National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Prostate Cancer

Version 2.2026 — September 15, 2025

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

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

Nabil Adra, MD, MSc †
Indiana University Melvin and Bren Simon Comprehensive Cancer Center

Bilawal Ahmed, MD †
The University of Tennessee Health Science Center

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

Rhonda Bitting, MD †
Duke Cancer Institute

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

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

Steve Y. Cho, MD φ
University of Wisconsin Carbone Cancer Center

Anthony Victor D'Amico, MD, PhD §
Dana-Farber/Brigham and Women's Cancer Center | Mass General 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, BSEE ¥**
Prostate Health Education Network (PHEN)

***Xin Gao, MD †**
Dana-Farber/Brigham and Women's Cancer Center | Mass General Cancer Center

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

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

R. Jeffrey Karnes, MD ω
Mayo Clinic Comprehensive Cancer Center

Amar Kishan, MD §
UCLA Jonsson Comprehensive Cancer Center

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

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

Daniel Lee, MD, MS ω
Abramson Cancer Center at The University of Pennsylvania

Tamara Lotan, MD ≠
Johns Hopkins Kimmel Cancer Center

Andrew McDonald, MD, MS §
O'Neal Comprehensive Cancer Center at UAB

Todd Morgan, MD ω
University of Michigan Rogel Cancer Center

Rodrigo Pessoa, MD, PhD ω
Moffitt Cancer Center

Soroush Rais-Bahrami, MD, MBA ω
O'Neal Comprehensive Cancer Center at UAB

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

Kristen R. Scarpato, MD, MPH ω
Vanderbilt-Ingram Cancer Center

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

Russell Szmulewitz, MD ‡ †
The UChicago Medicine Comprehensive Cancer Center

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

David VanderWeele, MD, PhD †
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Jessica Karen Wong, MD §
Fox Chase Cancer Center

NCCN
Deborah Freedman-Cass, PhD
Emily Kovach

[NCCN Guidelines Panel Disclosures]

∩ Diagnostic/Interventional radiology
‡ Hematology/Hematology oncology
† Medical oncology
φ Nuclear medicine
≠ Pathology
¥ Patient advocate
§ Radiotherapy/Radiation oncology
ω Urology
¶ Surgery/Surgical oncology
* Discussion Section Writing Committee

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 2.2026 of the NCCN Guidelines for Prostate Cancer from Version 1.2026 include:

MS-1
- The sections of the Discussion regarding mCSPC and mCRPC were updated to reflect the changes in the algorithm.

Updates in Version 1.2026 of the NCCN Guidelines for Prostate Cancer from Version 2.2025 include:

Global
- Very-low-risk group has been removed from the Guidelines.
- Androgen receptor pathway inhibitors ("ARPIs") has replaced "other hormonal agents" throughout the Guidelines.
- References have been updated throughout the Guidelines.

PROS-1
- Workup
  - Top pathway
    - ◊ Bullet 3 modified: Perform and/or collect prostate-specific antigen (PSA) ~~and calculate PSA density.~~
    - ◊ Bullet 4 modified:~~Obtain and~~ Review diagnostic prostate biopsies.
  - Bottom pathway
    - ◊ Bullet 3 modified: *Consider* ~~Perform~~ DRE to confirm clinical stage.
    - ◊ Last column, pathway added: See Workup and Treatment of High-Volume M1 CSPC (PROS-15).
- Footnote d added: Refer to the NCCN Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).
- Footnote h added: See "Number of Metastatic Sites" in the Principles of MDT (PROS-M). (Also for PROS-2A, 7A, -8A, -9A, -10A, -11, -12, -13, and -15A, and 18A)

PROS-2
- Additional Evaluation for Intermediate, High, and Very high, sub-bullets for soft-tissue imaging
  - Sub-bullet 1 modified: If regional ~~or distant~~ metastases are found, see PROS-7 ~~or~~
  - Sub-bullet added: If distant metastases are found, see PROS-14 for Low-Volume M1 (Metachronous or Synchronous) or Synchronous Oligometastatic CSPC or PROS-15 for High-Volume M1 CSPC.

PROS-2A
- Footnote removed: An ultrasound-, 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.

PROS-3
- Footnote n added: Principles of Focal/Subtotal Therapy or Whole Gland Ablative Therapy (PROS-I). (Also for PROS-4, -5, -6, and -7A)

PROS-6
- ≤5 y and asymptomatic
  - Initial therapy modified: Observation or RT ± *ADT* ~~or ADT ± RT~~.

PROS-7A
- Footnote x modified: Adverse ~~laboratory/~~pathologic features include: positive margin(s), seminal vesicle invasion, *or* extracapsular extension~~, or detectable PSA~~.
- Footnote removed: 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.
- Footnote removed: The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended option). (Also for PROS-9A, -10A, -15A)

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Prostate Cancer from Version 2.2025 include:

PROS-9
- PSA persistence/recurrence
  - Life expectancy >5 y: treatment recommendations extensively revised based on No evidence of M1 and M1 disease.

PROS-9A
- Footnote q, sentence 1 modified: Observation involves monitoring the course of disease with the expectation to deliver *definitive or* palliative therapy for the development of symptoms or a change in examination or PSA that suggests symptoms are imminent.
- Footnote jj added: Treatment for a first biochemical recurrence has historically been referred to as 'salvage' therapy. In efforts to use language that is more sensitive to patients, the NCCN Guidelines for Prostate Cancer refer to treatment in this setting as 'secondary' therapy. (Also for PROS-10A)
- Footnote ll added: For patients with PSA progression who have not received treatment for a first BCR, continue monitoring or consider treatment for first PSA persistence/recurrence. See PROS-9 for RP PSA persistence/recurrent or PROS-10 for RT recurrence. (Also for PROS-10A)
- Footnote removed: If considering treatment, reinitiate the PROS-10 algorithm.

PROS-10
- PSA recurrence or positive DRE
  - Life expectancy >5 y: treatment recommendations extensively revised based on No evidence of M1 and M1 disease.

PROS-11
- New page added: Second Biochemical Recurrence (BCR2).

PROS-12
- Page changed
  - New algorithm added: Treatment and Monitoring for Second Biochemical Recurrence (N0M0).
  - Algorithm removed: Treatment and Monitoring for Progressive M0 Castration-Sensitive Prostate Cancer (CSPC) After Maximal Pelvic Therapy.
- Footnote pp added: PSA level and PSADT should be considered when deciding whether to begin ADT for patients considered to have low risk disease. High-risk BCR has different definitions in different clinical trials that generally includes a PSADT ≤9 months and other adverse prognostic features.
- Footnote qq modified: ~~For patients with non-metastatic castration-sensitive disease, (by CT, MRI, or bone scan) who are not candidates for pelvic therapy, monitoring until diagnosis of metastatic disease is preferred. PSADT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease. For ADT alone~~ *If favorable PSA response, an* intermittent ADT *approach should be considered*. ~~can be considered to reduce toxicity.~~

PROS-13
- New page added: Workup and Treatment of Metachronous Oligometastatic CSPC.

PROS-14
- Page header modified: Workup and Treatment of *Low-Volume* M1 *(Metachronous or Synchronous)* or *Synchronous Oligometastatic* CSPC.
- Synchronous low-volume metastases or Synchronous oligometastatic disease, second option modified: ADT with docetaxel and one of the following *(low-volume disease only).*
- Progression modified: Progression *on ADT ± ARPI*.

PROS-15
- Page header modified: Workup and Treatment of *High-Volume* M1 CSPC.

PROS-15A
- Footnote zz added: Concurrent MDT can be considered in select patients with oligometastatic disease. See Principles of MDT (PROS-M).
- Footnote removed: Stereotactic body RT (SBRT) to metastases can be considered in appropriate clinical situations. See Principles of Radiation Therapy (PROS-I).

PROS-18
- Systemic Therapy for M1 CRPC: Adenocarcinoma
  - Page extensively revised and reorganized by Pre-ARPI, Post-ARPI/Pre-Docetaxel, Post-ARPI/Post-Docetaxel, Additional Options Irrespective of Prior ARPI or Prior Docetaxel.

Continued
UPDATES

Updates in Version 1.2026 of the NCCN Guidelines for Prostate Cancer from Version 2.2025 include:

PROS-18A
- Footnote kkk modified: ~~Novel hormone~~ *ARPI* therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered *post-ARPI* ~~prior novel hormone therapy~~.
- Footnote mmm added: Principles of MDT (PROS-M).
- Footnote ooo, sentence 3 added: There are limited data to support the efficacy of Sipuleucel-T in the post-chemotherapy setting.
- Footnote removed: Principles of Radiation Therapy (PROS-I).
- Footnote removed: Visceral metastases refers to liver, lung, adrenal, peritoneal, and brain metastases. Soft tissue/lymph node sites are not considered visceral metastases.
- Footnote removed: Pan-cancer, tumor-agnostic treatments can be considered for patients with actionable mutations.
- Footnote removed: The fine-particle formulation of abiraterone can be used instead of the standard form (other recommended option).
- Footnote removed: The fine-particle (category 2B; other recommended option) or standard formulation of abiraterone can be given with single-agent niraparib as a substitute for the combination of niraparib/abiraterone tablet.

PROS-B
- Section renamed: Principles of Survivorship.

PROS-B (5 of 6)
- New page added: Cardiovascular Disease in Prostate Cancer.

PROS-B (6 of 6)
- New page added: Cardiovascular Disease in Prostate Cancer: Risk Assessment.

PROS-D
- Bullet 5 added: Consider geriatric assessment. See NCCN Guidelines for Older Adult Oncology for tools to aid optimal assessment and management of disease in older adults.
- Bullet 6 added: Refer to the NCCN Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).

PROS-E (2 of 5)
- Bone Imaging
  - Bullet 2 modified: Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 piflufolastat prostate-specific membrane antigen (PSMA), Ga-68 PSMA-11, F-18 flotufolastat PSMA, *F-18 fluciclovine*, F-18 sodium fluoride, or C-11 choline can be considered for equivocal results on initial bone scan.

PROS-E (3 of 5)
- Full Body Imaging
  - Positron Emission Tomography
    - Bullet 1
      - Sub-bullet 1, last sentence modified: See Table *1 on PROS-E (5 of 5)* ~~2 in the discussion section~~ for more details.
      - Sub-bullet 3 modified: PSMA-PET/CT or PET/MRI can be considered as an alternative to CT, MRI, and bone scans for initial staging *in unfavorable intemediate-, high-, and very-high-risk disease,* the detection...
      - Sub-bullet 4 added: PSMA-PET imaging should only be used in the setting of M1 CRPC to determine if a patient is a candidate for Lu-177-PSMA-617.
      - Sub-bullet 5 added: Changes in systemic therapy should not be made solely based on a positive PSMA-PET in patients with M0 CRPC.
      - Sub-bullet 6 added: Bone scans can be considered to confirm osseous uptake on PET scans.
      - Sub-bullet 8 modified: C-11 choline *or F-18 fluciclovine* PET/CT or PET/MRI...
      - Sub-bullet 9 modified: 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 *(eg, <0.5 ng/mL).*

Continued
UPDATES

Updates in Version 1.2026 of the NCCN Guidelines for Prostate Cancer from Version 2.2025 include:

PROS-E (4 of 5)

- Sub-bullet modified (continued from PROS-E [3 of 5]) ...interpretation of scans. *The use of a standardized reporting system is encouraged.* ~~Several reporting systems have been proposed but will not have been validated or widely used.~~
- Sub-bullet 3 modified: Table *1 on PROS-E (5 of 5)* ~~in the discussion section~~ provides a summary of the main imaging tracers utilized for study in prostate cancer ~~both before definitive therapy and at recurrence~~.
- Imaging as Workup for Progression
  - Bullet 2 modified: Imaging for patients with progressive ~~m~~*CRPC* should included chest CT, bone imaging, and abdomen/pelvis CT with contrast or abdomen/pelvis MRI with and without contrast.
  - Bullet 3 modified: There is a lack of evidenced to support the use of PET imaging in ~~this~~ *the CRPC* setting *and it should only be used in the setting of M1 CRPC to determine if a patient is a candidate for Lu-177-PSMA-617. Changes in treatment should not be made solely based on a positive PSMA-PET in patients with M0 CRPC.*

PROS-E (5 of 5)

- New table added: FDA-Cleared PET Imaging Tracers Studied in Prostate Cancer.
- Footnote a added: Interpret with caution. Wherever possible, studies were included that used histopathologic confirmation, but not all studies used confirmatory histology as the gold standard. Values may vary depending upon the site of the lesion and phase of the disease process.
- Footnote b added: CLR: Correct localization rate. Patient-level positive predictive value + anatomic lesion co-localization. Preferred over sensitivity and specificity in analyses of patients with BCR.

PROS-F

- Principles of Active Surveillance: Section extensively revised.

PROS-G (1 of 6)

- Neoadjuvant, Concurrent, and/or Adjuvant ADT with RT
  - Bullet 4 modified: *First* M0 RP PSA persistence/recurrence ~~(without maximal pelvic therapy)~~.
  - Notes
    - ◊ Bullet 1 added: ADT is not recommended with RT for most patients with favorable intermediate-risk prostate cancer. If it is given (see Principles of Risk Stratification), the duration should be short term (4–6 months).
    - ◊ Bullet 4 modified: For high-risk ~~and very-high-risk~~ prostate cancer...
    - ◊ Bullet 6 modified: *First* M0 PSA persistence/recurrence:
      - – Sub-bullet 3 added: For patients treated with secondary RT in the setting of first RP recurrence, if ADT is given, it should be for a duration of 6 to 24 months.

PROS-G (2 of 6)

- ADT for Patients with M0 CSPC, bullet 2 modified: *First* M0 RT recurrence ~~(without maximal pelvic therapy)~~.

PROS-G (3 of 6)

- ADT for Patients with M0 CSPC *BCR2* ~~After Maximal Pelvic Therapy~~.
  - Useful in Certain Circumstances
    - ◊ Bullet 1 modified: Enzalutamide with or without leuprolide *(for high-risk BCR2).*
    - ◊ Bullet 2 modified: Apalutamide with LHRH agonist or LHRH antagonist ~~(category 2B)~~ *(for high-risk BCR2)*.
  - Notes, bullet 1 modified: Monitoring until diagnosis of metastatic disease is preferred for patients with *M0 CSPC in the low-risk BCR2 setting* ~~non-metastatic castration-sensitive disease who are not candidates for pelvic therapy~~.
  - Footnote c added: For patients receiving MDT with ADT, the ADT options are LHRH agonist or LHRH antagonist.

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Prostate Cancer from Version 2.2025 include:

PROS-G (5 of 6)

- ADT Monotherapy
  - Notes
    - ◊ Bullet 1 modified: ADT monotherapy is appropriate for patients with life expectancy ≤5 years whose cancer progressed on observation of localized disease, who are symptomatic or who have N1M0 disease ~~and in select patients with high- or very-high-risk disease, where complications, such as hydronephrosis or metastasis, can be expected within 5 years~~.
    - ◊ Bullet 2 modified: ADT monotherapy is also used for asymptomatic patients with ~~high-risk, very-high-risk, and~~ regional disease and life expectancy ≤5 years whether or not RT is given.
- Footnote h added: In the mCRPC setting, this option should only be used for select patients who are not candidates for other recommended mCRPC therapies.

PROS-G (6 of 6)

- Optimal ADT, bullet removed: Data are limited on long-term adherence to oral relugolix and the potential effects on optimal ADT. Ongoing monitoring for sustained suppression of testosterone (<50 ng/dL) can be considered, and relugolix may not be a preferred agent if adherence to the prescribed regimen is uncertain.

PROS-I

- New section added: Principles of Focal/Subtotal Therapy or Whole Gland Ablative Therapy.

PROS-J

- Principles of Radiation Therapy: Section extensively revised.

PROS-K

- Pelvic Lymph Node Dissection
  - Bullet 1, sub-bullet 5 modified: PLND can be performed using an open, laparascopic, or robotic technique *and can provide staging and prognostic information.*
  - Bullet removed: While PLND at the time of RP has not been shown to improve oncologic outcomes, it can provide staging and prognostic information.

PROS-L (1 of 2)

- Bullet 1 modified: Patients with biopsy-proven recurrence in the prostate after prior RT and without distant metastatic disease can be considered for local therapy. *Monitoring is also an option (see PROS-10). ADT may also be included, but it should not be reflexively ordered.*
- Bullet 3 modified: Local therapy options for patients with recurrence in the prostate ~~only~~ include:...
  - Sub-bullet 2 modified: High-intensity focused ultrasound (HIFU) ~~(category 2B)~~.
  - Sub-bullet 3 added: Irreversible electroporation (IRE) (category 2B).
  - Sub-bullet removed: Non-surgical strategies.
- Bullet and sub-bullets removed: Local therapy options for patients with recurrence in the regional nodes with or without prostate recurrence include: ADT + pelvic lymph node radiation (if not previously done), ADT + pelvic lymph node reirradiation (category 2B), ADT + PLND (category 2B), Pelvic lymph node radiation, PLND.
- Footnote a added: Reirradiation with LDR brachytherapy, HDR brachytherapy, and SBRT is supported by phase II trials with >36 months of median follow-up and should be strongly considered as an option in patients with >2 years interval from prior radiation who do not have ongoing moderate or higher grade radiation-associated toxicities. Phase II data with >36 months of median follow-up are available, albeit to a more limited scope, for secondary RP, cryotherapy, and HIFU.
- Footnote b added: Currently, all phase II and/or prospectively accrued registries reporting oncologic outcomes with >36 months of follow-up have pursued whole gland treatments. Focal therapy for prostate-only recurrences is the subject of active investigation. See Principles of Focal/Subtotal Therapy or Whole Gland Ablative Therapy (PROS-I).
- Footnote c added: There are no prospective data to guide the use and duration of ADT with reirradiation for prostate-only recurrences. The Panel recommends extrapolation from the definitive treatment setting to suggest that adding ADT or prolonging it in this setting likely offers an improvement in biochemical control. See Principles of Radiation Therapy (PROS-J).

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Prostate Cancer from Version 2.2025 include:

PROS-M
- New section added: Principles of Metastasis-Directed Therapy.

PROS-N (1 of 4)
- Non-Hormonal Systemic Therapy for M1 Castration-Sensitive Prostate Cancer
  - Bullet 1 modified: ~~Patients with low-volume synchronous or high-volume castration-sensitive metastatic prostate cancer who are fit for chemotherapy should be considered for~~ Triple therapy with ADT, certain ARPIs, and docetaxel *is an option for certain patients with mCSPC who are fit for chemotherapy* based on phase 3 studies:

PROS-N (2 of 4)
- Non-Hormonal Systemic Therapy for M1 CRPC
  - Chemotherapy
    - Bullet 1
      - Sub-bullet 4 modified: Docetaxel retreatment can be attempted after progression on *an ARPI and docetaxel* ~~novel hormone therapy~~ in patients with mCRPC whose cancer has not yet demonstrated definitive evidence of progression on prior docetaxel therapy in *either* the castration-sensitive setting *or the mCRPC setting*.
      - Sub-bullet 5 added: Rare patients may have exposure to docetaxel without prior ARPI (ie, in the setting of EBRT to the primary tumor for low-volume synchronous mCSPC). Docetaxel rechallenge is not recommended for such patients in the pre-ARPI mCRPC setting.
  - Bullet 2, sub-bullet 5 added: Biweekly cabazitaxel at 16 mg/m^2 dose with G-CSF in patients ≥65 years in a Phase 3 trial. Clinical outcomes were comparable between the 2 groups.

PROS-N (3 of 4)
- Non-Hormonal Systemic Therapy for M1 CRPC
  - PARP Inhibitors With or Without ARPIs: Subsection extensively revised.
  - Immunotherapy
    - Bullet 2 modified: Pembrolizumab is an option for certain patients with *MSI-H/dMMR* mCRPC ~~and MSI-H, dMMR, or TMB ≥10 mut/mB~~ (PROS-18).
      - Sub-bullet 2 added: Limited data suggest that pembrolizumab may be associated with some benefit in patients with mCRPC and TMB ≥10 mut/mB. Lenis AT, et al. Clin Canc Res 2024;30:3894-3903.
    - Bullet removed: Patients with asymptomatic or minimally symptomatic mCRPC may consider immunotherapy.

PROS-N (4 of 4)
- Table added: Table 1. PARP Inhibitors with or without ARPIs.

INITIAL PROSTATE CANCER DIAGNOSIS[a,b,c,d]

WORKUP

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

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

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

Regional prostate cancer (Any T, N1, M0) →

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

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

→ **Regional Prostate Cancer (PROS-7)**

→ **Workup and Treatment of Low-Volume M1 (Metachronous or Synchronous) or Synchronous Oligometastatic[h] Castration-Sensitive Prostate Cancer (CSPC) (PROS-14)**

→ **Workup and Treatment of High-Volume M1 CSPC (PROS-15)**

[a] See NCCN Guidelines for Older Adult Oncology for tools to aid optimal assessment and management of disease in older adults.
[b] NCCN Guidelines for Prostate Cancer Early Detection.
[c] Principles of Survivorship in Prostate Cancer (PROS-B).
[d] Refer to the NCCN Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).
[e] Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[f] Principles of Quality of Life and Shared Decision-Making (PROS-D).
[g] Principles of Imaging (PROS-E).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).

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

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

Risk Group	Clinical/Pathologic Features (Staging, ST-1)			Additional Evaluation[g,l]	Initial Therapy
Low[j]	Has all of the following: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-3
Intermediate[j]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[k]	• Confirmatory testing can be used to assess the appropriateness of active surveillance (PROS-F 2 of 5)	PROS-4
		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)[k]	• Soft tissue imaging and consider bone imaging[g] ▸ If regional metastases are found, see PROS-7 ▸ If distant metastases are found, see PROS-14 for Low-Volume M1(Metachronous or Synchronous) or Synchronous Oligometastatic[h] CSPC or PROS-15 for High-Volume M1 CSPC	PROS-5
High	Has one or more high-risk features, but does not meet criteria for very high risk: • cT3–cT4 • Grade Group 4 or Grade Group 5 • PSA >20 ng/mL			Bone and soft tissue imaging[g] ▸ If regional metastases are found, see PROS-7 ▸ If distant metastases are found, see PROS-14 for Low-Volume M1 (Metachronous or Synchronous) or Synchronous Oligometastatic[h] CSPC or PROS-15 for High-Volume M1 CSPC	PROS-6
Very high	Has at least two of the following: • cT3–cT4 • Grade Group 4 or 5 • PSA >40 ng/mL			Bone and soft tissue imaging[g] ▸ If regional metastases are found, see PROS-7 ▸ If distant metastases are found, see PROS-14 for Low-Volume M1 (Metachronous or Synchronous) or Synchronous Oligometastatic[h] CSPC or PROS-15 for High-Volume M1 CSPC	PROS-6

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

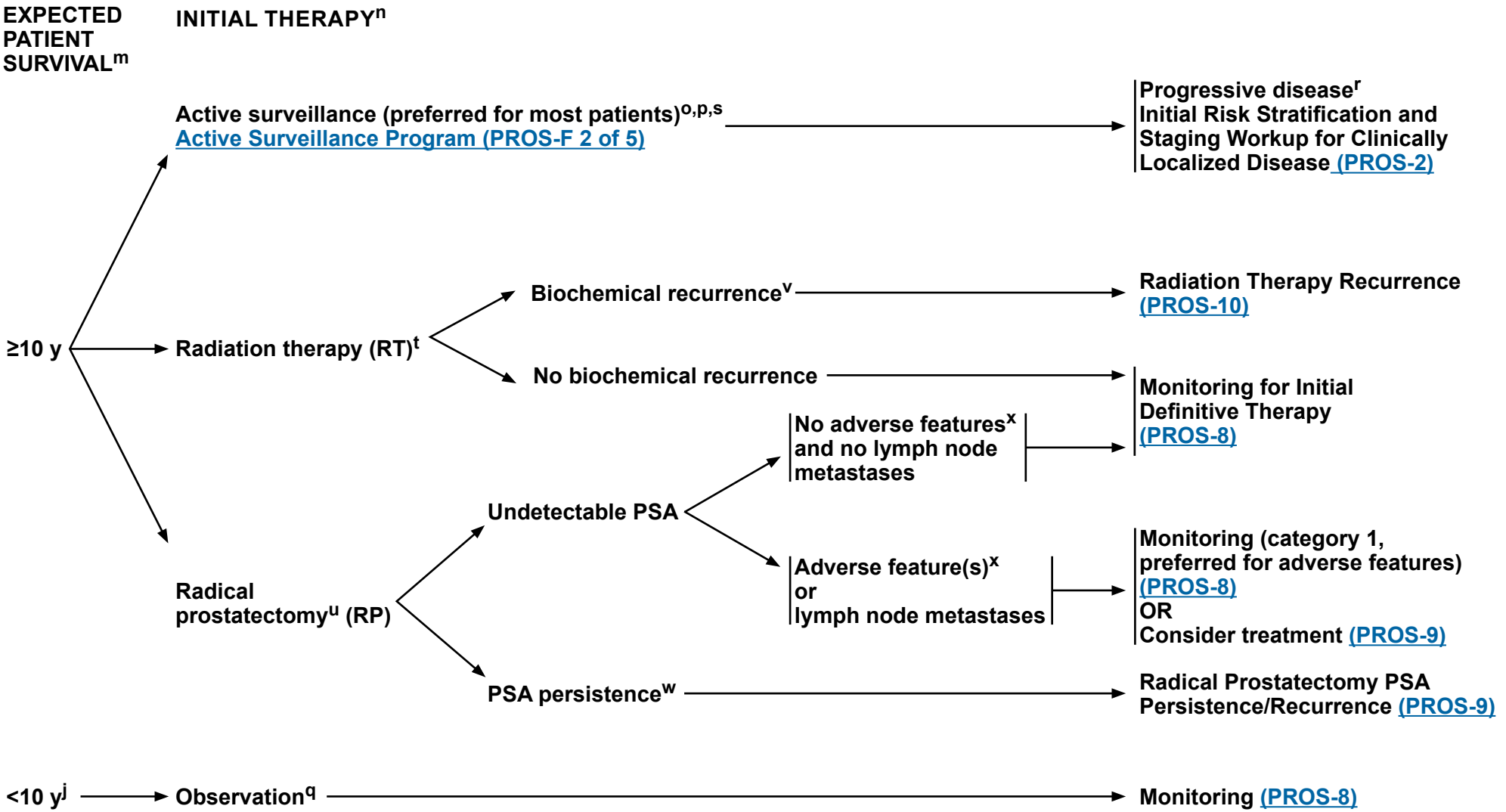
Footnotes on PROS-2A

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

[g] Principles of Imaging (PROS-E).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).
[i] Tumor-based molecular assays and germline genetic testing are other tools that can assist with risk stratification. See CRIT-6 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate and HRS-3 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric to determine if a patient is an appropriate candidate for germline genetic testing, and see Principles of Risk Stratification and Biomarkers (PROS-H) to determine if a patient is an appropriate candidate for tumor-based molecular assays.
[j] For patients who are asymptomatic in 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 [Principles of Imaging (PROS-E)] and androgen deprivation therapy (ADT) should be given [Principles of Androgen Deprivation Therapy (PROS-G)].
[k] Percentage of positive cores in the intermediate-risk group is based on biopsies that include systematic biopsies with or without targeted MRI-guided biopsies. The Panel considers biopsies from a single region of interest (ROI) to count as a single sample.
[l] Bone imaging should be performed for any patient with symptoms consistent with bone metastases.

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

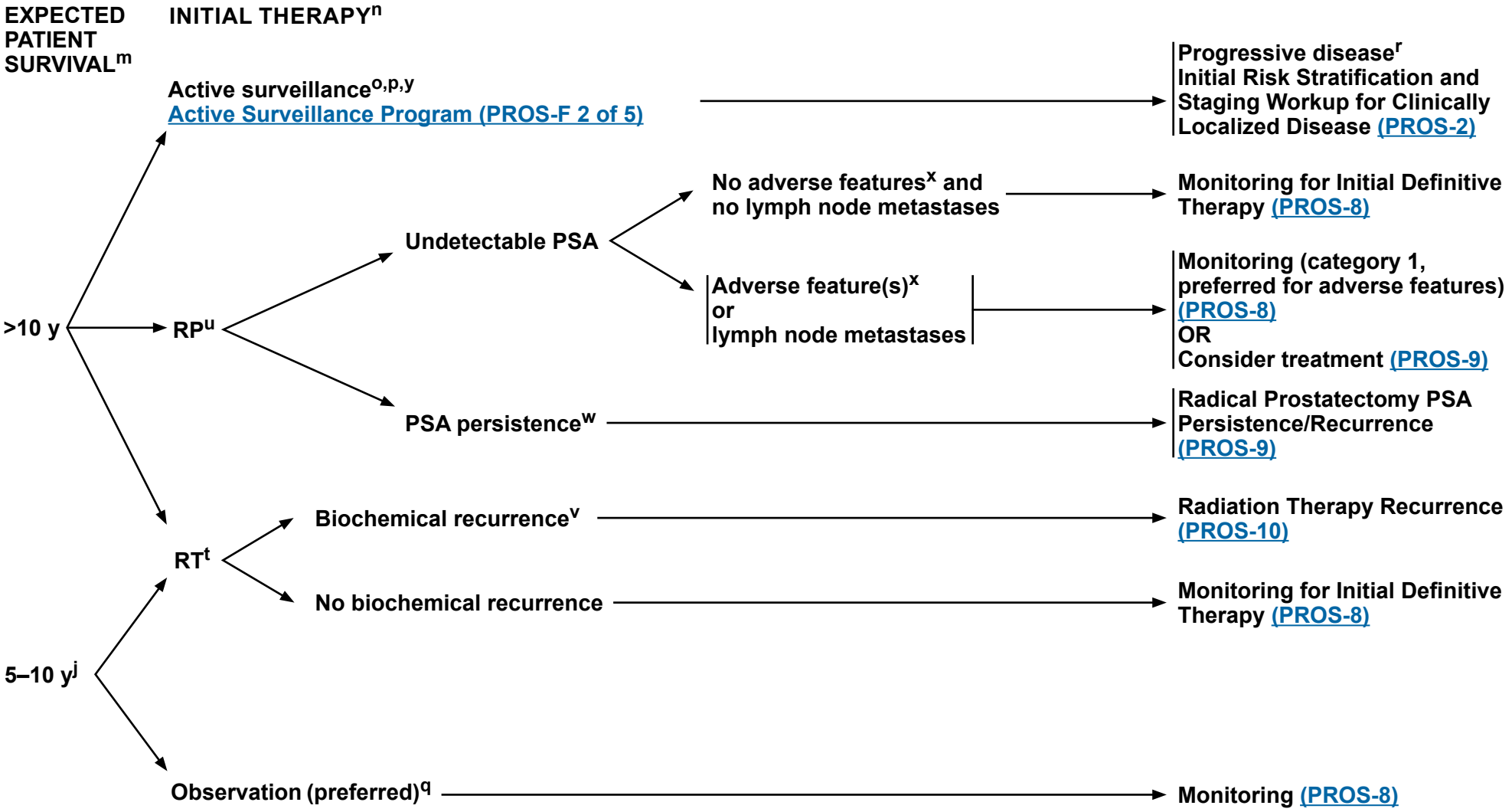
LOW-RISK GROUP



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

Footnotes on PROS-7A

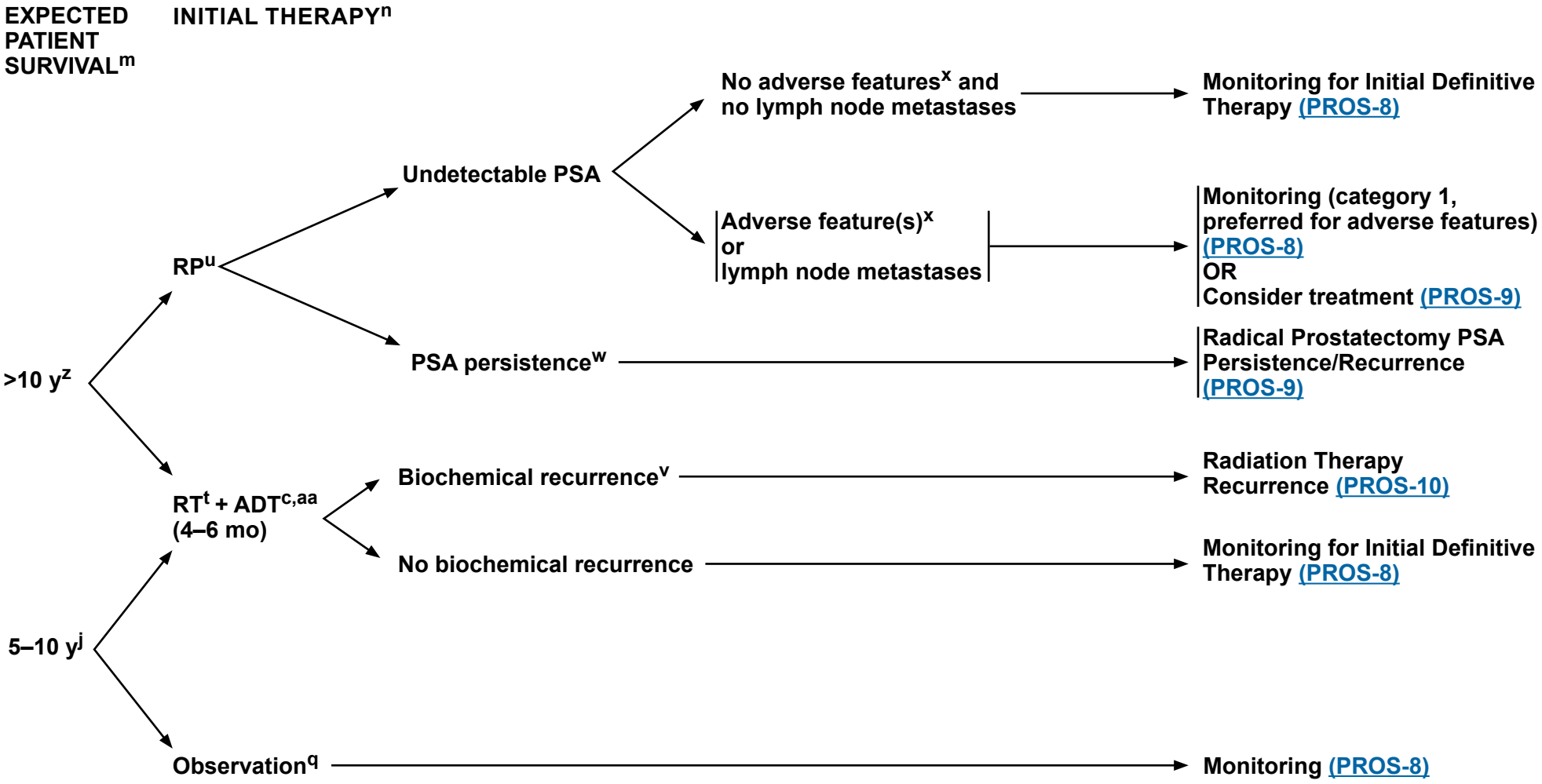
FAVORABLE INTERMEDIATE-RISK GROUP



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

Footnotes on PROS-7A

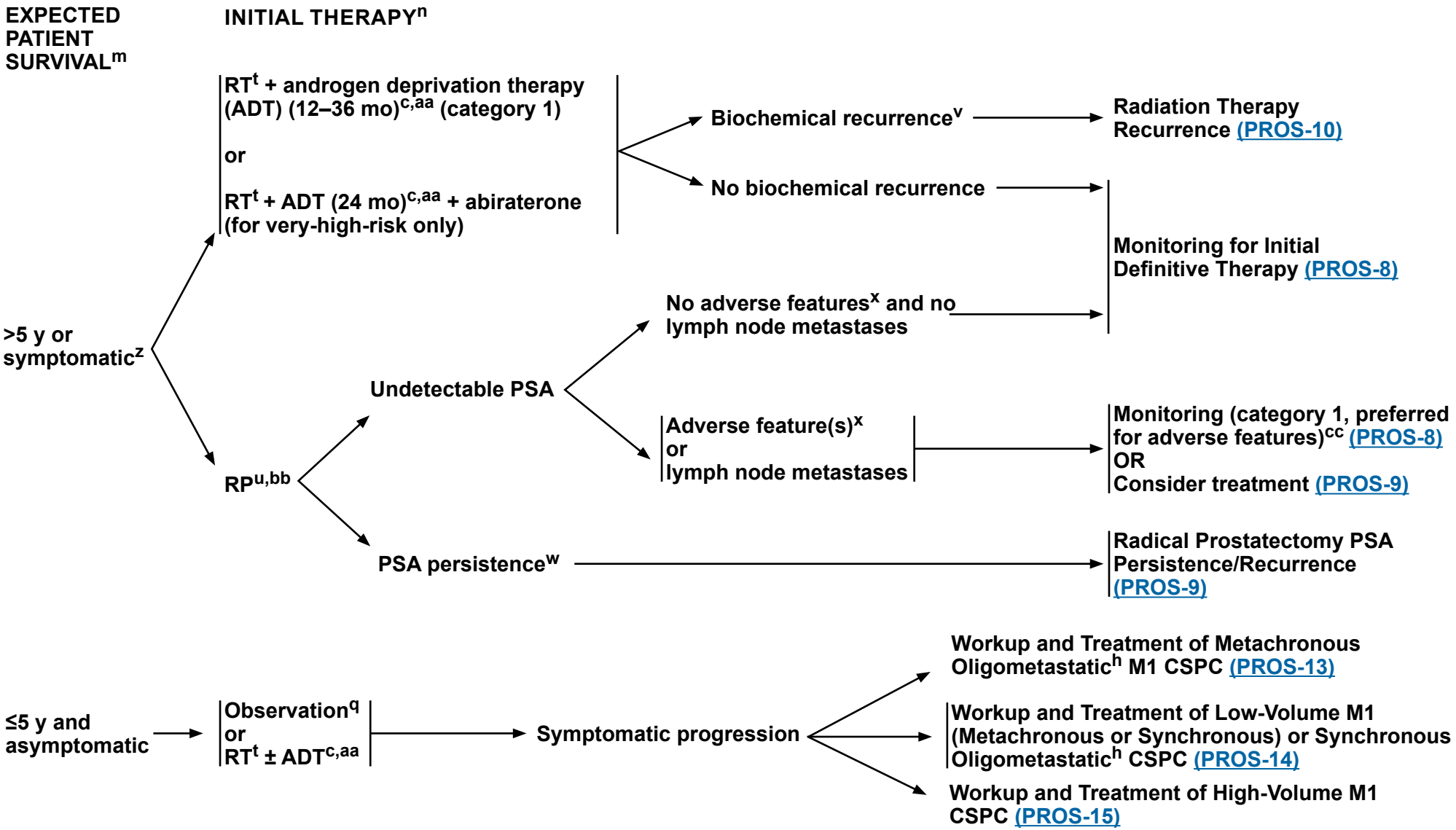
UNFAVORABLE INTERMEDIATE-RISK GROUP



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

Footnotes on PROS-7A

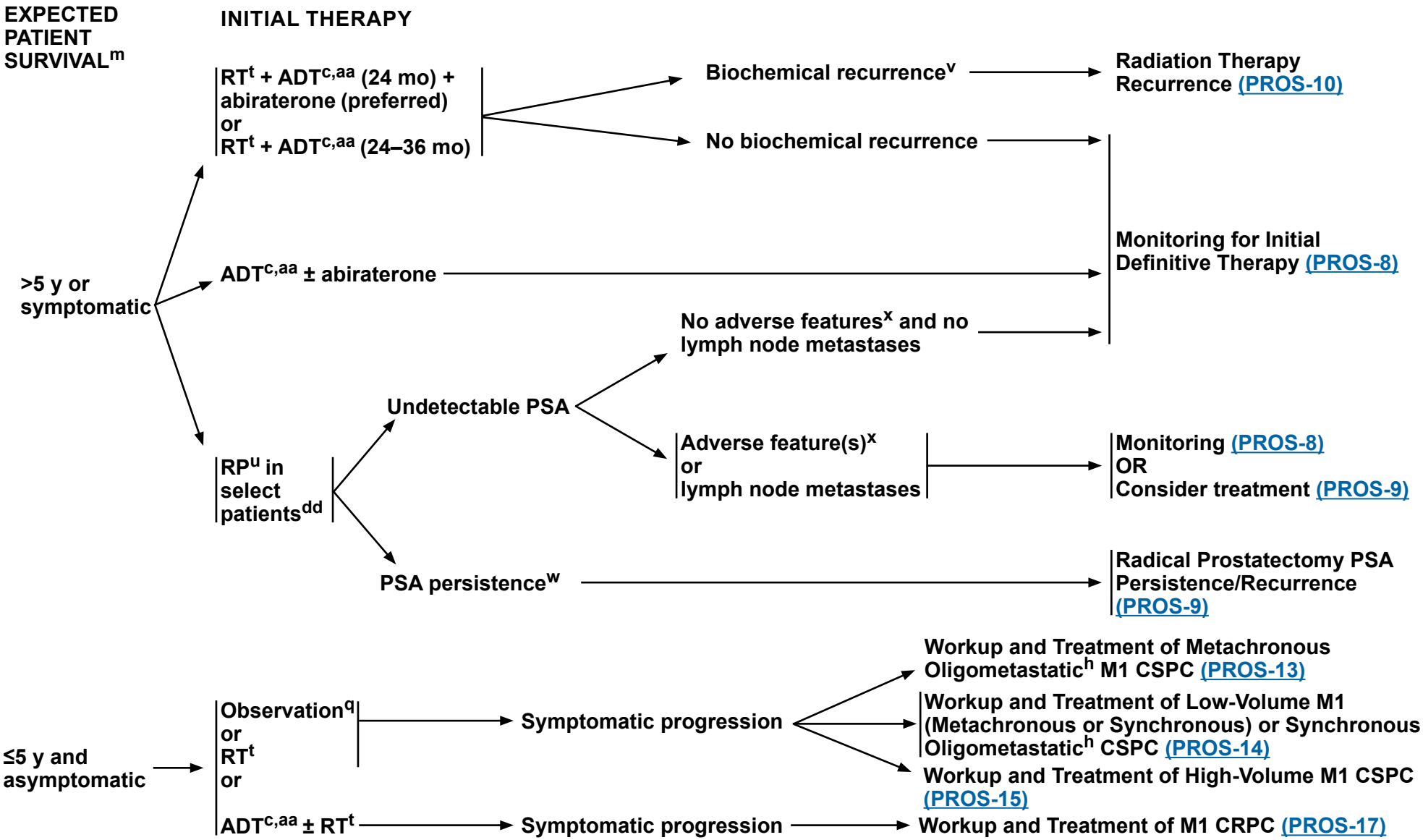
HIGH- OR VERY-HIGH-RISK GROUP



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

Footnotes on PROS-7A

REGIONAL PROSTATE CANCER (ANY T, N1, M0)



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

Footnotes on PROS-7A

FOOTNOTES

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

[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).

[j] For patients who are asymptomatic in 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 [Principles of Imaging (PROS-E)] and ADT should be given [Principles of Androgen Deprivation Therapy (PROS-G)].

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

[n] Principles of Focal/Subtotal Therapy or Whole Gland Ablative Therapy (PROS-I).

[o] 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).

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

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

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

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

[t] Principles of Radiation Therapy (PROS-J).

[u] Principles of Surgery (PROS-K).

[v] RTOG-ASTRO (Radiation Therapy Oncology Group - American Society for Radiation Oncology) Phoenix Consensus: 1) PSA increase by ≥2 ng/mL above the nadir PSA is the standard definition for PSA recurrence after external beam RT (EBRT) with or without hormone therapy; and 2) a recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is <2 ng/mL, especially in candidates for secondary local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in patients who are younger or healthier.

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

[x] Adverse pathologic features include: positive margin(s), seminal vesicle invasion, or extracapsular extension.

[y] 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).

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

[aa] For details on the use of ADT and androgen receptor pathway inhibitors (ARPIs) , see Principles of Androgen Deprivation Therapy (PROS-G) and Discussion.

[bb] RP + pelvic lymph node dissection (PLND) can be considered in patients who are younger and healthier without tumor fixation to the pelvic sidewall.

