emerging Technology Committee. Int J Radiat Oncol Biol Phys 2010;76:1297-1304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20338473.

440. Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiat Oncol 2011;6:3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21219625.

441. Kang JK, Cho CK, Choi CW, et al. Image-guided stereotactic body radiation therapy for localized prostate cancer. Tumori 2011;97:43-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21528663.

442. Madsen BL, Hsi RA, Pham HT, et al. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. Int J Radiat Oncol Biol Phys 2007;67:1099-1105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17336216.

443. Chen LN, Suy S, Uhm S, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. Radiat Oncol 2013;8:58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23497695.

444. Katz AJ, Santoro M, Diblasio F, Ashley R. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. Radiat Oncol 2013;8:118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23668632.

445. King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol 2013;109:217-221. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24060175.

446. Kishan AU, Dang A, Katz AJ, et al. Long-term outcomes of stereotactic body radiotherapy for low-risk and intermediate-risk prostate cancer. JAMA Netw Open 2019;2:e188006. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30735235.

447. Yu JB, Cramer LD, Herrin J, et al. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. J Clin Oncol 2014;32:1195-1201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24616315.

448. Hannan R, Tumati V, Xie XJ, et al. Stereotactic body radiation therapy for low and intermediate risk prostate cancer-Results from a multi-institutional clinical trial. Eur J Cancer 2016;59:142-151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27035363.

449. Halpern JA, Sedrakyan A, Hsu WC, et al. Use, complications, and costs of stereotactic body radiotherapy for localized prostate cancer. Cancer 2016;122:2496-2504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27224858.

450. Jackson WC, Silva J, Hartman HE, et al. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. Int J Radiat Oncol Biol Phys 2019;104:778-789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30959121.

451. Vargas CE, Schmidt MQ, Niska JR, et al. Initial toxicity, quality-of-life outcomes, and dosimetric impact in a randomized phase 3 trial of hypofractionated versus standard fractionated proton therapy for low-risk prostate cancer. Adv Radiat Oncol 2018;3:322-330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30202801.

452. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol 2019;20:1531-1543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31540791.

453. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet 2019;394:385-395. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31227373.

454. Brachman DG, Thomas T, Hilbe J, Beyer DC. Failure-free survival following brachytherapy alone or external beam irradiation alone for T1-2 prostate tumors in 2222 patients: results from a single practice. Int J Radiat Oncol Biol Phys 2000;48:111-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10924979.

455. Masson S, Persad R, Bahl A. HDR brachytherapy in the management of high-risk prostate cancer. Adv Urol 2012;2012:980841. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22461791.

456. Spratt DE, Soni PD, McLaughlin PW, et al. American Brachytherapy Society Task Group Report: Combination of brachytherapy and external beam radiation for high-risk prostate cancer. Brachytherapy 2017;16:1-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27771243.

457. Merrick GS, Butler WM, Wallner KE, et al. Permanent interstitial brachytherapy in younger patients with clinically organ-confined prostate cancer. Urology 2004;64:754-759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15491715.

458. Eade TN, Horwitz EM, Ruth K, et al. A comparison of acute and chronic toxicity for men with low-risk prostate cancer treated with intensity-modulated radiation therapy or (125)I permanent implant. Int J Radiat Oncol Biol Phys 2008;71:338-345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18207665.

459. Wong WW, Vora SA, Schild SE, et al. Radiation dose escalation for localized prostate cancer: intensity-modulated radiotherapy versus permanent transperineal brachytherapy. Cancer 2009;115:5596-5606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19670452.

460. Nag S, Bice W, DeWyngaert K, et al. The American Brachytherapy Society recommendations for permanent prostate brachytherapy postimplant dosimetric analysis. Int J Radiat Oncol Biol Phys 2000;46:221-230. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10656396.

461. Hoskin P. High dose rate brachytherapy for prostate cancer. Cancer Radiother 2008;12:512-514. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18755623.

462. Grills IS, Martinez AA, Hollander M, et al. High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. J Urol 2004;171:1098-1104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14767279.

463. Vargas C, Ghilezan M, Hollander M, et al. A new model using number of needles and androgen deprivation to predict chronic urinary toxicity for high or low dose rate prostate brachytherapy. J Urol 2005;174:882-887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16093980.

464. Badakhshi H, Graf R, Budach V, Wust P. Permanent interstitial low-dose-rate brachytherapy for patients with low risk prostate cancer: An interim analysis of 312 cases. Strahlenther Onkol 2015;191:303-309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25339309.

465. Krauss DJ, Ye H, Martinez AA, et al. Favorable preliminary outcomes for men with low- and intermediate-risk prostate cancer treated with 19-Gy single-fraction high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2017;97:98-106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27979460.

466. Lazarev S, Thompson MR, Stone NN, Stock RG. Low-dose-rate brachytherapy for prostate cancer: outcomes at >10 years of follow-up. BJU Int 2018;121:781-790. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29319928.

467. Rasmusson E, Gunnlaugsson A, Kjellen E, et al. Low-dose rate brachytherapy with I-125 seeds has an excellent 5-year outcome with few side effects in patients with low-risk prostate cancer. Acta Oncol 2016;55:1016-1021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27174603.

468. Matzkin H, Chen J, Agai R, et al. Long-term biochemical progression-free survival following brachytherapy for prostate cancer: Further insight into the role of short-term androgen deprivation and intermediate risk group subclassification. PLoS One 2019;14:e0215582. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31002732.

469. Frank SJ, Pugh TJ, Blanchard P, et al. Prospective phase 2 trial of permanent seed implantation prostate brachytherapy for intermediate-risk localized prostate cancer: Efficacy, toxicity, and quality of life outcomes. Int J Radiat Oncol Biol Phys 2018;100:374-382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29229325.

470. Giberti C, Gallo F, Schenone M, et al. Robotic prostatectomy versus brachytherapy for the treatment of low risk prostate cancer. Can J Urol 2017;24:8728-8733. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28436359.

471. Al-Salihi O, Mitra A, Payne H. Challenge of dose escalation in locally advanced unfavourable prostate cancer using HDR brachytherapy. Prostate Cancer Prostatic Dis 2006;9:370-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16832383.

472. Fang FM, Wang YM, Wang CJ, et al. Comparison of the outcome and morbidity for localized or locally advanced prostate cancer treated by high-dose-rate brachytherapy plus external beam radiotherapy (EBRT) versus EBRT alone. Jpn J Clin Oncol 2008;38:474-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18621848.

473. Soumarova R, Homola L, Perkova H, Stursa M. Three-dimensional conformal external beam radiotherapy versus the combination of external radiotherapy with high-dose rate brachytherapy in localized carcinoma of the prostate: comparison of acute toxicity. Tumori 2007;93:37-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17455870.

474. Pieters BR, van de Kamer JB, van Herten YR, et al. Comparison of biologically equivalent dose-volume parameters for the treatment of prostate cancer with concomitant boost IMRT versus IMRT combined with brachytherapy. Radiother Oncol 2008;88:46-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18378028.

475. Sathya JR, Davis IR, Julian JA, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. J Clin Oncol 2005;23:1192-1199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15718316.

476. Hoskin PJ, Motohashi K, Bownes P, et al. High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial. Radiother Oncol 2007;84:114-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17531335.

477. Hoskin PJ, Rojas AM, Bownes PJ, et al. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. Radiother Oncol 2012;103:217-222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22341794.

478. Shen X, Keith SW, Mishra MV, et al. The impact of brachytherapy on prostate cancer-specific mortality for definitive radiation therapy of high-grade prostate cancer: a population-based analysis. Int J Radiat Oncol Biol Phys 2012;83:1154-1159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22270175.

479. Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT trial): An analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:275-285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28262473.

480. Rodda S, Tyldesley S, Morris WJ, et al. Ascende-rt: An analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:286-295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28433432.

481. Rodda S, Morris WJ, Hamm J, Duncan G. ASCENDE-RT: An analysis of health-related quality of life for a randomized trial comparing low-dose-rate brachytherapy boost with dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol Biol Phys 2017;98:581-589. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28581398.

482. Spratt DE, Carroll PR. Optimal radical therapy for localized prostate cancer: Recreation of the self-fulfilling prophecy with combination brachytherapy? J Clin Oncol 2018;36:2914-2917. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29782208.

483. Bittner N, Merrick GS, Butler WM, et al. Long-term outcome for very high-risk prostate cancer treated primarily with a triple modality approach to include permanent interstitial brachytherapy. Brachytherapy 2012;11:250-255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22436516.

484. Martinez-Monge R, Moreno M, Ciervide R, et al. External-beam radiation therapy and high-dose rate brachytherapy combined with long-term androgen deprivation therapy in high and very high prostate cancer: preliminary data on clinical outcome. Int J Radiat Oncol Biol Phys 2012;82:e469-476. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22284039.

485. D'Amico AV, Moran BJ, Braccioforte MH, et al. Risk of death from prostate cancer after brachytherapy alone or with radiation, androgen suppression therapy, or both in men with high-risk disease. J Clin Oncol 2009;27:3923-3928. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19597029.

