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Prostate Cancer – Evaluation of Newly Diagnosed

**Evaluation of Newly Diagnosed Prostate Cancer** → **Initial Diagnosis and Workup** → **Assess risk group**

- Assess PSA
- Assess risk factors
- Digital rectal exam
- Assess life expectancy
- Biopsy and existing imaging

Clinical trial(s) always considered on pathway.

- **Risk Factors** Race, Agent Orange exposure, family history, known germline mutation
- **Risk Groups** Refer to risk stratification and corresponding pathways
# Prostate Cancer – Risk Stratification

<table>
<thead>
<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>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>All the following:</td>
<td></td>
<td>Recommended for any of the following:</td>
<td>Follow Very Low Risk pathway</td>
</tr>
<tr>
<td></td>
<td>- T1c</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- Grade group 1</td>
<td></td>
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<td></td>
<td>- PSA &lt; 10 ng/ml</td>
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<td></td>
<td>- &lt; 3 prostate biopsy fragments/cores positive; ≤ 50% cancer in each fragment/core</td>
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<td></td>
<td>- PSA density &lt; 0.15 ng/ml</td>
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<tr>
<td>Low</td>
<td>All the following:</td>
<td></td>
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<td>Follow Risk pathway</td>
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<tr>
<td></td>
<td>- T1-T2a</td>
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<tr>
<td></td>
<td>- Grade Group 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- PSA &lt; 10 ng/ml</td>
<td></td>
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<tr>
<td>Intermediate</td>
<td>All the following:</td>
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<td>Follow Intermediate Risk pathway</td>
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<tr>
<td></td>
<td>- No high-risk group features</td>
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</tr>
<tr>
<td></td>
<td>- No very high-risk group features</td>
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</tr>
<tr>
<td></td>
<td>- One or more intermediate risk factors (IRF)</td>
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<tr>
<td></td>
<td>- T2b-T2c</td>
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<tr>
<td></td>
<td>- Grade Group 2 or 3</td>
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<tr>
<td></td>
<td>- PSA 10-20 ng/ml</td>
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<td></td>
<td><strong>Favorable Intermediate</strong></td>
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<tr>
<td></td>
<td>- One IRF</td>
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<tr>
<td></td>
<td>- Grade Group 1 or 2</td>
<td></td>
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<tr>
<td></td>
<td>- &lt; 50% positive biopsy cores</td>
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<tr>
<td></td>
<td><strong>Unfavorable Intermediate</strong></td>
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<td>Follow Unfavorable Intermediate Risk pathway</td>
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<td></td>
<td>- At least one of the following:</td>
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<tr>
<td></td>
<td>- 2 or 3 IRFs</td>
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<td></td>
<td>- Grade Group 3</td>
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<tr>
<td></td>
<td>- ≥ 50% positive biopsy cores</td>
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<td><strong>Bone and Soft Tissue Imaging:</strong></td>
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<tr>
<td></td>
<td>- Use PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging</td>
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<tr>
<td></td>
<td>- With either Td99m-MDP/HDP SPECT/CT, F18-NAF PET/CT</td>
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<tr>
<td></td>
<td>- Soft tissue imaging (with CT, MRI)</td>
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<tr>
<td>High</td>
<td>At least one high-risk feature:</td>
<td></td>
<td></td>
<td>Follow High or Very High-Risk pathway</td>
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<tr>
<td></td>
<td>- T3a</td>
<td></td>
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<tr>
<td></td>
<td>- Grade Group 4 or 5</td>
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<td></td>
<td>- PSA &gt; 20 ng/ml</td>
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<tr>
<td></td>
<td><strong>Bone and Soft Tissue Imaging:</strong></td>
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<td></td>
<td>Recommended</td>
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<td></td>
<td>- Use PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging</td>
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<tr>
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<tr>
<td></td>
<td>- Soft tissue imaging (with CT, MRI)</td>
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<tr>
<td>Very High</td>
<td>At least one of the following:</td>
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<td></td>
<td>Recommended</td>
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<tr>
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<td>- T3b-T4</td>
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</tr>
<tr>
<td></td>
<td>- Primary Gleason pattern 5</td>
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<tr>
<td></td>
<td>- 2 or 3 high-risk features</td>
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<tr>
<td></td>
<td>- &gt; 4 cores with Grade Group 4 or 5</td>
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<tr>
<td></td>
<td><strong>Bone and Soft Tissue Imaging:</strong></td>
<td></td>
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<td>Recommended</td>
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<td>- Use PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging</td>
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<tr>
<td></td>
<td>- With either Td99m-MDP/HDP SPECT/CT, F18-NAF PET/CT</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>- Soft tissue imaging (with CT, MRI)</td>
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<td></td>
</tr>
<tr>
<td>Regional</td>
<td>Any T, N1, MD. Consider testing tumor for HRRm and MSI or dMMR</td>
<td></td>
<td></td>
<td>Follow Regional Risk pathway</td>
</tr>
<tr>
<td>Metastatic</td>
<td>Any T, Any N, M1: Recommend testing tumor for HRRm and MSI or dMMR</td>
<td></td>
<td></td>
<td>Follow CSPC M1 pathway</td>
</tr>
</tbody>
</table>
Prostate Cancer – Very Low Risk Group

- **Very Low Risk**
  - Life expectancy?
    - >20 years → Multidisciplinary discussion a
    - 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.

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

Low Risk

Life expectancy?

- >10 years: Multidisciplinary discussion
- <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 – Favorable Intermediate Risk Group

Favorable Intermediate Risk → Life expectancy?