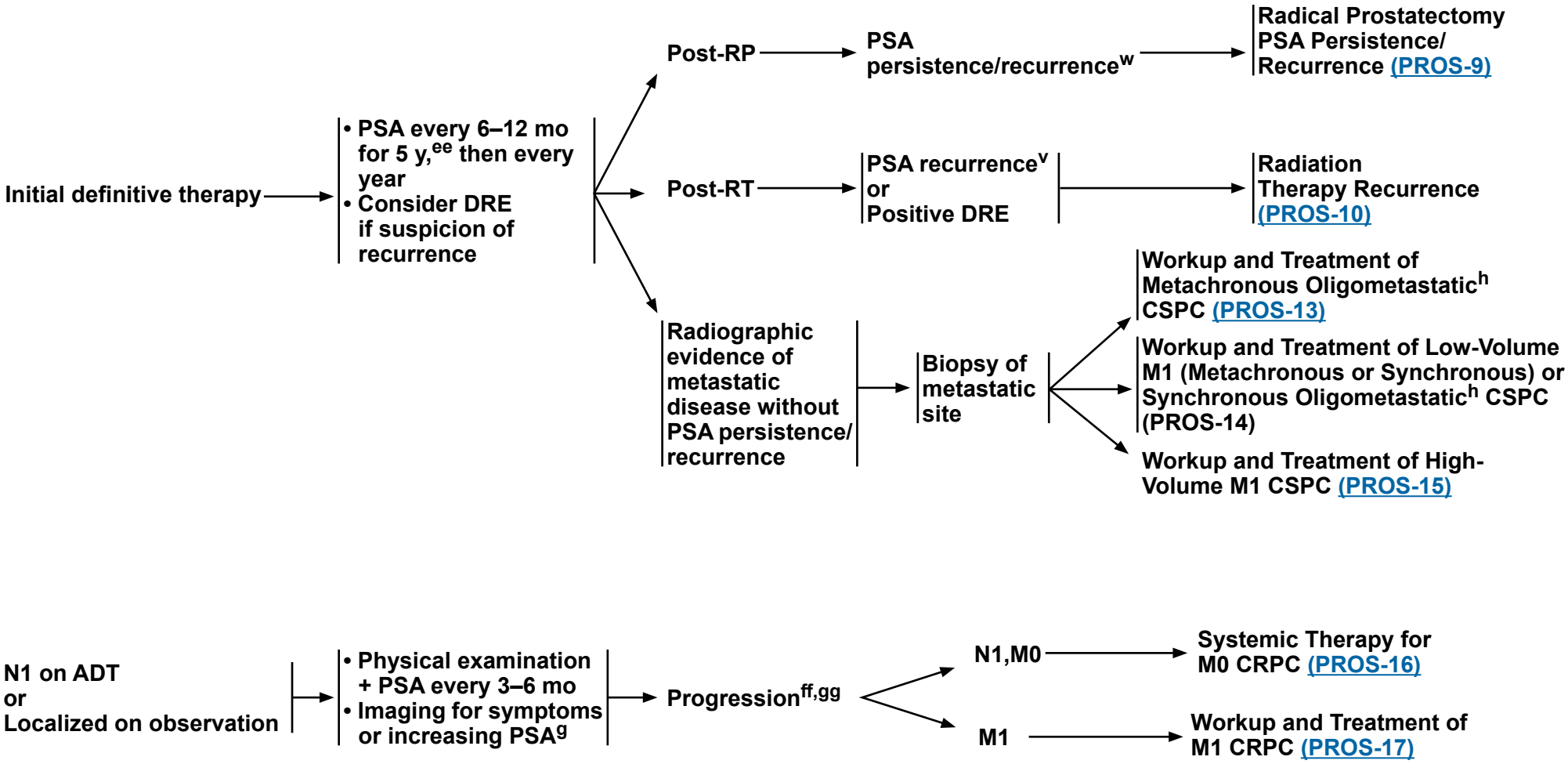
[cc] Monitoring is not preferred for patients with multiple high-risk features.

[dd] 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.

MONITORING
See NCCN Guidelines for Survivorship

RECURRENCE



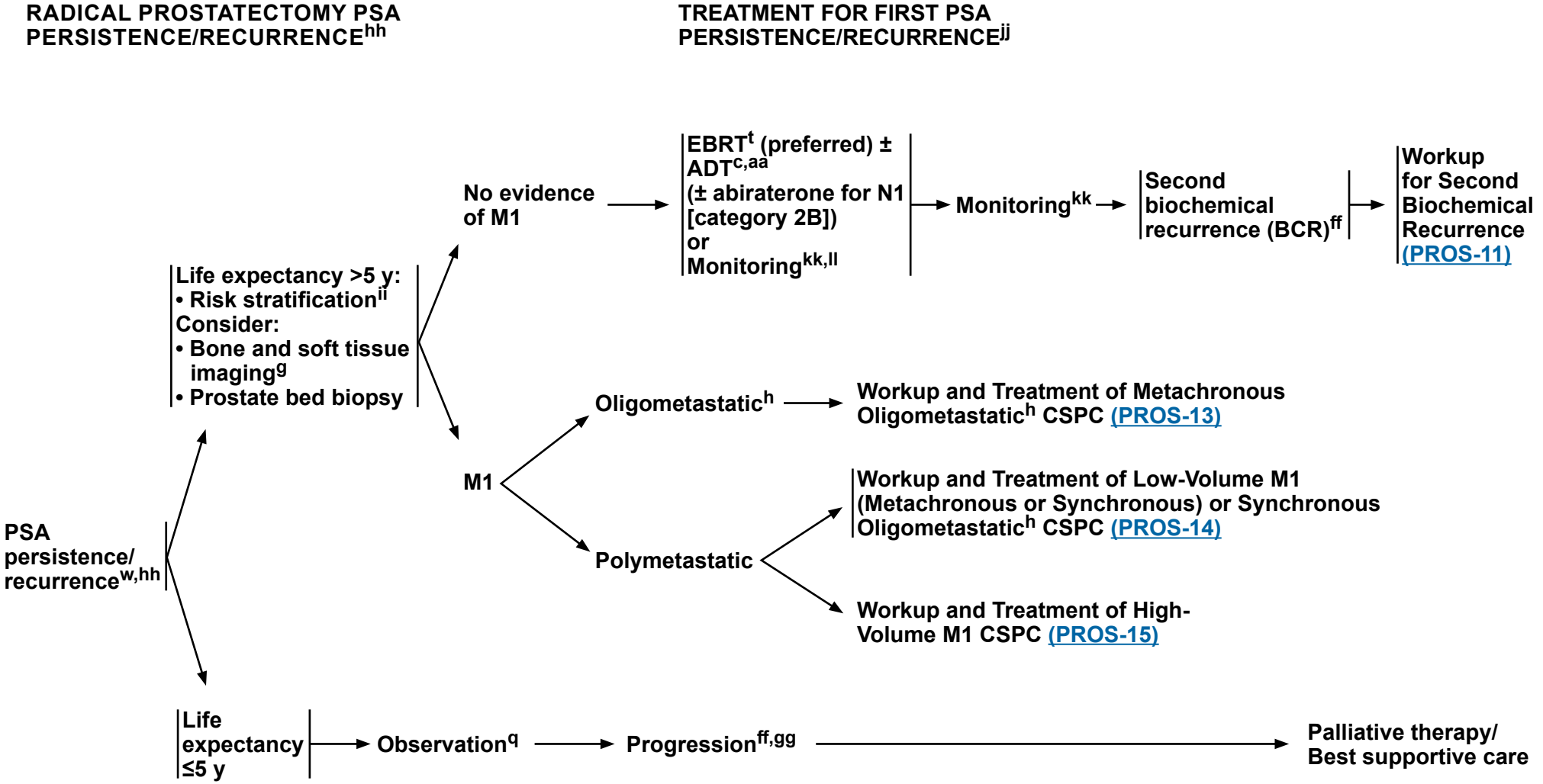
Note: All recommendations are category 2A unless otherwise indicated.

Footnotes on PROS-8A

MONITORING AND RECURRENCE FOOTNOTES

[g] Principles of Imaging (PROS-E).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).
[v] RTOG-ASTRO Phoenix Consensus: 1) PSA increase by ≥2 ng/mL above the nadir PSA is the standard definition for PSA recurrence after EBRT with or without hormone therapy; and 2) a recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is <2 ng/mL, especially in candidates for secondary local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in patients who are younger or healthier.
[w] PSA persistence/recurrence after RP is defined as when PSA does not fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on ≥2 determinations (PSA recurrence) or increases to PSA >0.1 ng/mL. Trials indicating non-inferiority of early RT compared with adjuvant RT after RP have used a PSA threshold of 0.1 or 0.2 ng/mL to trigger treatment. Imaging and treatment at lower PSA levels may be appropriate in patients at high risk for progression based on pretreatment risk factors, pathologic parameters, timing of recurrence, and GC score, among other factors.
[ee] PSA as frequently as every 3 mo may be necessary to clarify disease status, especially in patients at high risk of recurrence.
[ff] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. See Principles of Imaging (PROS-E).
[gg] Treatment for patients with life expectancy ≤5 y whose cancer progressed on observation of localized disease is ADT. See Principles of Androgen Deprivation Therapy (PROS-G).

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



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

Footnotes on PROS-9A

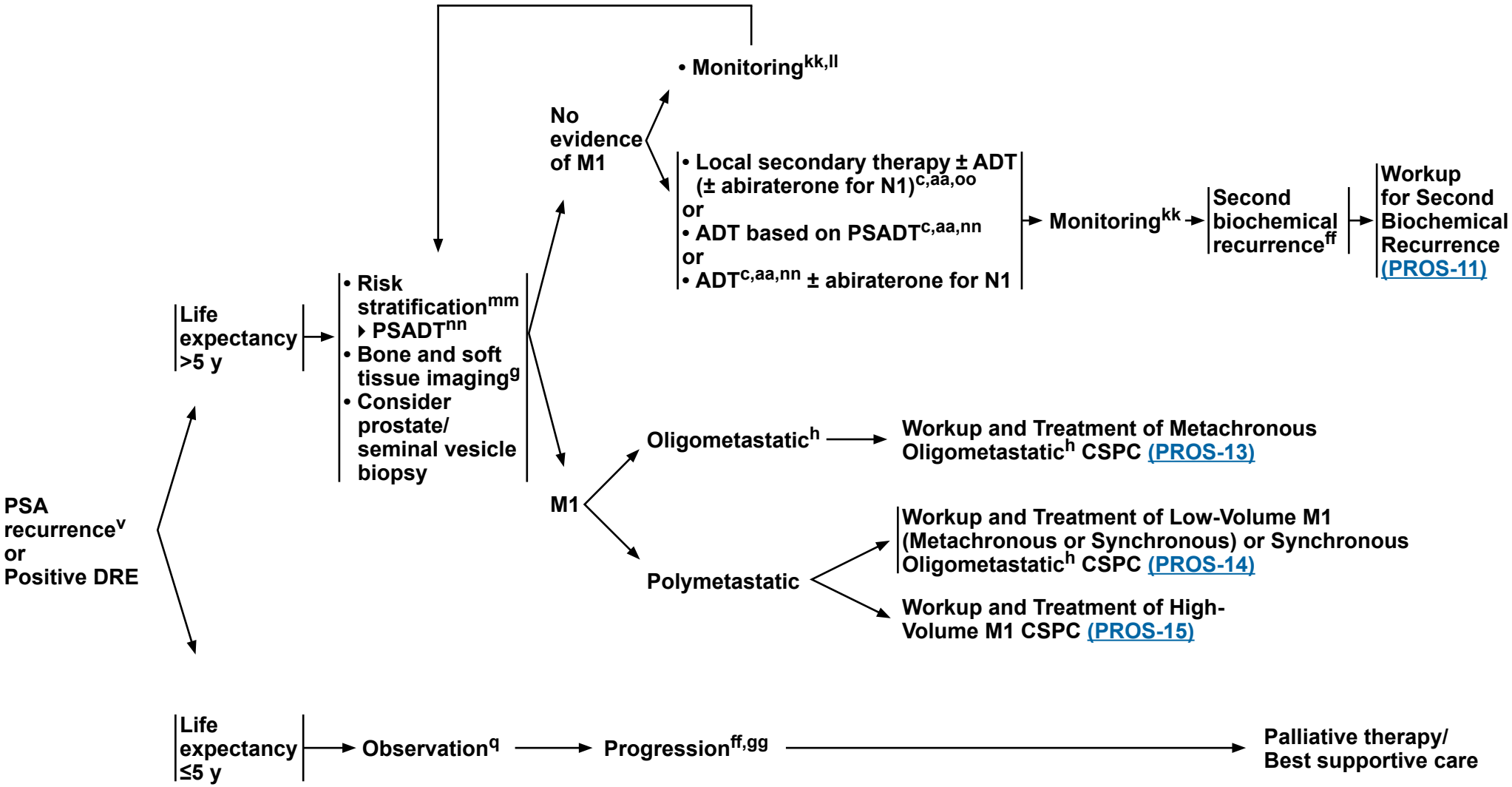
RADICAL PROSTATECTOMY PSA PERSISTENCE/RECURRENCE FOOTNOTES

[c] Principles of Survivorship in Prostate Cancer (PROS-B).
[g] Principles of Imaging (PROS-E).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).
[q] Observation involves monitoring the course of disease with the expectation to deliver definitive or palliative therapy for the development of symptoms or a change in examination or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-F).
[t] Principles of Radiation Therapy (PROS-J).
[w] PSA persistence/recurrence after RP is defined as when PSA does not fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on ≥2 determinations (PSA recurrence) or increases to PSA >0.1 ng/mL. Trials indicating noninferiority of early RT compared with adjuvant RT after RP have used a PSA threshold of 0.1 or 0.2 ng/mL to trigger treatment. Imaging and treatment at lower PSA levels may be appropriate in patients at high risk for progression based on pretreatment risk factors, pathologic parameters, timing of recurrence, and GC score, among other factors.
[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G) and Discussion.
[ff] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. See Principles of Imaging (PROS-E).
[gg] Treatment for patients with life expectancy ≤5 y whose cancer progressed on observation of localized disease is ADT. See Principles of Androgen Deprivation Therapy (PROS-G).
[hh] Recommendations for RP PSA persistence/recurrence may also apply to patients with undetectable PSA with multiple adverse features or lymph node metastases if treatment is being considered.
[ii] Principles of Risk Stratification and Biomarkers (PROS-H).
[jj] Treatment for a first biochemical recurrence has historically been referred to as 'salvage' therapy. In efforts to use language that is more sensitive to patients, the NCCN Guidelines for Prostate Cancer refer to treatment in this setting as 'secondary' therapy.
[kk] Monitoring should include physical exam, PSA every 3–6 months, and imaging for symptoms or increasing PSA.
[ll] For patients with PSA progression who have not received treatment for a first biochemical recurrence (BCR), continue monitoring or consider treatment for first PSA persistence/recurrence. See PROS-9 for RP PSA persistence/recurrence or PROS-10 for RT recurrence.

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

RADIATION THERAPY RECURRENCE

TREATMENT FOR FIRST RECURRENCE[jj]



Footnotes on PROS-10A

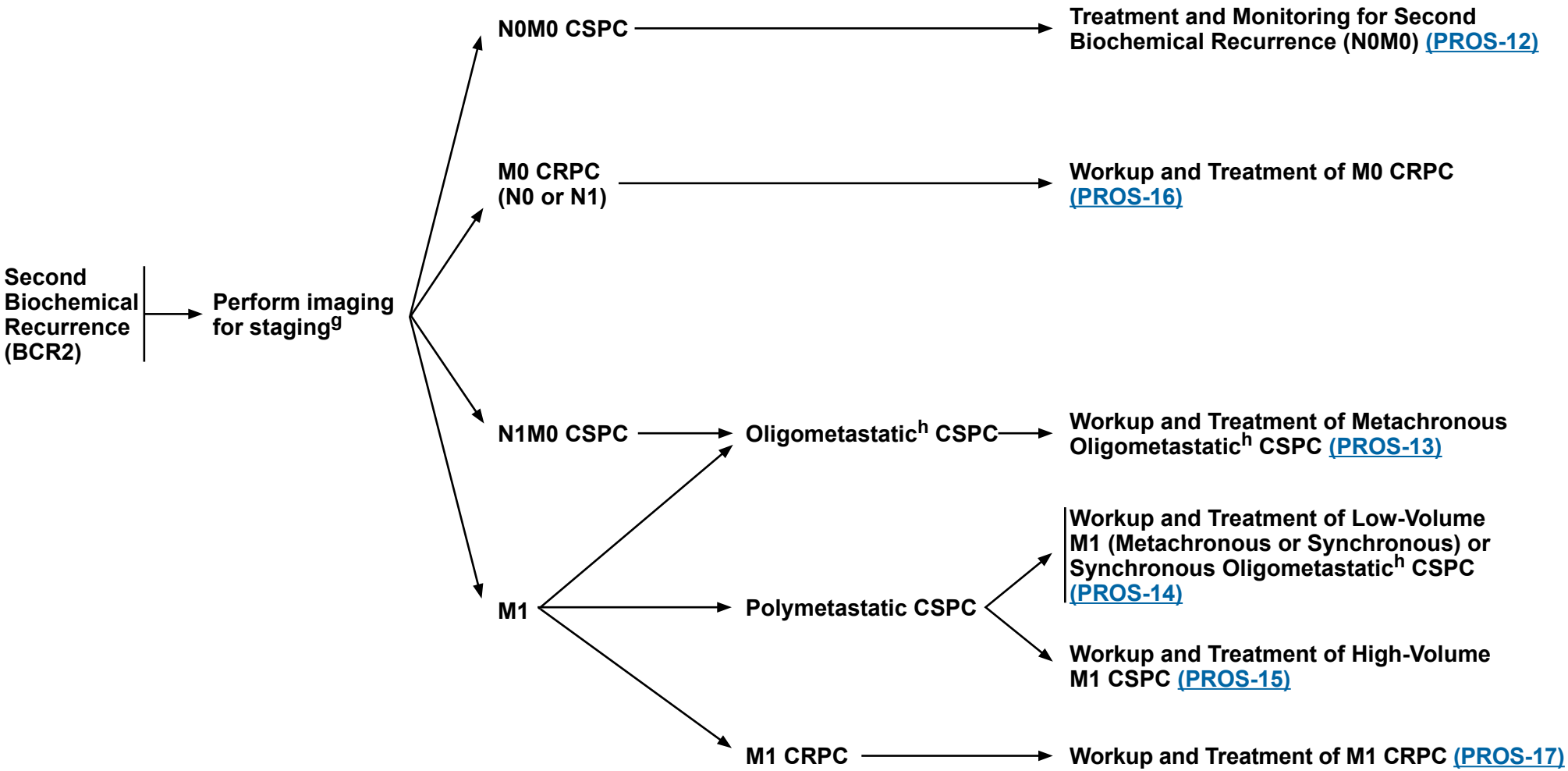
Note: All recommendations are category 2A unless otherwise indicated.

RADIATION THERAPY RECURRENCE FOOTNOTES

[c] Principles of Survivorship in Prostate Cancer (PROS-B).
[g] Principles of Imaging (PROS-E).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).
[q] Observation involves monitoring the course of disease with the expectation to deliver definitive or palliative therapy for the development of symptoms or a change in examination or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-F).
[v] RTOG-ASTRO Phoenix Consensus: 1) PSA increase by ≥2 ng/mL above the nadir PSA is the standard definition for PSA recurrence after EBRT with or without hormone therapy; and 2) A recurrence evaluation should be considered when PSA has been confirmed to be increasing after radiation even if the increase above nadir is <2 ng/mL, especially in candidates for secondary local therapy who are young and healthy. Retaining a strict version of the ASTRO definition allows comparison with a large existing body of literature. Rapid increase of PSA may warrant evaluation (prostate biopsy) prior to meeting the Phoenix definition, especially in patients who are younger or healthier.
[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G) and Discussion.
[ff] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. See Principles of Imaging (PROS-E).
[gg] Treatment for patients with life expectancy ≤5 y whose cancer progressed on observation of localized disease is ADT. See Principles of Androgen Deprivation Therapy (PROS-G).
[jj] Treatment for a first biochemical recurrence has historically been referred to as 'salvage' therapy. In efforts to use language that is more sensitive to patients, the NCCN Guidelines for Prostate Cancer refer to treatment in this setting as 'secondary' therapy.
[kk] Monitoring should include physical exam, PSA every 3–6 mo, and imaging for symptoms or increasing PSA.
[ll] For patients with PSA progression who have not received treatment for a first BCR, continue monitoring or consider treatment for first PSA persistence/recurrence. See PROS-9 for RP PSA persistence/recurrence or PROS-10 for RT recurrence.
[mm] PSADT can be calculated to inform nomogram use and counseling.
[nn] PSADT and Grade Group should be considered when deciding whether to begin ADT. See Principles of Androgen Deprivation Therapy (PROS-G).
[oo] Principles of Local Secondary Post-Recurrence Therapy (PROS-L).

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

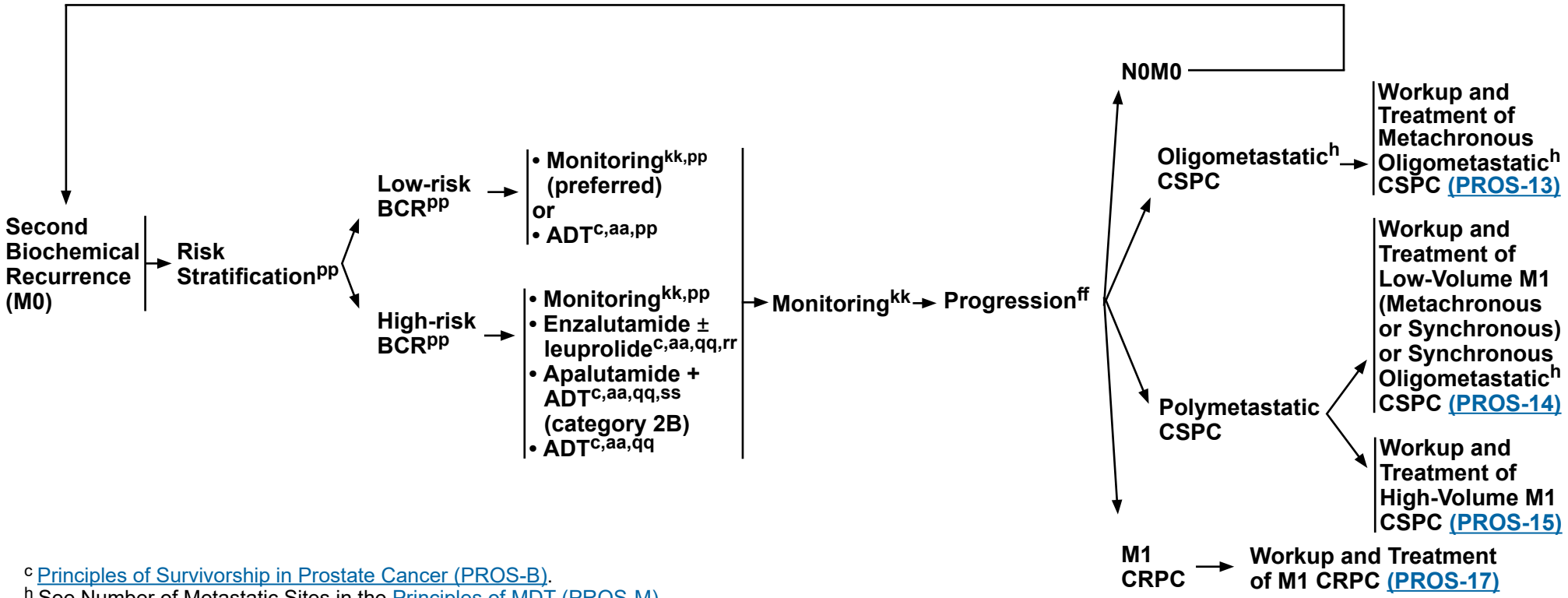
WORKUP FOR SECOND BIOCHEMICAL RECURRENCE (BCR2)



[g] Principles of Imaging (PROS-E).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).

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

TREATMENT AND MONITORING FOR SECOND BIOCHEMICAL RECURRENCE (N0M0)



[c] Principles of Survivorship in Prostate Cancer (PROS-B).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).
[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G) and Discussion.
[ff] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. See Principles of Imaging (PROS-E).
[kk] Monitoring should include physical exam, PSA every 3–6 months, and imaging for symptoms or increasing PSA.
[pp] PSA level and PSADT should be considered when deciding whether to begin ADT for patients considered to have lower risk disease. High-risk BCR has different definitions in different clinical trials that generally include a PSADT ≤9 months and other adverse prognostic features.
[qq] If favorable PSA response, an intermittent ADT approach should be considered.
[rr] Enzalutamide with or without leuprolide is an option for patients who have the following high-risk criteria: M0 by CT, MRI, or bone scan; PSADT ≤9 months; PSA ≥2 ng/mL above nadir after RT or ≥1 ng/mL after RP with or without postoperative RT; and not considered a candidate for pelvic-directed therapy (Freedland SJ, et al. N Engl J Med 2023;389:1453-1465). See Principles of Androgen Deprivation Therapy (PROS-G).
[ss] Apalutamide plus ADT is an option for patients with biochemical recurrence after RP who meet the following high-risk criteria: PSADT ≤9 months; PSA ≥0.5 ng/mL; and prior adjuvant or secondary RT or not considered a candidate for RT (Aggarwal R, et al. J Clin Oncol 2024;42:1114-1123.) See Principles of Androgen Deprivation Therapy (PROS-G).

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

WORKUP AND TREATMENT OF METACHRONOUS OLIGOMETASTATIC CSPC[c,h,tt,uu,vv,ww]

WORKUP FOR METASTASES[xx]

- Perform physical exam
- Perform imaging for staging[g]
- Perform and/or collect PSA and calculate PSADT
- Estimate life expectancy (Principles of Life Expectancy Estimation [PROS-A])
- Perform germline and somatic genetic testing[e] (if not previously done)
- Obtain family history[e]
- Assess quality-of-life measures[f]

→ MDT[yy] ± ADT[aa] or For M1 only, treat as metachronous low-volume M1 (see PROS-14)

→ • Physical examination + PSA every 3–6 mo
• Imaging for symptoms[g]
• Consider periodic imaging to monitor treatment response

→ Progression[ff]

→ Workup and Treatment of Low-Volume M1 (Metachronous or Synchronous) or Synchronous Oligometastatic[h] CSPC (PROS-14)

→ Workup and Treatment of High-Volume M1 CSPC (PROS-15)

→ Workup and Treatment of M1 CRPC (PROS-17)

[c] Principles of Survivorship in Prostate Cancer (PROS-B).
[e] Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[f] Principles of Quality of Life and Shared Decision-Making (PROS-D).
[g] Principles of Imaging (PROS-E).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).
[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G) and Discussion.
[ff] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. See Principles of Imaging (PROS-E).
[tt] EBRT to sites of bone metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.
[uu] Bone antiresorptive therapy is indicated for elevated fracture risk based upon FRAX in the castration-sensitive setting. See PROS-B.
[vv] The term "castration-sensitive" is used to define disease in patients who have not been treated with ADT and those who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-sensitive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of RT provided they have recovered testicular function.
[ww] ADT is strongly recommended in combination therapy for metastatic castration-sensitive disease. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy. If ADT monotherapy is given, intermittent ADT can be considered to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-G).
[xx] ADT alone (PROS-G) or observation are recommended for asymptomatic patients with metastatic disease or M0 CRPC and life expectancy ≤5 years.
[yy] See Principles of MDT (PROS-M).

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

WORKUP AND TREATMENT OF LOW-VOLUME M1 (METACHRONOUS OR SYNCHRONOUS) OR SYNCHRONOUS OLIGOMETASTATIC CSPC[c,h,tt,uu,vv,ww]

WORKUP FOR METASTASES[xx]

- Perform physical exam
- Perform imaging for staging[g]
- Perform and/or collect PSA and calculate PSADT
- Estimate life expectancy (Principles of Life Expectancy Estimation [PROS-A])
- Perform germline and somatic genetic testing[e] (if not previously done)
- Obtain family history[e]
- Assess quality-of-life measures[f]

Synchronous low-volume metastases or Synchronous oligometastatic disease

→ ADT[aa,zz] with one of the following:
- Preferred:
  - Abiraterone (category 1)[aa]
  - Apalutamide (category 1)[aa]
  - Enzalutamide (category 1)[aa]
- Other Recommended:
  - Darolutamide (category 2B)[aa]

or

ADT[aa,zz] with docetaxel and one of the following (low-volume disease only):
- Abiraterone (category 2B)[aa]
- Apalutamide (category 2B)[aa]
- Darolutamide (category 2B)[aa]
- Enzalutamide (category 2B)[aa]

or

ADT[aa,zz] with EBRT[t] to the primary tumor[aaa] alone or with one of the following:
- Abiraterone[aa]
- Apalutamide (category 2B)[aa]
- Docetaxel (category 2B)[aa]
- Enzalutamide (category 2B)[aa]

Metachronous low-volume metastases

→ ADT[aa,zz] with one of the following:
- Preferred:
  - Abiraterone (category 1)[aa]
  - Apalutamide (category 1)[aa]
  - Enzalutamide (category 1)[aa]
- Other Recommended:
  - Darolutamide (category 2B)[aa]

→
- Physical examination + PSA every 3–6 mo
- Imaging for symptoms[g]
- Periodic imaging to monitor treatment response

→ Progression[ff] on ADT ± androgen receptor pathway inhibitor (ARPI)

→ Workup and Treatment of M1 CRPC (PROS-17)

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

Footnotes on PROS-15A

WORKUP AND TREATMENT OF HIGH-VOLUME M1 CSPC[c,tt,uu,vv,ww,bbb]

WORKUP FOR METASTASES[xx]

- Perform physical exam
- Perform imaging for staging[g]
- Perform and/or collect PSA and calculate PSADT
- Estimate life expectancy (Principles of Life Expectancy Estimation [PROS-A])
- Perform germline and somatic genetic testing[e] (if not previously done)
- Obtain family history[e]
- Assess quality-of-life measures[f]

→ Synchronous or metachronous high-volume[bbb] metastases

→ ADT[aa] with docetaxel and one of the following:
- Preferred:
  - Abiraterone (category 1)[aa]
  - Darolutamide (category 1)[aa]
- Other Recommended:
  - Apalutamide (category 2B)[aa]
  - Enzalutamide (category 2B)[aa]

or

ADT[aa] with one of the following:
- Preferred:
  - Abiraterone (category 1)[aa]
  - Apalutamide (category 1)[aa]
  - Enzalutamide (category 1)[aa]
- Other Recommended:
  - Darolutamide[aa]

→
- Physical examination + PSA every 3–6 mo
- Imaging for symptoms[g]
- Periodic imaging to monitor treatment response

→ Progression[ff] → Workup and Treatment of M1 CRPC (PROS-17)

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

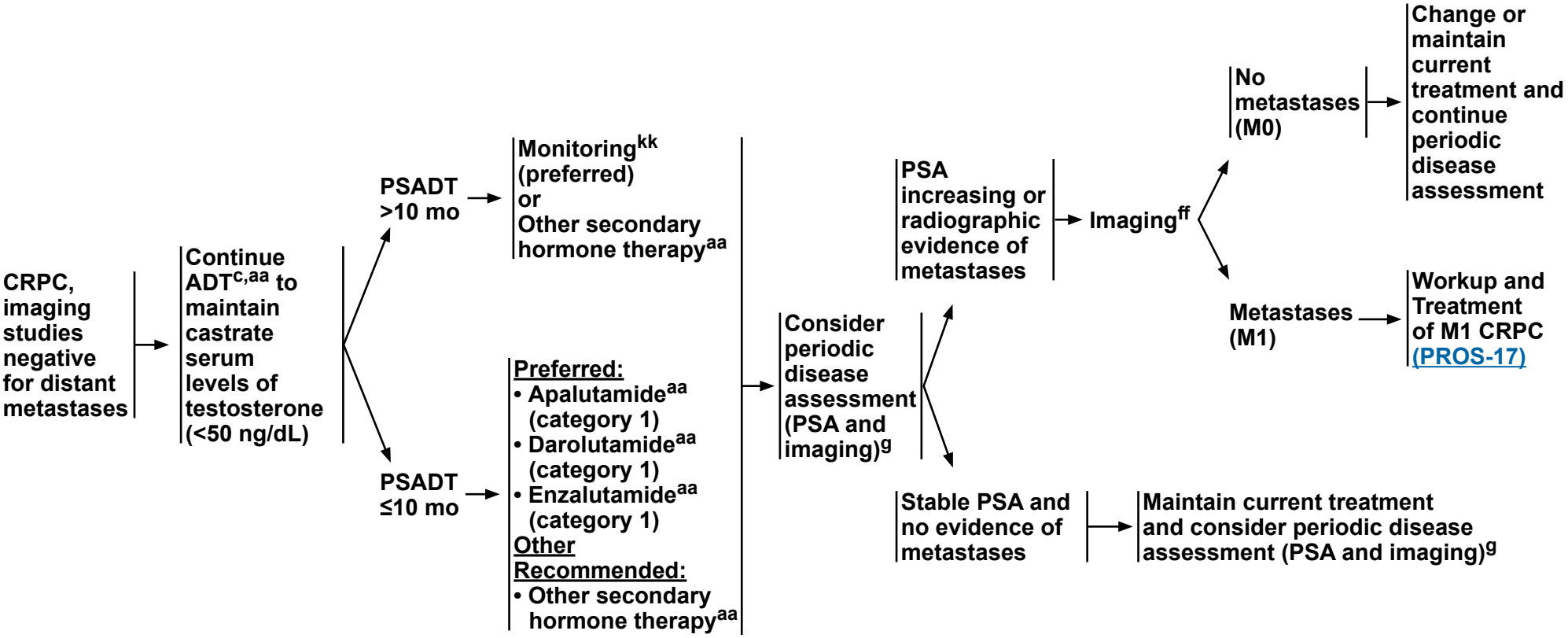
Footnotes on PROS-15A

FOOTNOTES

[c] Principles of Survivorship in Prostate Cancer (PROS-B).
[e] Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[f] Principles of Quality of Life and Shared Decision-Making (PROS-D).
[g] Principles of Imaging (PROS-E).
[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).
[t] Principles of Radiation Therapy (PROS-J).
[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G) and Discussion.
[ff] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. See Principles of Imaging (PROS-E).
[tt] EBRT to sites of bone metastases can be considered if metastases are in weight-bearing bones or if the patient is symptomatic.
[uu] Bone antiresorptive therapy is indicated for elevated fracture risk based upon FRAX in the castration-sensitive setting. See PROS-B.
[vv] The term "castration-sensitive" is used to define disease in patients who have not been treated with ADT and those who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-sensitive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of RT provided they have recovered testicular function.
[ww] ADT is strongly recommended in combination therapy for metastatic castration-sensitive disease. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy. If ADT monotherapy is given, intermittent ADT can be considered to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-G).
[xx] ADT alone (PROS-G) or observation are recommended for asymptomatic patients with metastatic disease or M0 CRPC and life expectancy ≤5 years.
[zz] Concurrent MDT can be considered in select patients with oligometastatic disease. See Principles of MDT (PROS-M).
[aaa] EBRT to the primary tumor is associated with an overall survival (OS) benefit in patients with low metastatic burden at the time of diagnosis of metastatic disease, which is defined by bone scan and CT or MRI 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-J).
[bbb] High-volume disease in this setting is defined based on CHAARTED criteria (the presence of visceral metastasis or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis).

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

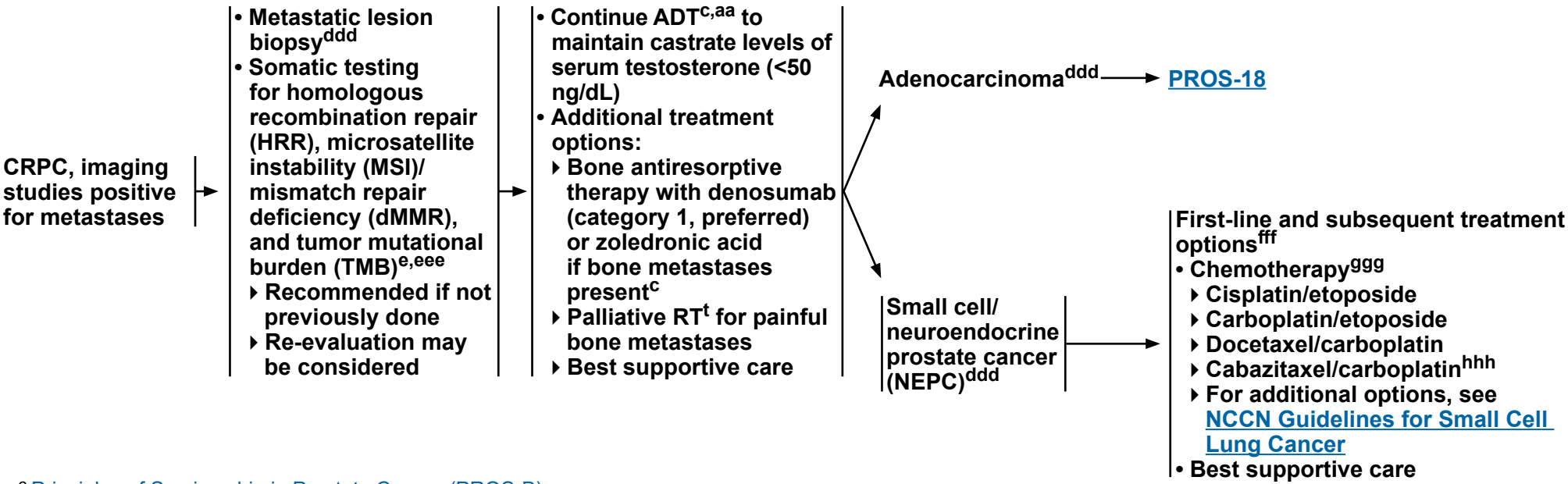
WORKUP AND TREATMENT OF M0 CASTRATION-RESISTANT PROSTATE CANCER (CRPC)[xx,ccc]



[c] Principles of Survivorship in Prostate Cancer (PROS-B).
[g] Principles of Imaging (PROS-E).
[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G) and Discussion.
[ff] Document castrate levels of testosterone if clinically indicated. Workup for progression should include bone and soft tissue evaluation. See Principles of Imaging (PROS-E).
[kk] Monitoring should include physical exam, PSA every 3–6 mo, and imaging for symptoms or increasing PSA.
[xx] ADT alone (PROS-G) or observation are recommended for asymptomatic patients with metastatic disease or M0 CRPC and life expectancy ≤5 years.
[ccc] 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.

WORKUP AND TREATMENT OF M1 CRPC[xx,ccc]



[c] Principles of Survivorship in Prostate Cancer (PROS-B).
[e] Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[t] Principles of Radiation Therapy (PROS-J).
[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G) and Discussion.
[xx] ADT alone (PROS-G) or observation are recommended for asymptomatic patients with metastatic disease or M0 CRPC and life expectancy ≤5 years.
[ccc] 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.
[ddd] 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.
[eee] Germline testing for HRR mutations is recommended if not performed previously. See Principles of Genetics and Molecular/Biomarker Analysis (PROS-C).
[fff] Document castrate levels of testosterone if progression occurs on ADT. See Principles of Imaging (PROS-E) and Discussion.
[ggg] For details on the efficacy and safety of these agents, see Principles of Non-Hormonal Systemic Therapy (PROS-N).
[hhh] Cabazitaxel 20 or 25 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 metastatic CRPC (mCRPC) (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.

SYSTEMATIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[g,aa,iii,jjj]

Pre-ARPI[aa,kkk]	Post-ARPI[kkk]/Pre-Docetaxel[aa]	Post-ARPI[kkk]/Post-Docetaxel[aa]
Preferred: • Abiraterone (category 1) • Enzalutamide (category 1) **Other Recommended:** • Docetaxel[ggg] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Niraparib/abiraterone[lll] (category 1) ◊ Olaparib/abiraterone[lll] (category 1) ◊ Talazoparib/enzalutamide[lll] (category 1) ▸ *HRRm* (other than BRCA1/2) ◊ Talazoparib/enzalutamide[lll] (category 1) • Disease State-Specific Therapy ▸ Bone metastases ◊ Radium-223[nnn]/enzalutamide	**Preferred:** • Docetaxel[ggg] (category 1) **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[lll] (category 1, preferred) ◊ Rucaparib[lll] (category 1, preferred) ◊ Niraparib/abiraterone[lll] (category 2B) ◊ Talazoparib/enzalutamide[lll] (category 2B) ▸ *HRRm* (other than BRCA1/2) ◊ Olaparib[lll] ◊ Talazoparib/enzalutamide[lll] (category 2B) • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lutetium Lu 177 vipivotide tetraxetan (Lu-177-PSMA-617)[ppp] ▸ Aggressive variant[hhh] ◊ Cabazitaxel/Carboplatin[ggg]	**Preferred:** • Cabazitaxel[ggg] (category 1) • Docetaxel rechallenge[ggg] **Useful in Certain Circumstances:** • Molecular Biomarker-Directed Therapy ▸ *BRCA* mutation ◊ Olaparib[lll] (category 1) ◊ Rucaparib[lll] ▸ *HRRm* (other than *BRCA1/2*) ◊ Olaparib[lll] ▸ Other FDA-approved agents for tissue agnostic indications[ggg] • Disease State-Specific Therapy ▸ PSMA-positive metastases ◊ Lu-177-PSMA-617[ppp] (category 1) ▸ Aggressive variant[hhh] ◊ Cabazitaxel/carboplatin[ggg] ▸ Palliation for symptomatic patients unable to tolerate other therapies ◊ Mitoxantrone[ggg]

Additional Options Irrespective of Prior ARPI or Prior Docetaxel (Useful in Certain Circumstances)

• Disease State-Specific Therapy
▸ Asymptomatic without visceral metastases
◊ Sipuleucel-T[ggg,ooo]
▸ Oligometastatic[h]/Oligoprogressive disease
◊ Metastasis-directed therapy[mmm] with metastatic castration-resistant prostate cancer (mCRPC) systemic therapy
▸ Symptomatic bone-predominant metastases
◊ Radium-223[nnn] (category 1)

• Molecular Biomarker-Directed Therapy
▸ MSI-High (MSI-H)/dMMR
◊ Pembrolizumab[ggg] (category 2B)

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

Footnotes on PROS-18A

THERAPY FOR M1 CRPC: ADENOCARCINOMA
FOOTNOTES

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

[h] See Number of Metastatic Sites in the Principles of MDT (PROS-M).

[aa] For details on the use of ADT and ARPIs, see Principles of Androgen Deprivation Therapy (PROS-G) and Discussion.

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

[hhh] Cabazitaxel 20 or 25 mg/m² plus carboplatin AUC 4 mg/mL per min with growth factor support can be considered for fit patients with aggressive variant mCRPC (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.

[iii] Document castrate levels of testosterone if progression occurs on ADT. Consider metastatic lesion biopsy. If small cell neuroendocrine is found, see PROS-17.

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

[kkk] ARPI therapies include abiraterone, enzalutamide, darolutamide, or apalutamide. Abiraterone given as part of neoadjuvant/concomitant/adjuvant ADT with EBRT is not considered post-ARPI.

[lll] PARP inhibitors with or without ARPI have different biomarker and previous treatment requirements. See Principles of Non-Hormonal Systemic Therapy (PROS-N).

[mmm] Principles of MDT (PROS-M).

[nnn] Radium-223 should not be used in patients with visceral metastases. Concurrent use with systemic therapies other than enzalutamide should be pursued with caution. Concomitant use of denosumab or zoledronic acid is recommended. See Principles of Radiation Therapy (PROS-J).

[ooo] Sipuleucel-T is recommended only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 months, 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. There are limited data to support the efficacy of Sipuleucel-T in the post-chemotherapy setting. Sipuleucel-T is not recommended for patients with small cell prostate cancer/NEPC.

[ppp] 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 or are considered appropriate to delay a taxane-based chemotherapy. Sartor O, et al. N Engl J Med 2021;385:1091-1103; Morris MJ, et al. Lancet 2024;404:1227-1239. See Principles of Radiation Therapy (PROS-J).

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

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)**
  - **University of California San Francisco (UCSF) Lee Schonberg Index (https://eprognosis.ucsf.edu/leeschonberg.php)**
- **If using a life expectancy table, life expectancy should be adjusted using the clinician's assessment of overall health as follows:**
  - **Best quartile of health - add 50%**
  - **Worst quartile of health - subtract 50%**
  - **Middle two quartiles of health - no adjustment**
- **Examples of upper, middle, and lower quartiles of life expectancy at selected ages are included in the NCCN Guidelines for Older Adult Oncology for life expectancy estimation.**

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

PRINCIPLES OF SURVIVORSHIP
BONE HEALTH IN PROSTATE CANCER

Treatment-Related Bone Loss

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

References on PROS-B 4 of 6

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

PRINCIPLES OF SURVIVORSHIP
BONE HEALTH IN PROSTATE CANCER

Treatment-Related Bone Loss Continued

- **The risk of osteonecrosis of the jaw is increased in patients who have tooth extractions, poor dental hygiene, or a dental appliance. To prevent osteonecrosis of the jaw, it is recommended that all patients have a comprehensive dental evaluation prior to initiating an osteoclast inhibitor.[3] If invasive dental procedures are required, bone-targeted therapy should be withheld until the dentist indicates that the patient has healed completely from all dental procedure(s). Stopping denosumab represents a dilemma is this context, and the clinician must carefully weigh the risk of rebound spine fractures versus the risk of osteonecrosis of the jaw.**

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

Table 1: Risk Assessment and Monitoring

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

References on PROS-B 4 of 6

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

PRINCIPLES OF SURVIVORSHIP
BONE HEALTH IN PROSTATE CANCER

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

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

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

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

References on PROS-B 4 of 6

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

PRINCIPLES OF SURVIVORSHIP
BONE HEALTH IN PROSTATE CANCER: REFERENCES

[1] LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2022;33:2049-2102.
[2] Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-controlled freedom trial and its extension. J Bone Miner Res 2018;33:190-198.
[3] Yarom N, Shapiro CL, Peterson DE, et al. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO Clinical practice guideline. J Clin Oncol 2019;37:2270-2290.
[4] 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.
[5] Clemons M, Ong M, Stober C, et al. A randomised trial of 4- versus 12-weekly administration of bone-targeted agents in patients with bone metastases from breast or castration-resistant prostate cancer. Eur J Cancer 2021;142:132-140.
[6] Smith M, Parker C, Saad F, et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:408-419.
[7] Smith MR, Halabi S, Ryan CJ, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202 (alliance). J Clin Oncol 2014;32:1143-1150.

