Trans-rectal interventional MRI: initial prostate biopsy experience

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ABSTRACT

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) of the prostate gland when evaluated along with T2-weighted images, diffusion-weighted images (DWI) and their corresponding apparent diffusion coefficient (ADC) maps can yield valuable information in patients with rising or elevated serum prostate-specific antigen (PSA) levels. In some cases, patients present with multiple negative trans-rectal ultrasound (TRUS) biopsies, often placing the patient into a cycle of active surveillance. Recently, more patients are undergoing TRIM for targeted biopsy of suspicious findings with a cancer yield of ~59% compared to 15% for second TRUS biopsy to solve this diagnostic dilemma and plan treatment. Patients were imaged in two separate sessions on a 1.5T magnet using a cardiac phased array parallel imaging coil. Automated CAD software was used to identify areas of wash-out. If a suspicious finding was identified on all sequences it was followed by a second imaging session. Under MRI-guidance, cores were acquired from each target region. In one case the microscopic diagnosis was prostatic intraepithelial neoplasia (PIN), in the other it was invasive adenocarcinoma. Patient 1 had two negative TRUS biopsies and a PSA level of 9ng/mL. Patient 2 had a PSA of 7.2ng/mL. He underwent TRUS biopsy which was negative for malignancy. He was able to go on to treatment for his prostate carcinoma (PCa). MRI may have an important role in a subset of patients with multiple negative TRUS biopsies and elevated or rising PSA.

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1. INTRODUCTION

Prostate cancer is a major medical problem not only in the United States, but worldwide. It is the second most fatal non-skin cancer in the United States among men. One in six men will be diagnosed with the disease and one in thirty-five will die of it. There is a growing trend to insert magnetic resonance imaging into the diagnostic work-up of patients who present with multiple negative TRUS biopsies in order to localize and target specific areas for biopsy with CAD under MR-guidance. Here we present the results of this technique in an outpatient setting.

1.1 Current clinical practice

Serum prostate specific antigen (PSA) and digital rectal examination (DRE) are standard tools for screening and diagnosis of PCa. Men who have elevated PSA frequently go on to TRUS biopsy, the gold standard for PCa diagnosis since 1989. It is estimated that over 1,000,000 TRUS biopsies are performed in the United States annually; however only about 20% detect cancer. When patients present year after year with increasing PSA velocity, saturation biopsy may also be performed, but it requires many more cores to be sampled. Additionally it requires pain management and carries a potential risk for increased morbidity. The random sampling of tissue with TRUS biopsy and the invasive nature of saturation biopsy raises questions about the possibility of a less invasive, more targeted approach. The key differentiator between TRUS and TRIM is MRI’s ability to localize not only the gland, but areas of suspicion within the gland.

1.2 Acquisition techniques

The high spatial and temporal resolution of MRI lends itself well to imaging the prostate gland. While only biopsy can diagnose cancer, MR imaging with a multi-parametric approach can assist with the characterization of areas within the gland that may warrant biopsy. Each pulse sequence has its own unique merits and limitations, but when used in combination can be helpful for selection of patients for TRIM biopsy for cancer detection. Most centers utilize four sequences to optimize successful imaging of the prostate gland. These include high resolution T2-weighted imaging in both axial and coronal planes. Image detail is improved by using dual coil technique with an 8 channel cardiac surface coil in conjunction with a 2 channel endorectal coil; but some groups are obtaining satisfactory imaging with surface coil technique alone. In attempts to improve diagnostic accuracy of prostate cancer detection, three additional function sequences can then be utilized. These include diffusion-weighted imaging (DWI), Dynamic contrast enhanced imaging (DCE) in conjunction with a dedicated post processing CAD system.
Before commencing with these diagnostic sequences; an axial T-1 weighted scan should be performed if the patient has undergone TRUS biopsy within 10 weeks of scanning; to evaluate possible residual gland hemorrhage; which can lower the sensitivity of the diagnostic scan. T2-weighted scanning is useful for assessment of gland size, evaluation of the normal high signal in the peripheral zone; central zone BPH nodules/prostatitis, neurovascular bundle, and the capsule of the gland. The seminal vessels are also evaluated best on the T-2 weighted sequence. Prostate cancer has been shown to usually represent a well defined focus of decreased signal intensity in the peripheral zone. The apex of the gland can be a blind area hard to target during TRUS; and approximately 20% of MRI depicted cancers can be identified in this location. Benign prostatic hyperplasia (BPH) nodules tend to be sharply marginated; and heterogeneous in signal intensity; and seen more in the central zone.

