Essentials for establishing a successful MR-US fusion biopsy program

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Introduction

• Multiparametric MRI with combined MRI and transrectal ultrasound (MRI/TRUS) fusion biopsy is being utilized across academic departments and private practices to aid in the detection, localization and risk stratification of patients with prostate cancer (PCa).

• Evidence suggests improved prostate cancer detection and stratification with mpMRI combined with MRI/TRUS fusion systems.

• ACR Appropriateness Criteria and AUA-SAR guidelines make recommendations concerning use of prostate MRI and MRI/TRUS for detection.

• We present the essentials to successfully establish a MR-US fusion program.

**The authors of this exhibit have no conflicts of interest to disclose**
Goals and Learning Objectives

• Review PI-RADS v2 recommendations for multiparametric MRI (mpMRI) with focus on the technical specifications, caveats and practical aspects with examples.

• Evaluate the literature supporting ability of prostate mpMRI to detect clinically significant prostate cancer.

• Review SAR/AUA prostate MRI and targeted biopsy guidelines.

• Review level of evidence supporting the efficacy of MR/US fusion biopsy with focus on types of devices and the efficacy of targeted vs. random vs. combined biopsy.

• Describe implementation of a simple quality assurance program with teaching modules.
Initial Prostate Cancer Diagnosis

**Baseline Evaluation**
- Family history
- Medications
- History of prostate disease and screening
- Race (i.e. AA men with relative with PCa diagnosed at < 65 yo.
- Genetics

**Risk Stratification of screening**
- Baseline serum PSA (high risk patients, beginning at age 50 for men with average risk with > 5 year life-expectancy
- Digital rectal examination (DRE)

**Indications for Biopsy**
- If PSA > 3.0 ng or suspicious DRE, then biopsy is considered.
- PSA velocity > 0.65 ng/mL/year is also used
- All others, repeat PSA at interval periods.

For biopsy, a standard 12-core TRUS is usually performed, but recent evidence suggests MR-US fusion biopsy after multiparametric MRI can increase detection.


NCCN Guidelines Version 3.2016 Prostate Cancer
Current indications for Prostate MRI (ACR Criteria)

- If clinically suspect PCa in a biopsy naïve patient, then prostate MRI may be performed before TRUS-guided biopsy so the targeted sample may be obtained using MRI or TRUS fusion. ACR Appropriateness Criteria Rating (AACR): 7.

- Clinically suspected PCa with prior TRUS-guided biopsy that is negative. **AACR: 8.** Findings defined by AACR is congruent with new AUA-SAR guidelines.

- Clinically established low risk PCa undergoing active surveillance (AS), intermediate risk PCa undergoing staging and/or active surveillance, and high risk PCa undergoing staging. **AACR: 8.**

Beyond staging for intermediate and high risk PCa, MRI may help in the following:
- New lesions in those patients undergoing AS
- Reveal disease that could benefit from androgen deprivation therapy
- Localizing dominant disease for focal therapy
- Guide surgical planning

ACR Appropriateness Criteria Rating (AACR) Scale:
- 1, 2, 3: Usually not appropriate
- 4, 5, 6: May be appropriate
- 7, 8, 9: Usually appropriate

Prostate Imaging Reporting and Data System (PI-RADS), Version 2 recently released to help standardized Prostate MRI

- PI-RADS version 2 (v2) (released in late 2014-early 2015) attempts to address shortcomings of PI-RADS v1 released in 2012 and to promote global standardization of image acquisition, interpretation and reporting of multiparametric MRI (mpMRI) of the prostate.

- PI-RADS v2 defines clinically significant cancer based on pathology/histology as Gleason score ≥7 (including 3+4 with prominent but not predominant Gleason 4 component), and/or volume ≥0.5cc, and/or extra prostatic extension (EPE).

- The newer version includes an algorithm for deriving overall score based on the T2WI, DWI, and DCE-MRI.

