MRI-directed cognitive fusion-guided biopsy of the anterior prostate tumors

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PURPOSE
We aimed to evaluate the efficacy of magnetic resonance imaging (MRI)-directed cognitive fusion transrectal ultrasonography (TRUS)-guided anterior prostate biopsy for diagnosis of anterior prostate tumors and to illustrate this technique.

METHODS
A total of 39 patients with previous negative TRUS biopsy, but high clinical suspicion of occult prostate cancer, prospectively underwent prostate MRI including diffusion-weighted imaging (DWI). Patients with a suspicious anterior lesion on MRI underwent targeted anterior gland TRUS-guided biopsy with cognitive fusion technique using sagittal probe orientation. PIRADS version 1 scores (T2, DWI, and overall), lesion size, prostate-specific antigen (PSA), PSA density, and prostate gland volume were compared between positive and negative biopsy groups and between clinically significant cancer and remaining cases. Logistic regression analysis of imaging parameters and prostate cancer diagnosis was performed.

RESULTS
Anterior gland prostate adenocarcinoma was diagnosed in 18 patients (46.2%) on targeted anterior gland TRUS-guided biopsy. Clinically significant prostate cancer was diagnosed in 13 patients (33.3%). MRI lesion size, T2, DWI, and overall PIRADS scores were significantly higher in patients with positive targeted biopsies and those with clinically significant cancer (P < 0.05). Biopsies were positive in 90%, 33%, and 29% of patients with overall PIRADS scores of 5, 4, and 3 respectively. Overall PIRADS score was an independent predictor of all prostate cancer diagnosis and of clinically significant prostate cancer diagnosis.

CONCLUSION
Targeted anterior gland TRUS-guided biopsy with MRI-directed cognitive fusion enables accurate sampling and may improve tumor detection yield of anterior prostate cancer.

Patients with clinical suspicion of malignant prostate neoplasm (i.e., elevated prostate-specific antigen [PSA], suspicious nodule on digital rectal examination) typically undergo systematic transrectal ultrasonography (TRUS)-guided sectoral biopsy; however, the overall yield of initial biopsy is 22%–29% (1, 2). Potential reasons for false negative TRUS biopsy include sampling error or technical limitation due to the location of tumor. Anteriorly located tumors, where the dominant tumor mass is anterior to the urethra represent a particular diagnostic challenge, as they are not sampled in standard systematic 12-core needle biopsy, and it is estimated that 21% of malignant prostate tumors occur in the anterior prostate (3, 4). Furthermore, when TRUS biopsy detects minimal volume/low-grade carcinoma, failure to sample a coexistent more aggressive anterior tumor may lead to an underestimation of disease burden and aggressiveness (5) and inappropriate management by enrollment in an active surveillance program.

In addition to an established role in the staging of prostate cancer (6–8), magnetic resonance imaging (MRI) has an increasing role for the localization of prostate tumors which can then be targeted for biopsy (9–11). For lesion localization, anatomic T2-weighted sequences are combined with one or more functional technique including diffusion-weighted imaging (DWI) (12), magnetic resonance spectroscopy (MRS) or dynamic contrast-enhanced (DCE) MRI (9–11). Based on suspicion of prostate cancer, targeted biopsy of the suspicious area can then be performed with either MRI guidance (10) or TRUS guidance. The level of suspicion of prostate cancer on MRI can be quantified using the Prostate Imaging Reporting and Data
System (PIRADS) (13). Where TRUS is used to guide targeted biopsy, electronic fusion of magnetic resonance images with TRUS images can be performed to guide biopsy (14, 15), or “cognitive fusion” can be used (16), by which the operator prospectively reviews the MRI appearances and uses TRUS to guide targeted sampling of the area of suspected tumor in the prostate gland.

Limited literature is available regarding the technique for TRUS-guided biopsy of the anterior apex of the prostate (17, 18). The goal of the current study is to evaluate the effectiveness of MRI-directed cognitive fusion TRUS-guided anterior prostate biopsy for diagnosis of anterior prostate tumors and to illustrate this technique.

Methods

Study design

The study was reviewed by the institutional ethics committee and approved as a clinical audit. In accordance with local policy, informed consent was not required. Patients were included if they had undergone MRI-directed targeted TRUS-guided anterior prostate biopsy in 2011–2014 because of suspicion of anterior tumor on MRI (Chart 1). All patients had undergone previous nontargeted TRUS-guided sectoral biopsy which was negative for carcinoma, but had undergone MRI for further evaluation due to persistent clinical concern for occult neoplasm.