1.3 Advanced imaging techniques

DWI imaging is a reflection of restricted free water; and prostate cancers typically have increased signal intensity on high b-value DWI sequences. These sequences tend to have lower spatial resolution; but positive DWI findings in conjunction with a suspicious focus on T2-weighted images has been associated with higher Gleason score; and a reasonable predictor of more aggressive disease. Many centers use b-values of 0, 500, 1000, and 1500. DCE imaging of the prostate utilizes similar principals for assessment of disease as breast MRI with DCE. However; the prostate differs in that the kinetics and biology tend to be much more rapid. This requires modifying the sequences to increase temporal resolution to 3 seconds/acquisition. On a high field scanner, many sites acquire images every 3 seconds for 5 minutes; which produces 100 time points for kinetic curve evaluation. As in breast MRI; rapid wash-in/wash-out is highly associated with suspicious foci. BPH nodules can occasionally have similar kinetic patterns, but their easily recognized anatomic findings make distinction fairly easy. Muti-voxel spectroscopy: MRS of the prostate was promoted as an accurate imaging technique by Kurhanewicz et al in the 1990’s¹¹, but many other centers were not able to replicate their experience. MRS is challenging to perform properly. The magnet requires a very tight shim. Endorectal coil is almost a requirement for optimal signal and spectral analysis. The balloon should be distended with either a perfluorocarbon, or concentrated barium/water mixture and not air or water to reduce spectroscopy susceptibility artifacts. Care must be taken in prescribing voxel placement to completely include the prostate gland, and minimize inclusion of the periprostatic fat. The voxel sizes tend to be 5x5x7mm for resolution. The challenge is that the pulse sequence requires 14-17 minutes on most scanners. The suspicious anatomic foci seen on T2-weighted images are evaluated; and spectral curves derived. The UCSF group uses as distinguishing threshold
of Choline +Creatine/Citrate ration of >0.5 on a 1.5T magnet. The NIH group uses a Choline/Citrate ration of >0.38 on a Philips 3T scanner\textsuperscript{12}. The higher the abnormal ration; the higher grade Gleason score tends to be identified. Some centers feel the diagnostic yield from MRS is low; and not worth the time penalty for the scan sequence. If the patient cannot tolerate an endorectal coil, performing the MRS can be omitted. Much of the recent literature on prostate MRI compare DWI versus T2-weighted imaging; or DCE versus T2-weighted imaging\textsuperscript{13}; but there has been little data that has analyzed the cumulative sensitivity, specificity and PPV of incorporating the data from all 4 pulse sequences. Some centers are creating a scoring system of probability by summarizing the data identified by these 3 functional sequences and the high resolution anatomic scan. If three or four of the sequences support a diagnosis of probable malignancy; it can be read as a high probability of cancer in a specific focus; if two sequences are positive; a moderate probability report can be generated; if only one sequence is positive; it can be classified as low probability; and follow up with repeat MRI scanning in 6-12 months can be recommended and correlated with PSA levels. TRIM is usually suggested as reasonable procedure for patients who have had a negative TRUS and have at least a moderate probable positive MRI\textsubscript{6}.

2. METHODS

2.1 Patient selection

Patients were selected based on PSA level\textsubscript{4}, clinical history and imaging findings following negative TRUS biopsy\textsubscript{2,6}.

