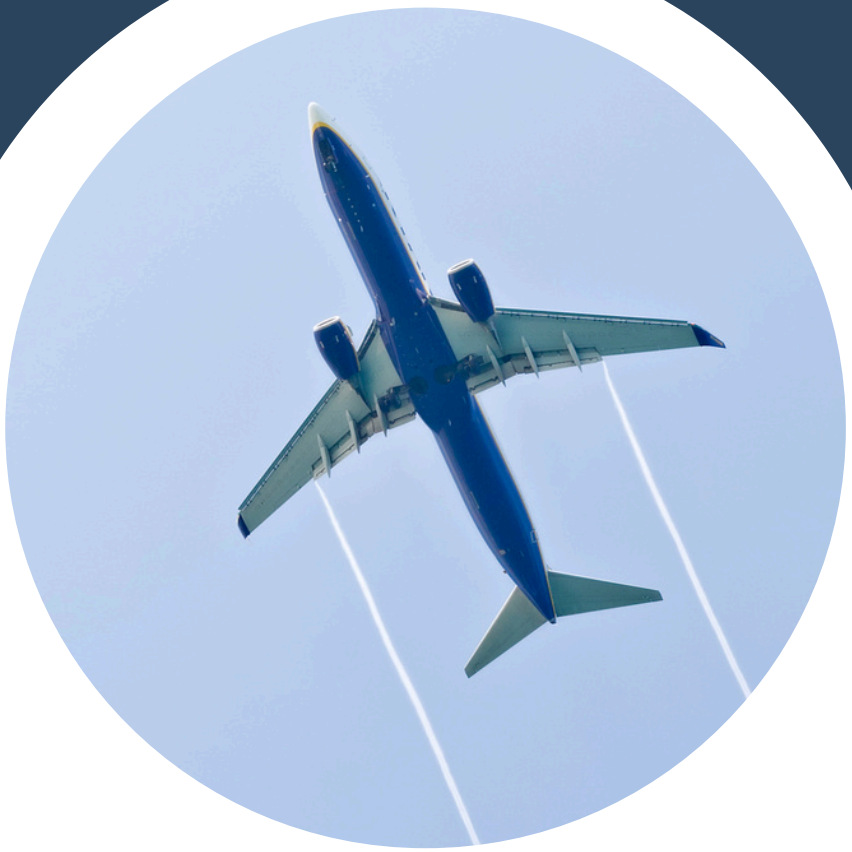
MUSIC
Michigan Urological Surgery Improvement Collaborative



MUSIC Flight Plan

Management of Patients with Favorable-Risk Prostate Cancer

MUSIC Michigan Urological Surgery Improvement Collaborative

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Management of Patients with Favorable-Risk Prostate Cancer

In our efforts to continuously improve the quality of prostate cancer care, the Michigan Urological Surgery Improvement Collaborative (MUSIC) has developed guidelines for management of patients with favorable-risk (FR) prostate cancer (PCa).

> We define FR PCa as early-stage tumors with Grade Group 1 (Gleason Score of 3+3=6) and select low-volume Grade Group 2 (Gleason Score 3+4=7) tumors. This document is not intended for patients with higher-risk (HR) PCa (i.e., high-volume Grade Group 2 (Gleason 3+4=7), Grade Group 3 or greater, intraductal carcinoma, cribriform pattern, etc.). For these patients, definitive local treatment is most commonly recommended, but we encourage shared decision-making to determine the best course of action for each individual patient.

After diagnosis, patients with FR disease should strongly consider Active Surveillance (AS) as the management option and should not default to immediate treatment as patients on AS have improved quality of life from avoidance of treatment-related side effects. However, high-quality AS follow-up testing is essential to ensure patient safety.

This plan provides a framework for the management of patients with FR PCa that was developed within the MUSIC collaborative.

Considering Active Surveillance

After initial biopsy, patient and provider should engage in shared decision-making to decide whether to pursue AS or treatment for their cancer. An important part of this process is to obtain an early Confirmatory Test if the patient did not have an MRI prior to the diagnostic biopsy.

Grade Group 1 (GG1) Prostate Cancer

AS is the preferred treatment for patients with GG1 PCa. There is predictable slow growth and near absent metastatic potential of GG1 prostate cancer. AS is safe and with high-quality surveillance, the risk of missing the ability to treat and cure the patient if/when needed in the future, is very low.