486. Demanes DJ, Brandt D, Schour L, Hill DR. Excellent results from high dose rate brachytherapy and external beam for prostate cancer are not improved by androgen deprivation. Am J Clin Oncol 2009;32:342-347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19398902.

487. Dattoli M, Wallner K, True L, et al. Long-term outcomes for patients with prostate cancer having intermediate and high-risk disease, treated with combination external beam irradiation and brachytherapy. J Oncol 2010;2010. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20847945.

488. Kishan AU, Cook RR, Ciezki JP, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with Gleason score 9-10 prostate cancer. JAMA 2018;319:896-905. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29509865.

489. Ennis RD, Hu L, Ryemon SN, et al. Brachytherapy-based radiotherapy and radical prostatectomy are associated with similar survival in high-risk localized prostate cancer. J Clin Oncol 2018;36:1192-1198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29489433.

490. Aaronson DS, Yamasaki I, Gottschalk A, et al. Salvage permanent perineal radioactive-seed implantation for treating recurrence of localized prostate adenocarcinoma after external beam radiotherapy. BJU Int 2009;104:600-604. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19245439.

491. Yamada Y, Kollmeier MA, Pei X, et al. A Phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. Brachytherapy 2014;13:111-116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24373762.

492. Crook JM, Zhang P, Pisansky TM, et al. A prospective phase II trial of trans-perineal ultrasound-guided brachytherapy for locally recurrent prostate cancer after external beam radiotherapy (NRG Oncology/RTOG - 0526). Int J Radiat Oncol Biol Phys 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30312717.

493. Georg D, Hopfgartner J, Gora J, et al. Dosimetric considerations to determine the optimal technique for localized prostate cancer among external photon, proton, or carbon-ion therapy and high-dose-rate or low-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys 2014;88:715-722. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24521685.

494. Coen JJ, Paly JJ, Niemierko A, et al. Long-term quality of life outcome after proton beam monotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2012;82:e201-209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21621343.

495. Yu JB, Soulos PR, Herrin J, et al. Proton versus intensity-modulated radiotherapy for prostate cancer: patterns of care and early toxicity. J Natl Cancer Inst 2013;105:25-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23243199.

496. Hoppe BS, Michalski JM, Mendenhall NP, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. Cancer 2014;120:1076-1082. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24382757.

497. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. JAMA 2012;307:1611-1620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22511689.

498. American Society of Radiation Oncology (ASTRO). Proton Beam Therapy Model Policy. 2014. Available at: https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/ASTRO%20PBT%20Model%20Policy%20FINAL.pdf. Accessed November 15, 2021.

499. Grewal AS, Schonewolf C, Min EJ, et al. Four-year outcomes from a prospective phase II clinical trial of moderately hypofractionated proton therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2019;105:713-722. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31199994.

500. Konski A, James J, Hartsell W, et al. Economic analysis of radiation therapy oncology group 97-14: multiple versus single fraction radiation treatment of patients with bone metastases. Am J Clin Oncol 2009;32:423-428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19546803.

501. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short-versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 2005;97:798-804. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15928300.

502. Chow E, van der Linden YM, Roos D, et al. Single versus multiple fractions of repeat radiation for painful bone metastases: a randomised, controlled, non-inferiority trial. Lancet Oncol 2014;15:164-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24369114.

503. Hoskin PJ, Hopkins K, Misra V, et al. Effect of single-fraction vs multifraction radiotherapy on ambulatory status among patients with spinal canal compression from metastatic cancer: The SCORAD randomized clinical trial. JAMA 2019;322:2084-2094. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31794625.

504. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: The ORIOLE phase 2 randomized clinical trial. JAMA Oncol 2020;6:650-659. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32215577.

505. Palma DA, Olson R, Harrow S, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. J Clin Oncol 2020;38:2830-2838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32484754.

506. Prescribing Information for lutetium Lu 177 vipivotide tetraxetan injection, for intravenous use. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215833s000lbl.pdf. Accessed May 9, 2022.

507. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2021;385:1091-1103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34161051.

508. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23863050.

509. Hoskin P, Sartor O, O'Sullivan JM, et al. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial. Lancet Oncol 2014;15:1397-1406. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25439694.

510. Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. Lancet Oncol 2014;15:738-746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24836273.

511. Nilsson S, Cislo P, Sartor O, et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. Ann Oncol 2016;27:868-874. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26912557.

512. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30738780.

513. Package Insert. XOFIGO (radium Ra 223 dichloride) Injection, for intravenous use. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203971s016lbl.pdf. Accessed November 15, 2021.

514. Janjan N, Lutz ST, Bedwinek JM, et al. Therapeutic guidelines for the treatment of bone metastasis: a report from the American College of Radiology Appropriateness Criteria Expert Panel on Radiation Oncology. J Palliat Med 2009;12:417-426. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19416037.

515. Pandit-Taskar N, Batraki M, Divgi CR. Radiopharmaceutical therapy for palliation of bone pain from osseous metastases. J Nucl Med 2004;45:1358-1365. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15299062.

516. Seider MJ, Pugh SL, Langer C, et al. Randomized phase III trial to evaluate radiopharmaceuticals and zoledronic acid in the palliation of osteoblastic metastases from lung, breast, and prostate cancer: report of the NRG Oncology RTOG 0517 trial. Ann Nucl Med 2018;32:553-560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30094545.

517. Barocas DA, Alvarez J, Resnick MJ, et al. Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years. JAMA 2017;317:1126-1140. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28324093.

518. Chen RC, Basak R, Meyer AM, et al. Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. JAMA 2017;317:1141-1150. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28324092.

519. Lardas M, Liew M, van den Bergh RC, et al. Quality of life outcomes after primary treatment for clinically localised prostate cancer: A systematic review. Eur Urol 2017;72:869-885. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28757301.

520. Hoffman KE, Penson DF, Zhao Z, et al. Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer. JAMA 2020;323:149-163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31935027.

521. Babaian RJ, Donnelly B, Bahn D, et al. Best practice statement on cryosurgery for the treatment of localized prostate cancer. J Urol 2008;180:1993-2004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18817934.

522. Bahn D, de Castro Abreu AL, Gill IS, et al. Focal cryotherapy for clinically unilateral, low-intermediate risk prostate cancer in 73 men with a median follow-up of 3.7 years. Eur Urol 2012;62:55-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22445223.

523. Donnelly BJ, Saliken JC, Brasher PM, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer. Cancer 2010;116:323-330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19937954.

524. Robinson JW, Donnelly BJ, Siever JE, et al. A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer: quality of life outcomes. Cancer 2009;115:4695-4704. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19691092.

525. Chin JL, Al-Zahrani AA, Autran-Gomez AM, et al. Extended followup oncologic outcome of randomized trial between cryoablation and external beam therapy for locally advanced prostate cancer (T2c-T3b). J Urol 2012;188:1170-1175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22901586.

526. de Castro Abreu AL, Bahn D, Leslie S, et al. Salvage focal and salvage total cryoablation for locally recurrent prostate cancer after primary radiation therapy. BJU Int 2013;112:298-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23826840.

527. Eisenberg ML, Shinohara K. Partial salvage cryoablation of the prostate for recurrent prostate cancer after radiotherapy failure. Urology 2008;72:1315-1318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18597824.

528. Li YH, Elshafei A, Agarwal G, et al. Salvage focal prostate cryoablation for locally recurrent prostate cancer after radiotherapy: initial results from the cryo on-line data registry. Prostate 2015;75:1-7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25283814.

529. Rischmann P, Gelet A, Riche B, et al. Focal high intensity focused ultrasound of unilateral localized prostate cancer: a prospective multicentric hemiablation study of 111 patients. Eur Urol 2017;71:267-273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27720531.

530. Albisinni S, Aoun F, Bellucci S, et al. Comparing high-intensity focal ultrasound hemiablation to robotic radical prostatectomy in the management of unilateral prostate cancer: a matched-pair analysis. J Endourol 2017;31:14-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27799004.

531. Guillaumier S, Peters M, Arya M, et al. A multicentre study of 5-year outcomes following focal therapy in treating clinically significant nonmetastatic prostate cancer. Eur Urol 2018;74:422-429. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29960750.

532. Glybochko PV, Amosov AV, Krupinov GE, et al. Hemiablation of localized prostate cancer by high-intensity focused ultrasound: A series of 35 cases. Oncology 2019;97:44-48. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31071712.

533. Abreu AL, Peretsman S, Iwata A, et al. High intensity focused ultrasound hemigland ablation for prostate cancer: Initial outcomes of a United States series. J Urol 2020;204:741-747. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32898975.

534. Ahmed HU, Cathcart P, McCartan N, et al. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. Cancer 2012;118:4148-4155. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22907704.

535. Baco E, Gelet A, Crouzet S, et al. Hemi salvage high-intensity focused ultrasound (HIFU) in unilateral radiorecurrent prostate cancer: a prospective two-centre study. BJU Int 2014;114:532-540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24930692.