2.2 Diagnostic imaging session

TECHNIQUE: This imaging study was accomplished using a 1.5Tesla MIR scanner (Intera Achieva XR, Philips Healthcare, Best, The Netherlands). High performance gradients (33 mT/m) and advanced software capabilities were utilized for enhanced image quality. Spectroscopy was not performed. Preliminary images were obtained before contrast material administration. Following uneventful intravenous infusion of 0.1 mmol/kg gadolinium contrast material (Omniscan, GE Healthcare, Waukesha, WI USA) via power injector (MEDRAD, Pittsburgh, PA USA) at 2.2 mL/sec. followed by 26cc saline flush, additional images were acquired. The pulse sequences and post processing functions that were obtained are summarized as follows:

<table>
<thead>
<tr>
<th>PLANE</th>
<th>THICKNESS</th>
<th>WEIGHTING</th>
<th>SEQUENCE</th>
<th>OPTION</th>
</tr>
</thead>
</table>
Axial 4.0 T1 TSE
Axial 4.0 T2 TSE
Coronal 4.0 T2 TSE
Sagittal 4.0 T2 TSE
Axial 3.0 DWI TSE
Axial 4.0 T1-3D FFE + Gad

2.3 Findings Patient 1

The prostate gland was enlarged measuring 5.0 cm AP x 6.8 cm transverse x 6.3 cm craniocaudad consistent with a prostatic gland volume of 111 cc. The inner gland of the prostate gland was enlarged and demonstrated inhomogeneous signal intensity most commonly due to benign prostatic hypertrophy. The dominant finding was a 1.1 cm x 0.8 cm ill-defined focus of T2 shortening in the left inner gland mid gland level that demonstrated mild restricted diffusion on the diffusion weighted imaging (Figure 1)

![Figure 1](image1.png)

Figure 1. T2-weighted axial image at the level of the left inner gland mid gland level with corresponding DWI image and ADC map.

and a rapid wash-out pattern of dynamic gadolinium contrast enhancement confirmed with computer-aided detection (Figure 2). A similar finding measuring 1.1 cm x 0.8 cm was seen in the right peripheral zone mid gland level.
There was a 1 cm focus of T1 shortening in the peripheral zone on the left mid gland level that most likely represented post biopsy change. There was also a 1.3 cm focus of T2 shortening in the left peripheral zone at the level of the base of the prostate gland that did not demonstrate associated restricted diffusion and did not demonstrate a rapid wash-out pattern of dynamic gadolinium contrast enhancement. This was most suggestive of fibrosis. No pelvic lymphadenopathy was seen. No invasion of the seminal vesicles was seen. There was no evidence of extension of an extracapsular mass arising from the prostate gland. The visualized osseous structures in the pelvis demonstrated no evidence of osseous metastatic disease. Based on these findings the patient was referred for TRIM biopsy.

Bi-exponential curve fits were used to smooth the appearance of the curves to better demonstrate wash-in and wash-out. The bi-exponential function is expressed as:

\[ C(t) = A_1 \exp(-m_1 t) + A_2 \exp(-m_2 t) \]  

(2)

This is a linear combination of two exponential decay functions. If one of them is positive, they can be combined into something that closely resembles typical enhancement curves, which are point-to-point representations of signal intensity change within a single pixel over the course of time. Utilization of curve fits minimizes the influence of noise and artifacts (such as susceptibility variations introduced by \( B_0 \) and \( B_1 \) inhomogeneities\textsuperscript{15} and artifacts introduced during first-pass contrast administration\textsuperscript{14.}) on the analysis of the contrast enhancement kinetics.
2.4 Findings Patient 2

The dominant finding was a 1.1 cm x 2.1 cm ill-defined focus of T2 shortening in the left peripheral zone mid gland level that demonstrated restricted diffusion on the diffusion-weighted imaging and a rapid wash-out pattern of dynamic gadolinium contrast enhancement confirmed with computer aided detection (Figure 3).

![Parametric overlay on DCE image with corresponding kinetic curve.](image)

On the coronal T2-weighted images there was some bulging of the contour of the surface of the prostate gland on the left associated with this finding. This finding was amenable to MR guided biopsy of the prostate gland (Figure 4).