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

PRINCIPLES OF SURVIVORSHIP
CARDIOVASCULAR DISEASE IN PROSTATE CANCER

- **Individuals with prostate cancer are at increased risk for cardiovascular disease (CVD) and cardiovascular events, and CVD is a leading cause of death in this population.[1]**
  - **The main cause for this increased risk is the cardiovascular effects of ADT and ARPIs.[2,3]**
  - **Shared risk factors for prostate cancer and CVD (ie, smoking, poor health behaviors) also likely contribute to the increased risk of CVD in this population.[4]**
- **CVD develops over time because of well-defined risk factors such as hypertension, hyperlipidemia, use of tobacco products, obesity, diabetes, and the cardiotoxic effects of cancer treatment.**
- **CVD-related morbidity and mortality can occur in both the short- and long-term in prostate cancer survivors.**
- **Control of modifiable risk factors can decrease the risk of subsequent cardiovascular events.**
- **Therefore, prostate cancer survivors should assessed for and counseled on:**
  - **Pre-existing and emerging CVD (eg, coronary artery disease, congestive heart failure, peripheral vascular disease, arrhythmias including atrial fibrillation)**
  - **Any increased risk of CVD based on prior treatment, comorbidity, or CVD risk factors (eg, hypertension, dyslipidemia, obesity, cigarette/tobacco use, diabetes mellitus)**
  - **Lifestyle modification and interventions for modifiable risk factors (see the ABCDEs of CVD Prevention, Table 1)**
- **Aggressive risk factor management is recommended for those deemed to be at higher risk, and referral to a cardiologist or cardio-oncologist in patients at elevated CVD risk should be considered at any stage of the prostate cancer journey.**
- **Cooperation and shared care with primary care providers, and cardiovascular specialists as needed, is key to optimizing cardiac and vascular outcomes in prostate cancer survivors.**
- **For further information on cardiovascular risk assessment in cancer survivors, see the NCCN Guidelines for Survivorship.**

[1] Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J 2019;40:3889-3897.
[2] Okwuosa TM, Morgans A, Rhee JW, et al. Impact of hormonal therapies for treatment of hormone-dependent cancers (breast and prostate) on the cardiovascular system: effects and modifications: a scientific statement from the American Heart Association. Circ Genom Precis Med 2021;14:e000082.
[3] El-Taji O, Taktak S, Jones C, et al. Cardiovascular events and androgen receptor signaling inhibitors in advanced prostate cancer: A systematic review and meta-analysis. JAMA Oncol 2024;20:874-884.
[4] Bergengren O, Pekala KR, Matsoukas K, et al. 2022 update on prostate cancer epidemiology and risk factors - a systematic review. Eur Urol 2023;84:191-206.

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

PRINCIPLES OF SURVIVORSHIP
CARDIOVASCULAR DISEASE IN PROSTATE CANCER: RISK ASSESSMENT[a]

Table 1: ABCDEs to Promote Cardiovascular Wellness in Cancer Survivors[b]	
A	• Awareness of risks and presentation of heart disease • Assessment of CVD and cardiovascular risk (consider use of a CVD risk assessment tool[c]) • Aspirin use as appropriate (indicated for secondary prevention; clinician-survivor discussion required for primary prevention with careful weighing of benefits and risks)[d]
B	• Blood pressure monitoring/management (with clinician-survivor discussion regarding the use of hypertension treatment and blood pressure goals)
C	• Cholesterol assessment/management (with clinician-survivor discussion regarding the use of statin therapy for primary prevention and lipid profile goals) • Cigarette/tobacco cessation (NCCN Guidelines for Smoking Cessation)
D	• Diet and weight management (see SNWM-1 in NCCN Guidelines for Survivorship) • Diabetes mellitus prevention/treatment
E	• Exercise (see SPA-1 in NCCN Guidelines for Survivorship)[e] • Echocardiogram (ECHO) and/or electrocardiogram (ECG) based on individual risk (consider use of a CVD risk assessment tool[c])

[a] Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:893-911.
[b] Adapted with permission from Montazeri K, Unitt C, Foody JM, et al. ABCDE steps to prevent heart disease in breast cancer survivors. Circulation 2014;130:e157-e159.
[c] The ASCVD Risk Estimator Plus from the American College of Cardiology is available at https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate and The American Heart Association's PREVENT Risk Calculator is available at https://professional.heart.org/en/guidelinesand-statements/prevent-calculator.
[d] U.S. Preventive Services Task Force; Davidson KW, Barry MJ, Mangione CM, et al. Aspirin use to prevent cardiovascular disease: U.S. Preventive Services Task Force Recommendation Statement. JAMA 2022;327:1577-1584.
[e] Gilchrist SC, et al. Circulation 2019;139:e997-e1012.

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

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, Pancreatic and Prostate

- **Pre-test Considerations**
  - **The Panel recommends inquiring about family and personal history of cancer, and known germline variants at time of initial diagnosis. Criteria for germline testing (see CRIT-6 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic and Prostate and HRS-3 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric) should be reviewed at time of initial diagnosis and, if relevant, at recurrence.**
  - **Germline testing is also recommended for patients with metastatic, regional (node positive), very-high-risk localized, or high-risk localized prostate cancer.**
  - **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, multigene testing is recommended (see GENE-1 in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate).**
- **Post-test Considerations**
  - **Post-test genetic counseling is strongly recommended if a germline mutation (pathogenic/likely pathogenic variant) is identified. Cascade testing for relatives is critical to inform the risk for familial cancers in all relatives.**
  - **Post-test genetic counseling is recommended if positive family history but no pathogenic variant OR if only germline variants of uncertain significance (VUS) are identified. This is to ensure accurate understanding of family implications and review indications for additional testing and/or follow-up (including clinical trials of reclassification).**
  - **Resources are available to review the available data supporting pathogenic consequences of specific variants (eg, https://www.ncbi.nlm.nih.gov/clinvar/; https://brcaexchange.org/about/app).**
  - **Individuals should be counseled to inform providers of any updates to family cancer history.**

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

PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

SOMATIC TUMOR TESTING

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

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

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 in a multidisciplinary manner regarding initial management of localized prostate cancer should include an explanation of the potential benefits and potential harms of each option. The provider should explain the likelihood of cure, recurrence, disease progression, and disease-specific mortality with each management option, taking into account disease severity and competing risks. In addition to the primary intended effects of treatment, the clinician should discuss the side effects of each treatment and predicted impact on quality of life, including urinary, sexual, and bowel function. Patient preferences should be elicited and should be incorporated into the disease management decision.[6]**
- **Consider geriatric assessment. See NCCN Guidelines for Older Adult Oncology for tools to aid optimal assessment and management of disease in older adults.**
- **Refer to the NCCN Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).**

[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.

PRINCIPLES OF IMAGING

Goals of Imaging

- Imaging is performed for the detection and characterization of disease to select treatment or guide change in disease management.
- Imaging techniques can evaluate anatomic or functional parameters.
  - Anatomic imaging techniques include ultrasound, CT, and MRI.
  - Functional imaging techniques include radionuclide bone scan, PET/CT, and advanced MRI techniques, such as spectroscopy and diffusion-weighted imaging (DWI).

Efficacy of Imaging

- The utility of imaging for patients with early PSA persistence/recurrence after RP depends on risk group prior to operation, pathologic Gleason grade and stage, PSA, and PSADT after recurrence. Low- and intermediate-risk groups with low serum PSAs postoperatively have a very low risk of positive bone scans or CT scans.
- Frequency of imaging should be based on individual risk, age, PSADT, Gleason score, and overall health.
- 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 is ≤8 months, where there appears to be an inflection point.

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.

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

PRINCIPLES OF IMAGING

Bone Imaging

- The use of the term "bone scan" refers to the 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 3D 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.
- Plain films, CT, MRI, or PET/CT or PET/MRI with F-18 piflufolastat prostate-specific membrane antigen (PSMA), Ga-68 PSMA-11, F-18 flotufolastat PSMA, F-18 fluciclovine, F-18 sodium fluoride, or C-11 choline can be considered for equivocal results on initial bone scan.
- Ga-68 PSMA-11, F-18 piflufolastat PSMA, or F-18 flotufolastat PSMA-PET/CT or PET/MRI (full body imaging) can be considered as an alternative to bone scan.
- Bone imaging is indicated in the initial evaluation of patients at high risk for skeletal metastases.
- Bone imaging can be considered for the evaluation of the patient post-prostatectomy when PSA does not fall to undetectable levels, or when there is undetectable PSA after RP with a subsequent detectable PSA that increases on ≥2 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.
- Bone scans are helpful to monitor metastatic prostate cancer to determine the clinical benefit of systemic therapy. However, new lesions seen on an initial post-treatment bone scan, compared to the pretreatment baseline scan, may not indicate disease progression.
- New lesions in the setting of a falling PSA or soft tissue response and in the absence of pain progression at that site may indicate bone scan flare or an osteoblastic healing reaction. For this reason, a confirmatory bone scan 8 to 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 to 12 months to monitor ADT. The need for soft tissue images remains unclear. In CRPC, 8- to 12-week imaging intervals appear reasonable.

- *Plain Radiography*
  - Plain radiography can be used to evaluate symptomatic regions in the skeleton. However, plain films 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.

Soft Tissue Imaging

- Soft tissue imaging of the pelvis, abdomen, and chest can include:
  - Chest CT and abdomen/pelvis CT or abdomen/pelvis MRI or
  - PSMA-PET/CT or PSMA-PET/MRI for bone and soft tissue (full body) imaging.

- *Computed Tomography*
  - CT provides a high level of anatomic detail, and may detect gross extracapsular disease, nodal metastatic disease, and/or visceral metastatic disease.
  - CT is generally not sufficient to evaluate the prostate gland.
  - CT may be performed with IV contrast, and CT technique should be optimized to maximize diagnostic utility while minimizing radiation dose.
  - CT can be used for examination of the pelvis and/or abdomen for initial evaluation (PROS-2) and as part of workup for recurrence or progression (see PROS-9 through PROS-18).

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

PRINCIPLES OF IMAGING

- *Magnetic Resonance Imaging*
  - The strengths of MRI include high soft tissue contrast and characterization, multiparametric image acquisition, multiplanar imaging capability, and the use of specific MRI sequences 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 a phased array/endorectal coil.
  - Standard MRI techniques can be used for examination of the pelvis and/or abdomen for initial evaluation (PROS-1) and as part of workup for recurrence or progression (see PROS-9 through PROS-18).
  - MRI may be considered in patients after RP when PSA does not fall to undetectable levels or when an undetectable PSA becomes detectable and increases on ≥2 subsequent determinations, or after RT for increasing PSA or positive DRE if the patient is a candidate for additional local therapy. MRI-ultrasound fusion biopsy may improve the detection of higher grade (Grade Group ≥2) cancers.
  - Multiparametric MRI (mpMRI) can be used in the staging and characterization of prostate cancer. mpMRI images are defined as images acquired with at least one more sequence in addition to the anatomical T2-weighted images, such as DWI or dynamic contrast-enhanced (DCE) images. mpMRI may be used to better risk stratify patients who are considering active surveillance. Additionally, mpMRI may detect large and poorly differentiated prostate cancer (Grade Group ≥2) and detect extracapsular extension (T staging) and is preferred over CT for abdomen/pelvis staging. mpMRI has been shown to be equivalent to CT scan for pelvic lymph node evaluation.

Full Body Imaging

- *Positron Emission Tomography*
  - PSMA-PET refers to a growing body of radiopharmaceuticals that target PSMA on the surface of prostate cells. There are multiple PSMA radiopharmaceuticals at various stages of investigation. At this time, the NCCN Guidelines only recommend the currently FDA-approved PSMA agents: F-18 piflufolastat PSMA (also known as F-18 DCFPyL), F-18 flotufolastat PSMA (also known as rh-PSMA-7.3), and Ga-68 PSMA-11 (also known as PSMA HBED-CC). Throughout these Guidelines, "PSMA-PET" refers to any of these FDA-approved PSMA ligands. See Table 1 on PROS-E (5 of 5) for more details.
  - F-18 flotufolastat PSMA is a PET imaging agent that is part of a class of tracers referred to as radiohybrid (rh) ligands. These tracers have two binding sites for radionuclides for both imaging and treatment, but the significance of this remains to be determined.
  - PSMA-PET/CT or PET/MRI can be considered as an alternative to CT, MRI, and bone scans for initial staging of unfavorable intermediate, high, and very-high-risk disease, the detection of biochemically recurrent disease, and as workup for progression.
  - In the setting of M1 CRPC, PSMA-PET imaging should only be used to determine if a patient is a candidate for Lu-177-PSMA-617.
  - Changes in systemic therapy should not be made solely based on a positive PSMA-PET in patients with M0 CRPC.
  - Bone scans can be considered to confirm osseous uptake on PET scans.
  - Synthesis of Ga-68 PSMA-11 requires that the PSMA-11 ligand is labeled with Ga-68 from a generator or cyclotron. Two commercial kits to perform this in nuclear pharmacies have been approved by the FDA.
  - C-11 choline or F-18 fluciclovine PET/CT or PET/MRI may be used to detect small-volume recurrent disease in soft tissues and in bone.
  - Studies suggest that PSMA-PET imaging has a higher sensitivity than C-11 choline or F-18 fluciclovine PET imaging, especially at very low PSA levels (eg, <0.5 ng/mL).
  - Because of the increased sensitivity and specificity of PSMA-PET tracers for detecting micrometastatic disease compared to CT, MRI, and bone scan at both initial staging and BCR, PSMA-PET/CT or PSMA-PET/MRI can serve as a more effective frontline imaging tool for these patients.
  - Histologic or radiographic confirmation of involvement detected by PET imaging is recommended whenever feasible due to the presence of false positives. Although false positives exist, literature suggests that these are outweighed by the increase in true positives detected by PET relative to CT, MRI, and bone scans. To reduce the false-positive rate, physicians should consider the

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

PRINCIPLES OF IMAGING

intensity of PSMA-PET uptake and correlative CT findings in the interpretation of scans. The use of a standardized reporting system is encouraged.

- 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 1 on PROS-E (5 of 5) provides a summary of FDA-approved PET imaging tracers utilized for study in prostate cancer.
- PET/CT or PET/MRI results may change treatment but may not change oncologic outcome.
- When patients with the worst prognosis move from one risk group to the higher risk group, the average outcome of both risk groups will improve even if treatment has no impact on disease. This phenomenon is known as the Will Rogers effect, in which the improved outcomes of both groups could be falsely attributed to improvement in treatment, but would be due only to improved risk group assignment. As an example, F-18 sodium fluoride PET/CT may categorize some patients as M1b who would have been categorized previously as M0 using a bone scan (stage migration). Absent any change in the effectiveness of therapy, the overall survival (OS) of both M1b and M0 groups would improve. The definition of M0 and M1 disease for randomized clinical trials that added docetaxel or abiraterone to ADT was based on CT and radionuclide bone scans. Results suggest that OS of M1 disease is improved, whereas progression-free but not OS of M0 disease is improved. Therefore, a subset of patients now diagnosed with M1 disease using F-18 sodium fluoride PET/CT might not benefit from the more intensive therapy used in these trials and could achieve equivalent OS from less intensive therapy aimed at M0 disease. Carefully designed clinical trials using proper staging will be necessary to prove therapeutic benefit, rather than making assumptions compromised by stage migration.
- Fluorodeoxyglucose (FDG)-PET/CT should not be used routinely for staging prostate cancer since data are limited in this setting.
- F-18 FDG-PET has been shown to be prognostic in patients with progressive CRPC.[1,2]
- The increasing use of PSMA-PET has identified the potential for considerable biological diversity among disease foci within a given individual with prostate cancer, especially mCRPC, and that this heterogeneity can be detected with a combination of PSMA-PET and FDG-PET. Initial data suggest that metastases with PSMA-negative/FDG-positive mismatches may exist in patients with mCRPC undergoing Lu-PSMA radioligand therapy and that patients with these mismatches may have worse outcomes. Currently, no robust clinical trial data exist to support the incorporation of FDG-PET into routine clinical use alongside PSMA-PET. To overcome the limitations of PSMA-PET in PSMA-negative metastatic disease, the Panel currently recommends the use of contrast-enhanced CT or MRI in these patients, as the non-contrast CT component of PSMA-PET/CT is insufficient to detect visceral metastatic disease.

Imaging as Workup for Progression

- Workup for progression should include bone and soft tissue evaluation.
  - See Bone Imaging (PROS-E [2 of 4]).
  - See Soft Tissue Imaging (PROS-E [2 of 4]).
- Imaging for patients with progressive CRPC should include chest CT, bone imaging, and abdomen/pelvis CT with contrast or abdomen/pelvis MRI with and without contrast.
- There is a lack of evidence to support the use of PET imaging in the CRPC setting and it should only be used in the setting of M1 CRPC to determine if a patient is a candidate for Lu-177-PSMA-617. Changes in treatment should not be made solely based on a positive PSMA-PET in patients with M0 CRPC.

[1] Buteau JP, Martin AJ, Emmett L, et al. PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [177Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): A biomarker analysis from a randomised, open-label, phase 2 trial. Lancet Oncol 2022;23:1389-1397.
[2] Pathmanandavel S, Crumbaker M, Nguyen A, et al. The prognostic value of posttreatment 68Ga-PSMA-11 PET/CT and 18F-FDG PET/CT in metastatic castration-resistant prostate cancer treated with 177Lu-PSMA-617 and NOX66 in a phase I/II trial (LuPIN). J Nucl Med 2023;64:69-74.

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

PRINCIPLES OF IMAGING

Table 1. FDA-Cleared PET Imaging Tracers Studied in Prostate Cancer

Tracer	Half-Life (min)	Excretion	Detection Rates[a]	Panel Recommendation
Ga-68 PSMA-11 (PSMA-HBED-CC)	68	Renal	• 40% sensitivity and 95% specificity to detect nodal involvement in primary staging of patients with intermediate-, high-, and very-high-risk disease • 92% patient-level PPV in BCR	• May be considered as an alternative to CT, MRI, and bone scans for initial staging, the detection of biochemically recurrent disease, and as workup for progression. • May be considered for equivocal results on initial bone scan
F-18 piflufolastat-PSMA (DCFPyL)	110	Renal	• 31%–42% sensitivity and 96%–99% specificity to detect nodal involvement in primary staging of patients with unfavorable intermediate-risk, high-risk, and very-high-risk disease • 85%–87% patient-level CLR[b] in BCR	
F-18 flotufolastat PSMA (rh-PSMA-7.3)	110	Renal	• 23%–30% sensitivity and 93%–97% specificity to detect nodal involvement in primary staging of patients with unfavorable-intermediate-, high-, and very-high-risk disease • 82% patient-level PPV in BCR	
C-11 choline	20	Hepatic and Renal	• 53%–96% PPV in BCR	• May be used to detect small-volume recurrent disease in soft tissues and in bone. • May be considered for equivocal results on initial bone scan
F-18 fluciclovine (FACBC)	110	Renal	• 87%–91% CLR[b] in BCR	
F-18 sodium fluoride	110	Renal	• 77%–94% sensitivity, 92%–99% specificity, and 82%–97% PPV for bone metastases	May be considered for equivocal results on initial bone scan

[a] Interpret with caution. Wherever possible, studies were included that used histopathologic confirmation, but not all studies used confirmatory histology as the gold standard. Values may vary depending upon the site of the lesion and phase of the disease process.
[b] CLR: Correct localization rate. Patient-level positive predictive value + anatomic lesion co-localization. Preferred over sensitivity and specificity in analyses of patients with BCR.

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

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **The NCCN Prostate Cancer Panel and the NCCN Prostate Cancer Early Detection Panel (NCCN Guidelines for Prostate Cancer Early Detection) remain concerned about overdiagnosis and overtreatment of prostate cancer. The Prostate Cancer Panel recommends that patients and their physicians carefully consider active surveillance based on the patient's prostate cancer risk profile and estimated life expectancy. In settings where the patient's age and comorbidities suggest a shorter life expectancy, observation may be more appropriate. Shared decision-making, after appropriate counseling on the risks and benefits of the various options, is critical.**
- **Life expectancy is a key determinant for the choice between observation and active surveillance. Multiple tools exist to assist in life expectancy estimation. See Principles of Life Expectancy Estimation (PROS-A).**
- **There remains no high-level evidence showing clinical benefit of advanced risk stratification tools (eg, gene expression biomarkers, germline or somatic testing, or artificial intelligence (AI)-based digital pathology models), to guide the candidacy for active surveillance.**

ACTIVE SURVEILLANCE[1]

- **Active surveillance involves actively monitoring the course of disease with the expectation to intervene with curative intent if the cancer progresses. It involves PSA monitoring and longitudinal serial pathologic assessments via a prostate biopsy, often guided by MRI.**
- **There are three phases of active surveillance: 1) candidacy, 2) confirmation of candidacy, and 3) active surveillance.**

- **Candidacy for Active Surveillance:**
  - **NCCN Low-Risk:**
    - **Active surveillance is the preferred management approach for patients with low-risk prostate cancer and a life expectancy ≥10 years.**
    - **The Panel recognizes that there is heterogeneity across this risk group.**
      - **Some factors may be associated with an increased probability of near-term grade reclassification including:**
        - **High PSA density (≥0.15)[2]**
        - **Increased number of positive cores[3]**
        - **Higher body mass index (BMI)[3]**
        - **Faster PSA kinetics[3]**
      - **Conversely a negative biopsy following diagnosis is associated with a decreased probability of grade reclassification.**
      - **The Canary PASS risk calculator can be used for more precise estimates of upgrading probability on active surveillance (Canary Pass Risk Calculator)**
      - **Higher risk features alone do not necessitate immediate treatment, but should be used as part of a shared-decision making discussion and in tailoring the intensity of active surveillance.**
    - **For patients who are at high-risk of suboptimal adherence to an active surveillance protocol, a careful discussion should be had about the potential risks of active surveillance. For some of these patients, upfront treatment with definitive RP or RT may be preferred.**

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

References on PROS-F 5 of 5

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **Candidacy for Active Surveillance (continued):**
  - **NCCN Favorable Intermediate-Risk (FIR)**
    - ◊ Patients with FIR prostate cancer and a life expectancy of >10 years may also consider active surveillance.
    - ◊ The FIR group was not created for optimal selection of active surveillance candidacy, and there is considerable heterogeneity in this risk group. Not all patients with FIR disease are suitable candidates for active surveillance. For example:
      - – A patient with Grade Group 1 in a single biopsy core, cT1c, PSA of 12 ng/mL, and PSA density of 0.15 ng/mL/g has FIR disease and a favorable prognostic outcome. Therefore, active surveillance is preferred.
      - – A patient with GG2 in 5 of 12 cores, cribriform architecture, cT1c, PSA of 8 ng/mL, and PSA density 0.30 ng/mL/g has FIR disease, but active surveillance would not be the preferred strategy.
    - ◊ In addition to prognostic factors listed for Low Risk, additional prognostic factors relevant for FIR include:
      - – Increased percentage pattern 4.
      - – Presence of unfavorable histology such as expansile/large cribriform histology and/or intraductal carcinoma.
    - ◊ Active surveillance is not recommended for patients with FIR and unfavorable histology (eg, expansile/large cribriform histology, intraductal carcinoma). See Discussion.
    - ◊ Intensity of active surveillance should generally be greater for patients with FIR disease.
    - ◊ Patients should be counseled that long-term data show that patients with GG2 disease managed with active monitoring or watchful waiting had an increase in the development of distant metastasis as compared to those receiving immediate radical treatment.[4] Continued refinements in active surveillance protocols and active surveillance candidacy are expected to improve the safety of active surveillance for GG2 FIR disease, and patients should be counseled on the importance of longitudinal follow-up.

- **Confirmation of Candidacy:**
  - **Goals of confirmation testing are to help facilitate early identification of patients who may be at a higher risk of grade reclassification or cancer progression.**
  - **An initial prostate biopsy may underestimate tumor grade or volume, thus confirmatory testing is strongly recommended for patients who are considering active surveillance.**
  - **A repeat biopsy is a routine component of confirmatory testing.**
    - ◊ The timing of repeat biopsy can be based on the patient's risk of progression. Patients with a higher risk should have a repeat biopsy earlier than those with a lower risk.
    - ◊ If the initial prostate biopsy was performed without mpMRI guidance, then the Panel recommends an earlier repeat biopsy (eg, within the first 6–12 months) and recommends mpMRI prior to the biopsy. A systematic biopsy should be included.
    - ◊ For most patients, the timing is generally within 6 to 24 months of diagnostic biopsy, but all patients on active surveillance should undergo a confirmatory prostate biopsy within 3 years of their diagnostic biopsy, irrespective of prior mpMRI findings.
  - **Confirmatory testing should also include mpMRI with calculation of PSA density.**
  - **Advanced risk stratification tools lack high level evidence to obviate other testing at this time.**
  - **Other forms of imaging are discouraged.**

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

References on PROS-F 5 of 5

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

- **Active Surveillance Program**
  - Patients who choose active surveillance should have regular follow-up.
  - Key principles include:
    - ◊ PSA no more often than every 6 months, unless clinically indicated.
    - ◊ DRE no more often than every 12 months, unless clinically indicated.
    - ◊ Repeat prostate biopsy no more often than every 12 months, unless clinically indicated. While the intensity of surveillance may be tailored based on patient and tumor factors (eg, grade, tumor volume), most patients should have prostate biopsies every 1 to 3 years as part of their monitoring. Longer intervals between biopsies may be considered if maintained on active surveillance for >3 years without progression.
    - ◊ Consider repeat prostate MRI no more than every 12 months, unless clinically indicated.
    - ◊ In patients with a suspicious lesion on prostate MRI, MRI-targeted biopsy improves the detection of higher grade (GG ≥2) cancers.
    - ◊ Patients should be transitioned to observation when life expectancy is <10 years.
    - ◊ A metastatic staging evaluation (PSMA PET, bone scan, CT scan, or whole-body MRI) should not be performed unless patient develops unfavorable intermediate or higher-risk disease, or has concerning symptoms not explainable by other causes.

- **Considerations for Treatment of Patients on Active Surveillance**
  - Low risk: Grade reclassification on repeat biopsy to GG2 or higher is the most common factor to transition off active surveillance to treatment. PSA alone or growth in size of the tumor on MRI (assuming organ confined) should not be used alone to stop active surveillance without histologic confirmation of progression.
  - FIR: Grade reclassification, increase in percent pattern 4, increase in tumor volume on biopsy or imaging, or rise in PSA density are common factors to transition off active surveillance to treatment.
  - Patient anxiety is commonly cited as a reason to transition off active surveillance. However, studies indicate patient anxiety is closely linked with provider education on the safety of active surveillance. Thus, if a patient is an excellent candidate for active surveillance and has anxiety, the provider should provide appropriate education on the safety of active surveillance.

- **Advantages of Active Surveillance**
  - Approximately 50% of those eligible for active surveillance may safely avoid treatment for 10 years.[5-7] This varies by baseline risk.
  - Patients will avoid or delay possible side effects of treatment. Quality of life will be less affected while on active surveillance.
  - Risk of unnecessary treatment of small, indolent cancers will be reduced.

- **Limitations of Active Surveillance**
  - According to current data, the majority of patients on active surveillance receive treatment by 15 years post-diagnosis.
  - Although the risk is very low for patients diagnosed with GG1 disease (<1% at 10 years and 5% at 15 years), it is possible for cancer to progress to a regional or metastatic stage.[5-8]
  - The majority of high quality evidence with >10 years of follow-up primarily limited active surveillance to patients with low-risk disease, low-volume and low PSA density.
  - In early series, GG2 disease had higher rates of progression to metastatic disease.[8] However, there has been grade migration, stage migration with MRI, and refinement in active surveillance candidacy with assessment of percentage pattern 4 and unfavorable histologic variants. Long-term follow-up (10–15 years) of patients with GG2 FIR disease continues to develop.

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

References on PROS-F 5 of 5

PRINCIPLES OF ACTIVE SURVEILLANCE AND OBSERVATION

OBSERVATION

- Observation involves monitoring with a history and physical examination no more often than every 12 months (without surveillance biopsies, imaging, or PSA monitoring) until symptoms develop or are thought to be imminent.
- Low risk
  - Observation is recommended for asymptomatic patients with life expectancy <10 years.
- FIR
  - Observation is recommended for asymptomatic patients with a life expectancy ≤5 years.
  - Observation is preferred for asymptomatic patients with a life expectancy between 5 to 10 years.
- Observation may be considered for asymptomatic patients with high-risk, very-high-risk, regional, and metastatic prostate cancer and a life expectancy ≤5 years.
- If patients under observation become symptomatic, an assessment of disease burden can be performed, and treatment per the appropriate disease setting or palliation can be considered.

- Advantages of Observation
  - Patients will avoid possible side effects of unnecessary confirmatory testing and definitive therapy with a low probability that this would compromise their survival.

- Limitations of Observation
  - There may be risk of local or systemic symptoms (eg, urinary retention, pathologic fracture) that could have been avoided with upfront definitive treatment.

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

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] Mcleod LC, Ellis WJ, Newcomb LF, et al. Timing of adverse prostate cancer reclassification on first surveillance biopsy: Results from the Canary prostate cancer active surveillance study. J Urol 2017;197:1026-1033.
[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] Wilt TJ, Vo TN, Langsetmo L, et al. Radical prostatectomy or observation for clinically localized prostate cancer: Extended follow-up of the prostate cancer intervention versus observation trial (PIVOT). Eur Urol 2020;77:713-724.
[5] 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.
[6] 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.
[7] 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.
[8] 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.

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

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Neoadjuvant, Concurrent, and/or Adjuvant ADT with RT[a]:
- **Clinically localized (N0, M0) disease**
- **Regional (N1, M0) disease**
- **Positive lymph nodes (pN1 disease) and/or adverse features post-RP**
- **First M0 RP PSA persistence/recurrence**

RT with one of the following ADT options:
- **Luteinizing hormone-releasing hormone (LHRH) agonist monotherapy**
  - Goserelin, leuprolide, or triptorelin
- **LHRH agonist (as above) plus first-generation antiandrogen**
  - Nilutamide, flutamide, or bicalutamide
- **LHRH antagonist**
  - Degarelix or relugolix

LHRH agonist or antagonist plus abiraterone[b] (2 years; only for very-high-risk localized disease or positive lymph nodes)

Notes:
- **ADT is not recommended with RT for most patients with favorable intermediate-risk prostate cancer. If it is given (see Principles of Risk Stratification), the duration should be short term (4–6 months).**
- **For unfavorable intermediate risk prostate cancer treated with RT, short-term ADT (ST-ADT) (4–6 months) is recommended. Concurrent/ adjuvant ADT is preferred over neoadjuvant ADT in this setting.**
- **For high- and very-high-risk prostate cancer treated with EBRT alone, long-term ADT (LT-ADT) (18–36 months) is recommended.**
- **For high-risk prostate cancer treated with combination EBRT + brachytherapy, a shortened duration of ADT (12 months) can be considered.**
- **For additional details on the use of RT with ADT by risk group, see PROS-J.**
- **First M0 PSA persistence/recurrence:**
  - **The timing of secondary treatment 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.**
  - **Earlier treatment may be better than delayed treatment, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early treatment 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 treatment earlier.**
  - **For patients treated with secondary RT in the setting of first RP recurrence, if ADT is given, it should be for a duration of 6 to 24 months.**
  - **Patients with prolonged PSADTs (>12 months) and who are older are candidates for observation or monitoring.**
  - **Patients who choose ADT monotherapy in the secondary treatment setting should consider intermittent ADT.**

[a] Specific recommendations, Categories of Evidence and Consensus, and Categories of Preference vary based on patient and disease characteristics (see PROS-5 through PROS-18). This chart delineates the forms of ADT that can be used and provides some additional details.

[b] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended). Abiraterone should be given with concurrent steroid: prednisone 5 mg PO once daily (in the CSPC setting without docetaxel) or twice daily (in the CSPC setting with docetaxel and in the CRPC setting) with the standard formulation or methylprednisolone 4 mg PO twice daily with the fine-particle formulation. The standard formulation of abiraterone can be given at 250 mg/day following a low-fat breakfast in patients who will not take or cannot afford the standard dose of 1000 mg/day after an overnight fast.

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

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Patients with M0 CSPC[a]:
- **Regional (N1, M0) disease**
- **First M0 RT recurrence**

ADT Options:
- **Orchiectomy**
- **LHRH agonist monotherapy**
  - Goserelin, leuprolide, or triptorelin
- **LHRH agonist (as above) plus first-generation antiandrogen**
  - Nilutamide, flutamide, or bicalutamide
- **LHRH antagonist**
  - Degarelix or relugolix
- **LHRH agonist, LHRH antagonist, or orchiectomy plus abiraterone[b] (only for positive lymph nodes)**

Notes:
- **M0 PSA persistence/recurrence:**
  - **The timing of secondary treatment 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.**
  - **Earlier treatment may be better than delayed treatment, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early treatment 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 treatment earlier.**
  - **Patients with prolonged PSADTs (>12 months) and who are older are candidates for observation or monitoring.**
  - **Patients who choose ADT monotherapy in the secondary treatment setting should consider intermittent ADT.**

[a] Specific recommendations, Categories of Evidence and Consensus, and Categories of Preference vary based on patient and disease characteristics (see PROS-5 through PROS-18). This chart delineates the forms of ADT that can be used and provides some additional details.

[b] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended). Abiraterone should be given with concurrent steroid: prednisone 5 mg PO once daily (in the CSPC setting without docetaxel) or twice daily (in the CSPC setting with docetaxel and in the CRPC setting) with the standard formulation or methylprednisolone 4 mg PO twice daily with the fine-particle formulation. The standard formulation of abiraterone can be given at 250 mg/day following a low-fat breakfast in patients who will not take or cannot afford the standard dose of 1000 mg/day after an overnight fast.

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

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Patients with M0 CSPC BCR2[a]:

ADT Options[c]:
- **Orchiectomy**
- **LHRH agonist monotherapy**
  - Goserelin, leuprolide, or triptorelin
- **LHRH agonist (as above) plus first-generation antiandrogen**
  - Nilutamide, flutamide, or bicalutamide
- **LHRH antagonist**
  - Degarelix or relugolix

Useful in Certain Circumstances:
- Enzalutamide with or without Leuprolide[d] (for high-risk BCR2)
- Apalutamide with LHRH agonist or LHRH antagonist[e] (for high-risk BCR2)

Notes:
- **Monitoring until diagnosis of metastatic disease is preferred for patients with M0 CSPC in the low-risk BCR2 setting.**
- **PSADT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease.**
- **ADT monotherapy is an option for these patients, and intermittent ADT can be considered to reduce toxicity.**

[a] Specific recommendations, Categories of Evidence and Consensus, and Categories of Preference vary based on patient and disease characteristics (see PROS-5 through PROS-18). This chart delineates the forms of ADT that can be used and provides some additional details.
[c] For patients receiving MDT with ADT, the ADT options are LHRH agonist or LHRH antagonist.
[d] Enzalutamide with or without leuprolide is an option for patients who have the following high-risk criteria: M0 by CT, MRI, or bone scan; PSADT ≤9 months; PSA ≥2 ng/mL above nadir after RT or ≥1 ng/mL after RP with or without postoperative RT; and not considered a candidate for pelvic-directed therapy.
[e] Apalutamide plus ADT is an option for patients with biochemical recurrence after RP who meet the following high-risk criteria: PSADT ≤ 9 months; PSA ≥0.5 ng/mL; and prior adjuvant or secondary RT or not considered a candidate for RT (Aggarwal R, et al. J Clin Oncol 2024;42:1114-1123).

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

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Patients with mCSPC[a]:

ADT with treatment intensification (systemic therapy):
- Orchiectomy plus abiraterone,[b] apalutamide, darolutamide, or enzalutamide
- LHRH agonist plus abiraterone,[b] apalutamide, darolutamide, or enzalutamide
- LHRH antagonist plus abiraterone,[b] apalutamide, darolutamide, or enzalutamide
- Orchiectomy plus docetaxel and either abiraterone,[b] apalutamide, darolutamide, or enzalutamide
- LHRH agonist plus docetaxel and either abiraterone,[b] apalutamide, darolutamide, or enzalutamide
- LHRH antagonist plus docetaxel and either abiraterone,[b] apalutamide, darolutamide, or enzalutamide

ADT with treatment intensification (EBRT to the primary tumor):
EBRT with:
- Orchiectomy alone or with abiraterone,[b] apalutamide, docetaxel, or enzalutamide
- LHRH agonist alone or with abiraterone,[b] apalutamide, docetaxel,[g] or enzalutamide
- LHRH antagonist alone or with abiraterone,[b] apalutamide, docetaxel, or enzalutamide

ADT alone for select patients[f]:
- **Orchiectomy**
- **LHRH agonist monotherapy[g]**
  - Goserelin, leuprolide, or triptorelin
- **LHRH agonist (as above) plus first-generation antiandrogen**
  - Nilutamide, flutamide, or bicalutamide
- **LHRH antagonist**
  - Degarelix or relugolix

[a] Specific recommendations, Categories of Evidence and Consensus, and Categories of Preference vary based on patient and disease characteristics (see PROS-5 through PROS-18). This chart delineates the forms of ADT that can be used and provides some additional details.
[b] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended). Abiraterone should be given with concurrent steroid: prednisone 5 mg PO once daily (in the CSPC setting without docetaxel) or twice daily (in the CSPC setting with docetaxel and in the CRPC setting) with the standard formulation or methylprednisolone 4 mg PO twice daily with the fine-particle formulation. The standard formulation of abiraterone can be given at 250 mg/day following a low-fat breakfast in patients who will not take or cannot afford the standard dose of 1000 mg/day after an overnight fast.
[f] ADT is strongly recommended in combination therapy for metastatic castration-sensitive disease. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy. If ADT monotherapy is given, intermittent ADT can be considered to reduce toxicity. 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.
[g] 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 or if there is a large prostate mass.

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

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Secondary Hormone Therapy for Patients with M0 or M1 CRPC[a]:

Castrate levels of testosterone (<50 ng/dL) should be maintained while additional therapies are applied:

- Orchiectomy, LHRH agonist, or LHRH antagonist with specific therapies noted on PROS-16 [M0 CRPC], PROS-17 [NEPC], and PROS-18 [M1 CRPC]
- Orchiectomy, LHRH agonist, or LHRH antagonist with other secondary hormone options:
  - **Abiraterone[b] or enzalutamide following progression on ARPIs (M1 only)**
  - **Abiraterone[b] plus 0.5 mg/day dexamethasone following progression on either formulation of abiraterone (M1 only)**
  - **Antiandrogen withdrawal[h]**
  - **Corticosteroids** (hydrocortisone, prednisone, or dexamethasone)[h]
  - **First-generation anti-androgen** (nilutamide, flutamide, or bicalutamide)[h]
  - **Ketoconazole plus hydrocortisone[h]**

Notes:

- **Although the optimal sequence of therapies remains undefined, some data are emerging that can help with treatment selection in some cases. See Discussion.**

ADT Monotherapy[a]:

ADT Options:

- **Orchiectomy**
- **LHRH agonist monotherapy[g]**
  - Goserelin, leuprolide, or triptorelin
- **LHRH antagonist**
  - Degarelix or relugolix

Notes:

- **ADT monotherapy is appropriate for patients with life expectancy ≤5 years whose cancer progressed on observation of localized disease, who are symptomatic, or who have N1M0 disease.**
- **ADT monotherapy is also used for asymptomatic patients with regional disease and life expectancy ≤5 years whether or not RT is given.**

[a] Specific recommendations, Categories of Evidence and Consensus, and Categories of Preference vary based on patient and disease characteristics (see PROS-5 through PROS-18). This chart delineates the forms of ADT that can be used and provides some additional details.
[b] The fine-particle formulation of abiraterone can be used instead of the standard form (category 2B; other recommended). Abiraterone should be given with concurrent steroid: prednisone 5 mg PO once daily (in the CSPC setting without docetaxel) or twice daily (in the CSPC setting with docetaxel and in the CRPC setting) with the standard formulation or methylprednisolone 4 mg PO twice daily with the fine-particle formulation. The standard formulation of abiraterone can be given at 250 mg/day following a low-fat breakfast in patients who will not take or cannot afford the standard dose of 1000 mg/day after an overnight fast.
[g] 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 or if there is a large prostate mass.
[h] In the mCRPC setting, this option should only be used for select patients who are not candidates for other recommended mCRPC therapies.

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

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Optimal ADT:

- **Medical castration (ie, LHRH agonist or antagonist) and surgical castration (ie, bilateral orchiectomy) are equally effective.**
- **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.**

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. See NCCN Guidelines for Survivorship. Patients and their medical providers should be advised about these risks prior to treatment.**

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

PRINCIPLES OF RISK STRATIFICATION AND BIOMARKERS

General Principles:

- Currently, the primary method for personalization of treatment from localized to advanced prostate cancer is based on prognostic risk stratification, rather than the use predictive biomarkers.
- NCCN uses multiple categories and subgroupings to capture prognostic risk to personalize treatment recommendations.
- The purpose of the NCCN categories and subgroupings are to provide a method for risk stratification to allow standardized treatment recommendations to be provided.
  - It is acknowledged that there are methods of risk stratification with superior prognostic performance to NCCN risk groups. However, they 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 continues to use NCCN categories and subgroups of risk as a framework.
  - Clinical trials have established the benefit of various treatments in prostate cancer and have commonly enrolled patients across a spectrum of risk. Subgroup analyses, absolute benefit estimates, and expert opinion are used to provide treatment recommendations for each NCCN risk group or disease state.
  - There is intrinsic heterogeneity in prognosis within a given NCCN category and subgroup. Thus, treatment recommendations for adjacent subgroups or categories of risk may be appropriate when using additional risk stratification methods.
  - The Panel acknowledges the ability to personalize treatment decisions through additional tools and have created this section to assist.
- Tools that are prognostic or predictive in one disease state may not be in other disease states, or they may have other forms of clinical utility beyond prognostication and prediction of treatment benefit.
  - For example, germline homologous recombination deficiency (HRD) mutations do not have an established prognostic or predictive role in localized prostate cancer, but specific HRD mutations have been demonstrated to have a prognostic and predictive role in advanced disease. Additionally, the utility of germline testing extends to inform screening recommendations for other cancers and cascade germline testing for family members.
- Imaging is also a biomarker (ie, MRI, PSMA-PET/CT) and can aid in risk stratification. See Principles of Imaging (PROS-E).

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

PRINCIPLES OF RISK STRATIFICATION AND BIOMARKERS

Biomarker Categories:

- **Biomarkers and risk stratification methods are tools that may assist in personalization of treatment. For clarity these tools are separated by type and category:**

  - **Type:**
    - ◊ **Standard Tools: These include clinical and/or pathologic variables routinely collected to assign a patient to an NCCN category and/or subgroup. Examples include TNM stage, Grade Group, PSA, and metastatic volume of disease.**
    - ◊ **Clinical and Pathologic Tools: These include clinical and/or pathologic tools that are generally derived from standard tools. Examples include multivariable models or nomograms, histologic variants, and PSA kinetics.**
    - ◊ **Advanced Tools: These involve an additional test above what is collected to assign an NCCN category or subgroup. These may include, but are not limited to, germline or somatic tests, gene expression tests, digital histopathology-based tests, imaging, and circulating markers.**

  - **Category:**
    - ◊ **Prognostic: Discriminates the risk of developing an oncologic endpoint (eg, distant metastasis). The relative benefit of a treatment (ie, the treatment effect or hazard ratio) is generally similar across a prognostic spectrum, although the absolute benefit of an intervention may vary by risk (ie, number needed to treat [NNT]).**
      - **– Ideally, prognostic biomarkers independently discriminate and are associated with a clinically meaningful endpoint above and beyond standard tools relevant to that disease setting that ultimately helps guide a therapeutic decision.**
    - ◊ **Predictive: Discriminates a difference in the relative benefit of a specific treatment for an oncologic endpoint.**
      - **– Ideally, predictive biomarkers have been demonstrated to measure a biomarker-treatment interaction that ultimately helps guide a therapeutic decision in the context of a randomized trial, specifically randomizing the treatment of interest.**

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

PRINCIPLES OF RISK STRATIFICATION AND BIOMARKERS

Clinical and Pathologic Tools:

- An extensive number of prognostic clinical or pathologic tools have been reported based on highly variable evidence quality (retrospective or registry study vs. randomized trial), validation rigor, strength of endpoint (adverse pathology or biochemical recurrence vs. distant metastasis), and univariable versus multivariable association with an outcome. Thus, while some of these tools may have value, these limitations hinder the ability to accurately provide guidance to specific treatment recommendations with confidence.
- A comprehensive list of these tools is outside the scope of this guideline.
  - Examples of such prognostic tools include multivariable models and nomograms (ie, CAPRA,[1] STAR-CAP,[2] MSKCC nomograms[3]), histopathology (ie, cribriform, intraductal carcinoma, percent Gleason pattern 4, total mm of cancer), and clinical variables (ie, PSA density, PSA velocity, PSA level, PSADT).

Advanced Tools:

- There are advanced tools that have demonstrated superior prognostic performance beyond standard tools and/or serve as a predictive biomarker that identifies patients who will differentially benefit from a specific treatment.
- These tools are an additional test that must be ordered, and thus are only recommended to be used when they have the potential ability to change management and should not be ordered reflexively.
- These tools are not recommended for patients with very-low-risk prostate cancer.
- There are an extensive number of these tools created with substantial variability in quality of reporting and model design, endpoint selection, and quality and caliber of validation. It is recommended to use models that have robust validation, ideally with high-quality, long-term clinical trial data, which usually comes from randomized trials and across multiple clinical trials.
- Only advanced tools with Simon level of evidence of I,[4] or specific alterations linked to FDA-approved treatments are shown in Table 1.
  - A comprehensive list of advanced tools that do not reach the threshold of level I evidence is outside the scope of this guideline, but examples of such tests include gene expression tests (ie, 31-gene assay [Prolaris] and 17-gene assay [Genomic Prostate Score]).