- **FOR LESION DETECTION, ALL COMPONENTS OF THE mpMRI SHOULD BE USED. SCORING OF THE LESION IS BASED ON SPECIFIC IMAGING CRITERIA AND DIFFERS SIGNIFICANTLY BETWEEN THE PERIPHERAL AND TRANSITIONAL ZONES.**

**Technical Specifications from PI-RADSv2**

<table>
<thead>
<tr>
<th>Magnet</th>
<th>3T preferable, or 1.5T (adequate with optimization) 1.5T is preferable in case of implanted devices that have been determined to be MR conditional at 1.5T, but not at 3T, and when there is concern for increased artifacts at 3T (e.g. bilateral metallic hip prosthesis).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coil</td>
<td>An endorectal coil (ERC) coil will increase signal-to-noise (SNR) at any magnet strength. However, the downsides of using an ERC include increased cost, gland deformation, patient discomfort and introduction of artifacts if the coil balloon is filled with air (some endorectal coils are solid, reusable and without balloons). For this reason, the balloon should be filled with liquid (ex. liquid perfluorocarbon or barium suspension). Use of an endorectal coil might be indispensable in older 1.5T scanners. Most 3T scanners and many modern/updated 1.5T scanners [with a high number of external phase array coil elements and RF channels (ex. 16 or more)] are capable of achieving adequate image quality/SNR without an ERC.</td>
</tr>
<tr>
<td>Sequence</td>
<td>All studies should include the following sequences <em>(with matched locations)</em>: T2-weighted (T2W), DWI, and DCE.</td>
</tr>
<tr>
<td>Field of View</td>
<td>12-20cm. At least one sequence should employ a large field of view to evaluate regional lymph nodes to the level of the aortic bifurcation.</td>
</tr>
<tr>
<td>CAE</td>
<td>Computer-Aided Evaluation (CAE) technology is not required for mpMRI interpretation but may improve workflow, provided quantitative pharmacodynamics data, and enhance lesion characterization.</td>
</tr>
</tbody>
</table>
| Patient Preparation (lack of consensus) | - Antispasmodic agents (ex. glucagon) reduce bowel peristalsis and may decrease artifact. Require nursing support for injection.  
- Enemas clear the rectum of stool decreasing artifact and allowing for easier placement of the ERC. May promote peristalsis and add to patient discomfort.  
- Have the patient evacuate his colon prior to the exam. Remove air from the rectum by imaging patient prone or decompressing with a small catheter. |
| Post TRUS biopsy | - Postponing the exam 6 weeks post biopsy will allow for hemorrhage to resolve, but it may not be feasible to wait that long. There is low likelihood for clinically significant cancer to be fully obscured by hemorrhage in setting of negative TRUS biopsy. “Hemorrhagic exclusion” effect of absence of citrate in the cancer will help preserve cancer imaging characteristics in presence of surrounding hemorrhage. |
Components of mpMRI

All studies should include the following sequences (with matched locations):

- **T2-weighted (T2W):** rapid acquisition with fast-spin-echo, 2-3 planes, slice thickness 3mm, FOV 12-20cm to include the prostate and seminal vesicles.

- **Diffusion weighting imaging (DWI):** 2-3 b values < 1000 for calculation of ADC. A separate high b value recommended (real or extrapolated) of ≥1400 sec/mm². Care should be taken to reduce distortion artifacts:
  - Left to Right phase encoding
  - Adequate ADC window and level - 1.650 and 1.675 × 10⁻⁶ mm²/s

- **Dynamic contrast enhanced (DCE):** rapid T1W gradient echo before/during/after IV bolus of gadolinium-based contrast. Early enhancement images most important.

- **MR spectroscopy (MRS):** Can detect cancer and predict lesion aggressiveness, but is not universally available. MRS is currently not a part of PI-RADS criteria.
**PI-RADS assessment for T2W (most important for transitional zone)**

**Transitional zone:**
- **BENIGN** – Homogeneously intermediate signal (1) or BPH nodule (2).
- **INDETERMINATE** - Note 2,4,5; heterogeneous, obscured margins.
- **MALIGNANT** – Non-circumscribed/lenticular with obscured margins and homogeneous T2 hypointensity (4). If (4) features and >1.5cm or with extraprostatic extension/local invasion give score of 5.

**PI-RADS assessment for DWI (most important for peripheral zone)**

**Peripheral/Transitional zone:**
- **BENIGN** – No abnormality on ADC and high b-value DWI (1) or indistinct hypointense on ADC (2).
- **INDETERMINATE** – Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI (3).
- **MALIGNANT** – Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI (4); if (4) features and >1.5cm or with extraprostatic extension/local invasion give score of 5.