MRI technique

All patients were scanned using 1.5 T MRI whole body scanner (GE Signa HDx or Siemens Avanto), with phased array external surface coil with parametric technique (T2-weighted imaging and DWI) (19). MRI scan technique included multiplanar T2-weighted imaging including high-resolution axial T2-weighted images (TR, 3720 ms; TE, minimum; NEX, 4; slice thickness, 3 mm; interslice gap, 1 mm; b value, 800 s/mm²).

MRI interpretation

For the purpose of this analysis, MRI findings of each patient were reviewed retrospectively by two radiologists with five and three years of experience in pelvic MRI interpretation. The studies were reviewed in a randomized order, with the radiologists blinded to the biopsy results. For each patient the anterior lesion suspected on MRI, which had prompted targeted biopsy, was scored using the PIRADS system (version 1) (13), with scores ranging 1–5 for T2 and DWI appearances. Interpretation of DWI data included both diffusion-weighted images and apparent diffusion coefficient (ADC) map, which were analyzed qualitatively. An overall score was also applied based on overall interpretation of MRI findings and scored 1–5. Additionally, the maximum dimension of the lesion on MRI was measured on the axial T2-weighted images, while visually referencing the diffusion-weighted images and ADC map. Two radiologists in consensus carried out all scoring and measurements.

The overall prostate volume was calculated by multiplying the maximum dimensions of the gland in three planes (anterior-to-posterior × transverse × craniocaudal) × 0.52.

Anterior TRUS biopsy technique

All biopsies were performed using either a BK ProFocus 2202 ultrasound machine (BK Medical) with the end-fire convex array of a multi-frequency 8818 transducer or a Philips iU22 ultrasound machine (Philips Healthcare), with an end-fire curved array C9-5ec transducer. All biopsies were performed by one of two radiologists with seven and 30 years of experience in TRUS prostate biopsy. At our institution, TRUS biopsies (both standard systematic and targeted) are typically performed with conscious sedation, peri-prostatic local anesthetic (10 mL 1% lidocaine) and a transverse plane of US and biopsy guidance. This limits effective sampling of the anterior gland. In a modification of technique described for apical anterior horn biopsy (17, 18), a sagittal plane of TRUS imaging and biopsy guidance was used. The endorectal ultrasound probe was positioned in the sagittal plane, such that the needle guide was positioned anteriorly with respect to the probe (Fig. 2). Cognitive fusion was employed to determine the exact location for biopsy sampling, following review of the patient’s MRI. The probe was then angled as needed in the sagittal plane such that the needle trajectory included the area of concern (Fig. 1). For lesions located more cranially, the biopsy needle was advanced 1–2 cm into the prostate gland prior to deploying the biopsy device. For more caudally located lesions, the biopsy device was activated from the prostate surface or with minimal advancement into the gland prior to triggering the device. Medial-to-lateral localization was performed by identifying the urethra in the midline as a landmark, then scanning laterally to the lateral margin of the gland to define the lateral border. Samples were taken more medially or laterally as needed based on the preprocedure MRI. Finally, if a concordant hypoechoic nodule was identified in a similar position to a suspicious lesion on MRI, the biopsy needle was directed into this area. At least two cores of tissue were obtained from the target area.

Clinical and biopsy data

Patient age and PSA levels prior to biopsy were recorded. PSA density was calculated by dividing serum PSA by prostate gland volume as determined on MRI. Gleason grade of biopsy samples positive for carcinoma were recorded in addition to the percentage of core biopsy sample involved by tumor. Clinically significant cancers were defined based on Epstein criteria: Gleason grade of ≥7; or percentage core biopsy involvement by tumor ≥50% (20, 21).

Statistical analysis

All analysis was performed using STATA Version 13.1 (Statacorp).

The primary hypothesis was that targeted anterior prostate biopsy would have a similar yield to that established in the existing literature for targeted prostate biopsy not limited to the anterior prostate gland. The yield of targeted TRUS biopsy based on MRI findings for the diagnosis of occult prostate cancer ranges from 39%–56% (10, 12, 16, 22, 23). For the purpose of sample size calculation, the null hypothesis was that the yield of anterior biopsy would be low (20%) and the alternative hypothesis was that the yield would be similar to the literature for targeted prostate biopsy not limited to the anterior prostate gland (45%). Sample size estimation was carried out using power analysis for a one sample Wald test with probability (power) of 0.9, and type I error probability of 0.05. This resulted in sample size estimation of 42.

Main points

- Transrectal targeted ultrasound-guided biopsy with cognitive fusion allows accurate sampling of clinically significant anterior prostate tumors suspected on MRI.
- In this setting, overall PIRADS score was an independent predictor of positive biopsy.
- PSA density was higher in those with positive biopsies; however, PSA was not.