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

PRINCIPLES OF RISK STRATIFICATION AND BIOMARKERS

Table 1. Advanced Tools

Localized

Category	Tool	Predictive	Prognostic	Prognostic Endpoint Trained For[a]	Treatment Implications
Gene Expression	22-gene genomic classifier (GC) (Decipher)[5-7]	Not determined	Yes	DM	See Table 2
AI-Pathology	Multimodal artificial intelligence (MMAI) (ArteraAI Prostate)[8-11]	Yes, for ST-ADT	Yes	DM, PCSM[b]	See Table 3

Post-RP

Category	Tool	Predictive	Prognostic	Prognostic Endpoint Trained For[a]	Treatment Implications
Gene Expression	22-gene GC[12,13]	Not determined	Yes	DM	See Table 2

mCRPC

Category	Tool	Predictive	Prognostic	Prognostic Endpoint Trained For[a]	Treatment Implications
Germline/Somatic	Select HRD mutations[14-17]	Yes, for PARP inhibitors	Variable	—	See PROS-C
Somatic	MSI-H; dMMR; TMB-high[18,19]	Yes, for pembrolizumab	Yes	—	See PROS-C
Imaging	PSMA-PET SUVmean[20]	Yes, for Lu-177–PSMA-617	Yes	—	See PROS-E
Imaging	FDG-PET/CT[20]	No	Yes	—	See PROS-E

DM = distant metastases; PCSM = prostate cancer-specific mortality; ST-ADT = short-term ADT; HRD = homologous recombination deficiency; SUVmean = Mean Standardized Uptake Value

[a] The listed models and biomarkers may have demonstrated they are prognostic for additional endpoints. This column indicates what the original model or biomarker was trained for.
[b] Separate models were trained and validated for each endpoint.

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

PRINCIPLES OF RISK STRATIFICATION AND BIOMARKERS

Table 2. Treatment Implications for Advanced Tools
Assay: 22-Gene Genomic Classifier (GC) Assay

Population	Score	Treatment Decision	Treatment Implications
NCCN Intermediate-Risk	**≤0.45 (low) vs. ≥0.60 (high)**	**RT vs. RT with ST-ADT**	**Evidence:** NRG/RTOG 0126 phase III randomized trial was profiled post-hoc with a prespecified analysis plan.[5] The study demonstrated the independent prognostic effect of GC on biochemical failure, secondary therapy, DM, PCSM, MFS, and OS. Patients receiving RT alone with low GC scores had 10-year DM rates of 4%, compared with 16% for GC high risk. **Evidence synthesis:** RT alone may be considered for patients with a low GC score and NCCN intermediate-risk disease. The addition of ST-ADT should be considered for patients with a high GC score given their increased risk of DM and significant benefit of ST-ADT on DM, irrespective of RT dose or brachytherapy boost.
NCCN High-Risk	**≤0.45 (low) vs. ≥0.60 (high)**	**RT + ST-ADT vs. RT + LT-ADT**	**Evidence:** A meta-analysis of three phase III randomized trials (NRG/RTOG 9202, 9413, and 9902) were profiled post-hoc with a prespecified analysis plan.[6] The study demonstrated the independent prognostic effect of GC on biochemical failure, DM, MFS, PCSM, and OS. Patients with low GC scores had 10-year DM rates of 6%, compared with 26% for GC high risk. The absolute benefit of LT-ADT over ST-ADT was 11% for patients with high GC scores (NNT of 9), and 3% for patients with low GC scores (NNT of 33). **Evidence synthesis:** RT + LT-ADT should be recommended for most patients with NCCN high-risk disease regardless of the GC score outside of a clinical trial, irrespective of RT dose or brachytherapy boost. However, patients with a GC low-risk score should be counseled that the absolute benefit of LT-ADT over ST-ADT is smaller than for patients with GC high-risk scores and when accounting for patient age, comorbidities, and patient preferences, it may be reasonable with shared decision-making to use a duration shorter than LT-ADT.
Post-RP BCR	**<0.6 (low/intermediate) vs. ≥0.60 (high)[c]**	**RT vs. RT + ADT**	**Evidence:** Two phase III randomized trials post-RP were profiled post-hoc with prespecified analysis plans. NRG/RTOG 9601 demonstrated the independent prognostic effect of GC on DM, PCSM, and OS, and found that for patients with lower entry PSAs (<0.7 ng/mL), the 12-year DM rate benefit from hormone therapy for patients with GC lower risk vs. GC higher risk was 0.4% vs. 11.2%.[12] The SAKK 09/10 phase III trial tested post-RP lower vs. higher dose RT alone. The study demonstrated the independent prognostic effect of GC on biochemical progression, clinical progression, secondary hormone therapy, DM, and MFS.[13] **Evidence synthesis:** For patients with node-negative disease post-RP planned for early secondary RT (PSA ≤0.5 ng/mL) with GC low or intermediate risk, use of RT alone should be considered. For patients planned for early secondary RT with a GC high-risk tumor, use of secondary RT with ADT is recommended. At this time, it is unclear how best to use GC for patients receiving late post-RP secondary RT (PSA >0.5 ng/mL). Optimal ADT duration (ie, 6 vs. 24 months) based on GC score is unknown at this time.

LT-ADT = long-term ADT; MFS = metastasis-free survival; NNT = number needed to treat; PCSS = prostate cancer-specific survival; ST-ADT = short-term ADT

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

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

PRINCIPLES OF RISK STRATIFICATION AND BIOMARKERS

Table 3. Treatment Implications for Advanced Tools
Assay: Multimodal Artificial Intelligence (MMAI, Artera Prostate Test)

Population	Score	Treatment Decision	Treatment Implications
NCCN Intermediate-Risk	**Biomarker (+) vs. (-)**	**RT vs. RT + ST-ADT**	**Evidence:** A predictive biomarker for benefit of ST-ADT to RT was trained in four phase III randomized trials and validated in NRG/RTOG 9408, a randomized trial of RT +/- 4 months of ST-ADT.[9] On validation, there was a significant biomarker-treatment interaction for DM (p-interaction 0.01). In patients with biomarker-positive disease, ST-ADT significantly reduced the risk of DM compared to RT alone (sHR = 0.34; 95% CI, 0.19–0.63; *P* < .001). There were no significant differences between treatment arms in the biomarker-negative subgroup (sHR = 0.92; 95% CI, 0.59–1.43; *P* = .71). **Evidence synthesis:** Patients with intermediate-risk prostate cancer planning to receive RT, those with biomarker-positive disease, and especially those with unfavorable intermediate-risk disease, should be recommended for the addition of ST-ADT regardless of RT dose or type, notwithstanding contraindications to ADT. Those with biomarker (-) tumors, especially tumors with more favorable prognostic risk, may consider the use of RT alone.
NCCN Low-, Intermediate-, and High-Risk	**Prognostic continuous score and 3-tier (low, intermediate, and high)**	**See Evidence synthesis**	**Evidence:** Published results from seven phase III randomized trials (NRG/RTOG 9202, 9408, 9413, 9902, 9910, 0126, and 0521) with post-hoc derivation of MMAI scores have been reported.[8,10,11] The MMAI model was superior for discrimination of DM and PCSM than standard clinical and pathologic variables and models (5-year DM AUC was 0.83 vs. 0.72 for MMAI vs. NCCN, respectively (*P* < .001)). For patients with high-risk prostate cancer treated with RT + ADT, MMAI was able to risk stratify patients with a 10-year DM risk of 8% for MMAI quartiles Q1–2 versus 26% for MMAI Q3–4.[10] **Evidence synthesis:** Specific MMAI cut points have not been published to date to precisely guide specific treatment decisions. Rather, the test may be used to provide more accurate risk stratification to enable improved shared decision-making. Note: Although the MMAI score incorporates clinical and pathologic variables, it is important to not confuse NCCN risk groups (low, intermediate, and high) with MMAI score groups (low, intermediate, and high).

AUC = area under the curve; BCR = biochemical recurrence; DM = distant metastases; PCSM = prostate cancer-specific mortality; OS = overall survival; sHR = subdistribution hazard ratio; ST-ADT = short term androgen deprivation therapy

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

PRINCIPLES OF RISK STRATIFICATION AND BIOMARKERS
REFERENCES

[1] 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. Erratum in: J Urol 2006;175:2369.
[2] 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.
[3] Memorial Sloan-Kettering Cancer Center. Pre-Radical Prostatectomy. Available at: https://www.mskcc.org/nomograms/prostate/pre_op.
[4] 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.
[5] Spratt DE, Liu VYT, Michalski J, et al. Genomic classifier performance in intermediate-risk prostate cancer: Results from NRG Oncology/RTOG 0126 randomized phase 3 trial. Int J Radiat Oncol Biol Phys 2023;117:370-377.
[6] Nguyen PL, Huang HR, Spratt DE, et al. Analysis of a biopsy-based genomic classifier in high-risk prostate cancer: Meta-analysis of the NRG Oncology/Radiation Therapy Oncology Group 9202, 9413, and 9902 phase 3 randomized trials. Int J Radiat Oncol Biol Phys 2023;116:521-529.
[7] Spratt DE, Zhang J, Santiago-Jiménez 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.
[8] 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. Erratum in: NPJ Digit Med 2023;6:27.
[9] Spratt DE, Tang S, Sun Y, et al. Artificial intelligence predictive model for hormone therapy use in prostate cancer. NEJM Evid 2023;2:EVIDoa2300023.
[10] Spratt DE, Liu VYT, Jia AY, et al. Meta-analysis of individual patient-level data for a multimodal artificial intelligence biomarker in high-risk prostate cancer: Results from six NRG/RTOG phase 3 randomized trials. Eur Urol 2024;86:369-371.
[11] Ross AE, Zhang J, Huang HC, et al. External validation of a digital pathology-based multimodal artificial intelligence architecture in the NRG/RTOG 9902 phase 3 trial. Eur Urol Oncol 2024;7:1024-1033.
[12] 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. Erratum in: JAMA Oncol 2021;7:639.
[13] Dal Pra A, Ghadjar P, Hayoz S, et al. Validation of the Decipher genomic classifier in patients receiving salvage radiotherapy without hormone therapy after radical prostatectomy - an ancillary study of the SAKK 09/10 randomized clinical trial. Ann Oncol 2022;33:950-958.
[14] Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 2020;383:2345-2357.
[15] Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet 2023;402:291-303. Erratum in: Lancet 2023;402:290.
[16] Chi KN, Rathkopf D, Smith MR, et al. Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. J Clin Oncol 2023;41:3339-3351.
[17] Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or physician's choice in metastatic prostate cancer. N Engl J Med 2023;388:719-732.
[18] 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.
[19] 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.
[20] Buteau JP, Martin AJ, Emmett L, et al. PSMA and FDG-PET as predictive and prognostic biomarkers in patients given [177Lu]Lu-PSMA-617 versus cabazitaxel for metastatic castration-resistant prostate cancer (TheraP): a biomarker analysis from a randomised, open-label, phase 2 trial. Lancet Oncol 2022;23:1389-1397.

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

PRINCIPLES OF FOCAL/SUBTOTAL THERAPY OR WHOLE GLAND ABLATIVE THERAPY

General

- **Ablative therapy refers to the use of a device to destroy tissue that can be directed at part of the prostate gland (termed partial gland, hemi-gland, or focal therapy [FT]) or the whole prostate gland.**
- **FT includes ablative therapies and non-ablative therapies, such as partial prostatectomy and focal radiation therapy.[a]**
- **Presently, FT is an experimental and emerging technology for the initial treatment of localized prostate cancer that lacks randomized controlled trial evidence with long-term follow-up showing its superiority or noninferiority to current recommended management strategies. As such, FT meets the criteria as an alternative therapy, or a non-standard treatment.**

Newly Diagnosed or Previously Untreated Prostate Cancer

- **Pathologic confirmation of prostate cancer and risk stratification is required prior to consideration of ablative or FT.**
- **Active surveillance is the preferred treatment for low-risk prostate cancer, and ablative and focal therapies are discouraged in this population.**
- **The Panel also believes that ablative FT should be discouraged in patients with high- or very-high-risk, regional, or metastatic prostate cancer outside of a clinical trial.**
- **There is currently insufficient comparative effectiveness evidence for FT to be recommended for patients with intermediate-risk prostate cancer, and the Panel believes there is uncertainty about the long-term efficacy and toxicity of these treatments. Therefore, ablative and focal therapies in this population should be utilized only in the context of a clinical trial.**
- **The following device categories are currently FDA approved or cleared for the initial treatment of prostate cancer, but randomized evidence to the superiority in long-term cancer control and/or quality of life are lacking when delivered as focal rather than whole gland therapy. These treatments may be considered as FT for patients with previously untreated, localized prostate cancer only in the context of a clinical trial:**
  - **External beam radiotherapy[a]**
  - **Brachytherapy**
  - **Cryotherapy ablation**
- **The following device categories are currently not FDA approved or cleared for the treatment of prostate cancer as focal or whole gland therapy, and should only be used for patients with previously untreated, localized prostate cancer in the context of a clinical trial:**
  - **High-intensity focused ultrasound (HIFU)**
  - **Transurethral ultrasound ablation (TULSA)**
  - **Focal laser ablation (FLA)**
  - **Radiofrequency ablation (RFA)**
  - **Irreversible electroporation (IRE)**
  - **Photodynamic therapy (PDT)**
  - **Histotripsy**
  - **Partial prostatectomy**

[a] Although ultra-hypofractionated EBRT, also known as stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), is considered by some as an ablative technology, it does not fall within the general class of ablative therapies. EBRT is recommended in multiple contexts for the treatment of prostate cancer, and when delivered to the prostate it is recommended to be delivered to the whole prostate gland (discussed within Principles of Radiation Therapy (PROS-J)). However, when delivered as FT it should be viewed within the context of other ablative therapies at this time given similar quality of evidence and risks of residual cancer and retreatment.

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

PRINCIPLES OF FOCAL/SUBTOTAL THERAPY OR WHOLE GLAND ABLATIVE THERAPY

- **Patients should be counseled prior to receiving FT or whole gland ablative therapy as follows:**
  - **HIFU, TULSA, FLA, RFA, IRE, PDT, and histotripsy are not FDA approved or cleared for the treatment of prostate cancer.**
  - **Currently, no treatment delivered as FT, including radiotherapy or partial prostatectomy, have demonstrated superiority or non-inferiority to guideline-recommended therapies in randomized trials with long-term follow-up. The importance of long-term follow-up is of increased importance in this setting given the high rates of secondary therapy after FTs and potential for increased toxicity.**
  - **For patients with low- and intermediate-risk disease[1-7]:**
    - ◊ **Biopsy-detected (any) cancer after FT is common within 2 years post-treatment (20%–70%).**
    - ◊ **Erectile dysfunction (10%–40%) and urinary incontinence (0%–20%) have been reported to occur of variable severity within 2 years post-treatment.**
  - **FT or whole gland ablative therapy may impact the safety and/or efficacy of subsequent local therapy.**
  - **Moderate toxicity (grade 2) is common, and severe toxicity (grade 3 or higher) is possible with reported rates in trials from approximately 1%–14% in the first 2 years post-FT.[1-7]**
  - **Currently, there is no evidence-based, universally agreed upon follow-up protocol after FT. Patients often undergo serial imaging and prostate biopsies.**

[1] Ehdaie B, Tempany CM, Holland F, et al. MRI-guided focused ultrasound focal therapy for patients with intermediate-risk prostate cancer: a phase 2b, multicentre study. Lancet Oncol 2022;23:910-918.
[2] Duwe G, Boehm K, Haack M, et al. Single-center, prospective phase 2 trial of high-intensity focused ultrasound (HIFU) in patients with unilateral localized prostate cancer: good functional results but ontologically not as safe as expected. World J Urol 2023;41:1293-1299.
[3] Ganzer R, Hadaschik B, Pahernik S, et al. Prospective multicenter phase II study on focal therapy (hemiablation) of the prostate with high intensity focused ultrasound. J Urol 2018;199:983-989.
[4] Ghai S, Finelli A, Corr K, et al. MRI-guided focused ultrasound focal therapy for intermediate-risk prostate cancer: final results from a 2-year phase II clinical trial. Radiol 2024;310:e231473.
[5] Klotz L, Pavlovich CP, Chin J, et al. Magnetic resonance imaging-guided transurethral ultrasound ablation of prostate cancer. J Urol 2021;205:769-779.
[6] Mehralivand S, George AK, Hoang AN, et al. MRI-guided focal laser ablation of prostate cancer: a prospective single-arm, single-center trial with 3 years follow-up. Diagn Interv Radiol 2021;27:394-400.
[7] Eggener SE, Yousuf A, Watson S, et al. Phase II evaluation of magnetic resonance imaging guided focal laser ablation of prostate cancer. J Urol 2016;196:1670-1675.

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

PRINCIPLES OF FOCAL/SUBTOTAL THERAPY OR WHOLE GLAND ABLATIVE THERAPY

Management of Recurrence After Focal Ablative or Whole Gland Ablative Therapy

- **Presently, the optimal management of residual or recurrent disease after receipt of these treatments is unknown and limited evidence exists. A multi-disciplinary discussion with experienced prostate cancer specialists is recommended.**
- **If there is suspicion of residual or recurrent prostate cancer, a biopsy should be performed to confirm the presence of residual or recurrent prostate cancer.**
  - **Histologic grading of the cancer is recommended if located in previously untreated areas of the prostate. Reliability of grading within a previously treated area of the prostate is unknown at this time, and patients should be informed of this uncertainty.**
- **Staging imaging should be performed based on the patient's NCCN risk group at time of recurrence (see PROS-2). However, PSA groupings as used for newly diagnosed prostate cancer may underestimate the burden of disease after prior FT or ablative therapy.**
  - **Interpretation of imaging (ie, assessment of cT3 disease by MRI near ablation zone) after FT or whole gland ablative therapy may be less reliable.[8]**
  - **Advanced risk stratification tools (eg, gene expression or digital pathology-based biomarkers) have not been adequately studied for use in the context of focal or whole gland ablative therapy and are not recommended to guide treatment decisions in this setting.**
- **Patients with a clinically significant recurrence after initial focal therapy should be offered radical prostatectomy or prostate RT if appropriate based on life expectancy.**
- **Patients should be counseled as follows:**
  - **There is limited evidence on how to optimally manage a FT or whole gland ablative therapy recurrence.**
  - **Patients are at an increased risk of toxicity from subsequent local therapy compared to the primary treatment setting.**
  - **It is not known if radical therapy has equivalent long-term success after FT or whole gland ablative therapy given lack of trials with long-term follow-up in this setting.**
  - **Secondary treatment should be reserved for patients with appropriate life expectancy and Grade Group 2 and higher recurrences detected on biopsy.**

Local Recurrence After Radiation Therapy

- **Patients with biopsy-proven recurrence in the prostate after prior RT and without distant metastatic disease can be considered for local secondary therapy.**
- **However, clinicians and patients should be aware that no local therapy currently has level 1 evidence for the management of a local recurrence after definitive RT.**
- **Treatments with higher quality of evidence are recommended. These are discussed in the Principles of Local Secondary Therapy Post-Radiation (PROS-L) and include select forms of FT or whole gland ablative therapy.**

[8] Lai AL, Velaga J, Tay KJ, et al. Multiparametric MRI before and after focal therapy for prostate cancer: pearls and pitfalls for the reporting radiologist. Radiol;7:e240269.

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

PRINCIPLES OF RADIATION THERAPY

All patients diagnosed with intermediate-, high-, very-high-, regional-risk, low-volume mCSPC, biochemically recurrent, low-volume metastatic castration-sensitive prostate cancer (mCSPC) and oligometastatic mCRPC are recommended to be evaluated by a radiation oncologist as part of a multidisciplinary discussion of treatment options.

General

- **EBRT**
  - **Treatment Planning: Intensity modulated RT (IMRT) is recommended over 3-dimensional conformal RT to improve dose conformality.**
  - **Image Guidance: Methods to improve accuracy of treatment delivery, thereby enabling reduction in planning target value (PTV) margins, which generally result in reduced toxicity are encouraged and may include one or more of the following:**
    - ◊ **Image guidance with daily 3D imaging is recommended with either a cone beam CT (CBCT) or MRI.**
    - ◊ **Devices that assist with optimal image guidance (fiducial markers) or reduce motion (endorectal balloons).**
    - ◊ **Real-time intrafraction volumetric tracking.**
    - ◊ **Online adaptive radiotherapy if target is near mobile organs (ie, performing a simultaneous integrated boost to a positive pelvic lymph node adjacent to bowel).**
  - **Beam Type: Photon and proton RT are acceptable forms of EBRT and appear to have similar outcomes in regard to toxicity, QOL, and tumor control. Potential financial toxicity should be discussed with patients.**
  - **Fractionation: An extensive list of fractionation schedules have been studied. These are grouped into three categories, conventional fractionation (1.8–2 Gy/fraction), moderate hypofractionation (>2.5 to 4 Gy/fraction), and ultra-hypofractionation (>6 Gy/fraction).[1] Common dose/fraction schedules are shown in Table 1. In general, iso-effective moderate hypofractionation dosing has demonstrated noninferior tumor control, toxicity, and QOL over conventional fractionation and is more convenient for patients and thus preferred. Similarly, ultra-hypofractionation has been demonstrated to be noninferior to both moderate hypofractionation and conventional fractionation.[2] Thus, use of conventionally fractionated radiotherapy is no longer preferred for localized prostate cancer.**
    - ◊ **Ultra-hypofractionation encompasses stereotactic body radiation therapy (SBRT), which requires precision treatment setup and required additional image guidance techniques.**
    - ◊ **SBRT is recommended and preferred specifically when:**
      - **– Performing metastasis-directed radiotherapy (MDRT) (see Principles of MDT [PROS-M])**
      - **– There is limited progression (eg, oligoprogression) or limited residual disease and the patient is on otherwise effective systemic therapy (eg, consolidation).**
      - **– The lesion occurs in or immediately adjacent to a previously irradiated treatment field.**
      - **– At physician discretion for more durable control of pain than achieved with typical palliative regimens.**

References on PROS-J 10 of 11

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

PRINCIPLES OF RADIATION THERAPY

- **Brachytherapy**
  - **Patient Selection: Providers 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 be considered in context of the balance between its additional toxicity with this benefit.**
  - **Dose Rate: Both low-dose rate (LDR) and high-dose rate (HDR) are acceptable to be used as either monotherapy or as a boost combined with EBRT in higher risk disease. Data indicates that HDR may have lower toxicity than LDR, and while efficacy appears similar between HDR and LDR when used as a boost combined with EBRT, it remains unknown if HDR as monotherapy provides equivalent tumor control to LDR given lack of robust randomized comparisons. Post-implant dosimetry must be performed for LDR implants to verify dosimetry.**
  - **Monotherapy: Brachytherapy monotherapy has been shown to have fewer side effects than when used with EBRT without compromising tumor control for intermediate-risk disease.[3]**
  - **Combination Therapy: EBRT with an LDR brachytherapy boost has been shown to improve biochemical control over conventionally fractionated EBRT with ADT (12 months) without a focal/micro EBRT boost.[4] This was at the expense of an increase in high-grade toxicity.[5] Thus, careful patient selection and contemporary planning, use of recognized organ at risk (OAR) dose constraints, and use of high-quality ultrasound and other imaging are essential.**

- **Elective Nodal Irradiation (ENI)**
  - **ENI can be considered in select patients.**
  - **Use of IMRT with image guidance is recommended when performing ENI. Advanced techniques that include online adaptive radiotherapy may be considered to reduce ENI planning target volume margins.**
  - **If performing ENI, it is recommended to include the common, internal, and external iliac, pre-sacral, and obturator lymph node stations. Peri-rectal/mesorectal lymph nodes may be included if there is evidence of lymph node involvement in this nodal station. Para-aortic lymph nodes should not be included in patients who do not have evidence of para-aortic lymph node involvement.**

Definitive RT

- **Biocompatible and biodegradable perirectal spacers:**
  - **These devices may be implanted between the prostate and rectum in patients undergoing radiation therapy to the prostate in order to displace the rectum from high radiation dose regions for the purpose of toxicity reduction. Patients with grossly apparent true posterior extraprostatic extension should not undergo perirectal spacer implantation. NCCN high-risk disease without posterior extraprostatic extension is not a contraindication to spacer use.**
  - **These devices should be placed by practitioners who can maintain a moderate to high volume of use to ensure quality.**
  - **Additional caution should be used in the re-irradiation setting due to potential changes in tissue planes.**

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

References on PROS-J 10 of 11

PRINCIPLES OF RADIATION THERAPY

Definitive RT (continued)

- **Low Risk**
  - **Patients with NCCN low-risk prostate cancer are encouraged to pursue active surveillance.[6]**
  - **Those electing treatment with RT may receive EBRT or brachytherapy as monotherapy.**
  - **The target should include the prostate and consideration of treatment of seminal vesicles (proximal).**
  - **Patients should not be treated with any of the following:**
    - ◊ **ENI**
    - ◊ **ADT**
    - ◊ **Combination brachytherapy boost with EBRT**

- **Favorable Intermediate Risk**
  - **The target should include the prostate and consideration of treatment of seminal vesicles (proximal or full).**
  - **Those electing treatment with RT may receive EBRT or brachytherapy as monotherapy.**
  - **Patients should not be treated with any of the following:**
    - ◊ **ENI**
    - ◊ **Combination brachytherapy boost with EBRT[3]**
  - **ADT is generally not recommended, but can be considered if additional risk assessments suggest aggressive tumor behavior or increased potential benefit from short-term ADT.[7,8]**

- **Unfavorable Intermediate Risk**
  - **The target should include the prostate and the seminal vesicles (proximal or full).**
  - **RT options include either EBRT, brachytherapy monotherapy, or EBRT with a brachytherapy boost.**
  - **Multiple randomized trials that included patients with unfavorable intermediate risk who did not demonstrate superiority of combination therapy over brachytherapy monotherapy.[3]**
  - **Focal boosting with isotoxic delivery can be considered if there is sufficient provider and practice expertise to delineate the dominant intraprostatic lesion (DIL) and OARs on MRI.[9]**
  - **ENI should not be used routinely.**
  - **ADT (level 1 data for ST-ADT) should be used unless additional risk assessments suggest less aggressive tumor behavior, or less predicted benefit, or if medically contraindicated.[8,10] Radiotherapy dose or modality has not clearly demonstrated the ability to obviate the benefit of ADT. ST-ADT is recommended to be used as a concurrent and adjuvant approach with RT rather than a neoadjuvant and concurrent approach.[11]**

References on PROS-J 10 of 11

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

PRINCIPLES OF RADIATION THERAPY

Definitive RT (continued)

- **High Risk**
  - The target should include the prostate and the seminal vesicles (full).
  - RT options include EBRT or brachytherapy boost combined with EBRT. Carefully selected patients may receive brachytherapy monotherapy.
  - Focal boosting with isotoxic delivery can be considered if there is sufficient provider and practice expertise to delineate the DIL and OARs on MRI.[9]
  - Clinical trials have demonstrated varied results regarding the benefit of ENI. Multiple randomized trials have not demonstrated improvement in outcomes from ENI. However, the benefit of ENI was shown in one trial of patients with high-risk prostate cancer staged primarily with PSMA-PET/CT and who had a risk of nodal involvement >20%. Currently, the use of ENI is at the discretion of the treating physician.
  - ADT (level 1 data for LT-ADT 12–36 months) is recommended for patients with life expectancy >5 years or who are symptomatic unless medically contraindicated. Radiotherapy dose or modality has not clearly demonstrated the ability to obviate the benefit of LT-ADT.[10]

- **Very-High-Risk**
  - The target should include the prostate and the seminal vesicles (full).
  - RT options include EBRT. Carefully selected patients may receive EBRT with a brachytherapy boost.
  - Focal boosting with isotoxic delivery can be considered if there is sufficient provider and practice expertise to delineate the DIL and OARs on MRI.
  - Combination brachytherapy boost with EBRT should not be used routinely. The primary randomized evidence to recommend combination brachytherapy boost with EBRT comes from the ASCENDE-RT trial, which excluded patients with PSA >40 ng/mL and T3b.[12]
  - ADT (level 1 data for LT-ADT 18–36 months) is recommended for patients with life expectancy >5 years or who are symptomatic unless medically contraindicated.
  - Currently, the use of ENI is at the discretion of the treating physician.
  - Addition of abiraterone should be used very selectively as the benefit in contemporary practice with modern staging is uncertain (see PROS-6 and PROS-G 1 of 5).[13] It is not recommended to be used routinely for patients with solely MRI defined T3a disease with low volume Gleason 8 disease. Studies validating the post-hoc subset analysis of STAMPEDE for the benefit of abiraterone in very high-risk prostate cancer using other ARPIs have not yet reported, and thus the benefit of using ARPIs with RT+LT-ADT remains uncertain in contemporary patients with very high risk N0M0 disease. Radiotherapy dose or modality has not clearly demonstrated the ability to obviate the benefit of LT-ADT.[10]

- **Regional Disease**
  - EBRT is recommended to include the prostate, seminal vesicles, and pelvic lymph nodes.
  - Simultaneous integrated boost to involved lymph nodes is recommended while respective adjacent OAR dose constraints.
  - Use of a brachytherapy boost is not recommended in these patients.
  - Addition of abiraterone is recommended (see PROS-7 and PROS-G [1 of 5]).[13]

References on PROS-J 10 of 11

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

PRINCIPLES OF RADIATION THERAPY

Postoperative RT:

- **Adjuvant RT: Adjuvant RT (aRT) involves the use of EBRT post-radical prostatectomy for patients with adverse pathologic features (ie, pT3 and/or positive surgical margins) in the setting of an undetectable postoperative PSA. This may result in some patients unnecessarily receiving aRT and experience potential additional side effects.**
  - **The early results and aggregate meta-analysis of three trials comparing aRT to early secondary RT (sRT) did not demonstrate a difference in biochemical recurrence for patients with generally a favorable prognosis. Thus, waiting for a detectable PSA and using an early sRT approach is recommended for most patients who undergo a RP rather than an immediate aRT approach to avoid over treatment and subsequent potential side effects.[14]**
  - **Use of aRT may be reasonable for patients with multiple adverse features and/or lymph node involvement.**
    - ◊ **Patients with multiple adverse features and/or lymph node involvement were underrepresented in these trials, and in the RADICALS-RT trial, the largest of the trials comparing aRT to early sRT, there was a significant reduction in prostate cancer-specific mortality with aRT and numerical trends in superior freedom-from-distant metastasis with aRT.[15] This raises uncertainty to the true noninferiority of early sRT in these patients with high risk of recurrence post-RP.**
  - **Multiple dose/fraction schedules have been used with aRT that include both conventionally fractionated (60–64 Gy in 30–36 fractions) and moderately hypofractionated regimens (52.5 Gy in 20 fractions).[16]**
- **Secondary RT is the use of EBRT post-RP when a patient has a detectable PSA; a lower limit is not defined and may be below 0.2 ng/mL.**
  - **Early sRT at a PSA of 0.1–0.2 ng/mL is recommended for most patients who experience BCR post-RP. The exception to this is in patients who have delayed recurrence many years post-RP with very slow PSA doubling times (ie, >24 months), especially when a patient has limited life expectancy.**
  - **Unlike in localized prostate cancer, the use of ADT in the post-RP setting has demonstrated survival improvements in only a small subset of patients, primarily in those with high pre-sRT PSAs receiving late sRT (PSA >0.7 ng/mL).[17] For patients receiving early sRT there is no clear OS benefit from the addition of ADT in any of the four published randomized trials, irrespective of ADT duration, or on meta-analysis.[18] ADT does significantly delay the incidence of biochemical recurrence.**
  - **Use of ADT with sRT should be personalized based on pre-RT PSA, clinicopathologic risk factors, patient age, life expectancy, comorbidities, and preferences, as well as advanced risk stratification tools (see PROS-H).[18,19]**
    - ◊ **Generally, ST-ADT is recommended to balance toxicity, QOL, and tumor control. However, LT-ADT may be preferred for patients receiving late sRT and/or those with multiple adverse pathologic features and/or lymph node involvement.**
    - ◊ **Treatment intensification with an ARPI has not demonstrated an improvement in metastasis-free survival or overall survival in this population in unselected patients.[20,21]**
  - **Multiple dose/fraction schedules have been used with sRT that include both conventionally fractionated (64–70.2 Gy in 32–39 fractions) and moderately hypofractionated regimens (52.5 Gy in 20 fractions or 62.5 Gy in 25 fractions).[16,22] The moderately hypofractionated regimens have demonstrated noninferior tumor control, toxicity, and QOL. Multiple single arm trials and early follow-up of phase II randomized trials have been reported using ultra-hypofractionated RT in the sRT setting, and generally are using 32.5–34 Gy in 5 fractions.[23,24] These studies often leverage either intrafraction motion monitoring, online adaptive radiotherapy, and strict image guidance with substantially modified contouring of target volumes to limit dose to OARs.**
  - **The addition of ENI to sRT plus ST-ADT has demonstrated improvements in biochemical control.[25] It appears the benefit is greater in patients with higher pre-sRT PSAs, as well as in patients who did not have their pelvic lymph nodes assessed, or minimally assessed, via a pelvic lymph node dissection. Use of PSMA PET/CT has not been shown to be sensitive enough to rule out the presence of pelvic lymph node micrometastases.**

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

References on PROS-J 10 of 11

PRINCIPLES OF RADIATION THERAPY

RT in Advanced Disease:

- **Synchronous mCSPC**
  - **Treatment of the primary tumor:**
    - **Minimizing toxicity is paramount when delivering RT to the primary tumor in patients with metastatic disease. As such, it is unclear if dose escalation (ie, brachytherapy or focal boost) improves outcomes.**
    - **Low Volume: Treatment of the primary is recommended with EBRT.[26,27]**
      - **Volume of disease should be defined according to CT and bone scan, if performed.**
      - **PET imaging should not be used to exclude a patient from treatment of the primary tumor.**
      - **The strongest data for a benefit of adding RT to the primary tumor are in patients receiving either ADT alone, ADT+ docetaxel, or ADT + abiraterone for those with ≤5 bony metastases.**
    - **High Volume: Treatment of the primary tumor with EBRT can be considered for select patients with high-volume mCSPC (category 2B).[27]**
      - **RT to the primary tumor in high volume mCSPC has demonstrated improvements in time to mCRPC and a reduction in the development of severe genitourinary adverse events when given in the context of ADT with variable use of docetaxel and/or abiraterone.**
  - **Treatment of Metastases**
    - **MDT, which typically uses SBRT, may be used for patients who have a limited burden of lymph node or osseous disease. See Principles of MDT (PROS-M).**

- **Metachronous mCSPC**
  - **A greater level of evidence supports the role of MDT in the metachronous setting as compared to synchronous mCSPC. This commonly is delivered using SBRT, but moderately hypofractionated RT may be considered.**
  - **Use of MDT in this setting has been shown to delay the need for ADT compared to observation,[28] the addition of RT to ADT has been shown to prolong a treatment free eugonadal interval as compared to ADT alone,[29] and the addition of ADT to RT has improved progression-free survival (PFS).[30]**
  - **See Principles of MDT (PROS-M).**

  - **mCRPC**
    - **The use of MDT has been shown to prolong PFS and rPFS when used for patients with oligometastatic CRPC treated with ADT+ARPI as compared to systemic therapy alone. MDT may be considered when the goal is to prolong PFS and extend duration of systemic therapy prior to needing to switch therapies.[31] See Principles of MDT (PROS-M).**

References on PROS-J 10 of 11

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

PRINCIPLES OF RADIATION THERAPY

Radiopharmaceutical Therapy

- Radiopharmaceutical therapies for prostate cancer are suitable options for improving survival and/or rPFS in select patients with advanced castration-resistant disease. Due to prior therapy exposure, specific targets, and hematologic effects of these therapies, careful selection and sequencing strategy with other therapies is important. This section discusses the two currently FDA-approved agents in use (Ra-223, Lu-177–PSMA-617).

- Radium-223
  - Radium-223 has been shown to extend survival in patients who have CRPC with symptomatic bone metastases, but no visceral metastases.[32] Radium-223 alone has not been shown to extend survival in patients with visceral metastases or bulky nodal disease (>3 to 4 cm).
  - Radium-223 is administered IV once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or radiation oncology facilities.
  - Concurrent use with enzalutamide and bone health agents may be considered given the overall survival benefit over enzalutamide alone.[33] Concurrent use with other systemic therapies should be pursued with caution.
  - Bone fracture risk: Radium-223 may increase fracture risk when given concomitantly with an ARPI without use of a bone health agent. Concomitant use of denosumab or zoledronic acid is recommended.[34]

- Lu-177–PSMA-617[16]
  - In patients with PSMA-positive disease, Lu-177–PSMA-617 has been shown to improve OS in patients with progressive mCRPC previously treated with androgen receptor inhibitors and taxane chemotherapy.[35] It has also been shown to improve rPFS in patients who have not received taxanes with PSMA-positive mCRPC who were previously treated with an androgen receptor inhibitor compared with changing to a different androgen receptor inhibitor.
  - This agent is approved for patients with mCRPC who have been treated with ARPI therapy and have received prior taxane-based chemotherapy or are considered appropriate to delay receipt of chemotherapy.[36]
  - Lu-177–PSMA-617 is not recommended in patients with dominant PSMA-negative lesions. PSMA-negative lesions are defined as metastatic disease that lack 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.
  - Use of PSMA PET/CT SUVmean and use of an FDG PET/CT scan may aid in identifying patients with lower PSMA expression and non-PSMA avid disease who will derive less or potentially no benefit from 177-Lu-PSMA-617.
  - Lu-177–PSMA-617 is typically administered IV 200 mCi (7.4 GBq) every 6 weeks for up to 6 treatments by an appropriately licensed facility.
  - Use of post-treatment SPECT or PET/CT imaging can be considered to monitor PSMA expression for adaptive dosing.
  - 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.
  - For information regarding the use of PSMA-PET to define PSMA-positive disease, see Principles of Imaging (PROS-E).

References on PROS-J 10 of 11

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

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 treatment pages and Principles of ADT (PROS-G) for other recommendations, including recommendations for neoadjuvant/concomitant/adjuvant ADT.

EBRT Regimen	Preferred Dose/Fraction	Definitive RT						Post-Treatment RT			Advanced Disease	
								Post-RP		Post-RT	Primary Tumor	Metastases
		Low	FIR	UIR	High	Very-High	Regional	aRT	sRT	sRT	mCSPC M0 CRPC mCRPC	MDT
Conventional	1.8–2 Gy x 37–45 fx			☼	☼	✓	✓				☼	
	1.8–2 Gy x 30–39 fx							✓	✓		☼	
Moderate Hypofractionation	3 Gy x 20 fx (preferred)[a] 2.7 Gy x 26 fx 2.5 Gy x 28 fx	☼	✓	✓	✓	✓	✓			☼	☼	☼
	2.63–2.75 Gy x 20 fx 2.5 Gy x 25 fx							✓	✓	☼	✓	☼
Ultra Hypofractionation (SBRT)	9.5 Gy x 4 fx 7.25–8 Gy x 5 fx 6 Gy x 6 fx 6.1 Gy x 7 fx	☼	✓	✓	✓	☼	☼		☼	✓	✓	✓
	9–10 Gy x 3 fx 12 Gy x 2 fx 16–24 Gy x 1 fx											✓
	6.2–6.4 Gy x 5 fx								☼			
EBRT Boost Techniques												
EBRT with simultaneous integrated boost	See footnote b.		☼	✓	✓	☼	☼		☼	☼	☼	
EBRT with sequential SBRT boost	*Prostate:* 1.8 Gy x 23–28 fx *Boost:* 6 Gy x 3 fx 9.5 Gy x 2 fx			☼	☼	☼						

(✓ Preferred; ☼ Acceptable based on clinical and medical need; Regimens shaded gray are not recommended)

Footnotes on PROS-J 8A of 11

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

PRINCIPLES OF RADIATION THERAPY
FOOTNOTES

[a] Based on the HYDRA individual patient meta-analysis of seven phase III randomized trials, isodose moderately hypofractionated radiotherapy (MHFRT) and dose-escalated MHFRT both have similar efficacy compared with conventionally fractionated radiotherapy (CFRT), but dose-escalated MHFRT was associated with higher toxicity. Isodose regimens (eg, 60 Gy in 20 fractions) are preferred for MHFRT for localized prostate cancer. Alternative regimens (eg, 70 Gy in 28 fractions) may be used, but patients should be counseled on potentially increased risk of toxicity.[1]

[b] EBRT to whole prostate 2.2 Gy x 35 fx plus micro-boost to MRI-dominant lesion to ≤95 Gy (fractions ≤2.7 Gy).[9] The micro-boost technique with level 1 data was established for a modestly hypofractionated regimen but has been extrapolated reasonably to other regimens in ongoing clinical trials. Care must be taken in doing so outside of clinical trials in order to respect normal tissue toxicity risk and above all in prioritizing normal organ tolerances over micro-boost coverage.

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

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 treatment pages and Principles of ADT (PROS-G) for other recommendations, including recommendations for neoadjuvant/concomitant/adjuvant ADT.

Brachytherapy	Preferred Dose/Fraction	Definitive RT						Post-Treatment RT			Advanced Disease	
								Post-RP		Post-RT	Primary	Metastases
		Low	FIR	UIR	High	Very-High	Regional	aRT	sRT	sRT	mCSPC M0 CRPC mCRPC	MDT
Monotherapy												
Iodine 125	145 Gy	☼	✓	✓	☼					✓		
Palladium 103	125 Gy											
Cesium 131	115 Gy											
Iridium 192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants											
EBRT + Brachytherapy Boost												
Iodine 125	110–115 Gy			☼	✓	☼						
Palladium 103	90–100 Gy											
Cesium 131	85 Gy											
Iridium 192	15 Gy x 1 fx 10.75 Gy x 2 fx											

(✓ Preferred; ☼ Acceptable based on clinical and medical need; Regimens shaded gray are not recommended)

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

References on PROS-J 10 of 11

PRINCIPLES OF RADIATION THERAPY
REFERENCES

[1] Kishan AU, Sun Y, Tree AC, et al. Hypofractionated radiotherapy for prostate cancer (HYDRA): an individual patient data meta-analysis of randomised trials in the MARCAP consortium. Lancet Oncol 2025;26:459-469.
[2] van As N, Griffin C, Tree A, et al. A Phase III randomized controlled trial of Stereotactic Body Radiotherapy in localized prostate cancer. N Engl J Med 2024;391:1413-1425.
[3] Michalski JM, Winter KA, Prestidge BR, et al. Effect of brachytherapy with external beam radiation therapy versus brachytherapy alone for intermediate-risk prostate cancer: NRG oncology RTOG 0232 randomized clinical trial. J Clin Oncol 2023;41:4035-4044.
[4] Oh J, Tyldesley S, Pai H, et al. An updated analysis of the survival endpoints of ASCENDE-RT. Int J Rad Oncol 2023;115:1061-1070.
[5] 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 Rad Onocl Biol Phys 2017;98:286-295.
[6] Hamdy FC, Donovan JL, Lane A, et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2023;388:1547-1558.
[7] 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.
[8] Krauss DJ, Karrison T, Martinez AA, et al. Dose-escalated radiotherapy alone or in combination with short-term androgen deprivation for intermediate-risk prostate cancer: results of a phase III multi-institutional trial. J Clin Oncol 2023;41:3203-3216.
[9] 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.
[10] Kishan AU, Sun Y, Hartman H, et al. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. Lancet Oncol 2022;23:304-316.
[11] Spratt DE, Malone S, Roy S, et al. Prostate radiotherapy with adjuvant androgen deprivation therapy (ADT) improves metastasis-free survival compared to neoadjuvant ADT: an individual patient meta-analysis. J Clin Oncol 2021;39:136-144.
[12] 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 Rad Oncol Biol Phys 2017;98:275-285.
[13] Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet 2022;399:447-460.
[14] 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;396:1422-1431.
[15] Parker CC, Petersen PM, Cook AD, et al. Timing of radiotherapy (RT) after radical prostatectomy (RP): long-term outcomes in the RADICALS-RT trial (NCT00541047). ESMO 2024;24;656-666.
[16] Petersen PM, Cook AD, Sydes MR, et al. Salvage radiation therapy after radical prostatectomy: analysis of toxicity by dose-fractionation in the RADICALS-RT trial. Int J Rad Oncol Biol Phys 2023;117:624-629.
[17] 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.
[18] Burdett S, Fisher DJ, Tierney JF, et al. Duration of androgen suppression with postoperative radiotherapy (DADSPORT) for nonmetastatic prostate cancer: a collaborative systematic review and meta-analysis of aggregate data. [online ahead of print] Eur Urol 2025;doi:/10.1016/j.eururo.2025.05.013.
[19] 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.
[20] Posadas EM, Gay HA, Rodgers JP, et al. Intensification of ADT with enzalutamide in high-risk patients with biochemical relapse following radical prostatectomy undergoing salvage radiation: Initial results from RTOG 3506 (STEEL). J Clin Oncol 2024;42:5101.