≥10 years → Multidisciplinary discussion *

<10 years → Multidisciplinary discussion *

Patient preference after shared decision making

Active surveillance
Radiation therapy
Radical prostatectomy
Observation preferred
Radiation therapy

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

Multidisciplinary discussion *

Clinical trial(s) always considered on pathway.

* Multidisciplinary discussion to include Radiation Oncology, Urology
Prostate Cancer – Unfavorable Intermediate Risk Group

Unfavorable Intermediate Risk

Life expectancy?

≥10 years

Multidisciplinary discussion

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

Patient preference after shared decision making

Radiation therapy plus 4-6 months ADT

Observation preferred

Multidisciplinary 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-fluoridovine PET) + PSMA PET/CT for equivocal findings

Multidisciplinary discussion to include Radiation Oncology, Urology, Medical Oncology
Prostate Cancer – High or Very High Risk Group

**Life expectancy?**

- **≥ 5 years or asymptomatic**: Multidisciplinary discussion

- **< 5 years and asymptomatic**: Patient preference after shared decision making

**Patient preference after shared decision making**

- Observation
- Radiation therapy
- ADT

**Radical prostatectomy plus pelvic lymph node dissection**

**Radiation therapy**

**T3 disease, PSA persistence or recurrence, positive margins?**

- Refer to Radiation Oncology

**Lymph node metastasis?**

- Multidisciplinary discussion

- **ADT +/- EBRT**

---

* 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

* Multidisciplinary discussion to include Radiation Oncology, Urology, Medical Oncology

* Prescribe abiraterone only for very high risk group patients; duration for maximum of 2 years
Prostate Cancer – Regional Risk Group

Regional Risk

Life expectancy?

≥ 5 years or symptomatic

Multidisciplinary discussion

Patient preference after informed decision making

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

< 5 years and asymptomatic

Patient preference after shared decision making

Observation

ADT

ADT +/- abiraterone

Clinical trial(s) always considered on pathway.

*Multidisciplinary discussion* to include Radiation Oncology, Urology, Medical Oncology
**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

- **Clinical trial(s) always considered on pathway.**

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

- **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)

- **Multidisciplinary discussion** to include Radiation Oncology, Urology, Medical Oncology

- **EBRT**: External Beam Radiation Therapy

- **Life expectancy?**
  - > 5 years
    - Multidisciplinary discussion
  - < 5 years
    - Observation or ADT

- **EBRT +/- ADT**

- **Observation**

---

**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

**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

**If PSMA PET imaging is 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** are 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 Tbil ≥ 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.

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

CRPC M0

PSA doubling time < 10 months?

Yes

Patient eligible for apalutamide? a

Yes

Apalutamide and continue ADT

No

Darolutamide and continue ADT

No

Continue ADT

Clinical trial(s) always considered on pathway.

a 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
  - No: Abiraterone and prednisone
  - Yes: Docetaxel

Second Line
- Abiraterone and prednisone
  - Yes: Enzalutamide
  - No: Docetaxel

Second Line
- Docetaxel
  - Yes: Pembrolizumab
  - No: Enzalutamide

Third Line
- Pembrolizumab
  - Yes: Cabazitaxel
  - No: Radium 223

Clinical trial(s) always considered on pathway.

- Consider biopsy in setting of visceral disease or atypical progression (scan worsening without overt PSA progression)
- Platinum-based combination No regimen proven more effective than another
- Abiraterone contraindications include hepatic dysfunction, significant cardiovascular disease, uncontrolled hypertension, or the inability to tolerate prednisone
- Docetaxel prescribe for relatively rapidly progressing symptomatic disease
- Enzalutamide contraindications include severe renal impairment (CrCl <30 ml/min), seizure history, and/or brain metastases/active epidural disease
- Pembrolizumab prescribe if patient has MSI-H (microsatellite instability-high), dMMR (deficient mismatch repair) or TMB high in tumor agnostic fashion
- Cabazitaxel favored for use after previous failure of one ART (enzalutamide/abiraterone); avoid repeat of previously used therapies
- Radium 223 prescribe if patient has symptomatic bone metastases and no visceral disease
- Olaparib prescribe if patient has HRRm (Homologous Recombination Repair mutation)
- Contraindications cannot be given with radium 223, cabazitaxel, or investigational product; patient can continue standard care i.e., AR-directed therapy
Prostate Cancer – Active Surveillance

Active Surveillance → Risk stratification

Consider early confirmatory prostate biopsy and/or MRI

PSA recommended every 6-12 months

DRE every 6 months or as clinically indicated

Repeat biopsy and/or MRI every 1-2 years

Concern for disease progression?

Yes → Prostate biopsy and/or MRI

No → Continue active surveillance

Progression to higher risk group?

Yes → Follow Risk Group pathway

No → Continue active surveillance

Surveillance Schedule

Clinical trial(s) always considered on pathway.

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**

1. **Is available tissue sufficient?**
   - **Yes**: Repeat biopsy
   - **No**: Repeat biopsy possible?
     - **Yes**: Repeat biopsy
     - **No**: Perform liquid biopsy if concern for progressive disease

2. **Order CGP on tumor tissue**
   - **Order germline genetic testing**
     - **Perform pretest informed consent for germline genetic testing**

**Notes:**

- **Comprehensive Genomic Profile (CGP)** for metastatic disease
- **Germline Testing** for high risk, very high risk, regional risk, and metastatic disease
Questions?

Contact VHAOncologyPathways@va.gov