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Continuous data (age, lesion size, PSA, prostate volume, PSA density) were compared between biopsy positive and negative groups using an independent samples t-test. In a similar way, continuous data were compared between clinically significant cancer cases and the remaining cases.

The positive predictive value of PIRADS overall score for prediction of a positive targeted biopsy and for the prediction of clinically significant cancer was calculated. Forward stepwise logistic regression analysis was performed for prediction of positive biopsy and for prediction of clinically significant cancer diagnosis.

**Results**

During the study period, 1984 TRUS-guided prostate biopsies were performed at this institution. Of these, 110 were targeted biopsies with MRI-directed cognitive fusion technique. Of these, 47 cases had biopsy targeted to an anterior prostate lesion. Excluding patients with previous positive biopsy (active surveillance candidates), 39 patients were eligible for the study. Mean age was 67.1±7.6 years. Case examples are shown in Figs. 3 and 4. Patient demographics, imaging and biochemical parameters are presented in Table 1.

Comparison of overall biopsy yield with PIRADS score, lesion size, PSA, prostate volume, and PSA density is presented in Table 2. Comparison of clinically significant prostate cancer yield with PIRADS score, lesion size, PSA, prostate volume, and PSA density is presented in Table 3. The overall PIRADS score, T2 score and DWI score were all significantly higher in the positive biopsy group compared with the negative biopsy group, and were also higher in cases of clinically significant cancer diagnosis. Serum PSA was not significantly different between positive and negative biopsy groups or between clinically significant cancer and remaining cases. However, PSA density was higher in patients with positive biopsies. Forward stepwise logistic regression analysis demonstrated that overall PIRADS score was an independent predictive factor for positive biopsy (odds ratio, 3.77; 95% confidence interval [CI], 1.40–10.16; \(P = 0.009\)) and for the diagnosis of clinically significant cancer (odds ratio, 3.91; 95% CI, 1.38–11.09; \(P = 0.011\)).

The positive predictive values of overall PIRADS 3, 4, and 5 score for positive anterior targeted biopsy were 29%, 33%, and 90%, respectively, and for clinically significant cancer were 21%, 13%, and 80%, respective-
Biopsies were more likely to be positive in larger lesions; the mean maximum diameter of lesions on MRI with subsequent positive biopsy was 20.2±8.7 mm vs. 13.4±5.3 mm for cases with negative biopsy (P = 0.005).

In 18 of 39 patients (46.2%), adenocarcinoma was identified in the anterior targeted biopsy samples. Clinically significant cancer was identified in 13 of 39 patients (33.3%). The mean age was 68.1±8.6 years in patients with positive targeted biopsy, and 66.1±6.7 years in those with negative biopsy.

On histology, the overall median tumor Gleason grade was 7 (range, 6–9). Six cases had Gleason 6 (3+3) tumors. Nine cases had Gleason 7 tumors, of which there were eight (3+4) and two (4+3) cases. There were three Gleason 9 (4+5) tumors. The mean percentage of involvement by tumor of each core sample was 30.6%±21.2%.

Review of microbiology records for positive urine cultures within one week following the biopsy date, and the radiology information system for complications revealed one case of postprocedural sepsis. The patient was successfully treated with intravenous antibiotics for five days (gentamycin and amoxicillin-clavulanate), with a subsequent course of oral antibiotics and sepsis resolved without long-term consequences.

**Discussion**

In this study, a technically feasible transrectal approach to targeting anterior prostate lesions identified with MRI for biopsy is described and validated by correlating results with MRI PIRADS score. The results indicate a close correlation of targeted biopsy results with PIRADS overall score, with 90% of biopsies positive in cases with the highest prebiopsy suspicion based on MRI PIRADS 5 score. The yield was moderate in cases with PIRADS 4 (33%) and PIRADS 3 (29%) lesions.

These targeted anterior biopsy results, with an overall yield of 46.2%, compare favorably with the existing literature for MRI-directed TRUS prostate biopsies for biopsy-occult tumors in other parts of the prostate (not confined to the anterior prostate), where cancer diagnosis ranges from 39% to 56% (10, 12, 16, 22, 23). For example, using a cognitive fusion technique, Park et al. (12) demonstrated an overall yield of 39.5% of prostate cancer in a study of 43 men with prior negative biopsy, persistent elevation of PSA, and suspicious lesion on MRI. MRI has been shown to correlate with anterior biopsy findings, but previous studies have used positive anterior biopsy as a starting point.
with MRI findings analyzed retrospectively (5, 24). The current study, however, includes all cases where an anterior targeted biopsy was performed based on MRI suspicion of prostate cancer (PIRADS 3 or greater).