Grade Group 2 (GG2) Prostate Cancer

Clinical trials and large cohort studies support the use of AS for a subset of patients with GG2 disease. The decision between AS and definitive treatment is more nuanced in this population owing to an increased risk of progression to treatment and small increased risk of biochemical recurrence and/or metastatic disease compared with upfront treatment. Shared decision-making is recommended for these patients to help align treatment decisions with patient priorities. For example, a patient with poor sexual function may be more likely to choose treatment over surveillance. Alternatively, patients with good sexual function may benefit from the quality of life gains with AS.

- Patients with low-volume (≤3 positive cores and ≤50% greatest involvement of an individual core) GG2 PCa should consider AS.
- Patients with moderate volume GG2 PCa can consider AS or treatment.

Life Expectancy and Prostate Cancer Outcomes

When deciding between treatment and surveillance, it can be beneficial to consult tools made for estimating life expectancy as well as the risk of adverse outcomes from PCa without treatment:

- Social Security: https://www.ssa.gov/OACT/population/longevity.html
  - Based on social security data, life expectancy for an average-healthy 76-year-old patient is ~10 years.
- MSKCC: https://www.mskcc.org/nomograms/prostate/male_life_expectancy
- Predict Prostate: https://prostate.predict.cam/tool

Treatment should always be considered in the context of a patient's overall health. Due to competing medical issues, some patients with indolent PCa and more serious comorbidities may be better suited for PSA-Only Surveillance rather than AS. This strategy limits the burden and morbidity of surveillance testing in patients with a limited life expectancy.

Confirmatory Testing

A critical consideration for patients diagnosed with FR PCa is the possibility of underestimating the true grade and/or volume of the tumor. Previous work from MUSIC, and elsewhere, has determined that the diagnostic biopsy can underestimate and/or under sample the true volume and grade of cancer in approximately 30% of patients. Confirmatory Testing is recommended to increase confidence that AS is an appropriate form of management. Results from such tests may indicate that definitive local treatment is more appropriate or can help risk stratify the patient for future surveillance monitoring.

MUSIC recommends an MRI* within 6 months of initial biopsy as a Confirmatory Test.

Patients with an MRI prior to diagnosis, additional Confirmatory Testing is not necessary.

**Can consider repeat biopsy or genomic testing if patient prefers.*

Interpretation of Confirmatory Testing

One or more of the recommended Confirmatory Tests should be performed within 6 months of diagnosis. Additionally, the results of the Confirmatory Test can help determine the intensity and frequency of surveillance monitoring.

Confirmatory Test Options	Reassuring Results
MRI	Absence of PIRADS 4 or 5 lesion **OR** PIRADS 4 lesion proven GG1 on biopsy
Repeat Prostate Biopsy	Biopsy grade and volume remain consistent with FR PCa
Tissue-Based Testing	**Decipher** Low-Risk Group **Genomic Prostate Score** Low Likelihood of Adverse Pathology at RP **Prolaris** <3.2% probability of PCa mortality

Once results of Confirmatory Test are available, engage again in shared decision-making. At this point, the conversation should reconsider the merits of definitive treatment versus AS based on the full set of information from estimation of life expectancy, tumor grade and volume, and interpretation of Confirmatory Test results. Patients with FR PCa and reassuring Confirmatory Tests should have increased confidence in the decision to pursue AS. Importantly, many patients with non-reassuring Confirmatory Tests may still be appropriate for AS, but they should undergo more intensive surveillance monitoring (see next section).

Performing Active Surveillance

When patients decide to pursue AS, they enter a period that involves regular follow-up and testing to monitor for changes in the risk of their cancer. This includes PSA testing and reassessments of tumor burden via repeat biopsy and MRI imaging. The goal of this section is to provide a plan for how to perform surveillance actively.

Selecting a Surveillance Plan

For patients who choose AS, it is important to determine the cadence for surveillance testing. Informed by MUSIC data, we have identified patients at standard vs. elevated risk of grade reclassification on surveillance biopsy.

Standard Risk: Patients meeting **all** the following criteria

- GG1 disease
- PSA density <0.15
- Reassuring Confirmatory Test*

Elevated Risk: Patients meeting **any one** of the following criteria

- GG2 disease
- PSA density ≥0.15
- Non-reassuring Confirmatory Test* or No Confirmatory Test

*Patients without pre-biopsy MRI should strongly consider MRI as a Confirmatory Test.