![T2-weighted coronal image of the left peripheral zone at the mid gland level with corresponding DWI image and ADC map.](image)

There was a nodular focus of T2 shortening in the right peripheral zone at the level of the base of the prostate gland adjacent to the right seminal vesicle measuring 1 cm x 1.5 cm. No associated restricted diffusion or malignant pattern of dynamic gadolinium contrast enhancement was identified. This finding was not amenable to MR guided biopsy of the prostate gland. There was a third focus of nodular T2 shortening involving the right
peripheral zone at the level of the apex of the prostate gland measuring 0.4 cm x 0.4 cm. While this finding demonstrated restricted diffusion on diffusion-weighted imaging, there was no malignant pattern of dynamic gadolinium contrast enhancement identified on the dynamic post-gadolinium images. This finding was too small to be amenable to MR guided biopsy. No pelvic lymphadenopathy was seen. No invasion of the seminal vesicles was seen. The visualized osseous structures in the pelvis demonstrate no evidence of osseous metastatic disease. Based on these findings the patient underwent TRIM biopsy.

### 3. BIOPSY PROCEDURE

#### 3.1 Trans-rectal interventional MRI device

The TRIM device is an MR-compatible solution to position biopsy instruments against the prostate gland to take targeted tissue samples. The MR-visible needle guide is introduced trans-rectally and connected to a clampstand. This allows precise adjustments according to the MRI findings in order to place the MR-compatible biopsy gun to acquire samples from the suspicious area. The device consists of four components (Figure 5):

![Figure 5. TRIM device components: prostate needle guide, patient pad, clampstand and baseplate.](image)

#### 3.2 Interventional imaging session

Patient 1 was a 71 year-old male with clinically elevated PSA, 9.0 in May, 2009 and history of two negative trans-rectal ultrasound guided biopsies. Based on prior diagnostic MR imaging findings, patient was referred for MRI-guided core biopsy. Patient 2 was a 60 year-old male with clinically elevated PSA, 7.2. Previous TRUS biopsy of the prostate was negative for malignancy. Again, based on prior diagnostic MR imaging findings, this
patient was also referred for MRI-guided prostate core biopsy. Both patients were instructed to obtain two adult fleet enemas and administer them two hours prior to their scheduled appointment. They were given a prescription for an antibiotic (Cipro 500 mg orally twice a day) to be taken one day prior to their biopsy, the actual day of the biopsy, and the day following the biopsy. It was explained that antibiotic prophylaxis decreases the risks of infection due to the trans-rectal approach of the procedure. Patients were also asked if they had a prosthetic heart valve or joint implant, requiring additional antibiotics. Patients were advised not to take aspirin, Motrin, Advil, Darvocet N100, or ibuprofen products for a period of 5 to 7 days prior to the biopsy due to their anticoagulant properties. Patients were questioned about anticoagulants such as Coumadin to reduce issues with bleeding. Because intestinal gas and bowel contents interfere with the procedure, patient were advised to avoid gum chewing, carbonated beverages, beans, and consuming members of the cabbage family during the 24 hours prior to their examination. Lastly, patients were asked about bleeding and bruising disorders.

3.3 Target localization Patient 1

For each procedure, the patient was placed on the MRI table in the prone position on the biopsy device (Figure 6).

![Figure 6. Patient positioning with needle sleeve in place.](image)

One coil was placed anteriorly and the other placed posteriorly in a phased-array configuration. Although the procedure requires no sedation or anesthesia, both patients chose the option of intravenous sedation to increase comfort and minimize memory of the procedure. Conscious sedation was performed with Versed injected at 0.5 mg increments over 1½ hours. Pulse rate and $O_2$ saturation were monitored throughout the procedure. $O_2$
saturation remained above 95% throughout the duration of the procedure. The needle sleeve biopsy guide was placed in the rectum (Figure X) without difficulty following DRE with viscous lidocaine. The localization device was attached to the biopsy guide and preliminary sequences were obtained to document optimal positioning. T2 sagittal (Figure 7)

![Sagittal T2-weighted acquisition for visualization of fiducial marker and calibration.](image1)

Figure 7. Sagittal T2-weighted acquisition for visualization of fiducial marker and calibration.

and coronal (Figure 8)

![T2-weighted coronal image with graphic overlay of needle trajectory.](image2)

