Oncology Clinical Pathways
Prostate Cancer

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Prostate Cancer – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran’s military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Vietnam Veterans – Agent Orange Exposure or Specified Locations
- Prostate cancer

Gulf War and Post 9/11 Veterans

If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if the patient served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:
- Reproductive cancers of any type

* The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov)
Prostate Cancer – Evaluation of Newly Diagnosed

**Risk Factors**
- Race
- Agent Orange exposure
- Family history
- Known germline mutation

**Risk Groups**
Refer to risk stratification and corresponding pathways

Clinical trial(s) always considered on pathway.

**Initial diagnosis and workup**
- Assess PSA
- Assess risk factors
- Digital rectal exam
- Assess life expectancy
- Biopsy and existing imaging

**Assess risk group**
# Prostate Cancer – Risk Stratification

<table>
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<tr>
<th>Risk Group</th>
<th>Defined by Clinical/Pathologic Features</th>
<th>Imaging for Nodal or Metastatic Disease</th>
<th>Germline Testing</th>
<th>Initial Therapy</th>
</tr>
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<tr>
<td>Very Low</td>
<td>- T1c &lt; 3 prostate biopsy fragments/cores positive; ≤ 50% cancer in each fragment/cores &lt; 10 ng/ml PSA density &lt; 0.15 ng/ml/g</td>
<td>Not Indicated</td>
<td>Recommended for any of the following: Ashkenazi Jewish ancestry</td>
<td>Follow Very Low Risk pathway</td>
</tr>
<tr>
<td>Low</td>
<td>- T1-T2a Grade group 1 PSA &lt; 10 ng/ml</td>
<td>Bone imaging not recommended for staging</td>
<td>Family history of high risk germline mutations</td>
<td>Follow Low Risk pathway</td>
</tr>
<tr>
<td>Intermediate</td>
<td>- No high-risk group features</td>
<td>Pelvic &amp; abdominal imaging recommended if nomogram predicts &gt;10% probability of pelvic LN involvement</td>
<td>Strong family history of cancer</td>
<td>Follow Favorable Intermediate Risk pathway</td>
</tr>
<tr>
<td></td>
<td>- One or more intermediate-risk factors (IRF)</td>
<td>Bone and Soft Tissue Imaging: PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging</td>
<td>Follow Unfavorable Intermediate Risk pathway</td>
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<tr>
<td></td>
<td>- T2b-T2c</td>
<td>(with either Tc99m-MDP/HDP SPECT/CT, F18-NAF PET/CT) + soft tissue imaging (with CT, MRI, 18-fluorocholine PET) + PSMA PET/CT for equivocal findings</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- Grade Group 2 or 3</td>
<td>Consider molecular imaging if available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>- At least one high-risk feature: T3a Grade Group 4 or 5 PSA &gt; 20 ng/ml</td>
<td>Bone and Soft Tissue Imaging: PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging</td>
<td>Follow High or Very High-Risk pathway</td>
<td></td>
</tr>
<tr>
<td>Very High</td>
<td>- At least one of the following: T3b-T4 Primary Gleason pattern 5 2 or 3 high-risk features &gt; 4 cores with Grade Group 4 or 5</td>
<td>Bone and Soft Tissue Imaging: PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging</td>
<td>Recommended</td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>Any T, N1, M0: Consider testing tumor for HRRm and MSI or dMMR</td>
<td>Bone and Soft Tissue Imaging: PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging</td>
<td>Follow Regional Risk pathway</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>Any T, Any N, M1: Recommend testing tumor for HRRm and MSI or dMMR</td>
<td>Bone and Soft Tissue Imaging: PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging</td>
<td>Follow CSPC M1 pathway</td>
<td></td>
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</table>
Prostate Cancer – Very Low Risk Group

Life expectancy?

- >20 years
  - Multidisciplinary discussion
  - Active surveillance

- 10-20 years
  - Active surveillance

- <10 years
  - Observation

Patient preference after shared decision making?

- Active surveillance preferred
- Radiation therapy
- Radical prostatectomy

Clinical trial(s) always considered on pathway.

* Multidisciplinary Discussion to include Radiation Oncology, Urology
Prostate Cancer – Low Risk Group

Low Risk

Life expectancy?

- >10 years: Multidisciplinary discussion \(^a\)
- <10 years: Observation

Patient preference after shared decision making?

- Active surveillance preferred
- Radiation therapy
- Radical prostatectomy

Clinical trial(s) always considered on pathway.