536. Crouzet S, Murat FJ, Pommier P, et al. Locally recurrent prostate cancer after initial radiation therapy: early salvage high-intensity focused ultrasound improves oncologic outcomes. Radiother Oncol 2012;105:198-202. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23068708.

537. Uddin Ahmed H, Cathcart P, Chalasani V, et al. Whole-gland salvage high-intensity focused ultrasound therapy for localized prostate cancer recurrence after external beam radiation therapy. Cancer 2012;118:3071-3078. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22071795.

538. Crouzet S, Blana A, Murat FJ, et al. Salvage high-intensity focused ultrasound (HIFU) for locally recurrent prostate cancer after failed radiation therapy: Multi-institutional analysis of 418 patients. BJU Int 2017;119:896-904. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28063191.

539. Palermo G, Totaro A, Sacco E, et al. High intensity focused ultrasound as first line salvage therapy in prostate cancer local relapse after radical prostatectomy: 4-year follow-up outcomes. Minerva Urol Nefrol 2017;69:93-100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27681490.

540. Kanthabalan A, Peters M, Van Vulpen M, et al. Focal salvage high-intensity focused ultrasound in radiorecurrent prostate cancer. BJU Int 2017;120:246-256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28258616.

541. Siddiqui KM, Billia M, Arifin A, et al. Pathological, oncologic and functional outcomes of a prospective registry of salvage high intensity focused ultrasound ablation for radiorecurrent prostate cancer. J Urol 2016;197:97-102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27422297.

542. Shah TT, Peters M, Kanthabalan A, et al. PSA nadir as a predictive factor for biochemical disease-free survival and overall survival following whole-gland salvage HIFU following radiotherapy failure. Prostate Cancer Prostatic Dis 2016;19:311-316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27431499.

543. Barret E, Ahallal Y, Sanchez-Salas R, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. Eur Urol 2013;63:618-622. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23265382.

544. Walser E, Nance A, Ynalvez L, et al. Focal laser ablation of prostate cancer: Results in 120 patients with low- to intermediate-risk disease. J Vasc Interv Radiol 2019;30:401-409 e402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30819483.

545. Azzouzi AR, Vincendeau S, Barret E, et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. Lancet Oncol 2016;18:181-191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28007457.

546. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281:1591-1597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10235151.

547. Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific

antigen doubling time. J Clin Oncol 2013;31:3800-3806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24043751.

548. Trabulsi EJ, Rumble RB, Jadvar H, et al. Optimum imaging strategies for advanced prostate cancer: ASCO guideline. J Clin Oncol 2020;38:1963-1996. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31940221.

549. Koulikov D, Mohler MC, Mehedint DC, et al. Low detectable prostate specific antigen after radical prostatectomy--treat or watch? J Urol 2014;192:1390-1396. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24859441.

550. Shinghal R, Yemoto C, McNeal JE, Brooks JD. Biochemical recurrence without PSA progression characterizes a subset of patients after radical prostatectomy. Prostate-specific antigen. Urology 2003;61:380-385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12597952.

551. Michalski JM, Lawton C, El Naqa I, et al. Development of RTOG consensus guidelines for the definition of the clinical target volume for postoperative conformal radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;76:361-368. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19394158.

552. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181:956-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19167731.

553. Swanson GP, Goldman B, Tangen CM, et al. The prognostic impact of seminal vesicle involvement found at prostatectomy and the effects of adjuvant radiation: data from Southwest Oncology Group 8794. J Urol 2008;180:2453-2457; discussion 2458. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18930488.

554. Van der Kwast TH, Bolla M, Van Poppel H, et al. Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911. J Clin Oncol 2007;25:4178-4186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17878474.

555. Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. Lancet 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33002429.

556. Sargos P, Chabaud S, Latorzeff I, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. Lancet Oncol 2020;21:1341-1352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33002438.

557. Kneebone A, Fraser-Browne C, Duchesne GM, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. Lancet Oncol 2020;21:1331-1340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33002437.

558. Hackman G, Taari K, Tammela TL, et al. Randomised trial of adjuvant radiotherapy following radical prostatectomy versus radical prostatectomy alone in prostate cancer patients with positive margins or extracapsular extension. Eur Urol 2019;76:586-595. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31375279.

559. Sachdev S, Carroll P, Sandler H, et al. Assessment of Postprostatectomy Radiotherapy as Adjuvant or Salvage Therapy in Patients With Prostate Cancer: A Systematic Review. JAMA Oncol 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32852528.

560. Vale CL, Fisher D, Kneebone A, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33002431.

561. Tilki D, Chen MH, Wu J, et al. Adjuvant Versus Early Salvage Radiation Therapy for Men at High Risk for Recurrence Following Radical

Prostatectomy for Prostate Cancer and the Risk of Death. J Clin Oncol 2021;39:2284-2293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34086480.

562. Feng FY, Huang HC, Spratt DE, et al. Validation of a 22-Gene Genomic Classifier in Patients With Recurrent Prostate Cancer: An Ancillary Study of the NRG/RTOG 9601 Randomized Clinical Trial. JAMA Oncol 2021;7:544-552. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33570548.

563. Pisansky TM, Thompson IM, Valicenti RK, et al. Adjuvant and salvage radiotherapy after prostatectomy: ASTRO/AUA guideline amendment 2018-2019. J Urol 2019;202:533-538. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31042111.

564. Millar J, Boyd R, Sutherland J. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions: in regard to Lawton et al. (Int J Radiat Oncol Biol Phys 2007;69:646-655.). Int J Radiat Oncol Biol Phys 2008;71:316; author reply 316. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18406900.

565. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. J Clin Oncol 2007;25:5366-5373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18048817.

566. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7:472-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16750497.

567. Touijer KA, Mazzola CR, Sjoberg DD, et al. Long-term outcomes of patients with lymph node metastasis treated with radical prostatectomy without adjuvant androgen-deprivation therapy. Eur Urol 2014;65:20-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23619390.

568. Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J Clin Oncol 2014;32:3939-3947. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25245445.

569. Da Pozzo LF, Cozzarini C, Briganti A, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. Eur Urol 2009;55:1003-1011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19211184.

570. Briganti A, Karnes RJ, Da Pozzo LF, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. Eur Urol 2011;59:832-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21354694.

571. Lin CC, Gray PJ, Jemal A, Efstathiou JA. Androgen deprivation with or without radiation therapy for clinically node-positive prostate cancer. J Natl Cancer Inst 2015;107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25957435.

572. Cheung R, Kamat AM, de Crevoisier R, et al. Outcome of salvage radiotherapy for biochemical failure after radical prostatectomy with or without hormonal therapy. Int J Radiat Oncol Biol Phys 2005;63:134-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16111581.

573. Lee AK, D'Amico AV. Utility of prostate-specific antigen kinetics in addition to clinical factors in the selection of patients for salvage local therapy. J Clin Oncol 2005;23:8192-8197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16278472.

574. Patel R, Lepor H, Thiel RP, Taneja SS. Prostate-specific antigen velocity accurately predicts response to salvage radiotherapy in men with biochemical relapse after radical prostatectomy. Urology 2005;65:942-946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15882728.

575. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA

2004;291:1325-1332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15026399.

576. Ward JF, Zincke H, Bergstralh EJ, et al. Prostate specific antigen doubling time subsequent to radical prostatectomy as a prognosticator of outcome following salvage radiotherapy. J Urol 2004;172:2244-2248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15538240.

577. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 2008;299:2760-2769. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18560003.

578. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25:2035-2041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17513807.

579. Kane CJ, Amling CL, Johnstone PA, et al. Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology 2003;61:607-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12639656.

580. Martino P, Scattoni V, Galosi AB, et al. Role of imaging and biopsy to assess local recurrence after definitive treatment for prostate carcinoma (surgery, radiotherapy, cryotherapy, HIFU). World J Urol 2011;29:595-605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21553276.

581. Dotan ZA, Bianco FJ, Jr., Rabbani F, et al. Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy. J Clin Oncol 2005;23:1962-1968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15774789.

582. Spratt DE, Yousefi K, Deheshi S, et al. Individual patient-level meta-analysis of the performance of the Decipher genomic classifier in high-risk men after prostatectomy to predict development of metastatic disease. J Clin Oncol 2017;35:1991-1998. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28358655.

583. Cher ML, Bianco FJ, Jr., Lam JS, et al. Limited role of radionuclide bone scintigraphy in patients with prostate specific antigen elevations after radical prostatectomy. J Urol 1998;160:1387-1391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9751361.

584. Cotter SE, Chen MH, Moul JW, et al. Salvage radiation in men after prostate-specific antigen failure and the risk of death. Cancer 2011;117:3925-3932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21437885.

585. D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Identifying patients at risk for significant versus clinically insignificant postoperative prostate-specific antigen failure. J Clin Oncol 2005;23:4975-4979. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16051949.

586. Carrie C, Hasbini A, de Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. Lancet Oncol 2016;17:747-756. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27160475.

587. Carrie C, Magne N, Burban-Provost P, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. Lancet Oncol 2019;20:1740-1749. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31629656.