Continued

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

PRINCIPLES OF RADIATION THERAPY
REFERENCES

[21] Nguyen PL, Kollmeier M, Rathkopf DE, et al. FORMULA-509: A multicenter randomized trial of post-operative salvage radiotherapy (SRT) and 6 months of GnRH agonist with or without abiraterone acetate/prednisone (AAP) and apalutamide (Apa) post-radical prostatectomy (RP). J Clin Oncol 2023;41:303.
[22] Buyyounouski MK, Pugh SL, Chen RC, et al. Noninferiority of hypofractionated vs conventional postprostatectomy radiotherapy for genitourinary and gastrointestinal symptoms: the NRG-GU003 Phase 3 randomized clinical trial. JAMA Oncol 2024;10:584-591.
[23] Nagar H, Diven MA, Rippon B, et al. A randomized controlled phase 2 trial comparing salvage radiotherapy for prostate cancer delivered in 4 versus 2 weeks (SHORTER): acute genitourinary and gastrointestinal patient-reported outcomes at a single institution. [online ahead of print] Eur Urol Oncol 2025;doi:10.1016/j.euo.2025.05.014.
[24] Ma TM, Ballas LK, Wilhalme H, et al. Quality-of-life outcomes and toxicity profile among patients with localized prostate cancer after radical prostatectomy treated with stereotactic body radiation: the SIMITAR multicenter phase 2 trial. Int J Rad Oncol Biol Phys 2023;115:142-152.
[25] Pollack A, Karrison TG, Balogh AG, 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.
[26] Parker CC, James ND, Brawley CD, et al. Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: Long-term results from the STAMPEDE randomised controlled trial. 2022;19:e1003998.
[27] Bossi A, Foulon S, Maldonado X, et al. Efficacy and safety of prostate radiotherapy in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design. Lancet 2024;404:2065-2076.
[28] Deek, MP, Van der Eecken K, Sutera P, et al. Long-term outcomes and genetic predictors of response to metastasis-directed therapy versus observation in oligometastatic prostate cancer: analysis of STOMP and ORIOLE trials. J Clin Oncol 2022;40:3377-3382.
[29] Tang C, Sherry AD, Haymaker C, et al. Addition of metastasis-directed therapy to intermittent hormone therapy for oligometastatic prostate cancer: the EXTEND phase 2 randomized clinical trial. JAMA Oncol 2023;9:825-834.
[30] Marvaso G, Corrao G, Zaffaroni M, et al. ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): a randomised, open-label, phase 2 clinical trial. Lancet Oncol 2025;26:300-311.
[31] Francolini G, Allegra AG, Detti B, et al. Stereotactic body radiation therapy and abiraterone acetate for patients affected by oligometastatic castrate-resistant prostate cancer: a randomized phase II trial (ARTO). J Clin Oncol 2023;41:5561-5568.
[32] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. NEJM 2013;369:213-223.
[33] Tombal B, Choudhury A, Saad F, et al. Enzalutamide plus radium-223 in metastatic castration-resistant prostate cancer: results of the EORTC 1333/PEACE-3 trial. [online ahead of print] ESMO 2025;doi: https://doi.org/10.1016/j.annonc.2025.05.011
[34] 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.
[35] 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.
[36] Morris MJ, Castellano D, Herrmann K, et al. 177Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. Lancet 2024;404:1227-1239.

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

PRINCIPLES OF SURGERY

Pelvic Lymph Node Dissection

- For patients undergoing RP:
  - Pelvic lymph node dissection (PLND) can be considered in patients with favorable intermediate-risk prostate cancer.
  - PLND is recommended in patients with unfavorable intermediate, high, very-high-risk, and regional prostate cancer.
  - 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%.[1-4]
  - 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%.[5,6] 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 and can provide staging and prognostic information.
- Extended PLND provides more complete staging and may cure some patients with microscopic metastases; therefore, an extended PLND is recommended 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.

Radical Prostatectomy

- RP is an appropriate therapy for any patient not on an active surveillance program with clinically localized prostate cancer that can be completely excised surgically, who has a life expectancy of ≥10 years, and who has no serious comorbid conditions that would contraindicate an elective operation.
- High-volume surgeons in high-volume centers generally provide better outcomes.
- Blood loss can be substantial with RP, but can be reduced by using laparoscopic or robotic assistance or by careful control of the dorsal vein complex and periprostatic vessels when performed as open surgery.
- Urinary incontinence can be reduced by preservation of urethral length beyond the apex of the prostate and avoiding damage to the distal sphincter mechanism. Bladder neck preservation may decrease the risk of incontinence. Anastomotic strictures increase the risk of long-term incontinence.
- Recovery of erectile function is directly related to age at RP, preoperative erectile function, and the degree of preservation of the cavernous nerves. Replacement of resected nerves with nerve grafts has not been shown to be beneficial. Early restoration of erections may improve late recovery.

Secondary Radical Prostatectomy

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

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

References on PROS-K 2 of 2

PRINCIPLES OF SURGERY
REFERENCES

[1] 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.
[2] 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.
[3] 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.
[4] 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 prostate cancer patients who should be considered for an extended pelvic lymph node dissection. Eur Urol 2020;78:138-142.
[5] 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.
[6] 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.

PRINCIPLES OF LOCAL SECONDARY THERAPY POST-RADIATION

Local Secondary Therapy for Recurrent Prostate Cancer After Definitive Radiotherapy:

- **Patients with biopsy-proven recurrence in the prostate after prior RT and without distant metastatic disease can be considered for local therapy. Monitoring is also an option (see PROS-10). ADT may also be included, but it should not be reflexively ordered.**
- **The Panel recommends that patients receive multidisciplinary counseling about the risks and benefits of each of these options in the context of the available comparative literature on this topic.[1,2]**
- **Local therapy options for patients with recurrence in the prostate include[a,b,c]:**
  - **Cryotherapy**
  - **High-intensity focused ultrasound (HIFU)**
  - **Irreversible electroporation (IRE) (category 2B)**
  - **Reirradiation**
  - **RP + PLND**
- **Reirradiation options include LDR brachytherapy, HDR brachytherapy, and SBRT.[1-7]**
- **There is no consensus as to the most appropriate reirradiation volume, and there are published experiences for both focal/partial and whole gland reirradiation. The Panel recommends that patients receiving local therapy for RT recurrence are treated within the context of clinical trials when available and/or at experienced centers.**

[a] Reirradiation with LDR brachytherapy, HDR brachytherapy, and SBRT is supported by phase II trials with >36 months of median follow-up and should be strongly considered as an option in patients with >2 years interval from prior radiation who do not have ongoing moderate or higher grade radiation-associated toxicities. Phase II data with >36 months of median follow-up are available, albeit to a more limited scope, for secondary RP, cryotherapy, and HIFU.

[b] Currently, all phase II and/or prospectively accrued registries reporting oncologic outcomes with >36 months of follow-up have pursued whole gland treatments. Focal therapy for prostate-only recurrences is the subject of active investigation. See Principles of Focal/Subtotal Therapy or Whole Gland Ablative Therapy (PROS-I).

[c] There are no prospective data to guide the use and duration of ADT with reirradiation for prostate-only recurrences. The Panel recommends extrapolation from the definitive treatment setting to suggest that adding ADT or prolonging it in this setting likely offers an improvement in biochemical control. See Principles of Radiation Therapy (PROS-J).

References on PROS-L 2 of 2

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

PRINCIPLES OF LOCAL SECONDARY THERAPY POST-RADIATION
REFERENCES

[1] Ingrosso G, Becherini C, Lancia A, et al. Nonsurgical salvage local therapies for radiorecurrent prostate cancer: A systematic review and meta-analysis. Eur Urol Oncol 2020;3:183-197.
[2] Valle LF, Lehrer EJ, Markovic D, et al. A systematic review and meta-analysis of local salvage therapies after radiotherapy for prostate cancer (MASTER). Eur Urol 2021;80:280-292.
[3] Crook J, Rodgers JP, Pisansky TM, et al. Salvage low-dose-rate prostate brachytherapy: Clinical outcomes of a phase 2 trial for local recurrence after external beam radiation therapy (NRG Oncology/RTOG 0526). Int J Radiat Oncol Biol Phys 2022;112:1115-1122.
[4] 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.
[5] Fuller DB, Chen RC, Crabtree T, et al. 10 year prostate stereotactic body radiotherapy outcomes: Relapse-free survival, PSA kinetics and toxicity from a pooled analysis of two multi-institutional trials. Int J Radiat Oncol 2020;108:e857-e858.
[6] Bergamin S, Eade T, Kneebone A, et al. Interim results of a prospective prostate-specific membrane antigen-directed focal stereotactic reirradiation trial for locally recurrent prostate cancer. Int J Radiat Oncol Biol Phys 2020;108:1172-1178.
[7] Pasquier D, Martinage G, Janoray G, et al. Salvage stereotactic body radiation therapy for local prostate cancer recurrence after radiation therapy: A retrospective multicenter study of the GETUG. Int J Radiat Oncol Biol Phys 2019;105:727-734.

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

PRINCIPLES OF METASTASIS-DIRECTED THERAPY (MDT)

General

- **MDT is the treatment of metastatic sites with a local therapy to improve oncologic outcomes, not simply to provide symptom palliation. MDT has been studied primarily with radiotherapy and with highly selected use of surgical resection in the form of lymph node dissections. MDT is not recommended to be performed with other local therapies.**
- **MDT is mostly commonly delivered in the form of MDRT, which specifically refers to the use of higher than palliative dose radiotherapy to provide durable local control of the areas targeted. This may be for the intended purpose of delaying the initiation of systemic therapy, improving PFS, radiographic PFS, or overall survival. Similar to systemic therapies in the polymetastatic setting, MDRT is uncommonly curative and should be viewed as a form of cytotoxic therapy, and it may need to be repeated.**

Disease State

- **The settings for which MDT may have utility with variable evidence quality are shown in Table 1:**

Table 1.

Treatment Regimen	mCSPC		mCRPC	
	Synchronous (de novo) Oligometastatic	Metachronous Oligorecurrent[a]	Oligometastatic	Oligoprogressive
MDT	☼	✓	✓	☼

(✓ Preferred; ☼ Acceptable based on clinical and medical need)

[a] Limited data suggest that lymphadenectomy may be beneficial for select patients with pelvic nodal recurrence after radical prostatectomy if they do not have evidence of distant metastases.

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

PRINCIPLES OF METASTASIS-DIRECTED THERAPY (MDT)

Number of Metastatic Sites

- **The number of metastatic sites to define oligometastatic disease remains an evolving space and is impacted by sensitivity of imaging used. Early studies limited metastatic sites to 1–3 or 1–5 by CT, MRI, or bone scan.[1-4] More recent studies have included up to 10 metastatic sites by PSMA-PET imaging (NCT04787744, NCT06150417, NCT03721341). The upper limit is not clearly established and is both a function of oncologic limitations and technical limitations of treating numerous metastatic sites.**
  - **If CT, MRI, or bone scan is used, >5 metastasis is generally an exclusion for MDT.**
  - **If PSMA-PET is used, >10 metastatic sites is generally an exclusion for MDT.**
- **Lymph nodes in the same drainage chain (eg, two adjacent para-aortic lymph nodes) are to be considered 1 metastatic site and would be treated together with one radiation therapy isocenter or plan.**
- **Discrete, non-contiguous bony metastases should be counted separately even if treated with one isocenter (eg, two discrete femur metastases).**
- **The goal of MDT is generally to treat all metastatic sites, which may include regional lymph nodes and potentially treatment of the primary tumor if untreated or evidence of local recurrence. The primary tumor in this setting should be counted as a site.**

Location of Metastatic Sites

- **The location of metastatic sites have generally consisted of lymph node and osseous metastatic sites, but some studies include lung and liver metastases. Brain metastases are generally not included in studies of MDRT in prostate cancer. MDT should not be used to delay systemic therapy when there is visceral organ involvement.**
- **Pelvic lymph nodes are also considered metastatic sites in the context of MDRT for metachronous mCSPC or mCRPC.**

[1] Marvaso G, Corrao G, Zaffaroni M, et al. ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): a randomised, open-label, phase 2 clinical trial. Lancet Oncol 2025;26:300-311.
[2] Tang C, Sherry AD, Haymaker C, et al. Addition of metastasis-directed therapy to intermittent hormone therapy for oligometastatic prostate cancer: the EXTEND phase 2 randomized clinical trial. JAMA Oncol 2023;9:825-834.
[3] Deek, MP, Van der Eecken K, Sutera P, et al. Long-term outcomes and genetic predictors of response to metastasis-directed therapy versus observation in oligometastatic prostate cancer: analysis of STOMP and ORIOLE trials. J Clin Oncol 2022;40:3377-3382.
[4] Francolini G, Allegra AG, Detti B, et al. Stereotactic body radiation therapy and abiraterone acetate for patients affected by oligometastatic castrate-resistant prostate cancer: a randomized phase II trial (ARTO). J Clin Oncol 2023;41:5561-5568.

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

PRINCIPLES OF METASTASIS-DIRECTED THERAPY (MDT)

Radiotherapy Details (Also see Principles of Radiation Therapy)

- Use of SBRT (also known in this setting as stereotactic ablative radiotherapy [SABR]) is most commonly recommended for MDRT. Established dose/fraction regimens should be used with strict OAR constraints. Daily 3D image guidance is required and motion management is recommended for thoracic and abdominal sites if relevant. Online adaptive radiotherapy, if available, may be preferred if treatment of a metastatic site is near an OAR with frequent day-to-day setup uncertainty. Appropriate clinical target volume (CTV) and PTV margins should be applied to account for microscopic spread and setup uncertainty.
- When treating a lymph node metastasis, one should generally include an elective nodal volume to the involved chain with a simultaneous integrated boost to the radiographic or biopsy confirmed lymph node. If lymph node(s) are in the pelvis, elective nodal irradiation fields should be considered, either ipsilateral or bilateral.
- Dose composites with special medical physics consults are required to account for prior radiotherapy or overlap of multiple treatment plans.
- If treatment involves more than two treatment plans simultaneously, consideration of splitting the treatment course into multiple sessions of SBRT may be required due to patient tolerance and safety (eg, 4 treatment plans for 4 metastatic sites may need to be delivered as 2 concurrent treatment plans as course 1, and then the other 2 treatment plans are delivered concurrently at a later date as a separate course of SBRT). Repeat simulation may be required based on potential for anatomy changes or use of alternative immobilization for other treatments sites.

Concurrent Systemic Therapy with MDRT

- Synchronous (de novo) oligometastatic mCSPC:
  - Systemic therapy, most commonly ADT+ARPI, and treatment of the primary tumor with RT is recommended for most patients. The concurrent addition of MDRT may be considered in select patients. For patient tolerance, it is reasonable to asynchronously treat the primary and metastatic sites in separate treatment courses.
- Metachronous oligorecurrent mCSPC:
  - Oligorecurrent disease detected primarily by PET imaging may be treated by MDRT alone or concurrently with short-term ADT (6 months). The addition of ADT improved clinical and biochemical PFS, but may simply delay the detection of recurrence rather than improve durable control of the disease.[1]
  - Trials have not been reported showing a benefit of the addition of triplet chemotherapy or an ARPI in the setting of MDRT+ADT.
- Oligometastatic mCRPC:
  - First-line treatment with ADT and an ARPI ± MDRT have demonstrated improvements in PFS and radiographic PFS from the addition of MDRT.[4] MDRT should not be used without recommended mCRPC systemic therapies.
- Oligoprogressive or oligopersistent mCRPC
  - For oligoprogressive or oligopersistent mCRPC, MDRT may be delivered concurrently with mCRPC systemic therapy.
  - MDRT should not be used concurrently with PARP inhibition (alone or in combination with abiraterone or enzalutamide) or chemotherapy outside of a clinical trial.
  - Use of MDRT may be considered for oligoprogression sequentially after approved systemic mCRPC treatments.

[1] Marvaso G, Corrao G, Zaffaroni M, et al. ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): a randomised, open-label, phase 2 clinical trial. Lancet Oncol 2025;26:300-311.
[4] Francolini G, Allegra AG, Detti B, et al. Stereotactic body radiation therapy and abiraterone acetate for patients affected by oligometastatic castrate-resistant prostate cancer: a randomized phase II trial (ARTO). J Clin Oncol 2023;41:5561-5568.

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

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

- **An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.**

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

- **Triplet therapy with ADT, certain ARPIs, and docetaxel is an option for certain patients with mCSPC who are fit for chemotherapy based on phase 3 studies:**
  - **ADT with docetaxel and abiraterone was compared to ADT alone or with docetaxel in an open-label, randomized, phase 3 study. Radiographic PFS was longer in patients who received abiraterone than in those who did not. The populations receiving the triplet and doublet therapies experienced similar rates of neutropenia, febrile neutropenia, fatigue, and neuropathy, although grade ≥3 adverse events occurred in 63% of patients who received the triplet combination compared with 52% of those receiving ADT and docetaxel.**
  - **ADT with docetaxel and darolutamide was compared with ADT with docetaxel and placebo in a randomized phase 3 trial. OS, time to CRPC, skeletal event-free survival, and time to initiation of subsequent systemic antineoplastic therapy were improved in the patients who received darolutamide. Adverse events of any grade, grade 3–5 adverse events, and serious adverse events occurred at similar incidence levels between the two arms. Many of these were known effects of docetaxel. Exceptions were rash (16.6% vs. 13.5%) and hypertension (13.7% vs. 9.2%), which are known effects of androgen receptor pathway inhibitors and were more frequent in the darolutamide group.**
  - **An open-label, randomized, phase 3 trial compared ADT with enzalutamide to ADT with a first-generation antiandrogen in this setting. Concurrent docetaxel was allowed and used for stratification. OS was improved with the use of enzalutamide over first-generation anti-androgen regardless of the addition of docetaxel. The most common grade ≥3 adverse events were febrile neutropenia associated with docetaxel use (6% in both groups), fatigue (1% in the control group vs. 6% in the enzalutamide group), and hypertension (6% vs. 10%). The incidence of grade 1–3 memory impairment was 4% versus 13%.**
- **The use of myeloid growth factors should follow the NCCN Guidelines for Hematopoietic Growth Factors, based on risk of neutropenic fever.**

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

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

Non-Hormonal Systemic Therapy for M1 CRPC

- ***Chemotherapy***
  - **Docetaxel with concurrent steroid**
    - ◊ Concurrent steroid includes daily prednisone, which may be omitted on the day of chemotherapy administration when dexamethasone is given.
    - ◊ Every–3-week docetaxel with concurrent steroid is the preferred first-line chemotherapy treatment based on phase 3 clinical trial data for patients with symptomatic mCRPC. Adverse events associated with docetaxel include neutropenia, leukopenia, febrile neutropenia, neutropenic infections, fluid retention, hypersensitivity reaction, hepatic function impairment, neuropathy, and other low-grade adverse events (eg, fatigue, nausea, vomiting, alopecia, diarrhea).
    - ◊ Only regimens utilizing docetaxel on an every–3-week schedule demonstrated beneficial impact on survival. The duration of therapy should be based on the assessment of benefit and toxicities. In the pivotal trials establishing survival advantage of docetaxel-based chemotherapy, patients received up to 10 cycles of treatment if no progression and no prohibitive toxicities were noted.
    - ◊ Docetaxel retreatment can be attempted after progression on an ARPI and docetaxel in patients with mCRPC whose cancer has not demonstrated definitive evidence of progression on prior docetaxel therapy in either the castration-sensitive setting or the mCRPC setting.
    - ◊ Rare patients may have exposure to docetaxel without prior ARPI (ie, in the setting of EBRT to the primary tumor for low-volume synchronous mCSPC). Docetaxel rechallenge is not recommended for such patients in the pre-ARPI mCRPC setting.
  - **Cabazitaxel with concurrent steroid**
    - ◊ Concurrent steroid includes daily prednisone, which may be omitted on the day of chemotherapy administration when dexamethasone is given.
    - ◊ Patients who are not candidates for docetaxel or who are intolerant of docetaxel should be considered for cabazitaxel with concurrent steroid, based on results that suggest clinical activity of cabazitaxel in mCRPC. Cabazitaxel was associated with lower rates of peripheral neuropathy than docetaxel, particularly at 20 mg/m² (12% vs. 25%) and may be appropriate in patients with pre-existing mild peripheral neuropathy. Current data do not support greater efficacy of cabazitaxel over docetaxel.
    - ◊ Cabazitaxel at 25 mg/m² with concurrent steroid has been shown in a randomized phase 3 study (TROPIC) to prolong OS, PFS, PSA response, and radiologic response when compared with mitoxantrone and prednisone and is FDA approved in the post-docetaxel second-line setting. Toxicity at this dose was significant and included febrile neutropenia, severe diarrhea, fatigue, nausea/vomiting, anemia, thrombocytopenia, sepsis, and renal failure. A recent trial, PROSELICA, compared cabazitaxel 25 mg/m² every 3 weeks to 20 mg/m² every 3 weeks. Cabazitaxel 20 mg/m² had less toxicity; febrile neutropenia, diarrhea, and fatigue were less frequent. Cabazitaxel at 20 mg/m² had a significantly lower PSA response rate but non-significantly lower radiographic response rate and non-significantly shorter PFS and OS (13.4 vs. 14.5 months) compared to 25 mg/m².
    - ◊ Cabazitaxel at 25 mg/m² with concurrent steroid improved radiographic PFS and reduced the risk of death compared with abiraterone or enzalutamide in patients with prior docetaxel treatment for mCRPC in the CARD study.
    - ◊ Biweekly cabazitaxel at 16 mg/m² with prophylactic G-CSF significantly reduced the risk of neutropenia/neutropenic complications compared to the 25 mg/m² dose with G-CSF in patients ≥65 years in a phase 3 trial. Clinical outcomes were comparable between the 2 groups.
    - ◊ No chemotherapy regimen to date has demonstrated improved survival or quality of life after cabazitaxel, and trial participation should be encouraged.
  - **Cabazitaxel/carboplatin with concurrent steroid**
    - ◊ Concurrent steroid includes daily prednisone, which may be omitted on the day of chemotherapy administration when dexamethasone is given.
    - ◊ Cabazitaxel 20 or 25 mg/m² plus carboplatin AUC 4 mg/mL per minute with growth factor support can be considered for fit patients with aggressive variant mCRPC (ie, visceral metastases, low PSA and bulky disease, high lactate dehydrogenase (LDH), high CEA, lytic bone metastases, NEPC histology) or unfavorable genomics (defects in at least 2 of *PTEN*, *TP53*, and *RB1*). The most common grade 3–5 adverse events were fatigue, anemia, neutropenia, and thrombocytopenia. Corn PG, et al. Lancet Oncol 2019;20:1432-1443.
      - – Cabazitaxel starting dose can be either 20 mg/m² or 25 mg/m² for patients with mCRPC whose cancer has progressed despite prior

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

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

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.

- Mitoxantrone with prednisone
  - ◊ Mitoxantrone with prednisone may provide palliation but has not been shown to extend survival in two randomized trials. Adverse events associated with mitoxantrone are similar to docetaxel, but with lower rates of grade 3 or 4 neutropenic fevers, cardiovascular events, nausea and vomiting, metabolic disturbances, and neurologic events.
- Increasing PSA should not be used as the sole criteria for progression. Assessment of response should incorporate clinical and radiographic criteria.
- See NCCN Guidelines for Hematopoietic Growth Factors for recommendations on growth factor support.

• *PARP Inhibitors with or without ARPIs*
- Inactivation of HRR genes has been associated with response to PARP inhibitor (PARPi) therapy, and a number of FDA-approved agents and combinations are now available (Table 1 and Discussion). Although there are multiple specific gene alterations included in the FDA labels for specific PARPi and combinations (see Table 1), the response rates have been most pronounced for patients with *BRCA2* mutation-associated prostate cancers. Treatment responses have been variable for other genes alterations, and this information should be taken into account in decisions about treatment sequencing and patient counseling. For example, responses have been less robust for patients whose cancers carry ATM mutations, and other recommended regimen options may be favored until more data are available on a gene-by-gene level.
- Loss of *BRCA2* may be especially associated with response to PARPi therapy compared to other HRR gene alterations.
- There has been heterogeneity of response to olaparib for non-*BRCA* mutations based on the specific gene mutation (Discussion).
- The fine-particle (category 2B; other recommended option) or standard formulation of abiraterone can be given with single-agent niraparib as a substitute for the combination niraparib/abiraterone tablet.
- The fine-particle abiraterone (category 2B; other recommended option) may be given with olaparib as a substitute for standard abiraterone.

• *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 prostate cancer/NEPC.
  - ◊ Sipuleucel-T has been shown in a phase 3 clinical trial to extend mean survival from 21.7 months in the control arm to 25.8 months in the treatment arm, which constitutes a 22% reduction in mortality risk.
  - ◊ Sipuleucel-T is well-tolerated; common complications include chills, pyrexia, and headache.
- Pembrolizumab is an option for certain patients with MSI-H/dMMR mCRPC (PROS-18).
  - ◊ Pembrolizumab may cause severe, life-threatening immune-mediated adverse reactions, which may include but are not limited to: pneumonitis, colitis, hepatitis, myocarditis, endocrinopathies, exfoliative dermatologic conditions, renal failure and nephritis, and ocular toxicities. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
  - ◊ Limited data suggest that pembrolizumab may be associated with some benefit in patients with mCRPC and TMB ≥10 mut/mB. Lenis AT, et al. Clin Canc Res 2024;30:3894-3903.

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

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

PRINCIPLES OF NON-HORMONAL SYSTEMIC THERAPY

Table 1. PARP Inhibitors with or without ARPIs

Treatment	FDA-Approved Disease State Indication	Biomarker Pathogenic variant or mutation in gene (germline and/or somatic)	Clinical Trial
Olaparib	mCRPC that has progressed following prior treatment with enzalutamide or abiraterone.	*BRCA2, BRCA1, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L*	PROfound[1]
Rucaparib	mCRPC that has been treated with androgen receptor-directed therapy and taxane-based chemotherapy	*BRCA2, BRCA1*	TRITON2[2,3]
Olaparib/ Abiraterone	mCRPC	*BRCA2, BRCA1*	PROPel[4]
Talazoparib/ Enzalutamide	mCRPC	*BRCA2, BRCA1, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, or RAD51C*	TALAPRO-2[5,6]
Niraparib/ Abiraterone	mCRPC	*BRCA2, BRCA1*	MAGNITUDE[7,8]

[1] de Bono JD, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. NEJM 2020;382:2091-2102.
[2] 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;38:3763-3772.
[3] Abida W, Campbell D, Patnaik A, et al. Rucaparib for the treatment of metastatic castration-resistant prostate cancer associated with a DNA damage repair gene alteration: final results from the Phase 2 TRITON2 study. Eur Urol 2023;84:321-330.
[4] Saad F, Clarke NW, Oya M, et al. Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24:1094-1108.
[5] Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet 2023;402:291-303.
[6] Fizazi K, Azad AA, Matsubara N, et al. First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial. 2023;30:257-264.
[7] Chi KN, Rathkopf D, Smith MR, et al. Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. J Clin Oncol 2023;41:339-3351.
[8] Chi KN, Sandhu S, Smith MR, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. 2023;34:772-782.

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

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.

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

Table 2. **AJCC Prognostic Groups**

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

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

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

Definition of Histologic Grade Group (G)
Recently, the Gleason system has been compressed into so-called Grade Groups.

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

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

ABBREVIATIONS

ACE-27	Adult Comorbidity Evaluation-27 Index
ADT	androgen deprivation therapy
AI	artificial intelligence
ARPI	androgen receptor pathway inhibitor
aRT	adjuvant RT
ASTRO	American Society for Radiation Oncology
AUC	area under the curve
BCR	biochemical recurrence
BED	biologically effective dose
BMI	body mass index
CBRT	cone beam CT
CEA	carcinoembryonic antigen
CHIP	clonal hematopoiesis of indeterminate potential
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
ctDNA	circulating tumor DNA
CVD	cardiovascular disease
DCE	dynamic contrast-enhanced
DEXA	dual-energy x-ray absorptiometry
DIL	dominant intraprostatic lesion
DM	distant metastases
dMMR	mismatch repair deficient
DRE	digital rectal examination
DWI	diffusion-weighted imaging
EBRT	external beam radiation therapy
ECG	electrocardiogram
ECHO	echocardiogram
ENI	elective nodal irradiation
FDG	fluorodeoxyglucose
FFS	failure-free survival
FIR	favorable intermediate-risk
FLA	focal laser ablation
FRAX	Fracture Risk Assessment Tool
FT	focal therapy
GC	genomic classifier
HDR	high dose rate
HIFU	high-intensity focused ultrasound
HRD	homologous recombination deficiency
HRR	homologous recombination repair
IGRT	image-guided radiation therapy
IMRT	intensity modulated RT
IRE	irreversible elecroporation
IRF	intermediate risk factor
ITT	intention to treat
LDH	lactate dehydrogenase
LDR	low dose rate
LHRH	luteinizing hormone-releasing hormone
LT-ADT	long-term androgen deprivation therapy
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MDRT	metastasis-directed radiotherapy
MFS	metastasis-free survival
MMAI	multimodal artificial intelligence
MMR	mismatch repair
mpMRI	multiparametric MRI
MSI	microsatellite instability
MSI-H	microsatellite instability-high

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

ABBREVIATIONS

NEPC	neuroendocrine prostate cancer
NNT	number needed to treat
OAR	organ at risk
OS	overall survival
PARPi	PARP inhibitor
PCSM	prostate cancer-specific mortality
PCSS	prostate cancer-specific survival
PDT	photodynamic therapy
PFS	progression-free survival
PLND	pelvic lymph node dissection
PNRT	prophylactic nodal radiotherapy
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
PSMA	prostate-specific membrane antigen
PTV	planning target value
QOL	quality of life
rh	radiohybrid
RFA	radiofrequency ablation
ROI	region of interest
RP	radical prostatectomy
rPFS	radiographic progression-free survival
RTOG	Radiation Therapy Oncology Group
SABR	stereotactic ablative radiotherapy
SBRT	stereotactic body radiation therapy
sHR	subdistribution hazard ratio
SPECT	single-photon emission computed tomography
SRE	skeletal-related event
sRT	secondary RT
ST-ADT	short-term androgen deprivation therapy
TMB	tumor mutational burden
TULSA	transurethral ultrasound ablation
VUS	variant of uncertain significance

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

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended	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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2026
Prostate Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Prostate Cancer. Sections on metastatic castration-sensitive prostate cancer and castration-resistant prostate cancer were updated on September 15, 2025. The remaining text was updated on May 10, 2022.

Table of Contents

Overview

An estimated 313,780 new cases of prostate cancer will be diagnosed in the United States in 2025, accounting for 30% of new cancer cases in men.[1] It is the most common cancer in men in the United States, who currently have a 1 in 8 lifetime risk of developing prostate cancer.[1] The incidence of prostate cancer declined by approximately 40% from 2007 to 2014, but since that time has increased at a rate of 3% annually. These trends largely reflect the changes in prostate-specific antigen (PSA) screening recommendations. The decrease in PSA screening that followed the 2012 USPSTF recommendations against routine testing was associated with a rise in the diagnosis of regional and metastatic disease.[2-10]

Researchers further estimate that prostate cancer will account for 11% of male cancer deaths in the United States in 2025, with an estimated 35,770 deaths.[1] The age-adjusted death rate from prostate cancer declined by 52% from 1993 to 2017, but the death rate has become more stable in recent years, with a 0.5% annual decrease from 2012 through 2022.[1] For all stages combined, the 5-year relative survival rate for prostate cancer is 97%.[1] The comparatively low death rate suggests that increased public awareness with earlier detection and treatment has affected mortality from this prevalent cancer, but is also complicated by screening-related lead-time bias and detection of indolent cancers. Maintenance of this low death rate is threatened by the rising prostate cancer incidence and diagnosis of advanced disease.

Unfortunately, large inequities exist in incidence of and mortality from prostate cancer across racial and ethnic groups. The incidence rate in Black individuals is 67% higher than in white individuals, with prostate cancer accounting for 44% of cancer diagnoses in Black men and a 1 in 6 lifetime risk of a prostate cancer diagnosis.[11] Black individuals are also more likely to be diagnosed with more aggressive disease and are less likely to have had a PSA test within the past year.[11] The mortality rate from prostate cancer in this population is two to four times higher than all other racial and ethnic groups; prostate cancer accounts for 17% of male cancer deaths in the United States.[1,11] However, the overall prognosis by race appears similar when patients are treated with the same guideline-concordant care.[12]

Use of PSA for early detection of potentially fatal prostate cancer coupled with the use of imaging and the consideration of risk calculators and/or biomarkers to improve the specificity of screening should decrease the risk of overdetection (see the NCCN Guidelines for Prostate Cancer Early Detection, available at www.NCCN.org). This reduced overdetection along with the use of active surveillance in appropriate patients should reduce overtreatment AND preserve the relatively low rates of prostate cancer mortality.

Guidelines Update Methodology

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

Literature Search Criteria

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

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice

Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

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

Initial Prostate Cancer Diagnosis

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

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The NCCN Guidelines Panel favors pathology synoptic reports from the College of American Pathologists (CAP) that comply with the Commission on Cancer (CoC) requirements.[16]

Estimates of Life Expectancy

Estimates of life expectancy have emerged as a key determinant of primary treatment, particularly when considering active surveillance or observation. Life expectancy can be estimated for groups of individuals, but it is difficult to extrapolate these estimates to an individual patient. Life expectancy can be estimated using the Minnesota Metropolitan Life Insurance Tables, the Social Security Administration Life Insurance Tables,[17] the WHO's Life Tables by Country,[18] or the Memorial Sloan Kettering Male Life Expectancy tool[19] and adjusted for individual patients by adding or subtracting 50% based on whether one believes the patient is in the healthiest quartile or the unhealthiest quartile, respectively.[20] As an example, the Social Security Administration Life Expectancy for a 65-year-old American male is 17.7 years. If judged to be in the upper quartile of health, a life expectancy of 26.5 years is assigned. If judged to be in the lower quartile of health, a life expectancy of 8.8 years is assigned. Thus, treatment recommendations could change dramatically using the NCCN Guidelines if a 65-year-old patient was judged to be in either poor or excellent health.

Prostate Cancer Genetics

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

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

treatment implications for patients with DNA repair defects (see *Treatment Options for Patients with DNA Repair Gene Mutations*, below).

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

Homologous DNA Repair Genes

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

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

An additional study showed that 9 of 125 patients with high-risk, very-high-risk, or metastatic prostate cancer (7.2%) had pathogenic germline mutations in *MUTYH* (4), *ATM* (2), *BRCA1* (1), *BRCA2* (1), and *BRIP1* (1).[40] In this study, the rate of metastatic disease among those with a mutation identified was high (28.6%, 2 of 7 patients). Although having a relative with breast cancer was associated with germline mutation identification (P = .035), only 45.5% of the mutation carriers in the study had mutations that were concordant with their personal and family history. Another study also found that a family history of breast cancer increased the chances of identifying a germline DNA repair gene mutation in patients with prostate cancer (OR, 1.89; 95% CI, 1.33–2.68; P = .003).[45] In a study of an unselected cohort of 3607 patients with a personal history of prostate cancer who had germline genetic testing based on clinician referral, 11.5% had germline mutations in *BRCA2*, *CHEK2*, *ATM*, *BRCA1*, or *PALB2*.[46]

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

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

DNA Mismatch Repair Genes

Tumor mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* may result in tumor microsatellite instability (MSI) and deficient MMR (dMMR; detected by

immunohistochemistry) and are sometimes associated with germline mutations and Lynch syndrome. Patients with Lynch syndrome may have an increased risk for prostate cancer. In particular, studies show an increased risk for prostate cancer in patients who are older and have germline *MSH2* mutations.[70,71]

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

Effect of Intraductal/Cribriform or Ductal Histology

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

Limited data suggest that acinar prostate adenocarcinoma with invasive cribriform pattern, intraductal carcinoma of prostate (IDC-P), or ductal adenocarcinoma component y have increased genomic instability.[75-78] In particular, tumors with these histologies may be more likely to harbor somatic MMR gene alterations than those with adenocarcinoma histology.[78-80] In addition, limited data suggest that germline homologous DNA repair gene mutations may be more common in prostate tumors of ductal or intraductal origin[81,82] and that intraductal histology is common in germline *BRCA2* mutation carriers with prostate cancer.[83] Overall, the panel believes that the data connecting histology and the presence of genomic alterations are stronger for intraductal than ductal histology at this time. Therefore, patients with presence of intraductal carcinoma on biopsy should have germline testing as described below.

Genetic Testing Recommendations

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

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

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

In addition, germline genetic testing should be considered in patients with a personal history of prostate cancer and 1) intermediate-risk prostate cancer and intraductal/cribriform histology or 2) a personal history of

exocrine pancreatic cancer, breast cancer, colorectal, gastric, melanoma, pancreatic cancer, upper tract urothelial cancer, glioblastoma, biliary tract cancer, and small intestinal cancer.

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

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

Somatic Tumor Testing Based on Risk Groups

Tumor testing recommendations are as follows:

1. Tumor testing for somatic homologous recombination gene mutations (eg, *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D*, *CHEK2, CDK12*) can be considered in patients with regional (N1) prostate cancer and is recommended for those with metastatic disease.
2. Tumor testing for MSI or dMMR can be considered in patients with regional or metastatic castration-naïve prostate cancer and is recommended in the metastatic CRPC setting.
3. Tumor mutational burden (TMB) testing may be considered in patients with metastatic CRPC.
4. Multigene molecular testing can be considered for patients with low-, intermediate-, and high-risk prostate cancer and life expectancy ≥10 years (see *Tumor Multigene Molecular Testing*, below).
5. The Decipher molecular assay is recommended to inform adjuvant treatment if adverse features are found post-radical prostatectomy, and can be considered as part of counseling for risk stratification in patients with PSA resistance/recurrence after radical prostatectomy (category 2B). See *Tumor Multigene Molecular Testing*, below).

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

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

Post-test genetic counseling is recommended if pathogenic/likely pathogenic somatic mutations in any gene that has clinical implications if

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

Additional Testing

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

Risk Stratification for Clinically Localized Disease

Optimal treatment of prostate cancer requires estimation of risk: How likely is a given cancer to be confined to the prostate or spread to the regional lymph nodes? How likely is the cancer to progress or metastasize after treatment? How likely is adjuvant or post-recurrence radiation to control cancer after an unsuccessful radical prostatectomy?

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

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

NCCN Risk Groups

The NCCN Guidelines have, for many years, incorporated a risk stratification scheme that uses a minimum of stage, Gleason grade, and PSA to assign patients to risk groups. These risk groups are used to select the appropriate options that should be considered and to predict the probability of biochemical recurrence after definitive local therapy.[92] Risk group stratification has been published widely and validated, and provides a better basis for treatment recommendations than clinical stage alone.[93,94]

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

- Grade Group 1: Gleason score ≤6; only individual discrete well-formed glands
- Grade Group 2: Gleason score 3+4=7; predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
- Grade Group 3: Gleason score 4+3=7; predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands
    - For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the

component of <5% well-formed glands is not factored into the grade.

- Grade Group 4: Gleason score 4+4=8; 3+5=8; 5+3=8
  - Only poorly formed/fused/cribriform glands; or
  - Predominantly well-formed glands and lesser component lacking glands (poorly formed/fused/cribriform glands can be a more minor component); or
  - Predominantly lacking glands and lesser component of well-formed glands (poorly formed/fused/cribriform glands can be a more minor component)
- Grade Group 5: Gleason score 9–10; lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands
  - For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well-formed glands is not factored into the grade.

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

The NCCN Guidelines Panel recognized that heterogeneity exists within each risk group. For example, an analysis of 12,821 patients showed that those assigned to the intermediate-risk group by clinical stage (T2b–T2c) had a lower risk of recurrence than those categorized according to Gleason score (7) or PSA level (10–20 ng/mL).[105] A similar trend of superior recurrence-free survival was observed in patients placed in the high-risk group by clinical stage (T3a) compared to those assigned by Gleason score (8–10) or PSA level (>20 ng/mL), although it did not reach statistical significance. Other studies have reported differences in outcomes in the high-risk group depending on risk factors or primary Gleason pattern.[106,107] Evidence also shows heterogeneity in the low-risk group, with PSA levels and percent positive cores affecting pathologic findings after radical prostatectomy.[108,109]

In a retrospective study, 1024 patients with intermediate-risk prostate cancer were treated with radiation with or without neoadjuvant and concurrent ADT.[110] Multivariate analysis revealed that primary Gleason pattern 4, number of positive biopsy cores ≥50%, and presence of >1 intermediate-risk factors (IRFs; ie, T2b-c, PSA 10–20 ng/mL, Gleason score 7) were significant predictors of increased incidence of distant metastasis. The authors used these factors to separate the patients into unfavorable and favorable intermediate-risk groups and determined that the unfavorable intermediate-risk group had worse PSA recurrence-free survival and higher rates of distant metastasis and prostate cancer-specific mortality than the favorable intermediate-risk group. The use of

active surveillance in patients with favorable intermediate-risk prostate cancer is discussed below (see *Active Surveillance in Favorable Intermediate Risk*). The NCCN Panel has included the separation of intermediate risk group into favorable and unfavorable subsets in their risk stratification scheme.

Nomograms

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

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

Tumor Multigene Molecular Testing

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

Several tissue-based molecular assays have been developed in an effort to improve decision-making in newly diagnosed patients considering active surveillance and in treated patients considering adjuvant therapy or treatment for recurrence. Uncertainty about the risk of disease progression can be reduced if such molecular assays can provide accurate and reproducible prognostic or predictive information beyond NCCN risk group assignment and currently available life expectancy tables and nomograms. Retrospective case cohort studies have shown that these assays provide prognostic information independent of NCCN or CAPRA risk groups, which include likelihood of death with conservative management, likelihood of biochemical recurrence after radical prostatectomy or EBRT, likelihood of adverse pathologic features after radical prostatectomy, and likelihood of developing metastasis after operation, definitive EBRT, or

post-recurrence EBRT.[143-155] Evaluation of diagnostic biopsy tissue from patients enrolled in the Canary PASS multicenter active surveillance cohort suggested that results of a molecular assay were not associated with adverse pathology either alone or in combination with clinical variables.[156]

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

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

Several of these assays are available, and four have received positive reviews by the Molecular Diagnostic Services Program (MolDX) and are likely to be covered by CMS (Centers for Medicare & Medicaid Services). Several other tests are under development, and the use of these assays is likely to increase in the coming years.

Table 1 lists these tests in alphabetical order and provides an overview of each test, populations where each test independently predicts outcome, and supporting references. These molecular biomarker tests have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous U.S. Food and Drug Administration (FDA) regulatory pathway for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that patients with low or favorable intermediate disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate, or Prolaris during initial risk stratification. Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris. In addition, Decipher may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence (category 2B for the latter setting). Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of patients with prostate cancer.

Initial Clinical Assessment and Staging Evaluation

For patients with very-low-, low-, and intermediate-risk prostate cancer and a life expectancy of 5 years or less and without clinical symptoms, further imaging and treatment should be delayed until symptoms develop, at which time imaging can be performed and ADT should be given. Those

with a life expectancy less than or equal to 5 years who fall into the high- or very-high-risk categories should undergo bone imaging and, if indicated by nomogram prediction of lymph node involvement, pelvic +/- abdominal imaging.

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

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

Retrospective evidence suggests that Gleason score and PSA levels are associated with positive bone scan findings.[160] Multivariate analysis of retrospective data on 643 patients with newly diagnosed prostate cancer who underwent staging CT found that PSA, Gleason score, and clinical T stage were associated independently with a positive finding ($P < .05$ for all).[161] mpMRI may detect large and poorly differentiated prostate cancer (Grade Group ≥2) and detect extracapsular extension (T staging) and is preferred over CT for abdominal/pelvic staging. mpMRI has been shown to be equivalent to CT scan for pelvic lymph node evaluation.

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

Imaging Techniques

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

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

More details on each technique are outlined in the algorithm under *Principles of Imaging*.