\(^a\) **Multidisciplinary Discussion** to include Radiation Oncology, Urology
Prostate Cancer – Favorable Intermediate Risk Group

- Favorable Intermediate Risk
  - Life expectancy?
    - >10 years
      - Multidisciplinary discussion *
        - Patient preference after shared decision making?
          - Active surveillance
          - Radiation therapy
          - Radical prostatectomy
    - <10 years
      - Multidisciplinary discussion *
        - Patient preference after shared decision making?
          - Observation preferred
          - Radiation therapy

* Multidisciplinary discussion to include Radiation Oncology, Urology

Clinical trial(s) always considered on pathway.
Prostate Cancer – Unfavorable Intermediate Risk Group

Unfavorable Intermediate Risk * → Life expectancy?

≥10 years → Multidisciplinary discussion b → Patient preference after shared decision making?

Patient preference after shared decision making?

Radiation therapy plus 4-6 months ADT

T3 disease, PSA persistence or recurrence, positive margins, lymph node metastasis?

<10 years → Multidisciplinary discussion b → Patient preference after shared decision making?

Radiation therapy plus 4-6 months ADT

Observation preferred

Clinical trial(s) always considered on pathway.

* Imaging: PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging (with either Tc99m-MDP/HDP SPECT/CT, F18-NAF PET/CT) + soft tissue imaging (with CT, MRI, F18-fluciclovine PET) + PSMA PET/CT for equivocal findings

b Multidisciplinary Discussion to include Radiation Oncology, Urology, Medical Oncology
High or Very High Risk

Life expectancy?

≥ 5 years or symptomatic
Multidisciplinary discussion
Patient preference after shared decision making?

Radical prostatectomy plus pelvic lymph node dissection

Radiation therapy plus 18-36 months ADT +/- abiraterone

Observation

< 5 years or asymptomatic
Patient preference after shared decision making?

Lymph node metastasis?
Multidisciplinary discussion
T3 disease, PSA persistence or recurrence, positive margins?

ADT +/- EBRT

Refer to Radiation Oncology

Radiation Oncology Discussion

Clinical trial(s) always considered on pathway.

* Imaging PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging (with either Tc99m-MDP/HDP SPECT/CT, F18-NAF PET/CT) + soft tissue imaging (with CT, MRI, F18-fluoride PET) + PSMA PET/CT for equivocal findings

b Multidisciplinary Discussion to include Radiation Oncology, Urology, Medical Oncology

c Abiraterone prescribe only for very high risk group patients; duration for maximum of 2 years
Prostate Cancer – Regional Risk Group

1. Regional Risk
2. Life expectancy?
   - ≥ 5 years or symptomatic
     - Multidisciplinary discussion
     - Patient preference after shared decision making?
   - ≤ 5 years and asymptomatic
     - Observation
     - ADT

Clinical trial(s) always considered on pathway.

*a Multidisciplinary Discussion to include Radiation Oncology, Urology, Medical Oncology

Radiation therapy (preferred) plus 24 months ADT +/- abiraterone

ADT +/- abiraterone
Prostate Cancer – Radical Prostatectomy PSA Persistence/Recurrence

Radical Prostatectomy PSA Persistence/Recurrence

Risk stratification

Negative for distant metastases

Life expectancy?

Positive for distant metastases

Follow CSPC M1 pathway

≥ 5 years

Multidisciplinary discussion

Observation or ADT

< 5 years

Observation

Clinical trial(s) always considered on pathway.

a PSA Persistence/Recurrence defined as rising, detectable PSA based on at least two determinations

b Risk Stratification PSADT; pathology report: PSMA PET imaging, if not available: fluciclovine PET/CT; CT chest/abdomen/pelvis; bone imaging with Tc99m-MDP/HDP SPECT/CT or F18 sodium fluoride PET/CT (or PET/MRI); MRI prostate/pelvis; provider appropriateness review and consideration should be made for imaging evaluation in the setting of early recurrence with low PSA values (<0.5 ng/ml)

c Multidisciplinary Discussion to include Radiation Oncology, Urology, Medical Oncology

EBRT External Beam Radiation Therapy
Prostate Cancer – Radiation Therapy Recurrence

1. Radiation Therapy Recurrence
2. PSMA PET
3. Local therapy candidate, PSA < 10, and life expectancy > 10 years?
   - Yes
     - Evidence of distant metastasis?
       - Yes
         - Follow CSPC M1 pathway
       - No
         - Biopsy of prostate
4. Evidence of distant metastasis?
   - Yes
     - Follow CSPC M1 pathway
   - No
     - Observation
5. Biopsy positive for cancer?
   - Yes
     - Observation, RP+PLND, brachytherapy, cryotherapy, ADT, or HIFU
   - No
     - Observation or ADT

Clinical trial(s) always considered on pathway.