588. Dess RT, Sun Y, Jackson WC, et al. Association of Presalvage Radiotherapy PSA Levels After Prostatectomy With Outcomes of Long-term Antiandrogen Therapy in Men With Prostate Cancer. JAMA Oncol 2020;6:735-743. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32215583.

589. Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 2017;376:417-428. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28146658.

590. Roach M, 3rd, Hanks G, Thames H, Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965-974. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16798415.

591. Mohler JL, Halabi S, Ryan ST, et al. Management of recurrent prostate cancer after radiotherapy: long-term results from CALGB 9687 (Alliance), a prospective multi-institutional salvage prostatectomy series. Prostate Cancer Prostatic Dis 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30385835.

592. Ismail M, Ahmed S, Kastner C, Davies J. Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients. BJU Int 2007;100:760-764. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17662081.

593. Allen GW, Howard AR, Jarrard DF, Ritter MA. Management of prostate cancer recurrences after radiation therapy-brachytherapy as a salvage option. Cancer 2007;110:1405-1416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17685384.

594. Lu-Yao GL, Albertsen PC, Moore DF, et al. Fifteen-year survival outcomes following primary androgen-deprivation therapy for localized prostate cancer. JAMA Intern Med 2014;174:1460-1467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25023796.

595. Potosky AL, Haque R, Cassidy-Bushrow AE, et al. Effectiveness of primary androgen-deprivation therapy for clinically localized prostate cancer. J Clin Oncol 2014;32:1324-1330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24638009.

596. McLeod DG, Iversen P, See WA, et al. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int 2006;97:247-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16430622.

597. McLeod DG, See WA, Klimberg I, et al. The bicalutamide 150 mg early prostate cancer program: findings of the North American trial at 7.7-year median followup. J Urol 2006;176:75-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16753373.

598. Klotz L, O'Callaghan C, Ding K, et al. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. J Clin Oncol 2015;33:1151-1156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25732157.

599. D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 2008;299:289-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18212313.

600. Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol 2011;12:451-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21440505.

601. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365:107-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21751904.

602. Roach M, 3rd, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol 2008;26:585-591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18172188.

603. Bolla M, Maingon P, Carrie C, et al. Short androgen suppression and radiation dose escalation for intermediate- and high-risk localized prostate cancer: results of EORTC trial 22991. J Clin Oncol 2016;34:1748-1756. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26976418.

604. Zumsteg ZS, Spratt DE, Daskivich TJ, et al. Effect of androgen deprivation on long-term outcomes of intermediate-risk prostate cancer stratified as favorable or unfavorable: A secondary analysis of the RTOG 9408 randomized clinical trial. JAMA Netw Open 2020;3:e2015083. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32902647.

605. Pisansky TM, Hunt D, Gomella LG, et al. Duration of androgen suppression before radiotherapy for localized prostate cancer: radiation therapy oncology group randomized clinical trial 9910. J Clin Oncol 2015;33:332-339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25534388.

606. Rosenthal SA, Bae K, Pienta KJ, et al. Phase III multi-institutional trial of adjuvant chemotherapy with paclitaxel, estramustine, and oral etoposide combined with long-term androgen suppression therapy and radiotherapy versus long-term androgen suppression plus radiotherapy alone for high-risk prostate cancer: preliminary toxicity analysis of RTOG 99-02. Int J Radiat Oncol Biol Phys 2009;73:672-678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18990504.

607. Rosenthal SA, Hunt D, Sartor AO, et al. A phase 3 trial of 2 years of androgen suppression and radiation therapy with or without adjuvant chemotherapy for high-risk prostate cancer: final results of Radiation Therapy Oncology Group phase 3 randomized trial NRG Oncology RTOG 9902. Int J Radiat Oncol Biol Phys 2015;93:294-302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26209502.

608. D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004;292:821-827. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15315996.

609. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513-1520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15470214.

610. Jackson WC, Hartman HE, Dess RT, et al. Addition of Androgen-Deprivation Therapy or Brachytherapy Boost to External Beam Radiotherapy for Localized Prostate Cancer: A Network Meta-Analysis of Randomized Trials. J Clin Oncol 2020;38:3024-3031. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32396488.

611. Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 2008;26:2497-2504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18413638.

612. Lawton CAF, Lin X, Hanks GE, et al. Duration of androgen deprivation in locally advanced prostate cancer: Long-term update of NRG Oncology RTOG 9202. Int J Radiat Oncol Biol Phys 2017;98:296-303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28463149.

613. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009;360:2516-2527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19516032.

614. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. Lancet Oncol 2015;16:320-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25702876.

615. Souhami L, Bae K, Pilepich M, Sandler H. Impact of the duration of adjuvant hormonal therapy in patients with locally advanced prostate cancer treated with radiotherapy: a secondary analysis of RTOG 85-31. J Clin Oncol 2009;27:2137-2143. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19307511.

616. Nabid A, Carrier N, Martin AG, et al. Duration of androgen deprivation therapy in high-risk prostate cancer: A randomized phase III trial. Eur Urol 2018;74:432-441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29980331.

617. Denham JW, Joseph D, Lamb DS, et al. Short-term androgen suppression and radiotherapy versus intermediate-term androgen suppression and radiotherapy, with or without zoledronic acid, in men with locally advanced prostate cancer (TROG 03.04 RADAR): 10-year results from a randomised, phase 3, factorial trial. Lancet Oncol 2019;20:267-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30579763.

618. Kishan AU, Wang X, Seiferheld W, et al. Association of Gleason grade with androgen deprivation therapy duration and survival outcomes: A systematic review and patient-level meta-analysis. JAMA Oncol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30326032.

619. Schroder FH, Kurth KH, Fossa SD, et al. Early versus delayed endocrine treatment of T2-T3 pN1-3 M0 prostate cancer without local treatment of the primary tumour: final results of European Organisation for the Research and Treatment of Cancer protocol 30846 after 13 years of follow-up (a randomised controlled trial). Eur Urol 2009;55:14-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18823693.

620. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999;341:1781-1788. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10588962.

621. Wong YN, Freedland S, Egleston B, et al. Role of androgen deprivation therapy for node-positive prostate cancer. J Clin Oncol 2009;27:100-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19047295.

622. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2007;25:1596-1605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17404365.

623. Trachtenberg J, Gittleman M, Steidle C, et al. A phase 3, multicenter, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. J Urol 2002;167:1670-1674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11912385.

624. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet 2000;355:1491-1498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10801170.

625. Samson DJ, Seidenfeld J, Schmitt B, et al. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer 2002;95:361-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12124837.

626. Laufer M, Denmeade SR, Sinibaldi VJ, et al. Complete androgen blockade for prostate cancer: what went wrong? J Urol 2000;164:3-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10840412.

627. Vitzthum LK, Straka C, Sarkar RR, et al. Combined androgen blockade in localized prostate cancer treated with definitive radiation therapy. J Natl Compr Canc Netw 2019;17:1497-1504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31805534.

628. Dijkstra S, Witjes WP, Roos EP, et al. The AVOCAT study: Bicalutamide monotherapy versus combined bicalutamide plus dutasteride therapy for patients with locally advanced or metastatic carcinoma of the prostate-a long-term follow-up comparison and quality of life analysis. Springerplus 2016;5:653. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27330919.

629. Kolinsky M, de Bono JS. The ongoing challenges of targeting the androgen receptor. Eur Urol 2016;69:841-843. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26585581.

630. Albertsen PC, Klotz L, Tombal B, et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol 2014;65:565-573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24210090.

631. Sun M, Choueiri TK, Hamnvik OP, et al. Comparison of gonadotropin-releasing hormone agonists and orchiectomy: effects of androgen-deprivation therapy. JAMA Oncol 2016;2:500-507. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26720632.

632. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med 2020;382:2187-2196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32469183.

633. D'Amico AV, Renshaw AA, Loffredo B, Chen MH. Duration of testosterone suppression and the risk of death from prostate cancer in men treated using radiation and 6 months of hormone therapy. Cancer 2007;110:1723-1728. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17828774.

634. Duchesne GM, Woo HH, Bassett JK, et al. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol 2016;17:727-737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27155740.

635. Duchesne GM, Woo HH, King M, et al. Health-related quality of life for immediate versus delayed androgen-deprivation therapy in patients with asymptomatic, non-curable prostate cancer (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol 2017;18:1192-1201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28760403.

636. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006;24:3984-3990. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16921051.

637. Labrie F, Dupont A, Belanger A, Lachance R. Flutamide eliminates the risk of disease flare in prostatic cancer patients treated with a luteinizing hormone-releasing hormone agonist. J Urol 1987;138:804-806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3309363.

638. Schulze H, Senge T. Influence of different types of antiandrogens on luteinizing hormone-releasing hormone analogue-induced testosterone surge in patients with metastatic carcinoma of the prostate. J Urol 1990;144:934-941. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2144596.

639. Package Insert. ZYTIGA® (abiraterone acetate) tablets. Horsham, PA: Janssen Biotech, Inc.; 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202379s025lbl.pdf. Accessed November 15, 2021.

640. Package Insert. ZYTIGA® (abiraterone acetate) tablets. Horsham, PA: Janssen Biotech, Inc.; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202379s035lbl.pdf. Accessed November 15, 2021.

641. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352-360. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28578607.

642. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 2019;20:686-700. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30987939.

643. Chi KN, Protheroe A, Rodriguez-Antolin A, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naive prostate cancer (LATITUDE): an international, randomised phase 3 trial. Lancet Oncol 2018;19:194-206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29326030.

644. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. J Clin Oncol 2018;36:1389-1395. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29590007.

645. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13-24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31150574.

646. Agarwal N, McQuarrie K, Bjartell A, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. Lancet Oncol 2019;20:1518-1530. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31578173.

647. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol 2021;39:2294-2303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33914595.

648. Package Insert. ERLEADA™ (apalutamide) tablets, for oral use. Horsham, PA: Janssen Products, LP; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210951s001lbl.pdf. Accessed November 15, 2021.

649. Package Insert. ERLEADA™ (apalutamide) tablets, for oral use. Horsham, PA: Janssen Products, LP; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210951s006lbl.pdf. Accessed November 15, 2021.

650. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 2019;381:121-131. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31157964.

651. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol 2019;37:2974-2986. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31329516.

652. Shaw GL, Wilson P, Cuzick J, et al. International study into the use of intermittent hormone therapy in the treatment of carcinoma of the prostate: a meta-analysis of 1446 patients. BJU Int 2007;99:1056-1065. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17346277.

653. Akakura K, Bruchovsky N, Goldenberg SL, et al. Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. Cancer 1993;71:2782-2790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7682149.

654. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med 2012;367:895-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22931259.

655. Higano CS. Intermittent versus continuous androgen deprivation therapy. J Natl Compr Canc Netw 2014;12:727-733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24812139.

656. Schulman C, Cornel E, Matveev V, et al. Intermittent Versus Continuous Androgen Deprivation Therapy in Patients with Relapsing or Locally Advanced Prostate Cancer: A Phase 3b Randomised Study (ICELAND). Eur Urol 2016;69:720-727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26520703.

657. Dong Z, Wang H, Xu M, et al. Intermittent hormone therapy versus continuous hormone therapy for locally advanced prostate cancer: a meta-analysis. Aging Male 2015;18:233-237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26225795.

658. Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368:1314-1325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23550669.

659. Hershman DL, Unger JM, Wright JD, et al. Adverse health events following intermittent and continuous androgen deprivation in patients with metastatic prostate cancer. JAMA Oncol 2016;2:453-461. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26720308.

660. Tsai HT, Pfeiffer RM, Philips GK, et al. Risks of serious toxicities from intermittent versus continuous androgen deprivation therapy for advanced prostate cancer: a population based study. J Urol 2017;197:1251-1257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27993663.

661. Botrel TE, Clark O, dos Reis RB, et al. Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis. BMC Urol 2014;14:9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24460605.

662. Magnan S, Zarychanski R, Pilote L, et al. Intermittent vs continuous androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. JAMA Oncol 2015:1-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26378418.

663. Niraula S, Le LW, Tannock IF. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. J Clin Oncol 2013;31:2029-2036. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23630216.

664. Hussain M, Tangen C, Higano C, et al. Evaluating intermittent androgen-deprivation therapy phase III clinical trials: the devil is in the details. J Clin Oncol 2015;34:280-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26552421.

665. Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. BJU Int 2013;111:543-548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23351025.

666. Gaztanaga M, Crook J. Androgen deprivation therapy: minimizing exposure and mitigating side effects. J Natl Compr Canc Netw 2012;10:1088-1095; quiz 1088, 1096. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22956808.

667. Lapi F, Azoulay L, Niazi MT, et al. Androgen deprivation therapy and risk of acute kidney injury in patients with prostate cancer. JAMA 2013;310:289-296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23860987.

668. Gonzalez BD, Jim HS, Booth-Jones M, et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. J Clin Oncol 2015;33:2021-2027. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25964245.

669. Nead KT, Gaskin G, Chester C, et al. Androgen deprivation therapy and future Alzheimer's Disease risk. J Clin Oncol 2015;34:566-571. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26644522.

670. Khosrow-Khavar F, Rej S, Yin H, et al. Androgen deprivation therapy and the risk of dementia in patients with prostate cancer. J Clin Oncol 2017;35:201-207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27870566.

671. Baik SH, Kury FSP, McDonald CJ. Risk of Alzheimer's disease among senior medicare beneficiaries treated with androgen deprivation therapy for prostate cancer. J Clin Oncol 2017;35:3401-3409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28841388.

672. Deka R, Simpson DR, Bryant AK, et al. Association of androgen deprivation therapy with dementia in men with prostate cancer who receive definitive radiation therapy. JAMA Oncol 2018;4:1616-1617. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30325986.

673. Jayadevappa R, Chhatre S, Malkowicz SB, et al. Association between androgen deprivation therapy use and diagnosis of dementia in men with prostate cancer. JAMA Netw Open 2019;2:e196562. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31268539.

674. Ospina-Romero M, Glymour MM, Hayes-Larson E, et al. Association Between Alzheimer Disease and Cancer With Evaluation of Study Biases: A Systematic Review and Meta-analysis. JAMA Netw Open 2020;3:e2025515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33185677.

675. Sari Motlagh R, Quhal F, Mori K, et al. The Risk of New Onset Dementia and/or Alzheimer Disease among Patients with Prostate Cancer Treated with Androgen Deprivation Therapy: A Systematic Review and

Meta-Analysis. J Urol 2021;205:60-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32856962.

676. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154-164. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15647578.

677. Smith MR, Boyce SP, Moyneur E, et al. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol 2006;175:136-139; discussion 139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16406890.

678. Smith MR, Lee WC, Brandman J, et al. Gonadotropin-releasing hormone agonists and fracture risk: a claims-based cohort study of men with nonmetastatic prostate cancer. J Clin Oncol 2005;23:7897-7903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16258089.

679. Daniell HW, Dunn SR, Ferguson DW, et al. Progressive osteoporosis during androgen deprivation therapy for prostate cancer. J Urol 2000;163:181-186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10604342.

680. Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer 1998;83:1561-1566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9781950.

681. Maillefert JF, Sibilia J, Michel F, et al. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol 1999;161:1219-1222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10081873.

682. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med 2001;345:948-955. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11575286.

683. Smith MR, Finkelstein JS, McGovern FJ, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2002;87:599-603. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11836291.

684. National Osteoporosis Foundation. Learn about Osteoporosis. Available at: http://nof.org/patients. Accessed November 15, 2021.

685. World Health Organisation. WHO Fracture Risk Assessment Tool. Available at: http://www.shef.ac.uk/FRAX/. Accessed November 15, 2021.

686. Smith MR, Eastham J, Gleason DM, et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol 2003;169:2008-2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12771706.

687. Michaelson MD, Kaufman DS, Lee H, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol 2007;25:1038-1042. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17369566.

688. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. Ann Intern Med 2007;146:416-424. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17371886.

689. Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009;361:745-755. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19671656.

690. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448-4456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16983113.

691. D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007;25:2420-2425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17557956.

692. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24:1868-1876. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16622261.

693. Tsai HK, D'Amico AV, Sadetsky N, et al. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. J Natl Cancer Inst 2007;99:1516-1524. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17925537.

694. Efstathiou JA, Bae K, Shipley WU, et al. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. J Clin Oncol 2009;27:92-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19047297.

695. Saigal CS, Gore JL, Krupski TL, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110:1493-1500. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17657815.

696. Nguyen PL, Je Y, Schutz FA, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. JAMA 2011;306:2359-2366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22147380.

697. Voog JC, Paulus R, Shipley WU, et al. Cardiovascular mortality following short-term androgen deprivation in clinically localized prostate cancer: An analysis of rtog 94-08. Eur Urol 2016;69:204-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26362090.

698. Jespersen CG, Norgaard M, Borre M. Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. Eur Urol 2014;65:704-709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23433805.

699. Schmid M, Sammon JD, Reznor G, et al. Dose-dependent effect of androgen deprivation therapy for localized prostate cancer on adverse cardiac events. BJU Int 2015;118:221-229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26074405.

700. Chen DY, See LC, Liu JR, et al. Risk of cardiovascular ischemic events after surgical castration and gonadotropin-releasing hormone agonist therapy for prostate cancer: A nationwide cohort study. J Clin Oncol 2017;35:3697-3705. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28968166.

701. Scailteux LM, Vincendeau S, Balusson F, et al. Androgen deprivation therapy and cardiovascular risk: No meaningful difference between GnRH antagonist and agonists-a nationwide population-based cohort study based on 2010-2013 French Health Insurance data. Eur J Cancer 2017;77:99-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28390298.

702. O'Farrell S, Garmo H, Holmberg L, et al. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J Clin Oncol 2015;33:1243-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25732167.

703. Gardner JR, Livingston PM, Fraser SF. Effects of exercise on treatment-related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. J Clin Oncol 2014;32:335-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24344218.

704. Berruti A, Dogliotti L, Terrone C, et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J Urol 2002;167:2361-2367; discussion 2367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11992038.