Standard Risk Pathway

<table>
<tr><th rowspan="2">Test</th><th colspan="3">Years after Diagnosis</th></tr>
<tr><th colspan="2">1-4</th><th>5+</th></tr>
<tr><td>PSA</td><td colspan="3">Every 6 months</td></tr>
<tr><td>Provider Visit</td><td colspan="3">Every 6 months with physician or APP*
*Patients should see a physician at least once every 18 months</td></tr>
<tr><td>MRI</td><td>At 1.5 years</td><td colspan="2">Every 1.5-3 years</td></tr>
<tr><td>Per-Protocol Biopsy</td><td colspan="2">At 3 years</td><td>Every 3 years
w/ shared decision making</td></tr>
<tr><td>For-Cause Biopsy</td><td colspan="3">Concerning PSA dynamics or MRI changes</td></tr>
</table>

- PSA every 6 months
- Provider visit every 6 months (physician or APP)*
  - *If APPs are utilized in your practice, the patient should see a physician at least every 18 months
- Obtain MRI at 18 months, and then every 18-36 months thereafter
- Per-protocol surveillance biopsy at 36 months and every 36 months with shared decision-making
- For-cause surveillance biopsy if:
  - Concerning PSA dynamics
    - High PSA velocity (>0.75ng/ml/year)
    - Change in PSA density
      - To ≥0.15 if <0.15 at diagnosis
    - PSA doubling time <3 years
  - After MRI changes
    - Emergence of new PIRADS 4-5 lesion

Elevated Risk Pathway

<table>
<tr><th rowspan="2">Test</th><th colspan="2">Years after Diagnosis</th></tr>
<tr><th>1-2</th><th>3+</th></tr>
<tr><td>PSA</td><td colspan="2">Every 6 months</td></tr>
<tr><td>Provider Visit</td><td colspan="2">Every 6 months with physician or APP*
*Patients should see a physician at least once every 18 months</td></tr>
<tr><td>MRI</td><td rowspan="2">At 1 - 1.5 years</td><td rowspan="2">Every 1 - 2 years</td></tr>
<tr><td>Per-Protocol Biopsy</td></tr>
<tr><td>For-Cause Biopsy</td><td colspan="2">Concerning PSA dynamics or MRI changes</td></tr>
</table>

- PSA every 6 months
- Provider visit every 6 months (physician or APP)*
  - *If APPs are utilized in your practice, the patient should see a physician at least every 18 months
- Obtain MRI and per protocol biopsy at 12-18 months after diagnosis
- In years two and beyond,
  - Per-protocol surveillance biopsy every 1-2 years
  - MRI every 1-2 years (may be staggered with biopsy)
- For-cause surveillance biopsy if:
  - Concerning PSA dynamics
    - High PSA velocity (>0.75ng/ml/year)
    - Change in PSA density
      - To ≥0.15 if <0.15 at diagnosis
      - If ≥0.15 at diagnosis, use clinical judgement
    - PSA doubling time <3 years
  - After MRI changes
    - Change in known PIRADS 4-5 lesion
    - Emergence of new PIRADS 4-5 lesion

PSA- Only Surveillance

PSA-Only Surveillance (akin to Watchful Waiting) is typically reserved for patients with an estimated life expectancy of <10 years.

Primary Pathway

- **PSA every 12 months**
  - Consider MRI/biopsy and/or staging scans for rapidly rising PSA that may suggest the presence of high-risk or metastatic disease that may require treatment

Transitioning to Treatment

If at some point in follow-up a patient's clinical profile or preferences change, a transition to an alternative management strategy may be warranted. For patients with GG1 and low-risk disease at diagnosis that continue to have GG1/low-risk disease during surveillance follow-up, we discourage transition to treatment based on patient preference alone. The decision to transition to treatment for men with GG2/favorable intermediate-risk disease at diagnosis or during follow-up is more nuanced, and patient goals of care, amongst other oncological factors, may influence the decision to stay on AS vs. transition to treatment.

Clinical results obtained in follow-up suggesting cancer progression or changing patient preferences may prompt a transition to treatment, such as surgery, radiation, or focal therapy. If any of the following test results occur, another round of shared decision-making to consider a transition is recommended.

Surveillance Test	**Result to Prompt Discussion about Transition to Definitive Treatment**
Biopsy	GG3 (Gleason score 4+3=7) Significant increase in GG2 or Pattern 4 disease New concerning pathological features (e.g., intraductal carcinoma, cribriform pattern, etc.)
MRI	New PI-RADS 4 or 5 lesion or significant change in known lesion *MRI changes should prompt further evaluation with biopsy. We recommend against direct transition to treatment based on imaging.*
Tissue-Based Test	Classification into a higher risk category *Serial testing is not recommended. Providers should use caution when using the results of prognostic tests to guide treatment decisions given the lack of prospective data.*
Patient Preference	Desire of patient to forego continued surveillance in favor of treatment *Transition to treatment for patients with low-risk disease based on preference should be discouraged.*

Transitioning to PSA-Only Surveillance: Should be considered if new health conditions suggest a patient's life expectancy drops below 10 years.