**Recurrence** defined as rising PSA >2 above Nadir or positive DRE post-curative intent radiation

PSA Bounce defined as a transient rise in PSA, at a median of 12-18 months after treatment; PSA bounce may occur in the absence of recurrent disease and does not necessarily signify a treatment failure or constitute an indication for intervention

**PSMA PET** if not available, recommend prostate MRI and fluciclovine PET/CT or CT chest/abdomen/pelvis and bone imaging (technetium bone scan or F-18 sodium fluoride PET)

RP Radical Prostatectomy
PLND Pelvic Lymph Node Dissection
HIFU High Intensity Focused Ultrasound
Prostate Cancer – Castrate Sensitive Prostate Cancer (CSPC) M1

- **First Generation Antiandrogens** not recommended for long-term use however short course may be administered to block testosterone flare.

- **Low-volume disease** defined as no visceral metastases and four or less bone metastases; **high volume disease** is differentiated from low-volume disease by visceral metastases and/or more than four bone metastases.

- **Abiraterone** contraindications include hepatic dysfunction, significant cardiovascular disease, uncontrolled hypertension, or the inability to tolerate prednisone.

- **Inclusion Criteria** includes ECOG 0-1 and distant metastasis (M1) detected on imaging.

- **Exclusion Criteria** includes CVA, MI, unstable angina, CHF (NYHA class III or IV) in the prior 6 months and/or uncontrolled HTN.

- **Hepatic Dysfunction** defined as baseline Tbilii > 1.5 x ULN (except in Gilbert’s Disease), AST or ALT > 2.5 x ULN (AST or ALT ≤ 5x ULN allowed in known liver metastases), and/or Child-Pugh Class C.

- **Significant CV disease** defined as MI or ATE in past 6 months, severe or unstable angina, NYHA Class III or IV heart failure, and/or EF < 50% at baseline.

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Clinical trial(s) always considered on pathway.
Prostate Cancer – Castrate Resistant Prostate Cancer (CRPC) M0

Clinical trial(s) always considered on pathway.

**Apalutamide contraindications include history of severe renal or hepatic dysfunction, cardiovascular or cerebrovascular event in prior 6 months, high fall risk, or seizure history**
Prostate Cancer – Castrate Resistant Prostate Cancer (CRPC) M1, First Line

- Adenocarcinoma ≤ 2 ECOG
- Candidate for abiraterone? *b*
  - Yes
    - BRCA mutation positive?
      - Yes
        - Olaparib and abiraterone
      - No
        - Abiraterone
  - No
    - Enzalutamide *d*

- Adenocarcinoma > 2 ECOG
  - Refer to Palliative Care
- Neuroendocrine Component
  - Platinum-based combination *e*

Clinical trial(s) always considered on pathway.

*a* Consider Biopsy in setting of visceral disease or atypical progression (scan worsening without overt PSA progression); continuous ADT with testosterone goal <50

*b* Abiraterone contraindications include hepatic dysfunction, significant cardiovascular disease, uncontrolled hypertension, or the inability to tolerate prednisone

*c* Docetaxel prescribe for relatively rapidly progressing symptomatic disease

*d* Enzalutamide contraindications include severe renal impaiement (CcCl <30 ml/min), seizure history, and/or brain metastases/active epidural disease

*e* Platinum-Based Combination No regimen proven more effective than another
Prostate Cancer – Castrate Resistant Prostate Cancer (CRPC) M1, Second Line

1. **Consider Biopsy** in setting of visceral disease or atypical progression (scan worsening without overt PSA progression); continuous ADT with testosterone goal <50 nmol/L.

2. **Docetaxel** prescribe for relatively rapidly progressing symptomatic disease.

3. **Pembrolizumab** prescribe if patient has MSI-H (microsatellite instability-high), dMMR (deficient mismatch repair) or TMB high in tumor agnostic fashion.

4. **Enzalutamide** prescribe if not previously received (response unlikely if previously progressed on abiraterone); contraindications include severe renal impairment (CrCl <30 ml/min), seizure history, and/or brain metastases/active epidural disease.

5. **Abiraterone** prescribe if not previously received (response unlikely if previously progressed on enzalutamide or other androgen receptor antagonist); contraindications include hepatic dysfunction, significant cardiovascular disease, uncontrolled hypertension, or the inability to tolerate prednisone.