**PI-RADS assessment for DCE**

**Peripheral/Transitional zone:** Binary score (+/-) given if there is focal and early enhancement relative to adjacent tissue.
PIRADS™ v2

In the peripheral zone (PZ), DWI is the dominant technique. For example, if DWI score is 4 and T2WI score is 2, then PI-RADSv2 should be 4.

**Peripheral Zone**
- **DWI**
  - Score 1/2 (benign)
  - Score 3 (indeterminate)
  - Score 4/5 (malignant)
- **DCE**
  - If DWI score is 3 (indeterminate), evaluate for early arterial enhancement. If yes, increase PIRADS score from 3 to 4.
- **T2WI**
  - Does not impact score in peripheral zone. May help with staging and detecting extracapsular extension.

In the transitional zone, T2W is the dominant sequence. If T2WI is 4 and DWI is 2, then PI-RADSv2 should be 4.

**Transitional Zone**
- **T2W**
  - Score 1/2 (benign)
  - Score 3 (indeterminate)
  - Score 4/5 (malignant)
- **DWI**
  - If T2W score is 3 (indeterminate), evaluate for restricted diffusion with marked hypointensity on ADC. If yes, increase PIRADS score from 3 to 4.
- **DCE**
  - Does not impact score for transitional zone lesions.

Please refer to the PI-RADS v2 document for scoring schema to be used in cases of inadequacy of one of the sequences.
Examples of PI-RADSv2 Peripheral Zone Lesions

**Peripheral Zone PI-RADS 4:** Less than 1.5cm lesion in the left mid gland shows significant restricted diffusion and also has early arterial enhancement. T2 hypointensity is noted, although does not factor in to the score. Pathology revealed Gleason 3+3 in all cores measuring up to 9mm in length.

**Peripheral Zone PI-RADS 5:** This non-circumscribed lesion measured 1.7cm and extended in to the transitional zone. Marked restricted diffusion, larger size and early enhancement determined the score. The moderate T2 hypointensity did not factor in scoring. Gleason 4+3.
Examples of PI-RADSv2 5 lesions in the Transitional Zone

**Transitional Zone PI-RADS 5:** Large lesion in the anterior fibromuscular stroma is T2 dark, shows intense early enhancement and marked restricted diffusion. Because of the broad base abutting the bladder, there was concern for extraprostatic extension. Pathology was Gleason 8.

**Transitional Zone PI-RADS 5:** A central gland lesion has non-circumscribed margins and is homogeneously T2 hypointense. Marked restricted diffusion is seen. Size >1.5cm. Pathology was Gleason 3+3 in all cores measuring up to 8mm in length.
ACCURACY OF PROSTATE MRI FOR LESION DETECTION: Characteristics of Detected and Missed Prostate Cancer Foci on 3T Multiparametric MRI Using an Endorectal Coil Correlated With Whole-Mount Thin-Section Histopathology.

Authors conclusions: Missed PCa lesions were smaller, low-grade (Gleason score 6) and more commonly satellite lesions, and located in prostate apex. Most Gleason 7 lesions, especially those with a predominant Gleason 4 pattern should be visualized on MRI.
Evaluation of current evidence supporting prostate mpMRI for staging.

Recent meta-analysis of 75 studies demonstrate high specificity but heterogeneous sensitivity of prostate MRI for local PCa staging. Pooled data indicates the following:

<table>
<thead>
<tr>
<th>Evidence For</th>
<th># of Studies</th>
<th># of patients</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracapsular Extension</td>
<td>45</td>
<td>5681</td>
<td>0.57 (0.49 - 0.64)</td>
<td>0.91 (0.88 - 0.93)</td>
</tr>
<tr>
<td>Seminal Vesicle Invasion</td>
<td>34</td>
<td>5677</td>
<td>0.58 (0.47 - 0.68)</td>
<td>0.96 (0.95 - 0.97)</td>
</tr>
<tr>
<td>Overall stage T3 detection</td>
<td>38</td>
<td>4001</td>
<td>0.61 (0.54 - 0.67)</td>
<td>0.88 (0.85 - 0.91)</td>
</tr>
</tbody>
</table>

Conclusions:
• There is low sensitivity and high specificity.
• Endorectal coil showed no additional benefit for ECE detection, but slightly improved sensitivity for SVI detection.
• Higher field strengths and the use of functional imaging techniques can slightly improve sensitivity.
Problems with Conventional Prostate Biopsy

- 12 cores are systematically acquired in the posterior portion of the prostate gland.
- The needle extends ~17 mm into the prostate leading the “misses” in the anterior gland.
- Only 0.45% of gland is sampled.
- 30% of cancer is missed by initial biopsy and is understaged.