Multiparametric MRI (mpMRI)

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

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

Evidence supports the implementation of mpMRI in several aspects of prostate cancer management.[162] ***First,*** mpMRI helps detect larger and/or more poorly differentiated cancers (ie, Grade Group ≥2).[165] mpMRI has been incorporated into MRI-TRUS fusion-targeted biopsy protocols, which has led to an increase in the diagnosis of high-grade cancers with fewer biopsy cores, while reducing detection of low-grade and insignificant cancers.[166-168] In fact, a recently published clinical study identified that MRI-targeted biopsy synergized with conventional systematic biopsy to identify more clinically significant cancers.[169] ***Second,*** mpMRI aids in better assessment of extracapsular extension (T staging), with high negative predictive values (NPVs) in patients with low-risk disease.[170] mpMRI results may inform decision-making regarding nerve-sparing operation.[171] ***Third,*** mpMRI is equivalent to CT scan for staging of pelvic lymph nodes.[172,173] Finally, mpMRI outperforms bone scan and targeted x-rays for detection of bone metastases, with a sensitivity of 98% to 100% and specificity of 98% to 100% (vs. sensitivity of 86% and specificity of 98%–100% for bone scan plus targeted x-rays).[174]

PET Imaging

The use of PET/CT or PET/MRI imaging using tracers other than F-18 fluorodeoxyglucose (FDG) for staging of small-volume recurrent or metastatic prostate cancer has rapidly expanded in recent years.[162] Currently, there are five PET tracers that are FDA approved for use in patients with prostate cancer: Ga-68 PSMA-11 (PSMA-HBED-CC), F-18 piflufolastat (DCFPyL), C-11 choline, F-18 fluciclovine, and F-18 sodium fluoride. Although these tracers are approved for the evaluation of patients with biochemical recurrence, the PSMA tracers Ga-68 PSMA-11 and F-18 piflufolastat are also approved for patients at initial staging with suspected metastatic disease. Tracer distribution in patients with prostate cancer can be imaged with either PET/CT or PET/MRI modalities. Although CT and MRI are equivalent in the assessment of lymphadenopathy, PET/MRI has the added advantage over PET/CT with enhanced tissue contrast that is especially important in evaluation of pelvic anatomy and prostate cancer assessment. Table 1 in the Principles of Imaging, above, summarizes the FDA-cleared PET imaging tracers studied in prostate cancer. F-18 FDG PET should not be used routinely, because data are limited in patients

with prostate cancer and suggest that its sensitivity is significantly lower than that seen with the above described tracers.[175-177]

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

Studies suggest that PSMA PET imaging has a higher sensitivity than C-11 choline or F-18 fluciclovine PET imaging, especially at very low PSA levels.[181-186] The reported sensitivity and specificity for PSMA-11 PET/CT in the detection of nodal involvement in primary staging of patients with intermediate-, high-, and very-high-risk disease is 40% and 95%, respectively.[187] The patient-level positive predictive value (PPV) in detection of lesions in patients with biochemical recurrence (BCR) is 92%.[188] Similarly, the reported sensitivity and specificity for piflufolastat PET/CT in the detection of nodal involvement in primary staging of patients with unfavorable intermediate-, high-, and very-high-risk disease is 31% to 42% and 96% to 99%, respectively.[189,190] The patient-level correct localization rate (CLR; patient-level PPV validated by anatomic lesion co-localization) for piflufolastat PET/CT is 85% to 87%.[191] Thus, PSMA-11 and piflufolastat are considered equivalent. Because of the increased sensitivity and specificity of PSMA PET tracers for detecting micrometastatic disease compared to conventional imaging (CT, MRI) at both initial staging and biochemical recurrence, the Panel does not feel that conventional imaging is a necessary prerequisite to PSMA-PET and that PSMA PET/CT or PSMA-PET/MRI can serve as an equally effective, if not more effective front-line imaging tool for these patients.

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

The use of these PET tracers can lead to changes in clinical management. The FALCON trial showed that results of F-18 fluciclovine PET/CT in 104 patients with biochemical recurrence after definitive therapy resulted in a change in disease management for 64% of patients.[206] In addition, the LOCATE trial demonstrated that fluciclovine frequently changed disease management plans in patients with biochemical recurrence.[207] In a similar fashion, data also show that PSMA PET has the ability to change radiation treatment planning in 53% (N = 45) of patients with high- and very-high-

risk prostate cancer using PSMA-11 as well as change disease management in over half of a prospective cohort of 635 patients with BCR.[208,209] However, whether changes to treatment planning because of PET tracers have an impact on long-term survival remains to be studied.

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

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

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

Risks of Imaging

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

Exposure to Ionizing Radiation

Deterministic and stochastic are two types of effects from exposure to ionizing radiation by x-ray, CT, or PET/CT. Deterministic effects are those that occur at a certain dose level, and include events such as cataracts and radiation burns. No effect is seen below the dose threshold. Medical imaging is always performed almost below the threshold for deterministic effects. Stochastic effects tend to occur late, increase in likelihood as dose increases, and have no known lower “safe” limit. The major stochastic effect of concern in medical imaging is radiation-induced malignancy. Unfortunately, no direct measurements are available to determine risk of cancer arising from one or more medical imaging events, so risks are calculated using other models (such as from survivors of radiation exposure). The literature is conflicting with regard to the precise risk of secondary malignancies in patients undergoing medical imaging procedures. There is a small but finite risk of developing secondary malignancies as a result of medical imaging procedures, and the risk is greatest in young patients. However, the absolute risk of fatal malignancy arising from a medical imaging procedure is very low, and is difficult to detect given the prevalence of cancer in the population and the multiple factors that contribute to oncogenesis.[218] Efforts should be made to minimize dose from these procedures, which begin with judicious use of imaging only when justified by the clinical situation. Harm may arise from

not imaging a patient, through disease non-detection, or from erroneous staging.

Adverse Reaction to Contrast Media

Many imaging studies make use of contrast material delivered by oral, intravenous, or rectal routes. The use of contrast material may improve study performance, but reactions to contrast material may occur and they should be used only when warranted. Some patients develop adverse reactions to iodinated intravenous contrast material. Most reactions are mild cutaneous reactions (eg, urticaria, pruritus) but occasionally severe reactions can be life-threatening (bronchospasm or anaphylaxis). The risk of severe reaction is low with non-ionic contrast materials.[219] Both iodinated CT contrast material and gadolinium-based MR contrast materials can be problematic in patients with reduced renal function. Gadolinium MR contrast media, in particular, is contraindicated in patients with acute renal failure or stage V chronic kidney disease (glomerular filtration rate [GFR] <15).[220] Patients in this category are significantly more likely to develop nephrogenic systemic fibrosis (NSF). Centers performing imaging studies with contrast materials should have policies in place to address the use of contrast in these patients.

False-Positive Scans and Overdetection

Every imaging test has limitations for sensitivity, specificity, and accuracy that involve both the nature of the imaging modality as well as the interpreting physician. Harm can arise when a tumor or tumor recurrence is not detected (ie, false negative), but harm to the patient and added expense to the medical system also can result from false-positive scans. Extensive workup of imaging findings that may otherwise be benign or indolent (ie, overdetection) can lead to significant patient anxiety, additional and unnecessary imaging, and invasive procedures that carry their own risks for adverse outcomes.

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

Medical imaging is a critical tool in the evaluation and comprehensive care of patients with malignancy. However, as with any medical procedure, imaging is not without risks to patients. Inappropriate use of imaging also has been identified as a significant contributor to health care costs in the United States and worldwide. Therefore, imaging should be performed only when medically appropriate, and in a manner that reduces risk (eg, minimizing radiation dose). An algorithmic approach to the use of imaging, such as by NCCN and the Appropriateness Criteria developed by the American College of Radiology,[221] can assist in medical decision-making.

Observation

Observation involves monitoring the course of prostate cancer with a history and physical exam no more often than every 12 months (without surveillance biopsies) until symptoms develop or are thought to be imminent. If patients under observation become symptomatic, an assessment of disease burden can be performed, and treatment or palliation can be considered. Observation thus differs from active surveillance. The goal of observation is to maintain quality of life (QOL) by avoiding noncurative treatment when prostate cancer is unlikely to cause mortality or significant morbidity. The main advantage of observation is avoidance of possible side effects of unnecessary definitive therapy or ADT. However, patients may develop urinary retention or pathologic fracture without prior symptoms or increasing PSA level.

Observation is applicable to patients who are older or frail with comorbidity that will likely out-compete prostate cancer for cause of death. Johansson and colleagues[222] observed that only 13% of patients developed metastases 15 years after diagnosis of T0–T2 disease and only 11% had died from prostate cancer. Because prostate cancer will not be treated for cure for patients with shorter life expectancies, observation for as long as possible is a reasonable option based on physician discretion. Monitoring should include PSA and physical exam no more often than every 6 months, but will not involve surveillance biopsies or radiographic imaging. When symptoms develop or are imminent, patients can begin palliative ADT.

Active Surveillance

Active surveillance (formerly referred to as watchful waiting, expectant management, or deferred treatment) involves actively monitoring the course of the disease with the expectation to deliver curative therapy if the cancer progresses. Unlike observation, active surveillance is mainly applicable to younger patients with seemingly indolent cancer with the goal to defer or avoid treatment and its potential side effects. Because these patients have a longer life expectancy, they should be followed closely and treatment should start promptly should the cancer progress so as not to miss the chance for cure.

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

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

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

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

Ultimately, a recommendation for active surveillance must be based on careful individualized weighing of a number of factors: life expectancy, general health condition, disease characteristics, potential side effects of treatment, and patient preference. Shared decision-making, after appropriate counseling on the risks and benefits of the various options, is critical.

The panel believes there is an urgent need for further clinical research regarding the criteria for recommending active surveillance, the criteria for reclassification on active surveillance, and the schedule for active surveillance especially as it pertains to prostate biopsies, which pose an increasing burden. One important ongoing study that can help answer these questions is the prospective multi-institutional Canary PASS cohort study, which has been funded by the NCI.[230] Nine hundred five patients, median age 63 years and median follow-up 28 months, demonstrated 19% conversion to therapy. Much should be learned about the criteria for selection of and progression on active surveillance as this cohort and research effort mature.

Rationale

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

The debate about the need to diagnose and treat every individual who has prostate cancer is fueled by the high prevalence of prostate cancer upon autopsy of the prostate[246]; the high frequency of positive prostate biopsies in individuals with normal DREs and serum PSA values[247]; the contrast between the incidence and mortality rates of prostate cancer; and the need to treat an estimated 37 patients with screen-detected prostate cancer[248,249] or 100 patients with low-risk prostate cancer[250] to prevent one death from the disease. The controversy regarding overtreatment of prostate cancer and the value of prostate cancer early detection[248-254] has been further informed by publication of the Goteborg study, a subset of the European Randomized Study of Screening for Prostate Cancer (ERSPC).[255,256] Many believe that this study best approximates proper use of PSA for early detection because it was population-based and involved a 1:1 randomization of 20,000 participants who received PSA every 2 years and used thresholds for prostate biopsy of PSA >3 and >2.5 since 2005. The 14-year follow-up reported in 2010 was longer than the European study as a whole (9 years) and the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial (11.5 years). Prostate cancer was diagnosed in 12.7% of the screened group compared to 8.2% of the control group. Prostate cancer mortality was 0.5% in the screened group and 0.9% in the control group, which gave a 40% absolute cumulative risk reduction of prostate cancer death (compared to ERSPC 20% and PLCO 0%).[255] Most impressively, 40% of the patients were initially on active surveillance and 28% were still on active surveillance at the time these results were analyzed. To prevent a prostate cancer death, 12 individuals would need to be diagnosed and treated as opposed to the ERSPC as a whole where 37 individuals needed to be treated. Analysis of 18-year follow-up data from the Goteborg study reduced the number needed to be diagnosed to prevent 1 prostate cancer death to 10.[257] Thus, early detection, when applied properly, should reduce prostate cancer mortality. However, that reduction comes at the expense of overtreatment that may occur in as many as 50% of patients treated for PSA-detected prostate cancer.[258]

The best models of prostate cancer detection and progression estimate that 23% to 42% of all U.S. screen-detected cancers were overtreated[259] and that PSA detection was responsible for up to 12.3 years of lead-time bias.[260] The NCCN Guidelines Panel responded to these evolving data with careful consideration of which patients should be recommended

active surveillance. However, the NCCN Guidelines Panel recognizes the uncertainty associated with the estimation of chance of competing causes of death; the definition of very-low-, low-, and favorable intermediate-risk prostate cancer; the ability to detect disease progression without compromising chance of cure; and the chance and consequences of treatment side effects.

Patient Selection

Epstein and colleagues[261] introduced clinical criteria to predict pathologically "insignificant" prostate cancer. Insignificant, or very-low-risk, prostate cancer is identified by: clinical stage T1c, biopsy Grade Group 1, the presence of disease in fewer than 3 biopsy cores, ≤50% prostate cancer involvement in any core, and PSA density <0.15 ng/mL/g. Despite the usefulness of these criteria, physicians are cautioned against using these as the sole decision maker. Studies have shown that as many as 8% of cancers that qualified as insignificant using the Epstein criteria were not organ-confined based on postoperative findings.[262,263] A new nomogram may be better.[264] Although many variations upon this definition have been proposed (reviewed by Bastian and colleagues[265]), a consensus of the NCCN Guidelines Panel was reached that insignificant prostate cancer, especially when detected early using serum PSA, poses little threat to individuals with a life expectancy of less than 20 years. The confidence that Americans with very-low-risk prostate cancer have a very small risk of prostate cancer death is enhanced by lead time bias introduced by PSA early detection that ranges from an estimated 12.3 years in a 55-year-old individual to 6 years in a 75-year-old individual.[260]

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

Active Surveillance in Low-Risk Disease

Panel consensus is that active surveillance is preferred for most patients with low-risk prostate cancer and a life expectancy greater than or equal to 10 years. However, the panel recognizes that there is heterogeneity across the low-risk group, and that some factors may be associated with an increased probability of near-term grade reclassification including high PSA density, a high number of positive cores (eg, ≥3), high genomic risk (from tissue-based molecular tumor analysis), and/or a known *BRCA2* germline mutation.[266-268] Of note, core involvement in the major active surveillance cohort studies was generally low (see *Table 1* in the *Principles of Active Surveillance and Observation*, in the algorithm above). Therefore, in some of patients with low-risk prostate cancer, upfront treatment with radical prostatectomy or prostate RT may be preferred based on shared decision-making with the patient.

Active Surveillance in Favorable Intermediate-Risk Disease

The literature on outcomes of active surveillance in patients with intermediate-risk prostate cancer is limited.[269] In the PIVOT trial, patients with clinically localized prostate cancer and a life expectancy greater than or equal to 10 years were randomized to radical prostatectomy or observation.[270] Of the 120 participants with intermediate-risk disease who were randomized to observation, 13 died from prostate cancer, a non-significant difference compared with 6 prostate cancer deaths in 129 participants with intermediate-risk disease in the radical prostatectomy arm (HR, 0.50; 95% CI, 0.21–1.21; P = .12). After longer follow-up (median 12.7 years), a small difference was seen in all-cause mortality in those with intermediate-risk disease (absolute difference, 14.5 percentage points; 95% CI, 2.8–25.6), but not in those with low-risk disease (absolute difference, 0.7 percentage points; 95% CI, -10.5–11.8).[271] Urinary incontinence and erectile and sexual dysfunction, however, were worse through 10 years in the radical prostatectomy group. These results and the

less-than-average health of participants in the PIVOT study[272] suggest that patients with competing risks may safely be offered active surveillance.

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

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

Role of Race in Decisions Regarding Active Surveillance

Race is emerging as an important factor to consider when contemplating active surveillance, particularly for African-American patients. A CDC analysis of population-based cancer registries found that from 2003 to 2017, the incidence of prostate cancer was higher in black individuals than in white individuals, Hispanic individuals, American Indian/Alaska natives, and Asian/Pacific islanders.[278] Five-year survival for all stages combined was higher for white patients than for black or Hispanic patients, but survival for distant stage disease was higher for black patients than white patients. In an analysis that spanned 2010 to 2012, African Americans had a higher lifetime risk of developing (18.2% vs. 13.3%) and dying from (4.4% vs. 2.4%) prostate cancer compared to Caucasian Americans.[279] In one study, the increase in prostate-cancer-specific mortality in African American patients was limited to those with grade group 1.[280] Multiple studies have shown that African Americans with very-low-risk prostate cancer may harbor high-grade (Grade Group ≥2) cancer that is not detected by pre-treatment biopsies. Compared to Caucasian Americans matched on clinical parameters, African Americans have been reported to have a 1.7- to 2.3-fold higher change of pathologic upgrading.[281,282] However, other studies have not seen different rates of upstaging or upgrading.[283,284] For example, in a retrospective study of 895 patients in the SEARCH database, no significant differences were seen in the rates of pathologic upgrading, upstaging, or biochemical recurrence between African American and Caucasian Americans.[283]

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

Reasons for these clinical disparities are under investigation, but treatment disparities and access to health care may play a significant role.[291,292] In fact, results of some studies suggest that racial disparities in prostate cancer outcomes are minimized when health care access is equal.[12,293-295]

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.[296]

Confirmatory Testing

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

Before starting on an active surveillance program, mpMRI with calculation of PSA density should be considered to confirm candidacy for active surveillance if not performed during initial workup.[297] Patients with PI-RADS 4 or 5 on mpMRI have an increased risk of biopsy progression during active surveillance.[298]

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

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

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

Active Surveillance Program

The current NCCN recommendations for the active surveillance program include PSA no more often than every 6 months unless clinically indicated; DRE no more often than every 12 months unless clinically indicated; repeat prostate biopsy no more often than every 12 months unless clinically indicated; and repeat mpMRI no more often than every 12 months unless clinically indicated. Repeat molecular tumor analysis is discouraged during active surveillance. Results of a study of 211 patients with Grade Group 1 prostate cancer who had initial and repeat mpMRIs and PSA monitoring suggest that a negative initial mpMRI predicts a low risk of Gleason upgrading by systematic biopsy.[299] 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.[300] 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.[301] Another study found the NPV of mpMRI to be 80%.[302]

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.[303] A repeat prostate biopsy should

also be considered if the prostate exam changes, if mpMRI (if done) suggests more aggressive disease, or if PSA increases. However, literature suggests that as many as 7% of patients undergoing prostate biopsy will suffer an adverse event,[252] and those who develop urinary tract infection are often fluoroquinolone-resistant.[304] Radical prostatectomy may become technically challenging after multiple sets of biopsies, especially as it pertains to potency preservation.[305] 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.[306]

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.[307-309] 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.[310-312]

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.[313] If repeat biopsy shows Grade Group ≥3 disease, or if tumor is found in a greater number of biopsy cores or in a higher percentage of a given biopsy core, cancer progression may have occurred. Grade reclassification on repeat biopsy is the most common factor influencing a change in management from active surveillance to treatment. Other factors affecting decisions to actively treat include: increase in tumor volume, a rise in PSA density, as well as patient anxiety. Considerations for a change in management strategy should be made in the context of the patient's life expectancy.

Each of the major active surveillance series has used different criteria for reclassification.[223,224,229-232,314-317] Reclassification criteria were met by 23% of patients with a median follow-up of 7 years in the Toronto experience,[315] 36% of patients with a median follow-up of 5 years in the Johns Hopkins experience,[223] and 16% of patients with a median follow-up of 3.5 years in the University of California, San Francisco (UCSF) experience[232] (Table 3). Uncertainty regarding reclassification criteria and the desire to avoid missing an opportunity for cure drove several reports that dealt with the validity of commonly used reclassification criteria. The Toronto group demonstrated that a PSA trigger point of PSADT less than 3 years could not be improved upon by using a PSA threshold of 10 or 20, PSADT calculated in various ways, or PSA velocity greater than 2 ng/mL/y.[318] 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.[319] Neither PSADT (area under the curve [AUC], 0.59) nor PSA velocity (AUC, 0.61) was associated with prostate biopsy reclassification. Both groups have concluded that PSA kinetics cannot replace regular prostate biopsy, although treatment of most patients who demonstrate reclassification on prostate biopsy prevents evaluation of biopsy reclassification as a criterion for treatment or reduction of survival. Treatment of all patients who developed Gleason pattern 4 on annual prostate biopsies has thus far resulted in only 2 prostate cancer deaths among 1298 patients (0.15%) in the Johns Hopkins study.[223] However, it remains uncertain whether treatment of all who progressed to Gleason pattern 4 was necessary. Studies remain in progress to identify the best

trigger points when interventions with curative intent may still be successful.

The Toronto group published findings on three patients who died of prostate cancer in their experience with 450 patients on active surveillance.[315] 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%.[315] Of the 30% (n = 145) of patients who progressed, 8% had an increase in Gleason grade, 14% had a PSADT less than 3 years, 1% developed a prostate nodule, and 3% were treated because of anxiety. One hundred thirty-five of these 145 patients were treated: 35 by radical prostatectomy, 90 by EBRT with or without ADT, and 10 with ADT alone. Follow-up is available for 110 of these patients, and 5-year biochemical PFS is 62% for those undergoing radical prostatectomy and 43% for those undergoing radiation. Longer-term follow-up of this cohort was reported in 2015.[224] The 10- and 15-year actuarial cause-specific survival rates for the entire cohort were 98.1% and 94.3%, respectively. Only 15 of 993 (1.5%) patients had died of prostate cancer, an additional 13 patients (1.3%) had developed metastatic disease, and only 36.5% of the cohort had received treatment by 10 years. In an analysis of 592 patients enrolled in this cohort who had 1 or more repeat prostate biopsies, 31.3% of cases were upgraded. Fifteen percent of upgraded cases were upgraded to Gleason ≥8, and 62% of total upgraded cases proceeded to active treatment.[320] 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%).[321] 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.[317] The two groups were similar by pathologic Gleason grade, pathologic stage, and margin positivity. All patients treated by radical prostatectomy after progression on active surveillance had freedom from biochemical progression at a median follow-up of 37.5 months, compared to 97% of those in the primary radical prostatectomy group at a median follow-up of 35.5 months. A later publication from this group showed that 23 of 287 patients who were treated after active surveillance (8%) experienced biochemical recurrence, and the rate was independent of the type of treatment.[223] Several studies have shown that delayed radical prostatectomy does not increase the rates of adverse pathology.[230,322-324]

Radical Prostatectomy

Radical prostatectomy is appropriate for any patient whose cancer appears clinically localized to the prostate. However, because of potential perioperative morbidity, radical prostatectomy should generally be reserved for patients whose life expectancy is 10 years or more. Stephenson and colleagues[121] reported a low 15-year prostate cancer-specific mortality of 12% in patients who underwent radical prostatectomy (5% for patients with low-risk disease), although it is unclear whether the favorable prognosis is due to the effectiveness of the procedure or the low lethality of cancers detected in the PSA era.

Radical prostatectomy was compared to watchful waiting in a randomized trial of 695 patients with early-stage prostate cancer (mostly T2).[325,326] 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.[325] The reduction in mortality was confirmed at 18 years of follow-up, with an

absolute difference of 11%.[326] Overall, 8 patients needed to be treated to avert one death; that number fell to 4 for patients <65 years of age. Longer follow-up results were also reported, in which the cumulative incidence of death from prostate cancer was 19.6% and 31.3% in the radical prostatectomy and watchful waiting groups, respectively, at 23 years, with a mean increase of 2.9 years of life in the radical prostatectomy group.[327] 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.[328] 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.[329-331] 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.[332]

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.[333,334] Overall and cancer-specific 10-year survival ranged from 54% to 89% and 70% to 83%, respectively.[333] 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.[335,336] Laparoscopic and robot-assisted radical prostatectomy are commonly used and are considered comparable to conventional approaches in experienced hands.[337-339] 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.[340] 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.[341] Oncologic outcome of a robotic versus open approach was similar when assessed by use of additional therapies[340] or rate of positive surgical margins,[342] 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.[342] 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[343] and potency recovery.[344] 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.[345,346] 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.[345]

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.[347] 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.[348]

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.[349] 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.[350,351] Replacement of resected nerves with nerve grafts does not appear to be effective for patients undergoing wide resection of the neurovascular bundles.[352] The ability of mpMRI to detect extracapsular extension can aid in decision-making in nerve-sparing surgery.[171]

Pelvic Lymph Node Dissection

The decision to perform PLND should be guided by the probability of nodal metastases. The NCCN Guidelines Panel chose 2% as the cutoff for PLND because this avoids 47.7% of PLNDs at a cost of missing 12.1% of positive pelvic lymph nodes.[126] A more recent analysis of 26,713 patients in the SEER database treated with radical prostatectomy and PLND between 2010 and 2013 found that the 2% nomogram threshold would avoid 22.3% of PLNDs at a cost of missing 3.0% of positive pelvic lymph nodes.[353] The Panel recommends use of a nomogram developed at Memorial Sloan Kettering Cancer Center that uses pretreatment PSA, clinical stage, and Gleason sum to predict the risk of pelvic lymph node metastases.[126]

PLND should be performed using an extended technique.[354,355] 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.[356-358] A survival advantage with more extensive lymphadenectomy has been suggested by several studies, possibly due to elimination of microscopic metastases,[357,359-361] although definitive proof of oncologic benefit is lacking.[362] 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.[363]

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

External Beam Radiation Therapy

Over the past several decades, EBRT techniques have evolved to allow higher doses of radiation to be administered safely. Three-dimensional (3D) CRT (3D-CRT) uses computer software to integrate CT images of the patients' internal anatomy in the treatment position, which allows higher cumulative doses to be delivered with lower risk of late effects.[137,364-366] The second-generation 3D technique, IMRT, has been used increasingly in practice.[367] 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.[368-371]

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.[372-381] Toxicity was similar between moderately hypofractionated and conventional regimens in some[372,376,379,380] but not all of the trials.[374,377,378] 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.[382] 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.[383] 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.[384]

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.[385-390] Kuban and colleagues[388] 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.[391] 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.[392] In light of these findings, the conventional 70 Gy dose is no longer considered adequate. A dose of 75.6 to 79.2 Gy in conventional fractions to the prostate (with or without seminal vesicles) is appropriate for patients with low-risk cancers. Patients Intermediate-risk and high-risk disease should receive doses of up to 81.0 Gy.[368,393,394]

Data suggested that EBRT and radical prostatectomy were effective for the treatment of localized prostate cancer.[395] 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.[396]

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.[396,397] 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.[398,399] 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.[400] 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.[401] Spacer implantation, however, is quite expensive and may be associated with rare complications such as rectum perforation and urethral damage.[402,403] 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.[404] 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.[405] 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.[406] 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.[407] In another study (RTOG 8531), 977 patients with T3 disease treated with EBRT were randomized to adjuvant ADT or ADT at relapse.[408] Two other randomized phase 3 trials evaluated long-term ADT with or without radiation in a population of patients who mostly had T3 disease.[409-412] 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.[413]

Prophylactic nodal radiation should be considered in this population. [414-416] 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.[417] The randomized phase 3 FLAME trial showed that a focal radiation boost to the mpMRI-visible lesion can improve biochemical DFS in this population.[418]

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.[419] 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.[420] 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; $P < .01$).[421] 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).[422]

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.[423]

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.[332] In this multicenter, international study, 2061 patients were randomized to lifelong ADT with or without EBRT to the primary tumor (either 55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6 weekly fractions over 6 weeks). The primary outcome of OS by intention-to-treat (ITT) analysis was not met (HR, 0.92; 95% CI, 0.80–1.06; $P = .266$), but EBRT improved the secondary outcome of FFS (HR, 0.76; 95% CI, 0.68–0.84; $P < .0001$). In a pre-planned subset analysis, outcomes of patients with high metastatic burden (defined as visceral metastases; ≥4 bone metastases with ≥1 outside the vertebral bodies or pelvis; or both) and those with low metastatic burden (all others) were determined. EBRT improved OS (adjusted HR, 0.68; 95% CI, 0.52–0.90), prostate cancer-specific survival (adjusted HR, 0.65; 95% CI, 0.47–0.90), FFS (adjusted HR, 0.59; 95% CI, 0.49–0.72), and PFS (adjusted HR, 0.78; 95% CI, 0.63–0.98) in patients with low metastatic burden, but not in patients with high metastatic burden. Randomized clinical trials are ongoing to better test the value of removal or radiation of the primary tumor in patients with low metastatic burden who are beginning ADT.[424-428]

The Panel recommends against EBRT to the primary tumor in the case of high-volume M1 disease based on the HORRAD and STAMPEDE trials.[332,429] 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,[430] 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.[431] 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.[430-436] 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.[437] 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.[438] 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).[439] Another phase 2 trial found increased toxicity with doses >47.5 Gy delivered in 5 fractions.[440] An analysis using the SEER database also reported that SBRT was more toxic than IMRT.[441] Overall, prospective evidence supports the use of SBRT in the setting of localized prostate cancer.[442]

Several phase 3 trials have been initiated comparing conventional regimens to SBRT.[443-445] 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.[445]

SBRT/extremely hypofractionated IG-IMRT regimens (6.5 Gy per fraction or greater) can be considered as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise. Longer follow-up and prospective multi-institutional data are required to evaluate longer-term results, especially because late toxicity theoretically could be worse in hypofractionated regimens compared to conventional fractionation (1.8–2.0 Gy per fraction).

Brachytherapy

Brachytherapy involves placing radioactive sources into the prostate tissue. Brachytherapy has been used traditionally for low-risk cases because earlier studies found it less effective than EBRT for high-risk disease.[94,446] 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.[447,448]

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.[449] 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.[397] 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.[450,451] 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.[452] 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).[453,454] Vargas and colleagues[455] 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.[456-460] A phase 2 trial in 300 patients with intermediate-risk prostate cancer also found LDR brachytherapy alone to be safe and effective.[461] 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).[462] 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.[463-466] This combination has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials, but with higher toxicity.[467-469] 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.[470]

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.[471] All patients were initially treated with 12 months of ADT and pelvic EBRT to 46 Gy. An ITT analysis found that the primary endpoint of biochemical PFS was 89% versus 84% at 5 years; 86% versus 75% at 7 years; and

83% versus 62% at 9 years for the LDR versus EBRT boost arms (log-rank $P < .001$). Toxicity was higher in the brachytherapy arm, with the cumulative incidence of grade 3 genitourinary events at 5 years of 18.4% for brachytherapy boost and 5.2% for EBRT boost ($P < .001$).[472] 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.[473] Whereas the toxicity is increased with the use of brachytherapy boost, this and other randomized controlled trials have not shown an improvement in OS or cancer-specific survival.[474]

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.[475,476] 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.[477] 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.[478,479]

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.[480] 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.[481]

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.[482] 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.[483] 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%.[484]

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.[485] 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.[486,487] 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.[488] 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.[487] 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.[486] 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.[489] 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.[487] 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.[490] 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.[491] 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.[492] 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).[493] 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.[494] The SCORAD randomized trial did not show non-inferiority for ambulatory status of single-fraction 8-Gy EBRT to 20 Gy in 5 fractions.[495]

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.[496] 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.[497] Sixteen patients had prostate cancer. After a median follow-up of 51 months, the 5-year OS rate was higher in the SABR group (17.7% vs. 42.3%; stratified log-rank *P* = .006), as was the 5-year PFS rate (3.2% vs. 17.3%; *P* = .001). No differences were seen in adverse events or QOL.

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

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

Comparison of Treatment Options for Localized Disease

Several large prospective, population/cohort-based studies have compared the outcomes of patients with localized prostate cancer treated with EBRT, brachytherapy, radical prostatectomy, observation, and/or active surveillance. Barocas et al compared radical prostatectomy, EBRT, and active surveillance in 2550 patients and found that, after 3 years, radical prostatectomy was associated with a greater decrease in urinary and sexual function than either EBRT or active surveillance.[498] 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.[499] 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.[500]

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.[501] By 5 years, most functional differences were minimal between management approaches. However, radical prostatectomy was associated with worse incontinence in the full cohort and with worse sexual function in those with unfavorable intermediate-, high-, or very-high-risk disease than those treated with EBRT and ADT.

Other Local Therapies

Many therapies have been investigated for the treatment of localized prostate cancer in the initial disease and recurrent settings, with the goals of reducing side effects and matching the cancer control of other therapies. Cryotherapy or other local therapies are not recommended as routine primary therapy for localized prostate cancer due to lack of long-term data comparing these treatments to radiation or radical prostatectomy. At this time, the panel recommends only cryosurgery and high-intensity focused ultrasound (HIFU; category 2B) as local therapy options for RT recurrence in the absence of metastatic disease.

Cryosurgery, also known as cryotherapy or cryoablation, is an evolving minimally invasive therapy that damages tumor tissue through local freezing. In the initial disease setting, the reported 5-year biochemical disease-free rate after cryotherapy ranged from 65% to 92% in patients with low-risk disease using different definitions of biochemical recurrence.[502] A report suggests that cryotherapy and radical prostatectomy give similar oncologic results for unilateral prostate cancer.[503] A study by Donnelly and colleagues[504] 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.[505] 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.[506]

Cryosurgery has been assessed in patients with recurrent disease after RT.[507-509] 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%).[509]

HIFU has been studied for treatment of initial disease.[510,511] A prospective multi-institutional study used HIFU in 111 patients with localized prostate cancer.[510] 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.[512] 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.[513,514]

HIFU also has been studied for treatment of radiation recurrence.[515-521] 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%.[522] Morbidity was acceptable, with a grade III/IV complication rate of 3.6%. Analysis of a separate prospective registry showed that 48% of those who received HIFU following radiotherapy recurrence were able to avoid ADT at a median follow-up of 64 months.[523]

Other emerging local therapies, such as focal laser ablation and vascular-targeted photodynamic (VTP) therapy have also been studied.[524,525] 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.[526] 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.[527] 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.[528]

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.[529] 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.[530,531] Serial PSA measurements can be helpful for stratifying patients at highest risk of progression and metastases.

Selecting patients appropriately for adjuvant radiation is difficult.

Adjuvant/Early Treatment for Adverse Features

Adjuvant radiation with or without ADT can be given to patients with PSA persistence (PSA does not fall to undetectable levels) or adverse pathologic features (ie, positive margins, seminal vesicle invasion, extracapsular extension) who do not have lymph node metastases. Positive surgical margins are unfavorable, especially if diffuse (>10-mm margin involvement or ≥3 sites of positivity) or associated with persistent serum levels of PSA. The defined target volumes include the prostate bed.[532] 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.[533-535] 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.[536] 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.[537,538] 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; $P < .001$).[539]

Systematic reviews come to conflicting conclusions on the utility of immediate post-prostatectomy radiation in patients with adverse features.[540,541] 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.[542]

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.[543] 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.[544]

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)[415,416,545,546]; 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*).[547] 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.[548] 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.[536-538] 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.[549-552]

Biochemical Recurrence After Radical Prostatectomy

Patients who experience biochemical recurrence after radical prostatectomy fall into three groups: 1) those whose PSA level does not fall to undetectable levels after radical prostatectomy (persistent disease); 2) those who achieve an undetectable PSA after radical prostatectomy with a subsequent detectable PSA level that increases on two or more subsequent laboratory determinations (PSA recurrence); or 3) the occasional case with persistent but low PSA levels attributed to slow PSA metabolism or residual benign tissue. Consensus has not defined a threshold level of PSA below which PSA is truly “undetectable.”[530] 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.[553-557] A large retrospective review of 501 patients who received radiation for detectable and increasing PSA after radical prostatectomy[556] 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.[558] Delivery of adjuvant or post-recurrence EBRT becomes both therapeutic and diagnostic—PSA response indicates local persistence/recurrence. Delayed biochemical recurrence requires

restaging, and a nomogram[118,559] 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.[560,561] 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%.[562]

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 ($P < .001$).[563]

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.[564] 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.[558,565] 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.[532] Treatment is most effective when pre-treatment PSA level is below 0.5 ng/mL.[559] 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,[558] 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.[565] Most patients with prolonged PSADT may be observed safely.[566]

Six months of concurrent/adjuvant ADT can be coadministered with radiation in patients with rising PSA levels based on the results of GETUG-16.[567,568] 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.[569] 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.[570] For 2 years of ADT, level 1 evidence supports 150 mg bicalutamide daily but an LHRH agonist could be considered as an alternative.[570]

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.[571] 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.[572] Other options for localized interventions include cryotherapy,[573] HIFU (category 2B),[515-518,522,523] and brachytherapy (reviewed by Allen and colleagues[574] and discussed in *Post-Recurrence Brachytherapy*, above). Treatment, however, needs to be individualized based on the patient's risk of progression, the likelihood of success, and the risks involved with therapy. For those with a life expectancy less than or equal to 10 years, positive biopsy, and no distant metastases, observation or ADT are appropriate options.

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

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

Androgen Deprivation Therapy

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

In the community, ADT has been commonly used as primary therapy for early-stage, low-risk disease, especially in the patients who are older. This practice has been challenged by a large cohort study of 66,717 patients ≥66 years of age with T1–T2 tumors.[575] 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.[576] 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.[577,578]

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.[579] 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).[570,580-582] Only a cancer-specific survival benefit was noted in a fourth trial that recruited mostly patients with high-risk disease (RTOG 8610).[583] Results of the EORTC 22991 trial showed that the addition of 6 months of ADT significantly improved biochemical DFS compared with radiation alone in those with intermediate-risk (75% of study population) and high-risk disease.[584] 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.[585]

RTOG 9910 and RTOG 9902 reinforced two important principles concerning the optimal duration of ADT and use of systemic chemotherapy in conjunction with EBRT.[586,587] 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.[582] 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.[588] 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.[588] 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).[589,590]

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.[407,408,410,411,591]

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.[592] 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).[593]

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.[594] The DART01/05 GICOR trial also reported similar results in patients with high-risk disease.[595] 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.[596] Two randomized phase 3 trials showed 1.5 years of ADT was not inferior to 3 years of ADT.[597,598]

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.[599]

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.[600] 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.[547] 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).[547,601] 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.[602] 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.[603] In addition, a cohort analysis of 731 patients with positive nodes did not demonstrate a survival benefit of ADT initiated within 4 months of radical prostatectomy compared to observation.[602] 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.[604]

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.[603] Meta-analysis data suggest that bicalutamide may provide an incremental relative improvement in OS by 5% to 20% over LHRH agonist monotherapy.[605,606] 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.[607,608] 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.[609]

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.[610] 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.[611] The heart and T lymphocytes have receptors for LHRH. Therefore, LHRH agonists may affect cardiac contractility, vascular plaque stability, and inflammation.[612]

A new LHRH antagonist, relugolix, has been studied as ADT in patients with advanced prostate cancer in the randomized phase 3 HERO trial.[613] In this study, 622 patients received relugolix (120 mg orally once daily) and 308 received leuprolide (injections every 3 months) for 48 weeks. The patients had recurrence after primary definitive therapy, newly diagnosed metastatic castration-naïve disease, or advanced localized disease deemed unlikely to be cured with definite therapy. The primary endpoint, sustained castrate levels of testosterone (<50 ng per deciliter) through 48 weeks, showed noninferiority and superiority of relugolix over leuprolide (96.7%; 95% CI, 94.9–97.9 vs. 88.8% [95% CI, 84.6–91.8]; $P < .001$ for superiority). The secondary endpoint of castrate levels of testosterone on day 4 was also improved in the relugolix arm (56% vs. 0%). However, relugolix did not achieve superiority in the key clinical secondary endpoint of castration resistance-free survival compared to leuprolide (74% vs.

75%; *P* = .84). The incidence of major adverse cardiovascular events was 2.9% in the relugolix arm and 6.2% in the leuprolide arm (HR, 0.46; 95% CI, 0.24–0.88). The Panel includes relugolix alone as an option for ADT in patients with castration-naïve disease. However, the Panel notes that data are limited on long-term adherence of oral relugolix and the potential effects non-adherence may have on optimal ADT. Ongoing monitoring for sustained suppression of testosterone (<50 ng/dL) can be considered, and relugolix may not be a preferred agent if adherence is uncertain.

It is important to note that the HERO trial did not include patients receiving curative intent therapy (ie, individuals getting definitive EBRT plus ADT). Furthermore, relugolix shows a shorter time to testosterone recovery, which might be associated with a higher risk of death from prostate cancer.[614] Therefore, although the Panel considers relugolix to be an acceptable option in the curative-intent setting, additional studies in this setting are needed.

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

ADT for M0 Biochemical Recurrence

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

Patients with an increasing PSA level and with no symptomatic or clinical evidence of cancer after definitive treatment present a therapeutic dilemma regarding the role of ADT. Some of these patients will ultimately die of their cancer. Timing of ADT for patients whose only evidence of cancer is increasing PSA is influenced by PSA velocity (PSADT), patient and physician anxiety, the short-term and long-term side effects of ADT, and underlying comorbidities of the patient. Early ADT is acceptable, but an alternative is close observation until progression of cancer, at which time appropriate therapeutic options may be considered. Earlier ADT may be better than delayed therapy, although the definitions of early and late (ie, what level of PSA) remain controversial. The multicenter phase 3 TROG 03.06/VCOG PR 01-03 [TOAD] trial randomized 293 patients with PSA relapse after operation or radiation (n = 261) or who were not considered for curative treatment (n = 32) to immediate ADT or ADT delayed by a recommended interval of greater than or equal to 2 years.[615] 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.[616] 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.[603] A PSA value ≤4 ng/mL after 7 months of ADT is associated with improved survival of patients newly diagnosed with metastatic prostate cancer.[617]

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.[618,619] 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.[620,621] 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.[622] 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.[622] 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; $P < .0001$).[623]

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.[622] 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.[624] 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.[622]

A second randomized trial (STAMPEDE) of 1917 patients with castration-naïve prostate cancer demonstrated similar OS benefits.[422] However, unlike LATITUDE, STAMPEDE eligibility permitted patients with high-risk N0,M0 disease (2 of 3 high-risk factors: stage T3/4, PSA >40, or Gleason score 8–10; n = 509), or N1,M0 disease (pelvic nodal metastases; n = 369) in addition to M1 patients, who made up the majority of patients (n = 941). The majority of patients were newly diagnosed, while a minority had recurrent, high-risk, or metastatic disease after local therapy (n = 98). Thus, STAMPEDE was a heterogeneous mix of patients with high-risk, non-metastatic, node-positive, or M1 disease. In M1 patients, treatment with abiraterone plus prednisone was continued until progression. In patients with N1 or M0 disease, 2 years of abiraterone plus prednisolone was used if curative-intent EBRT was utilized. OS was improved in the overall population (HR, 0.63; 95% CI, 0.5–0.76; $P < .0001$) and in the M1 and N1 subsets, without any heterogeneity of treatment effect by metastatic status. The survival benefit of abiraterone was larger in patients <70 years of age than those ≥70 years (HR, 0.94 vs. HR, 0.51). Patients who were older also suffered increased toxicities, which suggests heterogeneity in clinical benefits by age and comorbidity. The secondary endpoint of FFS, which included PSA recurrence, was improved overall (HR, 0.29; $P < .0001$) and in all subgroups regardless of M1 (HR, 0.31), N1 (HR, 0.29), or M0 (HR, 0.21) status. No heterogeneity for FFS was observed based on subgroups or by age. In this trial, subsequent life-prolonging therapy was received by 58% of those in the control group, which included 22% who received abiraterone and 26% who received enzalutamide. Thus, these data reflect a survival advantage of initial abiraterone in newly diagnosed patients compared with deferring therapy to the CRPC setting.

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

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

Abiraterone can be given at 250 mg/day and administered following a low-fat breakfast, as an alternative to the dose of 1000 mg/day after an overnight fast (see *Abiraterone Acetate in M1 CRPC*, below).[625] The cost savings may reduce financial toxicity and improve adherence.

Apalutamide in Castration-Naïve Prostate Cancer

The double-blind phase 3 TITAN clinical trial randomized 1052 patients with metastatic, castration-naïve prostate cancer to ADT with apalutamide (240 mg/day) or placebo.[626] 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.[627] 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 (not reached vs. 52.2 months; HR, 0.65; 95% CI, 0.53–0.79; $P < .001$)[628]

Apalutamide is a category 1 option for patients with M1 castration-naïve prostate cancer. The FDA approved this indication in September of 2019.[629,630]

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.[631] 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; $P < .001$).[632]

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.[631,632]

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.[633,634] 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.[635] 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).[635] 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.[636]

The multinational European ICELAND trial randomized 702 participants with locally advanced or biochemically recurrent prostate cancer to continuous or intermittent ADT.[637] 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.[638]

Intermittent ADT in Metastatic Disease

Hussain and colleagues[639] 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.[640]

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).[639] 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.[641] Furthermore, several meta-analyses of randomized controlled trials reported no difference in survival between intermittent ADT and continuous ADT.[642-644] Another recent analysis concluded that the non-inferiority of intermittent to continuous ADT in terms of survival has not been clearly demonstrated.[645] 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[617]: 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.[636] 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.[646-648] 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.[613] 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.[649-656]

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.[657-659] 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; $P = .01$).[612] ADT increases bone turnover and decreases bone mineral density,[660-663] 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,[664] and treatment-related sarcopenia appears to contribute to frailty and increased risk of falls in patients who are older.

The NCCN Guidelines Panel recommends screening and treatment for osteoporosis according to guidelines for the general population from the National Osteoporosis Foundation.[665] 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.[666] 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.[667-669] 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.[670] 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.[671] 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.[583,671-678] 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.[679] Other population-based studies resulted in similar findings.[612,680] However, a Taiwan National Health Insurance Research Database analysis found no difference in ischemic events with LHRH agonist therapy or orchiectomy.[681] A French database study showed the cardiovascular risk to be similar in patients taking LHRH agonists and antagonists.[682] 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.[611] Patients with a recent history of cardiovascular disease appear to have higher risk,[683] and increased physical activity may decrease the symptoms and cardiovascular side effects of patients treated with ADT.[684]

Several mechanisms may contribute to greater risk for diabetes and cardiovascular disease during ADT. ADT increases fat mass and decreases lean body mass.[664,685,686] ADT with an LHRH agonist increases fasting plasma insulin levels[687,688] and decreases insulin sensitivity.[689] ADT also increases serum levels of cholesterol and triglycerides.[687,690]

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

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

Management of mCSPC

ADT with treatment intensification is strongly recommended for patients with metastatic castration-sensitive prostate cancer (mCSPC). The use of ADT monotherapy in this setting is discouraged unless there are clear contraindications to combination therapy. Treatment intensification options include doublet therapy of ADT with an androgen receptor pathway inhibitor (ARPI; abiraterone, apalutamide, darolutamide, or enzalutamide); triplet therapy of ADT with docetaxel and one of the same ARPIs; metastasis-directed therapy (MDT) for oligometastases (see *MDT for Oligometastatic CSPC*, below); or ADT with EBRT to the primary tumor with or without docetaxel, abiraterone, apalutamide, or enzalutamide for low-metastatic burden (see *EBRT to the Primary Tumor in Low-Metastatic-Burden M1 Disease*, above). The specific recommended therapy options vary depending on whether the metastases were diagnosed in the synchronous or metachronous setting and on whether disease is oligometastatic, low-volume metastatic, or high-volume metastatic.

The data supporting doublet or triplet therapy in this setting are discussed below. For some of the combinations recommended by the Panel, supporting data are limited. They are included based on extrapolation from the studies of other agents, since the Panel considers the four ARPIs with approval in prostate cancer to be generally interchangeable.