6. **Cabazitaxel** favored for use after previous failure of one ART (enzalutamide/abiraterone); avoid repeat of previously used therapies.

7. **Radium 223** prescribe if patient has symptomatic bone metastases and no visceral disease.

8. **Olaparib** prescribe if not previously received and patient has HRRm (Homologous Recombination Repair mutation).

Clinical trial(s) always considered on pathway.
Prostate Cancer – Castrate Resistant Prostate Cancer (CRPC) M1, Third Line

**Consider biopsy** in setting of visceral disease or atypical progression (scan worsening without overt PSA progression); continuous ADT with testosterone goal <50 ng/dL.

**Lu177-PSMA** contraindications cannot be given with radium 223, cabazitaxel, or investigational product; patient can continue standard care i.e., AR-directed therapy without ADT.

**Cabazitaxel** favored for use after previous failure of one ART (enzalutamide/abiraterone); avoid repeat of previously used therapies.

**Pembrolizumab** prescribe if patient has MSI-H (microsatellite instability-high), dMMR (deficient mismatch repair) or TMB high in tumor agnostic fashion.

**Enzalutamide** prescribe if not previously received (response unlikely if previously progressed on abiraterone); contraindications include severe renal impairment (CcCl <30 ml/min), seizure history, and/or brain metastases/active epidural disease.

**Abiraterone** prescribe if not previously received (response unlikely if previously progressed on enzalutamide or other androgen receptor antagonist); contraindications include hepatic dysfunction, significant cardiovascular disease, uncontrolled hypertension, or the inability to tolerate prednisone.

**Radium 223** prescribe if patient has symptomatic bone metastases and no visceral disease.

**Olaparib** prescribe if not previously received and patient has HRRm (Homologous Recombination Repair mutation).
Risk Stratification based on a combination of factors that would impact the likelihood of clinically relevant disease progression including: life expectancy (reassess every 1-2 years; if limited life expectancy consider observation), risk group, PSA velocity, DRE, MRI findings, clinical concordance, and patient preference.

Confirmatory Prostate Biopsy consider if there is a discordance between pathologic and clinical findings or if initial biopsy is determined to be inadequate.

Concern for Disease Progression based on DRE, PSA, and/or MRI results.
Prostate Cancer – Molecular Testing

Molecular Testing → Tumor tissue sufficient?

- Yes: Perform CGP testing
- No: Repeat biopsy possible?
  - Yes: Repeat biopsy
  - No: Liquid biopsy if concern for progressive disease

- Perform germline testing

*CGP Testing* for metastatic disease

*Germline Testing* for high risk, very high risk, regional risk, and metastatic disease

CGP: Comprehensive Genomic Profiling
# Prostate Cancer – Molecular Testing Table

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<th>Eligibility</th>
<th>Test Category</th>
<th>Test Type</th>
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<tr>
<td>High risk or very high risk prostate cancer (non-metastatic, T3 or T4)</td>
<td>Germline NGS*</td>
<td>Germline prostate cancer panel or common hereditary panel (**POC) or referral to CGGS</td>
</tr>
<tr>
<td>Very low, low, or intermediate risk prostate cancer with:</td>
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<tr>
<td>1.) Ashkenazi Jewish ancestry (non-metastatic, T1 or T2),</td>
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<tr>
<td>2.) family history of high-risk germline mutations (non-metastatic, T1 or T2),</td>
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<td></td>
</tr>
<tr>
<td>3.) strong family history of cancer (non-metastatic, T1 or T2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional risk prostate cancer (any T, N1) non-metastatic</td>
<td>Germline NGS*</td>
<td>Germline prostate cancer panel or common hereditary panel (**POC) or referral to CGGS</td>
</tr>
<tr>
<td>Metastatic prostate cancer (any T, any N, M1)</td>
<td>Germline NGS*</td>
<td>Germline prostate cancer panel or common hereditary panel (**POC) or referral to CGGS</td>
</tr>
<tr>
<td>Somatic NGS</td>
<td>CGP (Solid);</td>
<td>CGP Liquid if tissue insufficient/NA</td>
</tr>
<tr>
<td>IHC</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td></td>
</tr>
<tr>
<td>*Germline NGS test should include BRCA1/2, ATM, CHEK2, HOXB13, MLH1, MSH2, MSH6, PMS2, NBN, TP53</td>
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<tr>
<td>** POC: Point of Care (Provider orders Germline genetic test)</td>
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Questions?

Contact VHAOncologyPathways@va.gov