Figure. Gold standard targets for 12 core biopsy are shown in green while actual biopsy sites performed by a urologist are shown in red.

Over 1 million patients undergo biopsies annually

MR-US Fusion for Targeted Prostate Biopsy

• Types of MR-guided biopsies
  1. In the magnet (in bore)
  2. MR-US Fusion
     a. Cognitive Fusion
     b. Software-based Fusion

• In-Bore and Software based fusion techniques are equivalent. Recent preliminary data suggests both are superior to cognitive fusion.

• MR-US fusion biopsy systems combine the powerful ability of MRI to visualize clinically relevant prostate cancer with sophisticated probe-tracking software to substantially improve the prostate biopsy technique.


MR-US Fusion for Targeted Prostate Biopsy

**Artemis System**

Artemis uses a robotic arm to scan the prostate and localize the target. The position of the needle and probe is tracked with angle-sensing encoders built in the joints of the arm.

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**UroNav System**

The UroNav system uses an external magnetic field generator to localize the lesion and track the biopsy probe. It allows for freehand use of the US probe during the biopsy which may be preferential to the proceduralist, but may increase room for error.

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Not frequently utilized in US: Koelis/Urostation (France), Hitachi/HI-RVS (Japan), and Geoscan/BioJet
Artemis MRI/TRUS Fusion system is used at VUMC

Image sent to Artemis after mpMRI, segmentation of prostate gland, and PI-RADS grading.

MR targets and standard or customized biopsy plans can be mapped

The exact path and coordinates of the biopsy needle are tracked for reference, planning and monitoring.

**Performance characteristics of MR-US fusion in the detection of prostate cancer for the two largest studies**

<table>
<thead>
<tr>
<th>First Author</th>
<th>First or subsequent biopsy</th>
<th>Overall Cancer Detection</th>
<th>Detection of Significant cancer</th>
<th>Detection of Insignificant cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Artemis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filson</td>
<td>Both</td>
<td>44% (359/825)</td>
<td>71% (229/321)</td>
<td>51% (132/261)</td>
</tr>
<tr>
<td><strong>UroNav</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siddiqui</td>
<td>Both</td>
<td>82% (461/564)</td>
<td>80% (244/304)</td>
<td>61% (213/352)</td>
</tr>
</tbody>
</table>

**FILSON (Artemis):** Combined biopsy (targeted plus standard) resulted in detection of more clinically significant and high-risk prostate cancers than either modality alone (p<0.001). In patients with normal prostate MRI, 16% were subsequently diagnosed with clinically significant cancer on standard biopsy further supporting a role for a combined biopsy approach.

**SIDDIQUI (UroNav):** 690 patients of the total cohort (69%) demonstrated exact agreement between targeted and standard biopsy pathologic risk categories. 304 out of 564 detected lesions were intermediate and high-risk. Targeted biopsy diagnosed a similar number of cancer cases (461 patients) to standard biopsy (469 patients). However, the 2 approaches differed in that targeted biopsy diagnosed 30% more high-risk cancers vs standard biopsy (173 vs 122 cases, P < .001) and 17% fewer low-risk cancers (213 vs 258 cases, P = .002). Approximately 20% of intermediate and high risk prostate cancers were detected only by standard biopsy and were hence not well visualized on MRI.
Some emerging literature provides strong evidence in favor of MRI to assist in tumor localization.

**Trial**: 223 biopsy naïve men participated in a single-institution, prospective study where all had mpMRI and TRUS-guided biopsy. Men with equivocal or suspicious lesions on mpMRI also underwent MR-guided biopsy.