Doublet Therapies for mCSPC

Abiraterone Acetate in mCSPC

In February 2018, the FDA approved abiraterone in combination with prednisone for mCSPC. This approval was based on two randomized phase 3 clinical trials of abiraterone and low-dose prednisone plus ADT in patients with newly diagnosed metastatic prostate cancer or high-risk or node-positive disease (STAMPEDE and LATITUDE) that demonstrated improved OS over ADT alone.[622]

In LATITUDE, 1199 patients with high-risk mCSPC 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.[622] 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-month 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 vs. 36.5 months; HR, 0.66; 95% CI, 0.56–0.78; $P < .0001$).[623]

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.[622] 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.[624] 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.[622]

The second randomized trial (STAMPEDE) of 1917 patients with CSPC demonstrated similar OS benefits.[422] 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 patients with metastatic disease, who made up the majority of patients (n = 941). Most 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 metastatic disease. In patients with M1 disease, treatment with abiraterone plus prednisone was continued until progression. In patients with N1 or M0 disease, 2 years of abiraterone plus prednisolone was used if curative-intent EBRT was utilized. OS was improved in the overall population (HR, 0.63; 95% CI, 0.5–0.76; *P* < .0001) and in the M1 and N1 subsets, without any heterogeneity of treatment effect by metastatic status. The survival benefit of abiraterone was larger in patients <70 years of age than those ≥70 years (HR, 0.94 vs. HR, 0.51). Patients ≥70 years also suffered increased toxicities, which suggests heterogeneity in clinical benefits by age and comorbidity. The secondary endpoint of FFS, which included PSA recurrence, was improved overall (HR, 0.29; *P* < .0001) and in all subgroups regardless of M1 (HR, 0.31), N1 (HR, 0.29), or M0 (HR, 0.21) status. No heterogeneity for FFS was observed based on subgroups or by age. In this trial, subsequent life-prolonging therapy was received by 58% of those in the control group, which included 22% who received abiraterone and 26% who received enzalutamide. Thus, these data reflect a survival advantage of initial abiraterone in newly diagnosed patients compared with deferring therapy to the CRPC setting.

Adverse events in STAMPEDE were similar to that reported in LATITUDE, but were increased in patients ≥70 years, 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 mCSPC (category 1). Alternatively, the fine-particle formulation of abiraterone can be used with 4 mg methylprednisolone PO twice daily (category 2B; see *Abiraterone Acetate in mCRPC*, below).

The standard formulation of 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 mCRPC*, below).[625] The cost savings may reduce financial toxicity and improve adherence in those who will not take or cannot afford the standard dose.

Apalutamide in mCSPC

The double-blind phase 3 TITAN clinical trial randomized 1052 patients with mCSPC to ADT with apalutamide (240 mg/day) or placebo.[626] 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.[627] 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 (not reached vs. 52.2 months; HR, 0.65; 95% CI, 0.53–0.79; *P* < .001).[628]

Apalutamide is a category 1 option for patients with mCSPC. The FDA approved this indication in September 2019.

Enzalutamide in mCSPC

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 mCSPC.[631] Stratification was by volume of disease, planned use of early docetaxel, planned use of bone antiresorptive therapy, comorbidity score, and trial site. The primary endpoint of OS was met at the first interim analysis with median follow-up of 34 months (HR for death, 0.67; 95% CI, 0.52–0.86; $P = .002$). Enzalutamide also improved secondary endpoints, such as PFS using PSA levels and clinical PFS. An additional analysis was triggered at 470 deaths.[691] After a median follow-up of 68 months, the 5-year OS rate was again lower in the first-generation antiandrogen group than in the enzalutamide group (HR, 0.70; 95% CI, 0.58–0.84; $P < .0001$). The median OS was not reached.

In the double-blind randomized phase 3 ARCHES clinical, 1150 patients with mCSPC 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; $P < .001$).[632] At the final, prespecified OS analysis, median OS was not met in either group, but a 34% reduction in the risk of death was observed in those receiving enzalutamide versus placebo (HR, 0.66; 95% CI, 0.53–0.81; $P < .001$).[692] This result could be an underestimate of the effect of enzalutamide, since approximately 32% of the patients assigned placebo crossed over to enzalutamide after unblinding.

The safety of enzalutamide in these trials was similar to that seen in previous trials in the castration-resistant setting. Adverse events associated with enzalutamide in these trials included fatigue, seizures, and hypertension.[631,632]

Enzalutamide is a category 1 option for patients with mCSPC. The FDA approved this indication in December 2019.

Darolutamide in mCSPC

The phase 3 ARANOTE trial assessed darolutamide with ADT compared with placebo and ADT in 669 patients with mCSPC.[693] The primary endpoint of radiological PFS was improved in the darolutamide arm compared with the placebo arm (HR, 0.54; 95% CI, 0.41–0.71; $P < .0001$). The benefit was consistent across the low- and high-volume subgroups. Some of the secondary endpoints were also met, including delayed time to mCRPC and time to pain progression. However, a significant improvement in OS was not evident in the current follow-up (HR, 0.81; 95% CI, 0.59–1.12).

The FDA approved this indication for darolutamide in June 2025. The Panel include darolutamide with ADT as an option for patients with low- and high-volume mCSPC. Because an OS benefit has not been demonstrated for darolutamide doublet therapy, it is not a category 1 recommendation at this time.

Docetaxel in mCSPC

Docetaxel with ADT has been studied as an upfront option for patients with mCSPC in two phase 3 trials (ECOG 3805/CHAARTED and STAMPEDE).[421,694] CHAARTED randomized 790 patients with mCSPC to docetaxel (75 mg/m^2 IV every 3 weeks x 6 doses) plus ADT or ADT alone.[694] After a median follow-up of 53.7 months, the patients in the combination arm experienced a longer OS than those in the ADT arm (57.6 vs. 47.2 months; HR, 0.72; 95% CI, 0.59–0.89; $P = .002$).[695]

Subgroup analysis showed that the survival benefit was more pronounced in the 65% of participants with high-volume disease (HR, 0.63; 95% CI, 0.50–0.79; *P* < .001). Patients with low metastatic burden in CHAARTED did not derive a survival benefit from the inclusion of docetaxel (HR, 1.04; 95% CI, 0.70–1.55; *P* = .86).

The STAMPEDE trial, a multi-arm, multi-stage phase 3 trial, included patients with both M0 and M1 CSPC.[421] The results in the M1 population confirmed the survival advantage of adding docetaxel (75 mg/m^2 IV every 3 weeks x 6 doses) to ADT seen in the CHAARTED trial. In STAMPEDE, extent of disease was not evaluated in the 1087 patients with metastatic disease, but the median OS for all patients with M1 disease was 5.4 years in the ADT-plus-docetaxel arm versus 3.6 years in the ADT-only arm (a difference of 1.8 years between groups compared with a 1.1-year difference in CHAARTED).

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

Triplet Therapies for mCSPC

Data from the PEACE-1 and ARASENS trials indicate that triplet therapies of ADT with docetaxel and an ARPI —either abiraterone or darolutamide— improve OS over ADT with docetaxel in patients with high-volume metastatic CSPC.[698,699] These trials are discussed below. Both of these combinations are included as category 1, preferred options for patients with high-volume mCSPC, and their use is encouraged for patients with high-volume disease who are fit for chemotherapy. However, the Panel notes that no studies have compared doublet therapies (ADT plus an ARPI; discussed above) to triplet therapies. Therefore, doublet therapies are also suitable options for patients with high-volume metastatic disease.

These triplet combinations are also included as options in the low-volume, synchronous CSPC setting based on results of a meta-analysis, although their use in this setting is controversial and should be reserved for patients who desire aggressive treatment.[700] No data support the use of triplet therapy in low-volume metachronous mCSPC, and they are not recommended in this setting.

Docetaxel Plus Abiraterone in CSPC

PEACE-1 was an international, open-label, randomized, phase 3 study conducted in seven European countries.[698] Using a 2 × 2 factorial design, 1173 patients with de novo metastatic prostate cancer were randomized at a 1:1:1:1 ratio to standard of care (ADT alone or with docetaxel), standard of care with RT, standard of care with abiraterone, or standard of care with radiation and abiraterone. The two primary endpoints of the trial were radiographic PFS and OS. Adjusted Cox regression modelling showed no interaction between abiraterone and RT, so data were pooled for the analysis of abiraterone efficacy. Consistent with results of older studies, at a median follow-up of 3.5 years, radiographic PFS was longer in patients who received abiraterone than in those that did not (HR, 0.54; 99.9% CI, 0.41–0.71; *P* < .0001) as was OS (HR, 0.82; 95.1% CI, 0.69–0.98; *P* = .030). An OS benefit with abiraterone was also seen in the subset of patients with high metastatic burden as defined by CHAARTED criteria (HR, 0.77 ;95% CI, 0.62–0.96), but was not seen in those with low metastatic burden (HR, 0.93 ;95% CI, 0.69–1.28).

As part of the analysis, the efficacy of abiraterone was assessed in the population that received docetaxel. As in the overall population, radiographic PFS (HR, 0.50; 99.9% CI, 0.34–0.71; *P* < .0001) and OS

(HR, 0.75; 95.1% CI, 0.59–0.95; *P* = .017) were longer in those receiving all three therapies compared with those only receiving ADT and docetaxel. The populations receiving the triplet and doublet therapies experienced similar rates neutropenia, febrile neutropenia, fatigue, and neuropathy, although grade ≥3 adverse events occurred in 63% of patients who received the triplet combination compared with 52% of those receiving ADT and docetaxel.

Based on these data, the Panel includes this regimen as a category 1 option for patients with high-volume mCSPC.

Docetaxel Plus Darolutamide in CSPC

The international, phase 3 trial ARASENS trial, the second phase 3 trial evaluating a triplet therapy, randomized 1306 patients with mCSPC to receive ADT and docetaxel with either darolutamide or matching placebo.[699] The primary endpoint, OS, was improved in the darolutamide group at 4 years (62.7%; 95% CI, 58.7–66.7) compared with the placebo group (50.4%; 95% CI, 46.3–54.6). The risk of death was lower in the darolutamide group by about 32% (HR, 0.68; 95% CI, 0.57–0.80; *P* < .001). The addition of darolutamide also showed significant benefits over placebo for secondary efficacy endpoints, including time to CRPC (HR, 0.36; 95% CI, 0.30–0.42; *P* < .001), skeletal event–free survival (HR, 0.61; 95% CI, 0.52–0.72; *P* < .001), and time to initiation of subsequent systemic antineoplastic therapy (HR, 0.39; 95% CI, 0.33–0.46; *P* < .001). Subgroup analysis showed a similar improvement in OS in those with high-volume disease as defined by CHAARTED criteria as in the overall population.[701] An OS benefit was not observed in those with low metastatic burden (HR, 0.68; 95% CI, 0.41–1.13), but median survival was not reached in either arm.

Adverse events of any grade, grade 3 to 5 adverse events, and serious adverse events occurred at similar incidence levels between the two arms. Many of these were known effects of docetaxel. The most frequent adverse events were alopecia (40.5% of patients in the darolutamide arm vs. 40.6% with placebo), neutropenia (39.3% vs. 38.8%), fatigue (33.1% vs. 32.9%), and anemia (27.8% vs. 25.1%). Exceptions were rash (16.6% vs. 13.5%) and hypertension (13.7% vs. 9.2%), which are known effects of androgen receptor pathway inhibitors and were more frequent in the darolutamide group.

The FDA approved this indication in August 2022, and the Panel includes this regimen as a category 1 option for patients with high-volume mCSPC.

EBRT to the Primary Tumor in Synchronous 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.[332] In this multicenter, international study, 2061 patients were randomized to lifelong ADT with or without EBRT to the primary tumor (either 55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6 weekly fractions over 6 weeks). The primary outcome of OS by intention-to-treat (ITT) analysis was not met (HR, 0.92; 95% CI, 0.80–1.06; *P* = .266), but EBRT improved the secondary outcome of failure-free survival (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. Long-term results have been reported, confirming the benefit of RT to the primary tumor in the setting of ADT with or without docetaxel.[702]

Abiraterone may be added to ADT with EBRT to the primary tumor in patients with low-volume synchronous metastases based on results of the PEACE-1, open-label, randomized trial.[703] In this trial, participants were randomized 1:1:1:1 to ADT alone or with docetaxel (standard of care, SOC), SOC with abiraterone, SOC with radiation to the prostate, or SOC with abiraterone and radiation to the prostate. Results demonstrated that the addition of RT to the primary tumor in patients with low-volume disease treated with abiraterone led to improvements in median radiographic PFS (4.4 vs. 7.5 years). RT to the primary tumor also reduced rates of serious genitourinary toxicity regardless of disease volume, and time to castration resistance was delayed in the full population. Thus, some patients with high-volume disease may also benefit from RT to the primary tumor.

In PEACE-1, the benefits of RT to the primary tumor were only seen in patients receiving abiraterone, not in those receiving ADT alone or with docetaxel.[703] However, in a secondary analysis of the STAMPEDE trial, the benefits of RT on OS and FFS in patients with low-volume disease were seen regardless of planned docetaxel use.[704] The panel therefore includes the addition of docetaxel to ADT and EBRT to the primary tumor as a category 2B recommendation for patients with low-volume synchronous mCSPC.

MDT for Oligometastatic CSPC

Treatment of metastatic sites with local therapy with the intent to improve oncologic outcomes (eg, delaying the initiation of systemic therapy or ADT; improving PFS, radiographic PFS, or OS) is known as metastasis-directed therapy, or MDT. MDT has been primarily studied as metastasis-directed RT (MDRT) and with the highly selected use of surgical lymph node dissection. MDRT is delivered at a higher-than-palliative dose to provide durable local control of the areas targeted and is the most used form of MDT.

MDT is used in patients with oligometastatic disease. The number of metastatic sites to define oligometastatic disease remains an evolving space and is impacted by the sensitivity of the imaging modality used. Early studies included patients with 1 to 3 or 1 to 5 metastatic sites by CT, MRI, or bone scan.[705-708] More recent studies allow for up to 10 metastatic sites by PSMA-PET imaging (NCT04787744, NCT06150417, NCT03721341). The upper limit is not clearly established and is both a function of oncologic limitations and technical limitations of treating numerous metastatic sites. It should be noted that the goal of MDT is generally to treat all metastatic sites, which may include regional lymph nodes and, potentially, the primary tumor if untreated or if there is evidence of local recurrence. The primary tumor in this setting should be counted as a site. The panel notes that general exclusion limits of >5 and >10 metastases by CT, MRI, or bone scan or by PSMA-PET imaging, respectively, are appropriate.

The best evidence supporting the use of MDT in the CSPC setting comes from randomized phase 2 studies in patients with metachronous oligorecurrent disease.[496,705,708,709] These trials mostly used MDRT and showed that the approach improved ADT-free survival or PFS over monitoring or ADT. For example, the ORIOLE trial included 54 previously treated patients with 1 to 3 metastases by conventional imaging who were randomized to receive MDRT or observation.[496] Median PFS was better in the MDRT group than in the observation group (not reached vs. 5.8 months; HR, 0.30; 95% CI, 0.11–0.81; P = .002), and the treatment was well tolerated. STOMP randomized 62 patients with biochemically recurrent CSPC and ≤3 metastases to surveillance or to MDT with surgery or RT.[709] The median ADT-free survival was improved in the MDT arm after a median 3-year follow-up (13 vs. 21 months; HR, 0.60; 80% CI, 0.40–0.90; log-rank P = .11). In a combined, longer-term analysis of ORIOLE and STOMP, median PFS was longer with MDT

compared with observation (pooled HR, 0.44; 95% CI, 0.29–0.66; *P* < .001) after a median follow-up of 52.5 months.[705]

The EXTEND trial included a more heterogeneous group of patients, as 24 of the 87 enrolled patients had no prior definitive therapy to the prostate and 7 patients had mCRPC.[708] Participants had ≤5 metastases amenable to MDRT and were randomized to MDRT with intermittent ADT or to intermittent ADT alone. After a median follow-up of 22 months, median PFS was improved in the MDRT/ADT group compared with the ADT-only group (not reached vs. 15.8 months; HR, 0.25; 95% CI, 0.12–0.55; *P* < .001). Analysis of a separate basket of participants in EXTEND who received continuous ADT have also been reported.[710] Results showed that the inclusion of MDT improved the primary endpoint of PFS improved in the participants who received continuous ADT (47 vs. 22 months; HR, 0.50; one-sided *P* = .036) and in the combined group of intermittent or continuous ADT (36 months vs. 17 months; HR, 0.45; *P* <.001).

The SABR-COMET phase 2 study, which enrolled patients with breast, lung, colorectal, and prostate cancers who had a controlled primary tumor and 1 to 5 metastases amenable to MDRT, showed an improvement on OS with an MDT approach.[497] SABR-COMET included 16 patients with prostate cancer; 14 were randomized to the MDRT arm, and 2 were randomized to receive palliative RT. Patients in both arms received palliative systemic therapy as appropriate. After a median follow-up of 51 months, improvements were seen in 5-year OS rate (17.7% vs. 42.3%; 95% CI, 0.28-0.56; stratified log-rank *P* = .006) in the total population of 99 patients. A post-hoc sensitivity analysis was used to address the imbalance in the distribution of patients with prostate cancer between the two arms of the study. When patients with prostate cancer were excluded from the analysis, the 5-year OS rate continued to trend in favor of the MDRT group (16.2% vs. 33.1%; stratified log-rank test *P* = .085).

The benefit of adding ADT to MDRT in patients with oligorecurrent CSPC was assessed in the randomized, phase 2 RADIOSA trial.[707] The 105 enrolled patients were randomized to 6 months of ADT with MDRT or MDRT alone. After a median follow-up of 31 months, the median clinical PFS was improved in the group receiving ADT (32.2 vs. 15.1 months; HR, 0.43; 95% CI, 0.26–0.72; *P* = .001).

Based on these data, the Panel recommends MDT with or without ADT as an option for patients with metachronous oligometastatic CSPC. These patients may alternatively be treated with ADT plus systemic therapy for low-volume mCSPC with or without concurrent MDT.

There is currently no randomized evidence in the synchronous oligometastatic setting, just single-arm prospective trials and retrospective cohorts. However, the Panel believes that concurrent MDT with recommended systemic therapy can be considered in select patients with synchronous oligometastatic disease.

Progression to and Management of CRPC

Most advanced disease eventually stops responding to traditional ADT and is categorized as castration-resistant (also known as castration-recurrent). CRPC is defined as prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL).[711] 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 orchiectomy or an LHRH agonist or antagonist should be continued to maintain castrate serum levels of testosterone (<50 ng/dL).

Patients with CRPC and no signs of distant metastasis on conventional imaging studies (M0) can consider monitoring with continued ADT if PSADT is >10 months (preferred), because these patients will have a relatively indolent disease history.[712] Secondary hormone therapy with continued ADT is an option mainly for patients with shorter PSADT (≤10 months) as described below.

For patients who develop mCRPC, metastatic lesion biopsy is recommended, as is MSI/MMR testing, if not previously performed. If MSI-H or dMMR is found, referral to genetic counseling should be made to assess for the possibility of Lynch syndrome. These patients should also have germline and tumor testing to check for mutations in homologous recombination repair (HRR) genes (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA, RAD51D, CHEK2, CDK12*) if not done previously.[713] This information may be used for genetic counseling, cascade germline testing for family members, early use of platinum chemotherapy, and understanding eligibility for biomarker-directed treatments or clinical trials. TMB testing is also recommended for patients with mCRPC.

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

The decision to initiate therapy in the CRPC setting after disease progression on one or more treatments should be based on the available high-level evidence of safety, efficacy, and tolerability of these agents and the application of this evidence to an individual patient. Prior exposures to therapeutic agents should be considered. Data to inform the optimal sequence for delivery of these agents in patients with mCRPC is evolving (see *Sequencing of Therapy in CRPC*, below). Choice of therapy is based largely on clinical considerations, which include patient preferences, prior treatment, presence or absence of visceral disease, symptoms, and potential side effects.

NCCN recommends that patients being treated for CRPC be closely monitored with radiologic imaging (ie, CT, bone imaging), PSA tests, and clinical exams for evidence of progression. Therapy should be continued until clinical progression or intolerability, with consideration of the fact that even in cases where PSA remains undetectable, bone imaging may reveal progression.[714,715] The sequential use of these agents is recommended in patients who remain candidates for further systemic therapy. The Panel also notes that Pan-cancer, tumor-agnostic treatments can be considered for patients with mCRPC who have actionable mutations. 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.[716,717] 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 ARPIs demonstrating efficacy in the non-metastatic CRPC and mCRPC settings dramatically changed the paradigm of CRPC treatment over the past two decades.

Abiraterone Acetate in mCRPC

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

docetaxel. This FDA approval in the post-docetaxel, mCRPC setting was based on the results of a phase 3, randomized, placebo-controlled trial (COU-AA-301) in patients with mCRPC previously treated with docetaxel-containing regimens.[718,719] 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).[719] Time to radiographic progression, PSA decline, and pain palliation also were improved by abiraterone.[719,720]

FDA approval in the pre-docetaxel setting occurred in December 2012, and was based on the randomized phase 3 COU-AA-302 trial of abiraterone and prednisone (n = 546) versus prednisone alone (n = 542) in patients with asymptomatic or minimally symptomatic, mCRPC.[721] 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 from 8.3 to 16.5 months with abiraterone (HR, 0.53; *P* < .001). OS was improved at final analysis with a median follow-up of 49.2 months (34.7 vs. 30.3 months; HR, 0.81; 95% CI, 0.70–0.93; *P* = .003).[722] Key secondary endpoints of time to symptomatic deterioration, time to chemotherapy initiation, time to pain progression, and PSA PFS improved significantly with abiraterone treatment; PSA declines (62% vs. 24% with >50% decline) and radiographic responses (36% vs. 16% RECIST responses) were more common.

The most common adverse reactions with abiraterone/prednisone (>5%) were fatigue (39%); back or joint discomfort (28%–32%); peripheral edema (28%); diarrhea, nausea, or constipation (22%); hypokalemia (17%); hypophosphatemia (24%); atrial fibrillation (4%); muscle discomfort (14%); hot flushes (22%); urinary tract infection; cough; hypertension (22%, severe hypertension in 4%); urinary frequency and nocturia; dyspepsia; or upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were increased aspartate aminotransferase and/or alanine aminotransferase (11%–12%), or cardiac disorders (19%, serious in 6%).

Based on the studies described here, abiraterone is a category 1, preferred option for mCRPC without prior ARPI therapy. It can also be considered in patients with mCRPC following progression on another ARPI, although other therapies are preferred in this setting.

In May 2018, the FDA approved a novel, fine-particle formulation of abiraterone, in combination with methylprednisolone, for the treatment of patients with mCRPC. In studies of healthy males, this formulation at 500 mg was shown to be bioequivalent to 1000 mg of the originator formulation.[723,724] In a phase 2 therapeutic equivalence study, 53 patients with mCRPC who were not treated previously with abiraterone, enzalutamide, radium-223, or chemotherapy (docetaxel for mCRPC 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.[725] 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 mCRPC (category 2A).

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 noninferiority study of 75 patients with mCRPC compared 1000 mg/day abiraterone after an overnight fast with 250 mg/day after a low-fat breakfast.[625] The primary endpoint was log change in PSA, with secondary endpoints of PSA response (≥50%) and PFS. The primary endpoint favored the low-dose arm (log change in PSA, -1.59 vs. -1.19), as did the PSA response rate (58% vs. 50%), with an equal PFS of 9 months in both arms. Noninferiority of the low dose was established according to the predefined criteria. Therefore, abiraterone can be given at 250 mg/day administered following a low-fat breakfast, as an alternative to the dose of 1000 mg/day after an overnight fast in patients who will not take or cannot afford the standard dose. The cost savings may reduce financial toxicity and improve adherence. Food impacts absorption unpredictably; therefore, 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 mCRPC

Switching from prednisone to dexamethasone 0.5 mg/day can be considered for patients with mCRPC with disease progression on either formulation of abiraterone. Trials show improved PSA responses and PFS and acceptable safety using this strategy.[726,727]

The SWITCH study was a single-arm, open-label, phase 2 study of this approach with 26 enrolled patients.[726] 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.[727] The primary endpoint of median PFS was 10.35 months, and PSA levels decreased or stabilized in 56% of patients after switching to dexamethasone.

Enzalutamide in M0 and M1 CRPC

In August 2012, the FDA approved enzalutamide, a next-generation antiandrogen, for treatment of patients with mCRPC who had received prior docetaxel chemotherapy. Approval was based on the results of the randomized, phase 3, placebo-controlled AFFIRM trial.[728,729] AFFIRM randomized 1199 patients to enzalutamide (160 mg daily) 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 were also 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 skeletal-related event (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. 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.[728,730]

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.[731,732] 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 vs. 5.4 months) and median OS (35.3 vs. 31.3 months). Improvements in all secondary endpoints were also observed (eg, the time until chemotherapy initiation or first SRE).

Thus, enzalutamide represents a category 1, preferred treatment option for patients with mCRPC without prior ARPI therapy. It can also be considered in patients with mCRPC with prior exposure to another ARPI, although other therapies are preferred in this setting.

The randomized, double-blind, placebo-controlled phase 3 PROSPER trial assessed the use of enzalutamide in 1401 patients with non-metastatic CRPC.[733] Patients with PSADT ≤10 months were stratified according to PSADT (<6 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 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 vs. 56.3 months; HR for death, 0.73; 95% CI, 0.61–0.89; $P = 0.001$).[734] 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.[735]

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

Patients receiving enzalutamide have no restrictions for food intake and concurrent prednisone is permitted but not required.[728]

Apalutamide in M0 CRPC

The FDA approved apalutamide for treatment of patients with non-metastatic CRPC in February 2018. This approval was based on the phase 3 SPARTAN trial of 1207 patients with M0 CRPC and PSADT ≤10 months.[736] Participants were stratified according to PSADT (>6 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 vs. 16.2 months; HR for metastasis or death, 0.28; 95% CI, 0.23–0.35; $P < .001$). Adverse events included rash (24% vs. 5.5%), fracture (11% vs. 6.5%), and hypothyroidism (8% vs. 2%). In a prespecified exploratory analysis of SPARTAN, health-related QOL was maintained in both the apalutamide and placebo groups.[737]

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 vs. 59.9 months; HR, 0.78; 95% CI, 0.64–0.96; $P = .016$).[738] 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 ≤10 months.

Darolutamide in M0 CRPC

The FDA approved darolutamide for treatment of patients with non-metastatic CRPC in July 2019. The phase 3 ARAMIS study randomized 1509 patients with M0 CRPC and PSADT ≤10 months 2:1 to darolutamide

(600 mg twice daily) or placebo.[739] Participants were stratified according to PSADT (>6 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 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).[740] 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%).[739]

Darolutamide is a category 1, preferred option for patients with M0 CRPC if PSADT is ≤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.[741-743] However, none of these strategies has been shown to prolong survival in randomized clinical trials. In the mCRPC setting, these options should only be used for select patients who are not candidates for other recommended mCRPC therapies.

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, mCRPC with prior progression on abiraterone.[744] BAT involves rapid cycling between high and low serum testosterone to disrupt the adaptive upregulation of the androgen receptor that occurs with low testosterone levels. Patients in the BAT arm received testosterone cypionate 400 mg intramuscularly once every 28 days. The PFS was 5.7 months in both arms (HR, 1.14; 95% CI, 0.83–1.55; *P* = .42). Crossover was allowed after disease progression, and OS was similar between the groups. BAT resulted in more favorable patient-reported QOL. The Panel awaits more data on this approach.

Chemotherapy, Immunotherapy, and Targeted Therapy for mCRPC

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

Docetaxel

Docetaxel was FDA-approved for mCRPC in May 2004. Two randomized phase 3 studies evaluated docetaxel-based regimens in symptomatic or rapidly progressive CRPC (TAX 327 and SWOG 9916).[590,745,746] TAX 327 compared docetaxel (every 3 weeks or weekly) plus prednisone to mitoxantrone plus prednisone in 1006 patients.[745] 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.[746] The SWOG 9916 study showed improved survival with docetaxel when combined with estramustine compared to mitoxantrone plus prednisone.[590]

Thus, docetaxel is a category 1 option for treatment of docetaxel-naïve mCRPC. It is the preferred option post-ARPI in patients without prior docetaxel exposure.

The standard regimen is 75 mg/m^2 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 mCRPC randomized to either every-2-week docetaxel or every-3-week docetaxel, each with maintenance of ADT and prednisone.[747] 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.

The duration of docetaxel therapy should be based on the assessment of benefit and toxicities. Treatment with ≥8 cycles of docetaxel may be associated with better OS than fewer cycles in the mCRPC setting.[748]

Retrospective analysis from the GETUG-AFU 15 trial suggests that docetaxel may benefit some patients with CRPC who received docetaxel in the CSPC setting.[749] Thus, the Panel believes that docetaxel can be given as a rechallenge after progression on an ARPI in the mCRPC setting if the patient's cancer did not demonstrate definitive evidence of progression on prior docetaxel therapy in either the castration-sensitive setting or the mCRPC setting.

Adverse events associated with docetaxel include neutropenia, leukopenia, febrile neutropenia, neutropenic infections, fluid retention, hypersensitivity reaction, hepatic function impairment, neuropathy, and other low-grade adverse events (eg, fatigue, nausea, vomiting, alopecia, diarrhea).

Cabazitaxel

In June 2010, the FDA approved cabazitaxel, a semi-synthetic taxane derivative, for patients with mCRPC previously treated with a docetaxel-containing regimen. An international randomized phase 3 trial (TROPIC) randomized 755 patients with progressive mCRPC to receive cabazitaxel 25 mg/m^2 or mitoxantrone 12 mg/m^2, each with daily prednisone.[750] 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 patients treated with cabazitaxel versus 1.3% of patients treated with mitoxantrone. The incidences of severe diarrhea (6%), fatigue (5%), nausea/vomiting (2%), anemia (11%), and thrombocytopenia (4%) also were higher in patients treated with cabazitaxel, 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.[751] 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.[752]

The multicenter CARD study was a randomized, open-label clinical trial that compared cabazitaxel with either abiraterone or enzalutamide in 255 patients with mCRPC who had previously received docetaxel and either abiraterone or enzalutamide.[753] 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.[754]

The phase 3 open-label, multinational, noninferiority PROSELICA study compared 20 mg/m^2 cabazitaxel with 25 mg/m^2 cabazitaxel in 1200 patients with mCRPC who progressed on docetaxel.[755] The lower dose was found to be noninferior to the higher dose for median OS (13.4 months [95% CI, 12.19–14.88] vs. 14.5 months [95% CI, 13.47–15.28]), and grade 3/4 adverse events were decreased (39.7% vs. 54.5%). In particular, grade ≥3 neutropenia rates were 41.8% and 73.3% for the lower and higher dose groups, respectively.

Results from the phase 3 FIRSTANA study suggest that cabazitaxel has clinical activity in patients with chemotherapy-naïve mCRPC.[756] Median OS, the primary endpoint, was similar between 20 mg/m^2 cabazitaxel, 25 mg/m^2 cabazitaxel, and 75 mg/m^2 docetaxel (24.5 months, 25.2 months, and 24.3 months, respectively). Cabazitaxel was associated with lower rates of peripheral sensory neuropathy than docetaxel, particularly at 20 mg/m^2 (12% vs. 25%). However, the Panel does not currently recommend cabazitaxel in docetaxel-naïve patients.

Based on these data, cabazitaxel is included in these Guidelines as a category 1, preferred option after exposure to docetaxel and an ARPI in patients with mCRPC. Cabazitaxel at 20 mg/m^2 every 3 weeks, with or without growth factor support, is the recommended dose for fit patients. Cabazitaxel at 25 mg/m^2 may be considered for healthy patients who opt for more aggressive treatment. Biweekly cabazitaxel at 16 mg/m^2 with prophylactic G-CSF is an option for patients ≥65 years based on results from the phase 3 CABASTY trial.[757] Using the lower dose significantly reduced the risk of neutropenia/neutropenic complications compared to the 25 mg/m^2 dose with G-CSF. Clinical outcomes were comparable between the 2 groups.

Cabazitaxel should be given with concurrent steroids (daily prednisone or dexamethasone on the day of chemotherapy). Physicians should follow current guidelines for prophylactic white blood cell growth factor use, particularly in this heavily pretreated 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.[758] 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 post-ARPI for fit patients with aggressive variant mCRPC (visceral metastases, low PSA and bulky disease, high lactate dehydrogenase [LDH], high carcinoembryonic antigen [CEA], lytic bone metastases, and neuroendocrine prostate cancer [NEPC] histology) or unfavorable genomics (defects in at least 2 of *PTEN*, *TP53*, and *RB1*). This recommendation is based on a phase 1–2, open label, randomized study.[759] In the phase 2 portion, 160 patients were randomized to receive cabazitaxel alone or with carboplatin, and the primary endpoint was investigator-assessed PFS. In the ITT population, median PFS was 4.5 months in the cabazitaxel arm versus 7.3 months in the cabazitaxel/carboplatin arm (HR, 0.69; 95% CI, 0.50–0.95; P = .018). The most common grade 3–5 adverse events (fatigue, anemia, neutropenia, and thrombocytopenia) were all more common in the combination arm. Post-hoc analyses showed that patients with aggressive variant disease had a longer median PFS in the combination arm than the cabazitaxel arm (7.5 vs. 1.7 months; P = .017). Patients without aggressive variant tumors, on the other hand, had similar median PFS regardless of treatment (6.5 vs. 6.3 months; P = .38).

Sipuleucel-T

In April 2010, sipuleucel-T became the first in a new class of cancer immunotherapeutic agents to be approved by the FDA. This autologous cancer "vaccine" involves collection of the white blood cell fraction-containing, antigen-presenting cells from each patient; exposure of the cells to the prostatic acid phosphatase-granulocyte macrophage colony-stimulating factor (PAP-GM-CSF recombinant fusion protein); and subsequent reinfusion of the cells. The pivotal study was a phase 3, multicenter, randomized, double-blind trial (D9902B).[760] Five hundred twelve patients with minimally symptomatic or asymptomatic mCRPC 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 mCRPC, PROCEED, enrolled 1976 patients from 2011 to 2017, who were followed for a median of 46.6 months.[761] 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 included in these Guidelines as an option for asymptomatic patients with mCRPC regardless of prior ARPI or docetaxel, although the Panel notes that the data supporting its use post-docetaxel is limited. Benefit of sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. Sipuleucel-T is also not recommended for patients with small cell prostate cancer/NEPC. The Panel prefers that sipuleucel-T be used as a therapy for asymptomatic or minimally symptomatic patients with mCRPC, so that disease burden is lower and immune function is potentially more intact. Patients should have good performance level (ECOG 0–1), estimated life expectancy >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.

Pembrolizumab

The FDA approved the tumor-agnostic use of pembrolizumab, an anti-PD-1 antibody, for treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors who have progressed on prior treatment and who have no satisfactory alternative treatment options in May 2017. This approval was based on the treatment of 149 patients across five clinical studies involving MSI-H or dMMR colorectal (n = 90) or non-colorectal (n = 59) cancer for an objective response rate of 40% (59/149).[730] All patients received ≥1 prior regimen. Among the non-colorectal cohorts, two patients had mCRPC: one achieved a partial objective response, and the other achieved stable disease for >9 months.

Outcomes of additional patients with mCRPC treated with pembrolizumab have been reported.[72,762-766] 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.[762] Some of the patients also had experienced disease progression on additional therapies (docetaxel for CSPC, abiraterone, and/or sipuleucel-T). Three of the 10 patients showed a near complete PSA response. Two of these three patients had radiographically measurable disease and achieved a partial radiographic

response (including a response in liver metastases). Of the remaining patients, three showed stable disease, and four displayed no evidence of clinical benefit. Genetic analysis of biopsy tissue revealed that one patient whose disease showed PSA response had an MSI-H tumor, whereas the other patient with responsive disease and two with non-responsive disease did not. The nonrandomized phase Ib KEYNOTE-028 trial included 23 patients with advanced, progressive prostate cancer, of whom 74% had received ≥2 previous therapies for metastatic disease.[764] 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 mCRPC and prior treatment with docetaxel and at least one ARPI that assessed pembrolizumab in patients regardless of MSI status.[767] Cohorts 1 and 2 included patients with programmed cell death ligand 1 (PD-L1)–positive (n = 133) and PD-L1–negative (n = 66) prostate cancer, respectively. Cohort 3 included those with bone-predominant disease with positive or negative PD-L1 expression (n = 59). The primary endpoint of overall response rate (ORR) was 5% (95% CI, 2%–11%) in cohort 1 and 3% (95% CI, <1% to 11%) in cohort 2. Responses were durable (range, 1.9 to ≥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 includes pembrolizumab as an option for patients with MSI-H or dMMR mCRPC (category 2B). The prevalence of MMR deficiency in metastatic CPRC is estimated at 2% to 5%,[36,763,768] 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 tumor-agnostic use in patients with unresectable or metastatic TMB-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Results from prospective biomarker analysis of the multicohort, non-randomized, open-label, phase 2 KEYNOTE-158 trial support this approval, but this trial did not include any patients with prostate cancer.[769] One retrospective study found that 1.5% of patients with prostate cancer had TMB-H tumors.[768] Of those patients, 8 had received an immune checkpoint inhibitor; 4 patients (50%) experienced a reduction in PSA of ≥50% that lasted at least 1 week. The Panel therefore notes that pembrolizumab may be associated with some benefit in patients with mCRPC and TMB ≥10 mut/Mb.

Mitoxantrone

Two randomized trials assessed the role of mitoxantrone in patients with mCRPC.[770,771] 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 mCRPC who cannot tolerate other therapies after disease progression on prior docetaxel and an ARPI.

Treatment Options for Patients with DNA Repair Gene Mutations

Early studies suggest germline and somatic mutations in HRR genes (eg, *BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2*) may be predictive of the clinical benefit of poly-ADP ribose polymerase (PARP) inhibitors.[772-774] PARP inhibitors are oral agents that exert their activity through the concept of synthetic lethality.[775] PARP inhibitor therapy options are discussed below.

DNA repair defects have also been reported to be predictive for sensitivity to platinum agents in CRPC and other cancers.[776-780] Platinum agents have shown some activity in patients with CRPC without molecular selection.[781] Studies of platinum agents in patients with CRPC that have DNA repair gene mutations are needed.

Results of one study suggested that patients with mCRPC and germline mutations in DNA repair genes may have better outcomes if treated with abiraterone or enzalutamide than with taxanes.[44] However, it should be noted that the response in patients with mCRPC and HRR gene mutations to standard therapies is similar to the response in patients without mutations.[782,783]

Patients with *CDK12* mutations tend to have aggressive disease, with high rates of metastases and short OS. Their disease also does not respond well to hormonal therapy, PARP inhibitors, or taxanes. Two large, multi-institutional, retrospective studies have shown that 11% to 33% of patients with mCRPC and *CDK12* mutations experienced disease response to PD-1 inhibitors (ie, nivolumab, pembrolizumab), some with durable responses.[784,785] There are also limited data from phase 2 trials indicating that ipilimumab plus nivolumab may have some activity against *CDK12*-mutated mCRPC.[786,787] 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.[773,774,788] 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).[789] Patients were required to have a somatic or germline HRR gene mutation, and were allocated to one of two cohorts: cohort A comprised patients with *BRCA1/2* or *ATM* mutations, and cohort B comprised patients with a mutation in at least one of 12 other HRR genes (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, or *RAD54L*). The primary endpoint of improving radiographic PFS with olaparib versus abiraterone/enzalutamide was met in cohort A (HR, 0.34; 95% CI, 0.25–0.47; $P < .001$), and radiographic PFS was also superior in the entire study population encompassing cohorts A+B (HR, 0.49; 95% CI, 0.38–0.63; $P < .001$).

In addition, final 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.[790]

The Panel notes that there may be heterogeneity of response to olaparib based on which gene has a mutation. Efficacy in PROfound appears to be driven by the cohort of patients with at least one alteration in *BRCA2*, *BRCA1*, or *ATM*, and in particular by patients with *BRCA2* or *BRCA1* mutations based on exploratory gene-by-gene analysis.[790] Patients with *BRCA2* mutations in PROfound experienced an OS benefit with olaparib (HR, 0.59; 95% CI, 0.37–0.95), whereas the HR for OS in patients with *ATM* mutations was 0.93 (95% CI, 0.53–1.75).[790] 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.[789] Patients with *PPP2R2A* mutations in PROfound experienced an unfavorable risk-benefit profile.

As a result of the favorable efficacy data from the PROfound trial, the FDA approved olaparib (300 mg twice daily) in May 2020 for use in patients with 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.

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.[789]

Since some patients in PROfound had prior taxane therapy, olaparib use might be reasonable in patients with mCRPC before or after docetaxel treatment. The Panel therefore recommends olaparib as an option for patients with mCRPC, previous ARPI, and an HRRm regardless of prior docetaxel therapy. 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*. Olaparib is included in the Guidelines as a category 1 recommendation for BRCAm mCRPC and is a preferred option for these patients if they have not yet received docetaxel.

Any commercially available analytically and clinically validated somatic tumor and germline assays can be used to identify patients for treatment. The Panel strongly recommends a metastatic biopsy for histologic and molecular evaluation; a plasma circulating tumor DNA (ctDNA) assay can be used if a metastatic biopsy is unsafe or not feasible.

Careful monitoring of complete blood counts and hepatic and renal function, along with type and screens and potential transfusion support and/or dose reductions as needed for severe anemia or intolerance are recommended during olaparib therapy.

Rucaparib

Rucaparib is another PARP inhibitor approved for use in patients with mCRPC. 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 an ARPI plus one taxane chemotherapy, were treated with rucaparib 600 mg twice daily.[791] The primary endpoint of TRITON2 was the objective response rate in patients with measurable disease, and was 43.5% (95% CI, 31.0%–56.7%) in this *BRCA1/2*-mutated population. Median radiographic PFS, a key secondary endpoint, was 9.0 months (95% CI, 8.3–13.5 months). The most common adverse events were asthenia/fatigue, nausea, and anemia/decreased hemoglobin, with grade ≥3 anemia/decreased hemoglobin in 25.2% of participants. Final analysis of TRITON2 confirmed results of the earlier analysis.[792]

In the randomized phase 3 TRITON3 study, patients with mCRPC and a germline or somatic *BRCA1/2* or *ATM* mutation who have previously received an ARPI but no chemotherapy for mCRPC were randomized 2:1 to rucaparib versus physician's choice of therapy (abiraterone, enzalutamide, or docetaxel).[793] The primary endpoint of TRITON3, the

median duration of imaging-based PFS, was significantly longer at 62 months in the group of 270 participants assigned to receive rucaparib than in the 135 participants who received a control medication (10.2 vs. 6.4 months; HR, 0.61; 95% CI, 0.47–0.80; $P < .001$). This effect was also seen in the 201 patients and 101 patients in each group with a *BRCA*m (11.2 vs. 6.4 months; HR, 0.50; 95% CI, 0.36–0.69). For those with *ATM* mutations, an exploratory analysis suggested a possible improvement as well (8.1 vs. 6.8 months; HR, 0.95; 95% CI, 0.59–1.52). As in TRITON2, the most frequent adverse events with rucaparib were fatigue and nausea.

The Panel recommends rucaparib as an option for patients with mCRPC, a *BRCA1* or *BRCA2* mutation, and prior treatment with an ARPI. It is a category 1, preferred option pre-docetaxel. Rucaparib should not be used in patients with HRR gene mutations other than *BRCA1/2*.[794] 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.[791,794]

The preferred method of selecting patients for rucaparib treatment is somatic and germline analysis of *BRCA1* and *BRCA2* from a metastatic biopsy. A ctDNA sample can be used if biopsy is unsafe or not feasible.

As with olaparib, careful monitoring of complete blood counts and hepatic and renal function, along with type and screens and potential transfusion support and/or dose reductions as needed for severe anemia or intolerance are recommended during treatment with rucaparib.

Olaparib Plus Abiraterone

Pre-clinical data suggest that PARP-1 promotes androgen receptor activity.[795] Additional pre-clinical data show that androgen receptor inhibitors can down-regulate DNA repair genes, creating a situation similar to that of HRR mutation.[796,797] These results suggest that the combination of PARP inhibition with androgen receptor inhibition may have an enhanced antitumor effect and that this effect may not be limited to patients with HRR mutations. In fact, a randomized phase 2 trial showed that the combination of abiraterone with olaparib increased radiographic PFS over abiraterone and placebo in patients with mCRPC regardless of HRR status (ITT population: HR, 0.65; 95% CI, 0.44–0.97; $P = .034$).[774]

The PROpel trial was an international, double-blind, phase 3 trial comparing abiraterone and olaparib with abiraterone and placebo in 796 patients with mCRPC regardless of HRR mutation status.[798] Prior docetaxel in the localized or mCSPC setting was allowed, but patients were untreated for CRPC. The primary endpoint, imaging-based PFS by investigator assessment in the ITT population, was significantly longer in the abiraterone/olaparib group than in the abiraterone/placebo group (24.8 vs. 16.6 months; HR, 0.66; 95% CI, 0.54–0.81; $P < .001$). HRR mutations were identified in tumors of 226 patients; 552 patients did not have HRR tumor mutations. The HR for the primary endpoint in those with HRR mutations was 0.50 (95% CI, 0.34–0.73). The safety profile of the olaparib/abiraterone combination was as expected based on the known safety profiles of the individual drugs, with the most common adverse events being anemia, fatigue/asthenia, and nausea.