705. Tayek JA, Heber D, Byerley LO, et al. Nutritional and metabolic effects of gonadotropin-releasing hormone agonist treatment for prostate cancer. Metabolism 1990;39:1314-1319. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2123281.

706. Dockery F, Bulpitt CJ, Agarwal S, et al. Testosterone suppression in men with prostate cancer leads to an increase in arterial stiffness and hyperinsulinaemia. Clin Sci (Lond) 2003;104:195-201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12546642.

707. Smith JC, Bennett S, Evans LM, et al. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab 2001;86:4261-4267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11549659.

708. Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. J Clin Endocrinol Metab 2006;91:1305-1308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16434464.

709. Eri LM, Urdal P, Bechensteen AG. Effects of the luteinizing hormone-releasing hormone agonist leuprolide on lipoproteins, fibrinogen and plasminogen activator inhibitor in patients with benign prostatic hyperplasia. J Urol 1995;154:100-104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7539852.

710. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148-1159. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18309951.

711. Smith MR, Kabbinavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 2005;23:2918-2925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15860850.

712. Abida W, Armenia J, Gopalan A, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 2017;2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28825054.

713. Ryan CJ, Shah S, Efstathiou E, et al. Phase II study of abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. Clin Cancer Res 2011;17:4854-4861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21632851.

714. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 2016;34:1402-1418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26903579.

715. Holzbeierlein J, Lal P, LaTulippe E, et al. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. Am J Pathol 2004;164:217-227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14695335.

716. Mohler JL, Gregory CW, Ford OH, 3rd, et al. The androgen axis in recurrent prostate cancer. Clin Cancer Res 2004;10:440-448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14760063.

717. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21612468.

718. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983-992. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22995653.

719. Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol 2012;13:1210-1217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23142059.

720. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138-148. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23228172.

721. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015;16:152-160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25601341.

722. Package Insert. YONSA® (abiraterone acetate) tablets, for oral use. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210308s000lbl.pdf. Accessed November 15, 2021.

723. Package Insert. YONSA® (abiraterone acetate) tablets, for oral use. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210308s001lbl.pdf. Accessed November 15, 2021.

724. Hussaini A, Olszanski AJ, Stein CA, et al. Impact of an alternative steroid on the relative bioavailability and bioequivalence of a novel versus the originator formulation of abiraterone acetate. Cancer Chemother Pharmacol 2017;80:479-486. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28695267.

725. Goldwater R, Hussaini A, Bosch B, Nemeth P. Comparison of a novel formulation of abiraterone acetate vs. The originator formulation in healthy male subjects: Two randomized, open-label, crossover studies. Clin Pharmacokinet 2017;56:803-813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28425029.

726. Stein CA, Levin R, Given R, et al. Randomized phase 2 therapeutic equivalence study of abiraterone acetate fine particle formulation vs. originator abiraterone acetate in patients with metastatic castration-resistant prostate cancer: The STAAR study. Urol Oncol 2018;36:81 e89-81 e16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29150328.

727. Romero-Laorden N, Lozano R, Jayaram A, et al. Phase II pilot study of the prednisone to dexamethasone switch in metastatic castration-resistant prostate cancer (mCRPC) patients with limited progression on abiraterone plus prednisone (SWITCH study). Br J Cancer 2018;119:1052-1059. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30131546.

728. Fenioux C, Louvet C, Charton E, et al. Switch from abiraterone plus prednisone to abiraterone plus dexamethasone at asymptomatic PSA progression in patients with metastatic castration-resistant prostate cancer. BJU Int 2019;123:300-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30099821.

729. Package Insert. XTANDI® (enzalutamide) capsules, for oral use. Northbrook, IL: Astellas Pharma US, Inc.; 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203415Orig1s014lbl.pdf. Accessed November 15, 2021.

730. Package Insert. XTANDI® (enzalutamide) capsules, for oral use. Northbrook, IL: Astellas Pharma US, Inc.; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203415s016lbl.pdf. Accessed November 15, 2021.

731. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187-1197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22894553.

732. Fizazi K, Scher HI, Miller K, et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-

resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. Lancet Oncol 2014;15:1147-1156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25104109.

733. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424-433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24881730.

734. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. Eur Urol 2017;71:151-154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27477525.

735. Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol 2016;17:153-163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26774508.

736. Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. J Clin Oncol 2016;34:2098-2106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26811535.

737. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018;378:2465-2474. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29949494.

738. Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2020;382:2197-2206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32469184.

739. Tombal B, Saad F, Penson D, et al. Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic, castration-resistant prostate cancer (PROSPER): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30770294.

740. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408-1418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29420164.

741. Saad F, Cella D, Basch E, et al. Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2018;19:1404-1416. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30213449.

742. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. Eur Urol 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32907777.

743. Package Insert. NUBEQA (darolutamide) tablets, for oral use. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212099Orig1s000lbl.pdf. Accessed November 15, 2021.

744. Package Insert. NUBEQA (darolutamide) tablets, for oral use. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212099s001lbl.pdf. Accessed November 15, 2021.

745. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019;380:1235-1246. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30763142.

746. Fizazi K, Shore N, Tammela TL, et al. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. N Engl J Med 2020;383:1040-1049. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32905676.

747. Small EJ, Halabi S, Dawson NA, et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). J Clin Oncol 2004;22:1025-1033. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15020604.

748. Dupont A, Gomez JL, Cusan L, et al. Response to flutamide withdrawal in advanced prostate cancer in progression under combination therapy. J Urol 1993;150:908-913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7688437.

749. Sartor AO, Tangen CM, Hussain MH, et al. Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). Cancer 2008;112:2393-2400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18383517.

750. Denmeade SR, Wang H, Agarwal N, et al. TRANSFORMER: A Randomized Phase II Study Comparing Bipolar Androgen Therapy Versus Enzalutamide in Asymptomatic Men With Castration-Resistant Metastatic Prostate Cancer. J Clin Oncol 2021;39:1371-1382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33617303.

751. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-1512. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15470213.

752. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008;26:242-245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182665.

753. Kellokumpu-Lehtinen PL, Harmenberg U, Joensuu T, et al. 2-Weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. Lancet Oncol 2013;14:117-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23294853.

754. de Morree ES, Vogelzang NJ, Petrylak DP, et al. Association of survival benefit with docetaxel in prostate cancer and total number of cycles administered: A post hoc analysis of the mainsail study. JAMA Oncol 2017;3:68-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27560549.

755. Lavaud P, Gravis G, Foulon S, et al. Anticancer activity and tolerance of treatments received beyond progression in men treated upfront with androgen deprivation therapy with or without docetaxel for metastatic castration-naive prostate cancer in the GETUG-AFU 15 phase 3 trial. Eur Urol 2018;73:696-703. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29074061.

756. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737-746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26244877.

757. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36:1080-1087. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29384722.

758. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:149-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23306100.

759. Gravis G, Boher JM, Joly F, et al. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol 2015;70:256-262. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26610858.

760. Abdel-Rahman O. Combined chemohormonal strategy in hormone-sensitive prostate cancer: A pooled analysis of randomized studies. Clin Genitourin Cancer 2016;14:203-209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26768966.

761. Tucci M, Bertaglia V, Vignani F, et al. Addition of docetaxel to androgen deprivation therapy for patients with hormone-sensitive metastatic prostate cancer: a systematic review and meta-analysis. Eur Urol 2015;69:563-573. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26422676.

762. Vale CL, Burdett S, Rydzewska LH, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol 2015;17:243-256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26718929.

763. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147-1154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20888992.

764. Bahl A, Oudard S, Tombal B, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol 2013;24:2402-2408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23723295.

765. Meisel A, von Felten S, Vogt DR, et al. Severe neutropenia during cabazitaxel treatment is associated with survival benefit in men with metastatic castration-resistant prostate cancer (mCRPC): A post-hoc analysis of the TROPIC phase III trial. Eur J Cancer 2016;56:93-100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26829012.

766. Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m(2)) and the currently approved dose (25 mg/m(2)) in postdocetaxel patients with metastatic castration-resistant prostate cancer-PROSELICA. J Clin Oncol 2017;35:3198-3206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28809610.

767. Oudard S, Fizazi K, Sengelov L, et al. Cabazitaxel versus docetaxel as first-line therapy for patients with metastatic castration-resistant prostate cancer: a randomized phase III trial-FIRSTANA. J Clin Oncol 2017:JCO2016721068. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28753384.

768. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 2019;381:2506-2518. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31566937.

769. Fizazi K, Kramer G, Eymard JC, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. Lancet Oncol 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32926841.

770. Sarantopoulos J, Mita AC, He A, et al. Safety and pharmacokinetics of cabazitaxel in patients with hepatic impairment: a phase I dose-escalation study. Cancer Chemother Pharmacol 2017;79:339-351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28058445.

771. Corn PG, Heath EI, Zurita A, et al. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1-2 trial. Lancet Oncol 2019;20:1432-1443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31515154.

772. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20818862.

773. Higano CS, Armstrong AJ, Sartor AO, et al. Real-world outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. Cancer 2019;125:4172-4180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31483485.