**Results**:
- 142 (63.7%) had PCa
- TRUSGB detected 126 cases of PCa in 223 men (56.5%) including 47 (37.3%) classed as low risk.
- MRGB detected 99 cases of PCa in 142 men (69.7%) with equivocal or suspicious mpMRI, of which 6 (6.1%) were low risk. The MRGB pathway reduced the need for biopsy by 51%, decreased the diagnosis of low-risk PCa by 89.4%, and increased the detection of intermediate/high-risk PCa by 17.7%.

AUA-SAR recently issued Joint Consensus Statement

- Applies to patients with prior negative biopsy.
- Prostate MRI and subsequent MRI-targeted cores appear to facilitate detection of clinically significant disease over repeat biopsy.
- MRI should be performed in accordance of PI-RADSv2.
- Patients receiving a PI-RADS assessment category of 4 & 5 warrant repeat biopsy with image guided targeting.
- Quality assurance program should be implemented.
- Cognitive fusion – good results. Can be pursued if operator well-versed.

AUA-SAR recently issued Joint Consensus Statement

- MR-US fusion – up to 3 mm mis-registration (importance of accurate segmentation for small lesions).
- At least 2 cores from each target. More dependent on the operator and confidence of fusion.
- Systematic biopsy - Depending on quality assurance program, may forego systematic biopsy, case by case basis.
- PIRADS 3 – insufficient data to routinely defer repeat biopsy, maybe deferred on basis of institutional results.
- IF MRI negative – consider PCA3, PHI, 4K, PSA density.
- IF PI-RADS 4 or 5 and negative targeted biopsy, earlier repeat targeted biopsy should be considered.

A Multidisciplinary team is required to implement a successful MR-US Biopsy Program

- Urologists
- Radiologists
- Pathologists
- NPs, Ancillary Staff, IT

Successful MR-US Biopsy Program
Quality Assurance Program at VUMC

We do approximately 8-12 MR-US fusion prostate biopsies a week.

• We have started implementing a Quarterly QA program.

• Slightly modified definition of clinically significant PCa (csPCa) – We include high volume Gleason 3+3 and Gleason 3+4 which are usually classified as intermediate risk in our cohort.

• Aim 1: Calculate PIRADS 4 and 5 (High Risk lesion), upgraded lesion (PI-RADS 3 to 4) and PIRADS 3 positivity rate.

• Aim 2: Identify cases where MRI misses high and intermediate risk cancer.
We are implementing the goals which have only been defined for previously biopsied patients to all populations including biopsy naïve patients for convenience.

- Suggested cancer detection rate (CDR) of csPCa by PI-RADS category:
  - PI-RADS 4: \(\geq 30\%\) of lesions.
  - PI-RADS 5: \(\geq 70\%\) of lesions.
  - Our institutional modified goal: PI-RADS 4 and 5 positive rate at 70\% or better, upgraded lesion (3 to 4) positive rate at 30\% or better.

- Maximum miss rate is also suggested based on comparison biopsies. MRI targeted bores should not miss more than:
  - 10\% of csPCa present on concurrently performed template biopsies.
  - 20\% of csPCa present on concurrently performed saturation biopsies.
  - 30\% of csPCA present on excised whole prostates.
  - Currently our QA program focuses on comparison with template biopsies.
Implementing a Prostate MRI teaching program at Vanderbilt.

- Resident and fellow lectures.
- On-line curated teaching modules with pre- and post tests.
- Micro-CME opportunities using mobile applications.

**ANSWER:** Peripheral Zone PI-RADS 4: A small right sided lesion shows mild ADC hypointensity and would be considered PI-RADS 3; however, the early arterial enhancement bumps up the score to PI-RADS 4. Note, T2 is not main determinant for scoring in the peripheral zone. Pathologic review was Gleason 3+3, high volume.
Conclusions

• High-quality MR imaging interpretation can be achieved by following PI-RADS v2 criteria.

• PI-RADS v2 grading is very accurate in detecting csPCa.

• The recent SAR-AUA joint consensus statement answers offers useful strategies to implement a MRI-TRUS fusion biopsy program.

• The role of the radiologist in diagnosis and treatment of prostate cancer continues to evolve into high-order care.

• One of the most important aspects for establishing a successful prostate MRI and targeted biopsy service is establishment of a QA program.
References


• NCCN Guidelines Version 3.2016 Prostate Cancer


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