Final OS data from PROpel showed that OS was not significantly improved with the abiraterone/olaparib combination therapy in the full cohort after a median follow up of approximately 36.5 months (42.1 vs 34.7 months; HR, 0.81; 95% CI, 0.67–1.00; $P = .054$).[799] In a post-hoc exploratory analysis, the BRCAm population saw an OS benefit, with a median OS of 23.0 months in the abiraterone arm and not reached in the combination arm (HR, 0.29; 95% CI, 0.14–0.56). A smaller OS benefit was

seen in the HRRm group overall, and no OS benefit was evident in the non-HRRm and the non-BRCAm/other HRRm subgroups.

In May 2023, the FDA approved the combination of olaparib with abiraterone for the treatment of adult patients with BRCAm mCRPC. Based on the results of PROpel, olaparib/abiraterone is included in the NCCN Guidelines as an option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet received an ARPI (category 1).

Talazoparib Plus Enzalutamide

Talazoparib is another PARP inhibitor; it has had an FDA indication in breast cancer. The open-label, international phase 2 TALAPRO-1 trial included 127 patients with an HRR mutation and progressive, mCRPC, all of whom received at least one dose of talazoparib.[800] The objective response rate after a median follow-up of 16.4 months was 29.8% (95% CI, 21.2–39.6). The most common grade 3–4 treatment-emergent adverse events were anemia (31%), thrombocytopenia (9%), and neutropenia (8%).

As noted above (see *Olaparib Plus Abiraterone*), pre-clinical data suggest that the PARP inhibition combined with androgen receptor inhibition may have an enhanced antitumor effect that may not be limited to those with HRR mutations. The randomized, double-blind, phase 3 TALAPRO-2 study compared enzalutamide plus talazoparib with enzalutamide plus placebo in 805 patients with untreated mCRPC.[801] HRR gene alteration status and treatment with docetaxel and/or abiraterone in the castration-sensitive setting were used to stratify the randomization. The primary endpoint was radiographic PFS in the ITT population. At the planned primary analysis, median radiographic PFS was not reached (95% CI, 27.5 months–not reached) for the talazoparib group and was 21.9 months (95% CI, 16.6–25.1) for the control group (HR, 0.63; 95% CI, 0.51–0.78; $P < .0001$).

HRR mutations were present in 21% of TALAPRO-2 participants, with *BRCA* alterations being the most common.[801] The HR for radiographic PFS in the HRR-deficient subgroup was more strongly in favor of the talazoparib combination than in the HRR-proficient/unknown population (0.46 [95% CI, 0.30–0.70; $P = .0003$] vs. 0.70 [95% CI, 0.54–0.89; $P = .0039$]). Among HRR mutations, talazoparib conferred a 77% lower risk of radiographic progression or death in those with tumor mutations in *BRCA1* or *BRCA2* (HR, 0.23; 95% CI, 0.10–0.53; $P = .0002$), whereas the corresponding reduction was 34% (HR, 0.66; 95% CI, 0.39–1.12; $P = .12$) in those with non-*BRCA* HRR alterations.

Prior therapy also affected the radiographic PFS outcomes in this trial.[801] In the 179 participants in TALAPRO-2 who had received docetaxel in earlier disease settings, the HR for radiographic PFS was 0.51 (95% CI, 0.32–0.81; $P = .0034$). In the small population of 50 participants in the ITT population who had received prior novel hormonal therapy, the corresponding HR was non-significant at 0.57 (95% CI, 0.28–1.16; $P = .12$).

Final results from an HRRm-only cohort of TALAPRO-2 at a median follow-up of 44.2 months showed that median OS was improved with the combination compared with enzalutamide alone (45.1 vs. 31.1 months; HR, 0.62; 95% CI, 0.48–0.81; two-sided $P = .0005$).[802] Median radiographic PFS was also improved with the talazoparib/enzalutamide group compared with the enzalutamide group (30.7 vs. 12.3 months; HR, 0.47; 95% CI, 0.36–0.61; $P < .0001$).

The safety profile of enzalutamide plus talazoparib was consistent with the known safety profiles of the individual drugs, with the most common adverse events in those who received talazoparib being anemia, neutropenia, and fatigue. However, hematologic adverse events were of higher grades and occurred more frequently than would be expected with talazoparib alone. Overall, the combination had significant toxicity, with

dose interruption due to adverse events in 75% of participants in the talazoparib group compared with 23% in the placebo group. Dose reductions due to adverse events occurred in 56% and 7% of the talazoparib and placebo groups, respectively.

Based on the results from the first TALAPRO-2 cohort, the FDA approved talazoparib plus enzalutamide for HRRm mCRPC in June 2023. The Panel includes talazoparib plus enzalutamide as a category 1 treatment option for patients with mCRPC and a pathogenic mutation (germline and/or somatic) in one of certain HRR and other DNA repair genes (*BRCA1, BRCA2, ATM, ATR, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2*, or *RAD51C*) who have not yet had treatment with an ARPI. Use of talazoparib/enzalutamide for those who have received prior ARPI therapy without prior docetaxel is controversial (category 2B) because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting, but responses are likely.

Niraparib Plus Abiraterone

Another PARP inhibitor, niraparib, has also been studied in combination with androgen inhibition in the setting of mCRPC. The randomized, double-blinded phase 3 MAGNITUDE trial compared niraparib plus abiraterone to placebo plus abiraterone in 423 patients with mCRPC and HRR mutations and an additional 247 patients without HRR mutations.[803] Prior chemotherapy and novel hormonal therapy were allowed in the mCSPC or M0 CRPC settings, and were received by 3.1% and 20.1% of the total HRRm cohort, respectively.

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

A second interim analysis of MAGNITUDE included a prespecified, inverse probability censoring weighting analysis of OS, which was designed to account for the receipt of subsequent therapies, including PARP inhibitors.[804] Results of this analysis suggest that there may be an OS benefit for the combination therapy (HR, 0.54; 95% CI, 0.33–0.90; nominal $P = .0181$).

The incidence of grade 3/4 adverse events was higher with the combination of niraparib plus abiraterone compared with placebo and abiraterone (67.0% vs. 46.4%).[803] Anemia (28.3% vs. 7.6%) and hypertension (14.6% vs. 12.3%) were the most reported grade ≥3 adverse events. Overall, the combination was tolerable and QOL was maintained.

Based on these results, the FDA approved niraparib plus abiraterone for the treatment of patients with BRCAm mCRPC in August 2023. The Panel includes niraparib plus abiraterone as a treatment option for patients with mCRPC and a pathogenic *BRCA1* or *BRCA2* mutation (germline and/or somatic) who have not yet had treatment in the setting of mCRPC. This is a category 1 recommendation for those without prior ARPI. Use of niraparib/abiraterone for those who have received a prior ARPI without prior docetaxel is controversial (category 2B) because a benefit of this combination over use of a PARP inhibitor alone has not been shown in this setting.

Radiopharmaceuticals for mCRPC

Lutetium Lu 177 vipivotide tetraxetan

Lu-177-PSMA-617 is a radiopharmaceutical that is administered intravenously and is indicated for PSMA-positive mCRPC that has been treated with androgen receptor pathway inhibition and taxane-based chemotherapy. The active moiety is a radionuclide that delivers radiation to PSMA-expressing and surrounding cells, which induces DNA damage and leads to cell death. The approval of Lu-177-PSMA-617 was based on the international, open-label phase III VISION trial of 831 patients with mCRPC and PSMA-positive metastatic lesions. Patients in VISION were previously treated with at least one androgen receptor-directed therapy and one or two taxane-based chemotherapy regimens.[805] Patients had at least one PSMA-positive metastatic lesion and no PSMA-negative lesions determined by Ga-68 labeled PSMA-11 PET/CT imaging. Patients were randomized in a 2:1 ratio to receive standard of care (abiraterone, enzalutamide, bisphosphonates, RT, denosumab, and/or glucocorticoids) and Lu-177-PSMA-617 (7.4 GBq or 200 mCi every 6 weeks for 4–6 cycles) or standard of care alone.

The median OS was improved in the Lu-177-PSMA-617 group compared to the control group (15.3 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 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. [805]

The FDA approved Lu-177-PSMA-617 in the post-ARPI setting in March 2022.

Another randomized controlled phase 3 trial, PSMAfore, assessed the efficacy of Lu-177-PSMA-617 pre-docetaxel in 468 patients with mCRPC who experienced disease progression on an ARPI.[806] The primary endpoint of rPFS in the ITT population was improved with Lu-177-PSMA-617 compared with a change in ARPI. At a median of 24.1 months after randomization, median radiographic PFS was 11.6 months in the Lu-177-PSMA-617 group versus 5.6 months in the control group (HR 0.49; 95% CI, 0.39–0.61). There was no difference in OS, but OS data are difficult to interpret because patients were allowed to crossover from an ARPI change to Lu-177-PSMA-617 upon radiographic progression, and 57% of patients in the control arm did so. Importantly, there were fewer grade 3–5 toxicities in Lu-177-PSMA-617 arm.

Based on the results of the PSMAfore trial, the FDA expanded the indication for Lu-177-PSMA-617 to include adult patients with PSMA-positive mCRPC who have progressed after ARPI therapy and are considered appropriate candidates for delaying taxane-based chemotherapy.

The NCCN Panel recommends Lu-177-PSMA-617 as a treatment option for patients with one or more PSMA-positive lesion and/or metastatic disease that is predominately PSMA-positive and with no dominant PSMA-negative metastatic lesions who have been treated previously with an ARPI and a taxane-based chemotherapy (category 1) or who have prior ARPI therapy and are considered appropriate to delay 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 Panel notes that Ga-68 PSMA-11, F-18 piflufolastat PSMA, or F-18 flotufolastat PSMA can be used to identify patients eligible for treatment with Lu-177–PSMA-617.

Radium-223

In May 2013, the FDA approved radium-223 dichloride, an alpha particle-emitting radioactive agent. This first-in-class radiopharmaceutical was approved for treatment of mCRPC 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.[807] 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 vs. 11.3 months; HR, 0.70; 95% CI, 0.058–0.83; $P < .001$) and prolonged time to first SRE (median 15.6 vs. 9.8 months). Preplanned subset analyses showed that the survival benefit of radium-223 was maintained regardless of prior docetaxel use.[808] ITT analyses from ALSYMPCA showed that radium-223 also may reduce the risk of symptomatic SREs.[809] Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), likely due to the short range of radioactivity.[807] 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.[810]

The multicenter, international, double-blind, placebo-controlled, phase 3 ERA 223 trial randomized patients with bone-metastatic chemotherapy-naïve CRPC to abiraterone with or without radium-223.[811] The patients were asymptomatic or mildly symptomatic. The primary endpoint of symptomatic skeletal event-free survival in the ITT population was not met. In fact, the addition of radium-223 to abiraterone was associated with an increased frequency of bone fractures compared with placebo.

The randomized PEACE-3 trial also compared radium-223 with or without an ARPI in patients who were ARPI-naive.[812] Radium-223 with enzalutamide was compared with enzalutamide therapy alone in 446 patients with mildly symptomatic mCRPC. The use of bone-protecting agents (denosumab or zoledronic acid) was made mandatory following results from ERA 223. The primary endpoint of radiological PFS was improved in the combination arm compared with enzalutamide alone (16.4 vs. 19.4 months; HR, 0.69; 95% CI, 0.54–0.87; $P = .0009$). At a preplanned interim OS analysis, median OS was also improved with the addition of radium-223 (35.0 vs. 42.3 months; HR, 0.69; 95% CI 0.52–0.90; $P = .0031$). Grade ≥3 adverse events occurred more commonly in the combination arm (65.6% vs. 55.8%) and included hypertension (in 34% of the combination arm), fatigue (6%), fracture (5%), anemia (5%), and neutropenia (5%). Fractures were also more common in the combination arm (24.3% vs. 13.4%).

In an earlier safety analysis of PEACE-3, the cumulative incidence of fractures at 1.5 years in patients who received a bone-protecting agent was 2.8% in participants receiving radium-223 plus enzalutamide and 3.9% in those receiving enzalutamide alone.[813] In the absence of bone agents, these numbers were 45.9% and 22.3%, respectively. This result suggests that radium-223 combined with an ARPI may be safe if preventive administration of a bone agent is used.

Radium-223 is a category 1 option to treat symptomatic bone metastases without visceral metastases in patients with mCRPC regardless of prior therapy. Radium-223 plus enzalutamide is included as an option for patients with bone-metastatic CRPC without prior exposure to an ARPI. Hematologic evaluation should be performed according to the FDA label before treatment initiation and before each subsequent dose.[730] Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial has the potential for additive myelosuppression.[730] Its use

in combination with docetaxel or any other systemic therapy except ADT or enzalutamide should be pursued with caution. It should not be used in patients with visceral metastases. All patients receiving radium-223 should be given concomitant denosumab or zoledronic acid.

MDT for mCRPC

Although most data supporting the use of MDT for oligometastatic prostate cancer is in the oligorecurrent CSPC setting, as discussed in detail above (see *MDT for Oligometastatic CSPC*), MDT has also been studied in the oligoprogressive CRPC. As noted above, the EXTEND trial included 7 patients with oligoprogressive CRPC, although results of MDT in this subset specifically were not reported.[708]

ARTO is a phase 2 study that included 157 patients with CRPC and 1 to 3 metastatic lesions who were randomized to receive abiraterone alone or abiraterone with MDRT.[706] The rate of biochemical response (defined as a ≥50% decrease in PSA levels at 6 months compared to baseline), which was the primary endpoint, was 92% in the MDRT group compared with 68.3% in the control group (OR, 4.22; 95% CI, 2.12–8.38; $P < .001$). PFS, a secondary endpoint was also improved with the use of MDRT (HR, 0.35; 95% CI, 0.21–0.57; $P < .001$). A subgroup analysis of ARTO further suggested that MDRT for oligoprogressive mCRPC may result in similar PFS as second-line systemic therapy.[814]

Initial results from the phase 2 GROUQ-PCS-9 were presented at the 2025 ASCO Genitourinary Cancers Symposium.[815] MDRT added to ADT and enzalutamide in oligometastatic CRPC (with 1–5 metastases) led to improvements in radiological PFS, biochemical PFS, and time to next line of therapy compared to ADT with enzalutamide alone.

The Panel includes MDT with mCRPC systemic therapy as an option for patients with oligometastatic or oligoprogressive CRPC regardless of prior therapy.

Small Cell/Neuroendocrine Prostate Cancer

De novo small cell carcinoma in untreated prostate cancer occurs rarely and is very aggressive.[816] Treatment-associated small cell prostate cancer/NEPC that occurs in patients with mCRPC is more common.[817] In a multi-institution prospective series of 202 consecutive patients with mCRPC, all of whom underwent metastatic biopsies, small cell/neuroendocrine histology was present in 17% of patients.[817] Patients with small cell/neuroendocrine tumors and prior abiraterone and/or enzalutamide had a shorter OS when compared with those with adenocarcinoma and prior abiraterone and/or enzalutamide (HR, 2.02; 95% CI, 1.07–3.82). Genomic analysis showed that DNA repair mutations and small cell/neuroendocrine histology were almost mutually exclusive.

Small cell/neuroendocrine carcinoma of the prostate should be considered in patients with disease that no longer responds to ADT and who test positive for metastases. These relatively rare tumors are associated with low PSA levels despite large metastatic burden and visceral disease.[818] Those with initial Grade Group 5 are especially at risk. Biopsy of accessible metastatic lesions to identify patients with small cell/neuroendocrine histomorphologic features is recommended in patients with mCRPC.

These patients may be treated with cytotoxic chemotherapy (ie, cisplatin/etoposide, carboplatin/etoposide, docetaxel/carboplatin, cabazitaxel/carboplatin).[759,819,820] Physicians should consult the NCCN Guidelines for Small Cell Lung Cancer for additional options in the first and subsequent lines of therapy (available at www.NCCN.org), because the behavior of small cell/neuroendocrine carcinoma of the prostate is similar to that of small cell carcinoma of the lung.

Additional Treatment Options for Bone Metastases

In a multicenter study, 643 patients with CRPC and asymptomatic or minimally symptomatic bone metastases were randomized to intravenous zoledronic acid every 3 weeks or placebo.[821] 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 vs. 321 days; *P* = .01).[822] No significant differences were found in OS. Other bisphosphonates have not been shown to be effective for prevention of disease-related skeletal complications.

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.[823] 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.[824] 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 noninferiority; *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).

Therefore, denosumab every 4 weeks (category 1, preferred) or zoledronic acid every 3 to 4 weeks is recommended for patients with CRPC and bone metastases to prevent or delay disease-associated SREs. SREs include pathologic fractures, spinal cord compression, operation, or EBRT to bone. The optimal duration of zoledronic acid or denosumab in patients with CRPC and bone metastases remains unclear. A multi-institutional, open-label, randomized trial in 1822 patients with bone-metastatic prostate cancer, breast cancer, or multiple myeloma found that zoledronic acid every 12 weeks was noninferior to zoledronic acid every 4 weeks.[825] In the every-12-week and every-4-week arms, 28.6% and 29.5% experienced at least 1 SRE within 2 years of randomization, respectively.

Use of zoledronic acid in patients with CSPC and bone metastases is not associated with lower risk for SREs.[826] Therefore, the routine use of these agents in bone-metastatic CSPC is not recommended. Bone antiresorptive agents should, however, be used for SRE prevention in patients with CSPC if they have treatment-related bone loss (see *Principles of Survivorship, Bone Health in Prostate Cancer*, in the algorithm above).

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.[827] Most, but not all, patients who develop ONJ have preexisting dental problems.[828] If invasive dental surgery is necessary, therapy should be deferred until the dentist confirms that the patient has healed completely from the dental procedure. Supplemental calcium and vitamin D are recommended to prevent hypocalcemia in patients receiving either denosumab or zoledronic acid.

Monitoring of creatinine clearance is required to guide dosing of zoledronic acid. Zoledronic acid should be dose reduced in patients with impaired

renal function (estimated creatinine clearance 30–60 mL/min) and held for creatinine clearance <30 mL/min. Denosumab may be administered to patients with impaired renal function or even patients on hemodialysis; however, the risk for severe hypocalcemia and hypophosphatemia is greater, and the dose, schedule, and safety of denosumab have not yet been defined. A single study of 55 patients with creatinine clearance <30 mL/min or on hemodialysis evaluated the use of 60-mg-dose denosumab.[730] 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 in patients with mCRPC without visceral metastases (see *Radium-223*, above). The use of palliative RT is also an option.

Clinical research on the prevention or delay of disease spread to bone continues. A phase 3 randomized trial of 1432 patients with non-metastatic CRPC at high risk of bone involvement showed that denosumab delayed bone metastasis by 4 months compared to placebo.[829] OS was not improved, and the FDA did not approve denosumab for the prevention of bone metastases.

Considerations for Visceral Metastases

The panel defines visceral metastases as those occurring in the liver, lung, adrenal gland, peritoneum, or brain. Soft tissue/lymph node sites are not considered visceral metastases. In general, there are fewer data on treatment of patients with CRPC and visceral metastases than for those without visceral metastases.

Sequencing of Therapy in CRPC

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

After abiraterone or enzalutamide, data suggest that giving the alternate ARPI may not be the optimal strategy considering the availability of other treatment options, including chemotherapy. The CARD trial, for instance, showed that treatment with cabazitaxel significantly improved clinical outcomes over enzalutamide or abiraterone in patients with mCRPC who had been previously treated with docetaxel and the alternate hormonal therapy (abiraterone or enzalutamide).[753] Furthermore, data suggest cross-resistance between abiraterone and enzalutamide.[830-833] Results of a randomized, open-label, phase 2, crossover trial suggest that the sequence of abiraterone followed by enzalutamide may be more efficacious than the reverse.[834]

Some data inform the sequencing of therapies in patients with PSMA-positive mCRPC. The multicenter, unblinded, randomized phase 2 TheraP trial compared PSA response after Lu-177-PSMA-617 versus cabazitaxel in 200 patients with PSMA-positive mCRPC who previously received docetaxel.[835] Prior androgen receptor-directed therapy was permitted. Among the ITT population, the PSA response rate was 66% in the Lu-177-PSMA-617 arm compared with 37% in the cabazitaxel arm (difference 29%; 95% CI, 16–42; $P < .0001$). These numbers were 66% and 44%, respectively, in those who received treatment (difference 23%; 95% CI, 9–37; $P = .0016$). Furthermore, grade 3–4 adverse events were less frequent in the Lu-177-PSMA-617 arm than in the cabazitaxel arm (33% vs. 53%). Results from the phase 3 PSMAfore trial as discussed above (see *Lutetium Lu 177 vipivotide tetraxetan*) showed that Lu-177-PSMA-617 improved rPFS compared with switching to a different ARPI in docetaxel-naïve patients.[806]

Data for patients with HRRm mCRPC are more limited, but comparative effectiveness research suggests that olaparib may result in superior

radiographic PFS than cabazitaxel in patients with *BRCA1* or *BRCA2* mutations and prior treatment with docetaxel.[836] Furthermore, data from PROfound and TRITON3 suggest that a PARP inhibitor is preferred over a different ARPI in patients with BRCAm mCRPC and prior ARPI exposure.[789,793]

No chemotherapy regimen has demonstrated improved survival or QOL after cabazitaxel or cabazitaxel/carboplatin in patients with mCRPC of adenocarcinoma histology, 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).[837-846] No survival benefit for any these combination regimens over sequential single-agent regimens has been demonstrated, and toxicity is higher. Treatment with these regimens could be considered after an informed discussion between the physician and an individual patient about treatment goals and risks/side effects and alternatives, which must include best supportive care. In patients not able to receive life prolonging therapy, prednisone and dexamethasone at low doses may provide palliative benefits.[847] Participation in a clinical trial is encouraged.

Summary

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

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

Test	Platform	Populations Studied	Outcome(s) Reported (Test independently predicts)	Selected References	Molecular Diagnostic Services Program (MolDX) Recommendations
Decipher	Whole-transcriptome 1.4M RNA expression (46,050 genes and noncoding RNA) oligonucleotide microarray optimized for FFPE tissue	Post radical prostatectomy (RP), adverse pathology/high-risk features	• Metastasis • Prostate cancer-specific mortality • Postoperative radiation sensitivity (PORTOS)	148,151,152,563,848-861	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	862-865	Not recommended
		Biopsy, low- to intermediate-risk treated with RP	• Non-organ-confined pT3 or Grade Group ≥4 disease on RP		
Oncotype DX Prostate	Quantitative RT-PCR for 12 prostate cancer-related genes and 5 housekeeping controls	Biopsy, very-low- to high-risk treated with RP	• Non-organ-confined pT3 or Grade Group 4 disease on RP • Biochemical recurrence • Metastases • Prostate cancer-specific mortality	150,866,867	Cover post-biopsy for NCCN very-low-, low-risk, and favorable intermediate-risk prostate cancer in patients with at least 10 years life expectancy who have not received treatment for prostate cancer and are candidates for active surveillance or definitive therapy
Prolaris	Quantitative RT-PCR for 31 cell cycle-related genes and 15 housekeeping controls	Biopsy, conservatively managed (active surveillance)	• Prostate cancer-specific mortality	143-146,868-870	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	871-875	Not recommended
		RP, high-risk localized disease	• Biochemical recurrence		

References

1. Siegel RL, Kratzer TB, Giaquinto AN, et al. Cancer statistics, 2025. CA Cancer J Clin 2025;75:10–45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39817679.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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;199:676–682. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28965781.

8. 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;124:2733–2739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29781117.

9. 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.

10. 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.

11. Saka AH, Giaquinto AN, McCullough LE, et al. Cancer statistics for African American and Black people, 2025. CA Cancer J Clin 2025;75:111–140. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39976243.

12. 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.

13. PubMed Overview. National Institutes of Health; Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed July 20, 2023.

14. Freedman-Cass DA, Fischer T, Alpert AB, et al. The value and process of inclusion: Using sensitive, respectful, and inclusive language and images in NCCN content. J Natl Compr Canc Netw 2023;21:434–441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37156485.

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

16. 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.

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

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

19. 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.

20. 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.

21. 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.

22. 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.

23. 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;36:JCO2017766907. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29652556.

24. 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.

25. Latham A, Srinivasan P, Kemel Y, et al. Microsatellite instability is associated with the presence of Lynch syndrome pan-cancer. J Clin Oncol 2018;37:JCO1800283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30376427.

26. 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.

27. 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.

28. 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.

29. 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.

30. 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.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. 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.

37. 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.

38. 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.

39. 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.

40. 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.

41. 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.

42. 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.

43. 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.

44. 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.

45. 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;79:333–339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30450585.

46. 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;5:523–528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30730552.

47. 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.

48. 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.

49. 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.

50. 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.

51. 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.

52. 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.

53. 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.

54. 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.

55. 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.

56. 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.

57. 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.

58. 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.

59. 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.

60. 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.

61. 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.

62. 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.

63. 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.

64. 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.

65. 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.

66. 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.

67. 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.

68. 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.

69. 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.

70. 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.

71. 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.

72. 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 2019;5:471–478. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30589920.

73. 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.

74. 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.

75. 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.

76. 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.

77. 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.

78. 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.

79. 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;75:378–382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30337059.

80. 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.

81. 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.

82. 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.

83. 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.

84. 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.

85. 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.

86. 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.

87. 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.

88. 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.

89. 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.

90. 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.

91. 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.

92. 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.

93. 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.

94. 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.

95. 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.

96. 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.

97. 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.

98. 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.

99. 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.

100. 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.

101. 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.

102. 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.

103. 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.

104. 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.

105. 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.

106. 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.

107. 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.

108. 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.

109. 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.

110. 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.

111. 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.

112. 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.

113. 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.

114. 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.

115. 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.

116. 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.

117. 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.

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

119. 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.

120. 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.

121. 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.

122. 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.

123. 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.

124. 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.

125. 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.

126. 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.

127. 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.

128. 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.

129. 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.

130. 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.

131. 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.

132. 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.

133. 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.

134. 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.

135. 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.

136. 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;34:3648–3654. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27528718.

137. 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.

138. 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.

139. 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.

140. 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.

141. 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.

142. 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.

143. 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.

144. 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.

145. 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.

146. 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.

147. 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.

148. 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.

149. 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.

150. 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.

151. 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;22:399–405. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30542054.

152. 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.

153. 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.

154. 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.

155. 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.

156. 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:

157. 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.

158. 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.

159. 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 2022;25:677–683. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34285350.

160. 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.

161. 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.

162. 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.

163. 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.

164. 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.

165. 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.

166. 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.

167. 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.

168. 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.

169. 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.

170. 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.

171. 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.

172. 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.

173. 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.

174. 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.

175. 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.

176. 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.

177. 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.

178. 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.

179. 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.

180. 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.

181. 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.

182. 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.

183. 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.

184. 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.

185. 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.

186. 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.

187. 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.

188. 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.

189. 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.

190. 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.

191. 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:

192. 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.

193. 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.

194. 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.

195. 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.

196. 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.

197. 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.

198. 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.

199. 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.

200. 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.

201. 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.

202. 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.

203. 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.

204. 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.

205. 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.

206. 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.

207. 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;201:322–331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30179618.

208. 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.

209. 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.

210. 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.

211. 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.

212. 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.

213. 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.

214. 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.

215. 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.

216. 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.

217. 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.

218. 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.

219. 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.

220. 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.

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

222. 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.

223. 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.

224. 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.

225. 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.

226. 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.

227. 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.

228. 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.

229. 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: https://www.ncbi.nlm.nih.gov/pubmed/27329565.

230. 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.

231. 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.

232. 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.

233. 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.

234. 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.

235. 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.

236. 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.

237. 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.

238. 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.

239. 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.

240. 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.

241. 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.

242. 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.

243. 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;319:2231–2233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29800017.

244. 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;321:704–706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30743264.

245. 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.

246. 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.

247. 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.

248. 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.

249. 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.

250. 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.

251. 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.

252. 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.

253. 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.

254. 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.

255. 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.

256. 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.

257. 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.

258. 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.

259. 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.

260. 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.

261. 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.

262. 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.

263. 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.

264. 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.

265. 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.

266. 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.

267. 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.

268. 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.

269. 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.

270. 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.

271. 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.

272. 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.

273. 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.

274. 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.

275. 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.

276. 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.

277. Loeb S, Folkvaljon Y, Bratt O, et al. Defining intermediate-risk prostate cancer suitable for active surveillance. J Urol 2018;201:292–299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30240688.

278. 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.

279. 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.

280. 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.

281. 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.

282. 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.

283. 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.

284. 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.

285. 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.

286. 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.

287. 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.

288. 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.

289. 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.

290. 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.

291. 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.

292. 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;73:445–451. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28778619.

293. 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.

294. 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.

295. 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.

296. 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.

297. 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;147:213–222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32946908.

298. 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.

299. 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;123:429–438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30113755.

300. 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;22:206–220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30487646.

301. 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.

302. 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.

303. 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.

304. 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.

305. 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.

306. 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.

307. 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.

308. 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.

309. 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.

310. 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.

311. 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.

312. 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.

313. 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.

314. 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.

315. 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.

316. 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.

317. 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.

318. 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.

319. 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.

320. 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.

321. 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.

322. 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.

323. 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.

324. 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.

325. 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.

326. 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.

327. 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.

328. 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.

329. 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:

330. 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:

331. 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:

332. 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;392:2353–2366. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30355464.

333. 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.

334. 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.

335. 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.

336. 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.

337. 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.

338. 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.

339. 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.

340. 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.

341. 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.

342. 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.

343. 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.

344. 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.

345. 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.

346. 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.

347. 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.

348. 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.

349. 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.

350. 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.

351. 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.

352. 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.

353. 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.

354. 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.

355. 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.

356. 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.

357. 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.

358. 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.

359. 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.

360. 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.

361. 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.

362. 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.

363. 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;36:JCO2017755371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29561693.

364. 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.

365. 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.

366. 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.

367. 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.

368. 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.

369. 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.

370. 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.

371. 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.

372. 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.

373. 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.

374. 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.

375. 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.

376. 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.

377. 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.

378. 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.

379. 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.

380. 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.

381. 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;5:664–670. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30763425.

382. 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.

383. 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.

384. 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;36:JCO1801097. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30307776.

385. 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.

386. 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.

387. 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.

388. 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.

389. 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.

390. 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.

391. 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.

392. 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.

393. 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.

394. 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.

395. 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.

396. 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.

397. 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.

398. 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.

399. 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.

400. 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.

401. 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.

402. 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.

403. 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.

404. 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.

405. 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.

406. 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;4:e180039. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29543933.

407. 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.

408. 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.

409. 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.

410. 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.

411. 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.

412. 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.

413. 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.

414. 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.

415. 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;19:1504–1515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30316827.

416. 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.

417. 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.

418. 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.

419. 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.

420. 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;37:JCO1802158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30860948.

421. 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.

422. 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.

423. 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.

424. 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.

425. 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.

426. 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.

427. 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; 2013. Available at: https://clinicaltrials.gov/study/NCT01751438. Accessed August 1, 2023.

428. Standard systemic therapy with or without definitive treatment in treating participants with metastatic prostate cancer. ClinicalTrials.gov; 2018. Available at: https://clinicaltrials.gov/study/NCT03678025. Accessed August 1, 2023.

429. 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.

430. 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.

431. 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.

432. 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.

433. 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.

434. 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.

435. 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.

436. 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.

437. 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.

438. 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.

439. 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.

440. 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.

441. 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.

442. 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.

443. 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.

444. 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.

445. 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.

446. 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.

447. 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.

448. 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.

449. 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.

450. 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.

451. 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.

452. 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.

453. 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.

454. 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.

455. 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.

456. 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.

457. 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.

458. 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.

459. 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.

460. 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.

461. 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.

462. 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.

463. 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.

464. 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.

465. 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.

466. 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.

467. 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.

468. 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.

469. 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.

470. 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.

471. 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.

472. 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.

473. 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.

474. 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.

475. 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.

476. 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.

477. 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.

478. 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.

479. 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.

480. 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.

481. 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.

482. 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.

483. 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.

484. 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;103:335–343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30312717.

485. 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.

486. 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.

487. 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.

488. 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.

489. 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.

490. 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.

491. 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.

492. 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.

493. 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.

494. 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.

495. 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.

496. 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.

497. 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.

498. 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.

499. 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.

500. 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.

501. 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.

502. 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.

503. 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.

504. 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.

505. 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.

506. 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.

507. 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.

508. 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.

509. 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.

510. 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.

511. 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.

512. 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.

513. 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.

514. 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.

515. 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.

516. 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.

517. 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.

518. 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.

519. 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.

520. 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.

521. 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.

522. 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.

523. 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.

524. 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.

525. 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.

526. 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.

527. 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.

528. 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.

529. 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.

530. 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.

531. 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.

532. 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.

533. 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.

534. 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.

535. 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.

536. Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. Lancet 2020;396:1413–1421. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33002429.

537. 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.

538. 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.

539. 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.

540. 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;6:1793–1800. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32852528.

541. 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;396:1422–1431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33002431.

542. 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.

543. 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.

544. 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.

545. 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.

546. 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.

547. 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.

548. 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.

549. 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.

550. 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.

551. 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.

552. 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.

553. 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.

554. 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.

555. 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.

556. 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.

557. 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.

558. 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.

559. 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.

560. 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.

561. 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.

562. 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.

563. 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.

564. 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.

565. 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.

566. 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.

567. 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.

568. 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.

569. 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.

570. 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.

571. 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.

572. 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;22:309–316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30385835.

573. 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.

574. 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.

575. 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.

576. 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.

577. 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.

578. 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.

579. 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.

580. 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.

581. 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.

582. 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.

583. 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.

584. 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.

585. 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.

586. 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.

587. 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.

588. 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.

589. 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.

590. 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.

591. 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.

592. 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.

593. 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.

594. 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.

595. 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.

596. 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.

597. 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.

598. 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.

599. 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;5:91–96. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30326032.

600. 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.

601. 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.

602. 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.

603. 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.

604. 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.

605. 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.

606. 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.

607. 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.

608. 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.

609. 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.

610. 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.

611. 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.

612. 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.

613. 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.

614. 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.

615. 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.

616. 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.

617. 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.

618. 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.

619. 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.

620. 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.

621. Prescribing Information for abiraterone acetate tablets. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202379s035lbl.pdf. Accessed November 15, 2021.

622. 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.

623. 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.

624. 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.

625. 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.

626. 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.

627. 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.

628. 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.

629. 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.

630. Prescribing Information for apalutamide tablets, for oral use. 2021. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210951s006lbl.pdf. Accessed November 15, 2021.

631. 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.

632. 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.

633. 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.

634. 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.

635. 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.

636. 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.

637. 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.

638. 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.

639. 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.

640. 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.

641. 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.

642. 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.

643. 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;1:1–10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26378418.

644. 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.

645. 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.

646. 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.

647. 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.

648. 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.

649. 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.

650. 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.

651. 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.

652. 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.

653. 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.

654. 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.

655. 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.

656. 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.

657. 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.

658. 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.

659. 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.

660. 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.

661. 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.

662. 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.

663. 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.

664. 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.

665. National Osteoporosis Foundation. Learn about Osteoporosis. Available at: http://nof.org/patients. Accessed November 15, 2021.

666. Fracture Risk Assessment Tool. University of Sheffield; Available at: http://www.shef.ac.uk/FRAX/. Accessed August 1, 2023.

667. 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.

668. 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.

669. 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.

670. 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.

671. 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.

672. 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.

673. 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.

674. 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.

675. 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.

676. 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.

677. 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.

678. 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.

679. 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.

680. 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.

681. 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.

682. 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.

683. 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.

684. 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.

685. 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.

686. 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.

687. 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.

688. 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.

689. 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.

690. 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.

691. Sweeney CJ, Martin AJ, Stockler MR, et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. Lancet Oncol 2023;24:323–334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36990608.

692. Armstrong AJ, Azad AA, Iguchi T, et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2022;40:1616–1622. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35420921.

693. Saad F, Vjaters E, Shore N, et al. Darolutamide in combination with androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer from the phase III ARANOTE trial. J Clin Oncol 2024;42:4271–4281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39279580.

694. 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.

695. 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.

696. 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.

697. 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.

698. Fizazi K, Foulon S, Carles J, et al. Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. Lancet 2022;399:1695–1707. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35405085.

699. Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med 2022;386:1132–1142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35179323.

700. Vale CL, Fisher DJ, Godolphin PJ, et al. Which patients with metastatic hormone-sensitive prostate cancer benefit from docetaxel: a systematic review and meta-analysis of individual participant data from randomised trials. Lancet Oncol 2023;24:783–797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37414011.

701. Hussain M, Tombal B, Saad F, et al. Darolutamide plus androgen-deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer by disease volume and risk subgroups in the phase III ARASENS trial. J Clin Oncol 2023;41:3595–3607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36795843.

702. Parker CC, James ND, Brawley CD, et al. Radiotherapy to the prostate for men with metastatic prostate cancer in the UK and Switzerland: Long-term results from the STAMPEDE randomised controlled trial. PLoS Med 2022;19:e1003998. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35671327.

703. Bossi A, Foulon S, Maldonado X, et al. Efficacy and safety of prostate radiotherapy in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 x 2 factorial design. Lancet 2024;404:2065–2076. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39580202.

704. Ali A, Hoyle A, Haran AM, 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33599706.

705. Deek MP, Van der Eecken K, Sutera P, et al. Long-term outcomes and genetic predictors of response to metastasis-directed therapy versus observation in oligometastatic prostate cancer: Analysis of STOMP and ORIOLE trials. J Clin Oncol 2022;40:3377–3382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36001857.

706. Francolini G, Allegra AG, Detti B, et al. Stereotactic body radiation therapy and abiraterone acetate for patients affected by oligometastatic castrate-resistant prostate cancer: A randomized phase II trial (ARTO). J Clin Oncol 2023;41:5561–5568. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37733977.

707. Marvaso G, Corrao G, Zaffaroni M, et al. ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): a randomised, open-label, phase 2 clinical trial. Lancet Oncol 2025;26:300–311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/40049196.

708. Tang C, Sherry AD, Haymaker C, et al. Addition of metastasis-directed therapy to intermittent hormone therapy for oligometastatic prostate cancer: The EXTEND phase 2 randomized clinical trial. JAMA Oncol 2023;9:825–834. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37022702.

709. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. J Clin Oncol 2018;36:446–453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29240541.

710. Sherry AD, Siddiqui BA, Haymaker C, et al. Continuous androgen deprivation therapy with or without metastasis-directed therapy for oligometastatic prostate cancer: The multicenter phase 2 randomized EXTEND trial. Eur Urol 2025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/40750497.

711. 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.

712. 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.

713. 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.

714. 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.

715. 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.

716. 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.

717. 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.

718. 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.

719. 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.

720. 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.

721. 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.

722. 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.

723. 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.

724. 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.

725. 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.

726. 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.

727. 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.

728. 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.

729. 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.

730. Drugs@FDA: FDA-Approved Drugs. U.S. Food & Drug Administration; Available at:

https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed August 15, 2025.

731. 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.

732. 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.

733. 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.

734. 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.

735. 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;20:556–569. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30770294.

736. 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.

737. 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.

738. Smith MR, Saad F, Chowdhury S, et al. Apalutamide and overall survival in prostate cancer. Eur Urol 2020;79:150–158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32907777.

739. 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.

740. 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.

741. 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.

742. 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.

743. 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.

744. 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.

745. 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.

746. 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.

747. 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.

748. 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.

749. 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.

750. 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.

751. 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.

752. 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.

753. 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.

754. 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;21:1513–1525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32926841.

755. 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.

756. 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;35:JCO2016721068. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28753384.

757. Oudard S, Ratta R, Voog E, et al. Biweekly vs triweekly cabazitaxel in older patients with metastatic castration-resistant prostate cancer: The CABASTY phase 3 randomized clinical trial. JAMA Oncol 2023;9:1629–1638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37883073.

758. 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.

759. 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.

760. 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.

761. 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.

762. 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.

763. 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.

764. 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.

765. 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.

766. 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.

767. 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.

768. Lenis AT, Ravichandran V, Brown S, et al. Microsatellite instability, tumor mutational burden, and response to immune checkpoint blockade in patients with prostate cancer. Clin Cancer Res 2024;30:3894–3903. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38949888.

769. 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.

770. 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.

771. 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.

772. 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.

773. 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.

774. 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.

775. 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.

776. 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.

777. 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.

778. 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.

779. 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.

780. 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.

781. 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.

782. 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.

783. 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.

784. 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.

785. 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.

786. Nguyen CB, Reimers MA, Perera C, et al. Evaluating immune checkpoint blockade in metastatic castration-resistant prostate cancers with deleterious CDK12 alterations in the phase 2 IMPACT trial. Clin Cancer Res 2024;30:3200–3210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38787530.

787. van Wilpe S, Kloots ISH, Slootbeek PHJ, et al. Ipilimumab with nivolumab in molecularly selected patients with castration-resistant prostate cancer: primary analysis of the phase II INSPIRE trial. Ann Oncol 2024;35:1126–1137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39293514.

788. 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.

789. 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.

790. Hussain M, Mateo J, Fizazi K, et al. Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 2020;383:2345–2357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32955174.

791. 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;38:3763–3772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32795228.

792. Abida W, Campbell D, Patnaik A, et al. Rucaparib for the treatment of metastatic castration-resistant prostate cancer associated with a DNA damage repair gene alteration: Final results from the phase 2 TRITON2 study. Eur Urol 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37277275.

793. Fizazi K, Piulats JM, Reaume MN, et al. Rucaparib or physician's choice in metastatic prostate cancer. N Engl J Med 2023;388:719–732. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36795891.

794. 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.

795. Schiewer MJ, Goodwin JF, Han S, et al. Dual roles of PARP-1 promote cancer growth and progression. Cancer Discov 2012;2:1134–1149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22993403.

796. Polkinghorn WR, Parker JS, Lee MX, et al. Androgen receptor signaling regulates DNA repair in prostate cancers. Cancer Discov 2013;3:1245–1253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24027196.

797. Li L, Karanika S, Yang G, et al. Androgen receptor inhibitor-induced "BRCAness" and PARP inhibition are synthetically lethal for castration-resistant prostate cancer. Sci Signal 2017;10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28536297.

798. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. NEJM Evidence 2022;1:EVIDoa2200043. Available at: https://evidence.nejm.org/doi/abs/10.1056/EVIDoa2200043

799. Saad F, Clarke NW, Oya M, et al. Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24:1094–1108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37714168.

800. de Bono JS, Mehra N, Scagliotti GV, et al. Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial. Lancet Oncol 2021;22:1250–1264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34388386.

801. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet 2023;402:291–303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37285865.

802. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial. Lancet 2025;406:447–460. Available at: https://www.ncbi.nlm.nih.gov/pubmed/40683290.

803. Chi KN, Rathkopf D, Smith MR, et al. Niraparib and abiraterone acetate for metastatic castration-resistant prostate cancer. J Clin Oncol 2023;41:3339–3351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36952634.

804. Chi KN, Sandhu S, Smith MR, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. Ann Oncol 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37399894.

805. 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.

806. Morris MJ, Castellano D, Herrmann K, et al. (177)Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): a phase 3, randomised, controlled trial. Lancet 2024;404:1227–1239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39293462.

807. 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.

808. 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.

809. 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.

810. 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.

811. 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.

812. Tombal B, Choudhury A, Saad F, et al. Enzalutamide plus radium-223 in metastatic castration-resistant prostate cancer: results of the EORTC 1333/PEACE-3 trial. Ann Oncol 2025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/40450503.

813. Gillessen S, Choudhury A, Rodriguez-Vida A, et al. Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACEIII trial combining Ra223 with enzalutamide versus enzalutamide alone: An updated safety analysis [abstract]. Journal of Clinical Oncology 2021;39:5002–5002. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.5002.

814. Francolini G, Bertini N, Di Cataldo V, et al. Impact of stereotactic body radiotherapy after progression in castrate resistant prostate cancer patients undergoing first line abiraterone treatment. A subgroup analysis from ARTO trial (NCT03449719). Prostate Cancer Prostatic Dis 2025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39972049.

815. Niazi T, Saad F, Koul R, et al. Metastases-directed therapy in addition to standard systemic therapy in oligometastatic castration resistant prostate cancer: A randomized phase II trial (GROUQ-PCS 9) [abstract]. Journal of Clinical Oncology 2025;43:22–22. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2025.43.5_suppl.22.

816. 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.

817. 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.

818. 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.

819. 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.

820. 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.

821. 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.

822. 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.

823. 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.

824. 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.

825. 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.

826. 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.

827. Coleman RE. Risks and benefits of bisphosphonates. Br J Cancer 2008;98:1736–1740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18506174.

828. 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.

829. 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.

830. 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.

831. 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.

832. 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.

833. 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.

834. 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.

835. Hofman MS, Emmett L, Sandhu S, et al. [(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet 2021;397:797–804. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33581798.

836. Wallis CJD, Klaassen Z, Jackson WC, et al. Olaparib vs cabazitaxel in metastatic castration-resistant prostate cancer. JAMA Netw Open 2021;4:e2110950. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34028551.

837. 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.

838. 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.

839. 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.

840. 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.

841. 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.

842. 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.

843. 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.

844. 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.

845. 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.

846. 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.

847. 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.

848. 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.

849. 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.

850. 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.

851. 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.

852. 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.

853. 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.

854. 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.

855. 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.

856. 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.

857. 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.

858. 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.

859. 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.

860. 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.

861. 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.

862. 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.

863. 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.

864. 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.

865. 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.

866. 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.

867. 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.

868. 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.

869. 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.

870. 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.

871. 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.

872. 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.

873. 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.

874. 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.

875. 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.