774. Package Insert. KEYTRUDA® (pembrolizumab). Whitehouse Station, NJ: Merck & Co, Inc.; 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s031lbl.pdf. Accessed November 15, 2021.

775. Package Insert. KEYTRUDA® (pembrolizumab). Whitehouse Station, NJ: Merck & Co, Inc.; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s117,s118lbl.pdf. Accessed October 7, 2021.

776. Graff JN, Alumkal JJ, Drake CG, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget 2016;7:52810-52817. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27429197.

777. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-413. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28596308.

778. Hansen AR, Massard C, Ott PA, et al. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. Ann Oncol 2018;29:1807-1813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29992241.

779. Tucker MD, Zhu J, Marin D, et al. Pembrolizumab in men with heavily treated metastatic castrate-resistant prostate cancer. Cancer Med 2019;8:4644-4655. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31270961.

780. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31682550.

781. Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: Multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol 2020;38:395-405. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31774688.

782. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353-1365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32919526.

783. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996;14:1756-1764. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8656243.

784. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. J Clin Oncol 1999;17:2506-2513. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561316.

785. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol 2015;33:244-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25366685.

786. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697-1708. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26510020.

787. Clarke N, Wiechno P, Alekseev B, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2018;19:975-986. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29880291.

788. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917-921. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15829967.

789. Package Insert. LYNPARZA® (olaparib) tablets, for oral use. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208558s019s020lbl.pdf. Accessed November 15, 2021.

790. Package Insert. RUBRACA® (rucaparib) tablets, for oral use. Boulder, CO: Clovis Oncology, Inc.; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209115s009lbl.pdf. Accessed November 15, 2021.

791. Imyanitov EN, Moiseyenko VM. Drug therapy for hereditary cancers. Hered Cancer Clin Pract 2011;9:5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21819606.

792. Cheng HH, Pritchard CC, Boyd T, et al. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer. Eur Urol 2016;69:992-995. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26724258.

793. Pomerantz MM, Spisak S, Jia L, et al. The association between germline BRCA2 variants and sensitivity to platinum-based chemotherapy among men with metastatic prostate cancer. Cancer 2017;123:3532-3539. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28608931.

794. Mota JM, Barnett E, Nauseef JT, et al. Platinum-based chemotherapy in metastatic prostate cancer with DNA repair gene alterations. JCO Precis Oncol 2020;4:355-366. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32856010.

795. Schmid S, Omlin A, Higano C, et al. Activity of Platinum-Based Chemotherapy in Patients With Advanced Prostate Cancer With and Without DNA Repair Gene Aberrations. JAMA Netw Open 2020;3:e2021692. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33112397.

796. Hager S, Ackermann CJ, Joerger M, et al. Anti-tumour activity of platinum compounds in advanced prostate cancer-a systematic literature review. Ann Oncol 2016;27:975-984. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27052650.

797. Antonarakis ES, Lu C, Luber B, et al. Germline DNA-repair gene mutations and outcomes in men with metastatic castration-resistant prostate cancer receiving first-line abiraterone and enzalutamide. Eur Urol 2018;74:218-225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29439820.

798. Mateo J, Cheng HH, Beltran H, et al. Clinical outcome of prostate cancer patients with germline DNA repair mutations: Retrospective analysis from an international study. Eur Urol 2018;73:687-693. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29429804.

799. Antonarakis ES, Isaacsson Velho P, Fu W, et al. CDK12-Altered Prostate Cancer: Clinical Features and Therapeutic Outcomes to Standard Systemic Therapies, Poly (ADP-Ribose) Polymerase Inhibitors, and PD-1 Inhibitors. JCO Precis Oncol 2020;4:370-381. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32462107.

800. Schweizer MT, Ha G, Gulati R, et al. CDK12-Mutated Prostate Cancer: Clinical Outcomes With Standard Therapies and Immune Checkpoint Blockade. JCO Precis Oncol 2020;4:382-392. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32671317.

801. Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 2020;21:162-174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31806540.

802. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091-2102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32343890.

803. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32955174.

804. Package Insert. LYNPARZA® (olaparib) tablets, for oral use. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf. Accessed November 15, 2021.

805. Abida W, Patnaik A, Campbell D, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. J Clin Oncol 2020:JCO2001035. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32795228.

806. Abida W, Campbell D, Patnaik A, et al. Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: Analysis from the phase II TRITON2 study. Clin Cancer Res 2020;26:2487-2496. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32086346.

807. Beltran H, Tagawa ST, Park K, et al. Challenges in recognizing treatment-related neuroendocrine prostate cancer. J Clin Oncol 2012;30:e386-389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23169519.

808. Aggarwal R, Huang J, Alumkal JJ, et al. Clinical and genomic characterization of treatment-emergent small-cell neuroendocrine prostate cancer: A multi-institutional prospective study. J Clin Oncol 2018;36:2492-2503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29985747.

809. Brennan SM, Gregory DL, Stillie A, et al. Should extrapulmonary small cell cancer be managed like small cell lung cancer? Cancer 2010;116:888-895. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20052730.

810. Yao JL, Madeb R, Bourne P, et al. Small cell carcinoma of the prostate: an immunohistochemical study. Am J Surg Pathol 2006;30:705-712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16723847.

811. Sella A, Konichezky M, Flex D, et al. Low PSA metastatic androgen-independent prostate cancer. Eur Urol 2000;38:250-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10940696.

812. Spiess PE, Pettaway CA, Vakar-Lopez F, et al. Treatment outcomes of small cell carcinoma of the prostate: a single-center study. Cancer 2007;110:1729-1737. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17786954.

813. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458-1468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12359855.

814. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004;96:879-882. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15173273.

815. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24590644.

816. James ND, Pirrie SJ, Pope AM, et al. Clinical outcomes and survival following treatment of metastatic castrate-refractory prostate cancer with docetaxel alone or with strontium-89, zoledronic acid, or both: The trapeze randomized clinical trial. JAMA Oncol 2016;2:493-499. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26794729.

817. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21353695.

818. Tarassoff P, Csermak K. Avascular necrosis of the jaws: risk factors in metastatic cancer patients. J Oral Maxillofac Surg 2003;61:1238-1239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14586868.

819. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: A randomized clinical trial. JAMA

2017;317:48-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28030702.

820. Coleman RE. Risks and benefits of bisphosphonates. Br J Cancer 2008;98:1736-1740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18506174.

821. Package Insert. Zometa® (zoledronic acid) Injection. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021223s041lbl.pdf. Accessed November 15, 2021.

822. Package Insert. Xgeva (denosumab) injection, for subcutaneous use. Thousand Oaks, CA: Amgen Inc.; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125320s207lbl.pdf. Accessed November 15, 2021.

823. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 2012;379:39-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22093187.

824. Abratt RP, Brune D, Dimopoulos MA, et al. Randomised phase III study of intravenous vinorelbine plus hormone therapy versus hormone therapy alone in hormone-refractory prostate cancer. Ann Oncol 2004;15:1613-1621. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15520061.

825. Aparicio AM, Harzstark AL, Corn PG, et al. Platinum-based chemotherapy for variant castrate-resistant prostate cancer. Clin Cancer Res 2013;19:3621-3630. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23649003.

826. Beer TM, Garzotto M, Katovic NM. High-dose calcitriol and carboplatin in metastatic androgen-independent prostate cancer. Am J Clin Oncol 2004;27:535-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15596926.

827. Cabrespine A, Guy L, Khenifar E, et al. Randomized Phase II study comparing paclitaxel and carboplatin versus mitoxantrone in patients with hormone-refractory prostate cancer. Urology 2006;67:354-359. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16442593.

828. Harris KA, Harney E, Small EJ. Liposomal doxorubicin for the treatment of hormone-refractory prostate cancer. Clin Prostate Cancer 2002;1:37-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15046711.

829. Ladoire S, Eymard JC, Zanetta S, et al. Metronomic oral cyclophosphamide prednisolone chemotherapy is an effective treatment for metastatic hormone-refractory prostate cancer after docetaxel failure. Anticancer Res 2010;30:4317-4323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21036758.

830. Lee JL, Ahn JH, Choi MK, et al. Gemcitabine-oxaliplatin plus prednisolone is active in patients with castration-resistant prostate cancer for whom docetaxel-based chemotherapy failed. Br J Cancer 2014;110:2472-2478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24736579.

831. Loriot Y, Massard C, Gross-Goupil M, et al. Combining carboplatin and etoposide in docetaxel-pretreated patients with castration-resistant prostate cancer: a prospective study evaluating also neuroendocrine features. Ann Oncol 2009;20:703-708. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19179557.

832. Nakabayashi M, Sartor O, Jacobus S, et al. Response to docetaxel/carboplatin-based chemotherapy as first- and second-line therapy in patients with metastatic hormone-refractory prostate cancer. BJU Int 2008;101:308-312. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18184327.

833. Torti FM, Aston D, Lum BL, et al. Weekly doxorubicin in endocrine-refractory carcinoma of the prostate. J Clin Oncol 1983;1:477-482. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6668511.