Figure 8. T2-weighted coronal image with graphic overlay of needle trajectory.
sequences were acquired. Utilizing prostate biopsy software, the lesion in the right mid gland peripheral zone was localized. The biopsy device was calibrated and the needle track pathway was then determined, obtaining coordinates for the localizer. Once the coordinates were obtained, the biopsy sleeve was adjusted in the sagittal, axial and coronal planes. An oblique axial confirmation scan was performed to confirm adequate needle track position through the lesion. Using the needle graphic confirmation dataset, an 18-gauge core biopsy needle was advanced into the lesion and a specimen was obtained. A follow-up scan before removal of the needle was performed to ensure optimal needle position. The needle was removed and the core was placed in the specimen container. In similar fashion, a second site was biopsied in the central zone mid gland to the left of midline as depicted in Figure 8. Following adequate acquisition of core material, the needle sleeve was then removed and the patient was allowed to ambulate. The patient voided without difficulty. No hematuria was observed. The patient tolerated the procedure well with no complication. The patient was discharged 30 minutes following the procedure in satisfactory condition without complaint. A post biopsy instruction sheet was reviewed with the patient. The patient was instructed to call if any complications arise such as unusual rectal bleeding, protracted hematuria longer than two to three days, or fever greater than 101°F. The patient was instructed to follow up with his personal physician regarding biopsy results in two to three days.

3.4 Target localization Patient 2

The patient was placed on the MRI table in the prone position. Conscious sedation was performed with Versed injected at 0.5 mg increments over 1½ hours. Pulse rate and O₂ saturation were monitored throughout the procedure. O₂ saturation remained above 95% throughout the duration of the procedure. The needle sleeve biopsy guide was placed in the rectum without difficulty. The localization device was attached to the biopsy guide and preliminary sequences were obtained to document optimal positioning. T2 axial and sagittal sequences were acquired. Utilizing prostate biopsy software, the lesion was localized in the left peripheral zone mid gland slightly anteriorly. The biopsy device was calibrated and the needle track pathway was then determined obtaining coordinates for the localizer. Once the coordinates were obtained, the biopsy sleeve was adjusted in the sagittal, axial and coronal planes. An oblique axial confirmation scan was performed to confirm adequate needle track position through the lesion (Figure 9).
Using the needle graphic confirmation dataset, an 18-gauge core biopsy needle was advanced into the lesion and a specimen was obtained. A follow-up scan before removal of the needle was performed to ensure optimal needle position. The needle was removed and the core was placed in the specimen container. The 0.4 cm nodular focus of signal abnormality in the right peripheral zone in the apex of the gland was localized. In similar fashion, a specimen was obtained with the 18-gauge core biopsy needle. Following adequate acquisition of core material, the needle sleeve was then removed and the patient was allowed to ambulate. The patient voided without difficulty. No hematuria was observed. The patient tolerated the procedure well with no complication. The patient was discharged 30 minutes following the procedure in satisfactory condition without complaint. A post biopsy instruction sheet was reviewed with the patient. The patient was instructed to call if any complications arise such as unusual rectal bleeding, protracted hematuria longer than two to three days, or fever greater than 101°F. The patient was instructed to follow up with his personal physician regarding biopsy results in two to three days.

3.5 Post-procedure care

Patients were reminded that due to the risk of infection that it was important to continue taking their antibiotics as directed and to drink plenty of fluids to increase urine output. They were informed to expect some or all of the following: A small amount of blood streaking of stool for three to five days, gross hematuria or passage of small clots for several days, and hematospermia with sexual activity for three to four weeks. They were also advised that in approximately 1 percent of patients, complications may occur which require immediate medical attention. These are: excessive bleeding per rectum, such as
bloody diarrhea or passage of numerous large clots, inability to urinate or voiding frequently small amounts, fever over 101°F, weakness, flushing, or shaking chills. Instructions were provided to contact medical staff or visit local hospital emergency departments should symptoms arise. Overall, both patients tolerated their procedures extremely well.

4. RESULTS

4.1 Pathology Patient 1

Gross description: (A) specimen received in formalin labeled “Right peripheral zone mid gland, slight anterior”. It consisted of two cylindrical segments of tan-white tissue measuring 0.6 and 0.7 cm in length x 0.1 cm in diameter. (B) specimen received in formalin labeled “Left inner gland and mid gland central zone”. It consisted of a cylindrical segment of tan-white tissue measuring 1.0 cm in length x 0.1 cm in diameter.

Microscopic description: core biopsies of the prostate were studied at three levels of each paraffin block represented by six slides, 35 sections. The right peripheral zone tissue demonstrated a pattern of hyperplasia with cytologic evidence of prostatic intraepithelial neoplasia (PIN). There were areas of ordinary hyperplasia in which columnar epithelial cells proliferate with basally situated, uniform nuclei, abundant pale cytoplasm and intraluminal papillary upheaval that focally creates a lattice. Elsewhere the papillations are composed of cells in which fusiform, hyperchromatic nuclei are organized with long axis perpendicular to basement membrane, with retained polarity, slight crowding and homogeneous, dark chromatin which presented a visual variance from the hyperplastic gland elsewhere. There were also areas in which the nuclei were pale with prominent nucleoli. Both nuclei and nucleoli exhibited size variation and disorder. These areas, too, were considered to represent PIN. The left inner gland biopsies were presented by muscle, precipitated fibrin, inert involuted glands, a lymphocytic infiltrate and a few glandular acini formed by cells whose nuclei were variable in size, contour and polarity, with vacuoles, nucleoli and crowding, also considered to reflect PIN. Diagnosis (Figure 10):
(A) prostatic intraepithelial neoplasia (PIN) with atypical hyperplasia, (B) focal microscopic PIN, chronic inflammation, involution of fibrin precipitation.

4.2 Pathology Patient 2

Gross description: (A) specimen received in formalin labeled, “Left peripheral zone mid gland (slight anterior), and consisted of three cylindrical segments of tan-white tissue measuring 0.7 to 1.1cm in length x 0.1cm in diameter. (B) the specimen was received in formalin labeled, “Right peripheral zone apex”, and consisted of a cylindrical segment of tan-white tissue measuring 0.7cm in length x 0.1cm in diameter. Microscopic description: core biopsies of prostate were studied at three levels of each paraffin block represented by 27 sections distributed on six slides. Samples from the left peripheral zone (A) confirm invasive adenocarcinoma representing 55% of the 1.1cm core, 20% of the 1.0cm core and 71% of the 0.7cm core. Measurements take in to account the sum of discontinuous segments. The neoplasm was arranged microarchitecturally in closely juxtaposed, compact glands of variable size, often with little or no intervening stroma, with microacini incinuated among the dominant expanses of glandular proliferation. Nuclei were round, hyperchromatic with textured chromatin and nucleoli of variable size and conspicuity. Open lumina contained pink-gray secretory accumulations. There were elements of cribriform and papilliform organization. The overall pattern was consistent with Gleason 3. However, areas of coalescence, streaming and luminal obscuration are evident for an element of Gleason 4. No perineural space invasion was identified. The intervening parenchyma varied from normal to hyperplastic with foci of involution. The right peripheral zone biopsies consist of smooth muscle, adipose tissue, rectal mucosa and a fragment of benign inert glandular tissue. Microscopic diagnosis (Figure 11):
Figure 11. Invasive adenocarcinoma (Patient 2).

(A) Invasive adenocarcinoma of the prostate, Gleason 3+4=7. (B) Benign inert glandular tissue, smooth muscle, adipose and rectal mucosa.

5. DISCUSSION

5.1 Diagnostic imaging options

The high false-negative rate of TRUS biopsy has led to many questions about improving the targeting of biopsy for detection of prostate disease. Laterally directed biopsies, sonographically targeting hyopoechoic areas, and performing saturation or extreme biopsies evolved over the years as techniques to improve diagnosis. MRI is evolving as a viable option for patients who present with rising or elevated PSA following negative TRUS.

5.2 Conclusion

Early detection and treatment of prostate disease in patients with rising or elevated PSA and negative TRUS biopsy may be possible with the insertion of MRI and TRIM biopsy into the diagnostic work-up. The ability of MRI to visualize areas within the prostate gland provides a useful diagnostic tool that also provides reliable information for targeting. TRIM prostate biopsy is easily performed in an outpatient setting and well-tolerated by patients.
REFERENCES