834. Shamash J, Powles T, Sarker SJ, et al. A multi-centre randomised phase III trial of dexamethasone vs dexamethasone and diethylstilbestrol in castration-resistant prostate cancer: immediate vs deferred diethylstilbestrol. Br J Cancer 2011;104:620-628. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21285990.

835. Noonan KL, North S, Bitting RL, et al. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol 2013;24:1802-1807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23585511.

836. Loriot Y, Bianchini D, Ileana E, et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol 2013;24:1807-1812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23576708.

837. Bianchini D, Lorente D, Rodriguez-Vida A, et al. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. Eur J Cancer 2014;50:78-84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24074764.

838. Smith MR, Saad F, Rathkopf DE, et al. Clinical outcomes from androgen signaling-directed therapy after treatment with abiraterone acetate and prednisone in patients with metastatic castration-resistant prostate cancer: Post hoc analysis of COU-AA-302. Eur Urol 2017;72:10-13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28314611.

839. Antonarakis ES, Armstrong AJ, Dehm SM, Luo J. Androgen receptor variant-driven prostate cancer: clinical implications and therapeutic targeting. Prostate Cancer Prostatic Dis 2016;19:231-241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27184811.

840. Khalaf DJ, Annala M, Taavitsainen S, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol 2019;20:1730-1739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31727538.

841. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014;371:1028-1038. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25184630.

842. Antonarakis ES, Lu C, Luber B, et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. JAMA Oncol 2015;1:582-591. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26181238.

843. Scher HI, Lu D, Schreiber NA, et al. Association of AR-V7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer. JAMA Oncol 2016;2:1441-1449. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27262168.

844. Scher HI, Graf RP, Schreiber NA, et al. Assessment of the validity of nuclear-localized androgen receptor splice variant 7 in circulating tumor cells as a predictive biomarker for castration-resistant prostate cancer. JAMA Oncol 2018;4:1179-1186. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29955787.

845. Armstrong AJ, Halabi S, Luo J, et al. Prospective multicenter validation of androgen receptor splice variant 7 and hormone therapy resistance in high-risk castration-resistant prostate cancer: The PROPHECY study. J Clin Oncol 2019;37:1120-1129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30865549.

846. Armstrong AJ, Luo J, Nanus DM, et al. Prospective Multicenter Study of Circulating Tumor Cell AR-V7 and Taxane Versus Hormonal Treatment Outcomes in Metastatic Castration-Resistant Prostate Cancer. JCO Precis Oncol 2020;4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33154984.

847. Erho N, Crisan A, Vergara IA, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. PLoS One 2013;8:e66855. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23826159.

848. Karnes RJ, Bergstralh EJ, Davicioni E, et al. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. J Urol 2013;190:2047-2053. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23770138.

849. Klein EA, Yousefi K, Haddad Z, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. Eur Urol 2015;67:778-786. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25466945.

850. Prensner JR, Zhao S, Erho N, et al. RNA biomarkers associated with metastatic progression in prostate cancer: a multi-institutional high-throughput analysis of SChLAP1. Lancet Oncol 2014;15:1469-1480. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25456366.

851. Tomlins SA, Alshalalfa M, Davicioni E, et al. Characterization of 1577 primary prostate cancers reveals novel biological and clinicopathologic insights into molecular subtypes. Eur Urol 2015;68:555-567. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25964175.

852. Ross AE, Johnson MH, Yousefi K, et al. Tissue-based genomics augments post-prostatectomy risk stratification in a natural history cohort of intermediate- and high-risk men. Eur Urol 2015;69:157-165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26058959.

853. Yamoah K, Johnson MH, Choeurng V, et al. Novel biomarker signature that may predict aggressive disease in African American men with prostate cancer. J Clin Oncol 2015;33:2789-2796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26195723.

854. Cooperberg MR, Davicioni E, Crisan A, et al. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. Eur Urol 2015;67:326-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24998118.

855. Ross AE, Feng FY, Ghadessi M, et al. A genomic classifier predicting metastatic disease progression in men with biochemical recurrence after prostatectomy. Prostate Cancer Prostatic Dis 2014;17:64-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24145624.

856. Den RB, Feng FY, Showalter TN, et al. Genomic prostate cancer classifier predicts biochemical failure and metastases in patients after postoperative radiation therapy. Int J Radiat Oncol Biol Phys 2014;89:1038-1046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25035207.

857. Den RB, Yousefi K, Trabulsi EJ, et al. Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy. J Clin Oncol 2015;33:944-951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25667284.

858. Freedland SJ, Choeurng V, Howard L, et al. Utilization of a genomic classifier for prediction of metastasis following salvage radiation therapy after radical prostatectomy. Eur Urol 2016;70:588-596. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26806658.

859. Klein EA, Santiago-Jimenez M, Yousefi K, et al. Molecular analysis of low grade prostate cancer using a genomic classifier of metastatic potential. J Urol 2017;197:122-128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27569435.

860. Karnes RJ, Choeurng V, Ross AE, et al. Validation of a genomic risk classifier to predict prostate cancer-specific mortality in men with adverse pathologic features. Eur Urol 2018;73:168-175. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28400167.

861. Khor LY, Bae K, Paulus R, et al. MDM2 and Ki-67 predict for distant metastasis and mortality in men treated with radiotherapy and androgen deprivation for prostate cancer: RTOG 92-02. J Clin Oncol 2009;27:3177-3184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19470936.

862. Verhoven B, Yan Y, Ritter M, et al. Ki-67 is an independent predictor of metastasis and cause-specific mortality for prostate cancer patients treated on Radiation Therapy Oncology Group (RTOG) 94-08. Int J Radiat Oncol Biol Phys 2013;86:317-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23474109.

863. Li R, Heydon K, Hammond ME, et al. Ki-67 staining index predicts distant metastasis and survival in locally advanced prostate cancer treated with radiotherapy: an analysis of patients in radiation therapy oncology group protocol 86-10. Clin Cancer Res 2004;10:4118-4124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15217948.

864. Fisher G, Yang ZH, Kudahetti S, et al. Prognostic value of Ki-67 for prostate cancer death in a conservatively managed cohort. Br J Cancer 2013;108:271-277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23329234.

865. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. Eur Urol 2014;66:550-560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24836057.

866. Cullen J, Rosner IL, Brand TC, et al. A biopsy-based 17-gene genomic prostate score predicts recurrence after radical prostatectomy and adverse surgical pathology in a racially diverse population of men with clinically low- and intermediate-risk prostate cancer. Eur Urol 2015;68:123-131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25465337.

867. Cuzick J, Stone S, Fisher G, et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. Br J Cancer 2015;113:382-389. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26103570.

868. Cooperberg MR, Simko JP, Cowan JE, et al. Validation of a cell-cycle progression gene panel to improve risk stratification in a contemporary prostatectomy cohort. J Clin Oncol 2013;31:1428-1434. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23460710.

869. Tosoian JJ, Chappidi MR, Bishoff JT, et al. Prognostic utility of biopsy-derived cell cycle progression score in patients with National Comprehensive Cancer Network low-risk prostate cancer undergoing radical prostatectomy: implications for treatment guidance. BJU Int 2017;120:808-814. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28481440.

870. Cuzick J, Yang ZH, Fisher G, et al. Prognostic value of PTEN loss in men with conservatively managed localised prostate cancer. Br J Cancer 2013;108:2582-2589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23695019.

871. Lotan TL, Carvalho FL, Peskoe SB, et al. PTEN loss is associated with upgrading of prostate cancer from biopsy to radical prostatectomy. Mod Pathol 2015;28:128-137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24993522.

872. Lotan TL, Gurel B, Sutcliffe S, et al. PTEN protein loss by immunostaining: analytic validation and prognostic indicator for a high risk surgical cohort of prostate cancer patients. Clin Cancer Res 2011;17:6563-6573. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21878536.

873. Lotan TL, Wei W, Ludkovski O, et al. Analytic validation of a clinical-grade PTEN immunohistochemistry assay in prostate cancer by comparison with PTEN FISH. Mod Pathol 2016;29:904-914. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27174589.

874. Troyer DA, Jamaspishvili T, Wei W, et al. A multicenter study shows PTEN deletion is strongly associated with seminal vesicle involvement and extracapsular extension in localized prostate cancer. Prostate 2015;75:1206-1215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25939393.

875. Package insert. Gallium Ga 68 PSMA-11 Injection, for intravenous use. Los Angeles, CA: University of California, Los Angeles 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212642s000lbl.pdf. Accessed June 23, 2021.

876. Package Insert. PYLARIFY® (piflufolastat F 18) injection, for intravenous use. Billerica, MA: Progenics Pharmaceuticals, Inc.; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214793s000lbl.pdf. Accessed October 11, 2021.

877. Package Insert. Choline C 11 Injection, for intravenous use. Rochester, Minnesota: Mayo Clinic PET Radiochemistry Facility; 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203155s000lbl.pdf. Accessed October 11, 2021.

878. Package Insert. AXUMIN (fluciclovine F 18) injection, for intravenous use. Oxford, UK: Blue Earth Diagnostics Ltd; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208054s034lbl.pdf. Accessed October 11, 2021.