The advantage of the technique utilized in this study is the use of widely available TRUS equipment and procedure performance with conscious sedation and local anesthetic. The results of the current study also compare favorably with the efficacy of transperineal template biopsy. For example, Taiira et al. (25) demonstrated a yield of 47% of prostate cancer in men with previous negative biopsy, with a high prevalence of occult anterior tumors diagnosed in that study, although results were not limited to anterior lesions. Additional alternative approaches include MRI-guided (in-bore) biopsies (26); however, the hardware and expertise for this approach is less widely available than.
for TRUS biopsy. Saturation biopsies can also be performed in the setting of clinical sus-
picion of biopsy-occult prostate cancer (27) but require a high number of biopsy passes,
without specifically targeting the areas of potentially highest yield. Another promising
technique is electronic fusion of magnetic resonance and TRUS images to guide biop-
sy. With this technique, software is used to coregister prior MRI data and real-time TRUS
images (14). This makes use of spatial posi-
tioning sensors attached to the endorectal ultrasound probe. Images from the MRI
are reconstructed to the real-time plane of TRUS imaging thereby providing increased
certainty that the TRUS-guided biopsy is effectively sampling the area of concern on
MRI (15).

Our study has some limitations. The study is a retrospective review. The MRI protocol
included DWI in addition to anatomic imag-
ing, a strategy that has been correlated with a high cancer detection rate particularly for
high Gleason grade disease (28). Howev-
er, the addition of a further functional se-
quence (DCE or MRS) may have refined the
overall PIRADS score, with potential effect on correlation with biopsy result. It is not-
oted that a b value of 800 s/mm² was used in this
study. Higher b value imaging may be advantageous, where adequate signal-to-
oise ratio (SNR) permits, as recommended by in the PIRADS version 2 guidelines (29).
Additionally, the use of a cognitive target-
ing technique to direct the biopsy makes it less certain that the exact location of the
abnormality characterized on MRI has been sampled. The finding that the average size
of lesions, which were positive for carcinoma on targeted biopsy was greater than those
which were negative (20.2 mm vs. 13.4 mm) highlights this potential sampling limitation.
However, it is interesting that such large
lesions were present in patients with prior
negative biopsies, highlighting the impor-
tance of strategies for diagnosis of occult an-
terior prostate tumors. Since the study group
did not all have radical prostatectomy, we
cannot determine the false negative biopsy
rate in this study. It is also worth noting that
the study does not include patients who had
no target for biopsy in the anterior prostate
gland, so the proportion of men with occult
anterior tumors in the clinical settings de-
scribed is not determined. A further consid-
eration is the impact of operator experience
on the efficacy of this technique. In the cur-
rent study, the operators had experience in
both prostate MRI and TRUS-guided biopsies
and an understanding of both modalities is
needed to perform the procedure effective-
ly. However, the transition from performing
sectoral nontargeted biopsies to manipu-
lating the biopsy needle into the portion of
the gland deemed suspicious for neoplas-
m on MRI proved straightforward for both op-
erators. It is noted that the targeted lesions
were sometimes visible on ultrasound. How-
ever, this was not routinely documented,
and the yield of visible lesions versus lesions
that were sampled purely based on anatomic
location could not be evaluated by this ret-
rospective study.

All of the targeted anterior biopsies in
this study were performed with a sagita-
tal approach, described in detail above. It is
hoped that this will be useful to the
reader, as the exact biopsy technique for
TRUS-guided targeted biopsy is often not
specifically described in existing literature
and this can be a barrier to implementing this
approach in local clinical practice. This
biopsy technique was well tolerated by all
patients. The specific yield of targeted an-
terior biopsy with sagittal approach com-
pared with axial approach was not directly
compared in this study. In smaller volume
prostate glands, based on local experience,
some anterior tumors can be sampled us-
ing a transaxial approach. However, it is
difficult to direct the biopsy needle into
the anterior-most aspect of the prostate
with axial TRUS imaging guidance in larger
glands. We did not routinely perform both
techniques, as performing both in all cases
would have resulted in unnecessary addi-
tional biopsy passes.

In general terms, targeted prostate biopsy
has a number of potential advantages. The
mobidity associated with prostate biopsy,
particularly procedure related sepsis has
been shown to be related to the number of
biopsy samples performed (30). In a study of
5802 biopsies in 2002, 50% had hemat-
spermia at three days, and 3.5% developed
sepsis (31). Targeted TRUS biopsy of the pro-
state has the potential to reduce the number
of cores required by reducing the need for
repeated extended (12-core) biopsies and
could potentially reduce the yield of clinically
insignificant prostate cancers (32).

In conclusion, MRI-directed targeted
TRUS-guided prostate biopsy with cogni-
tive fusion enables accurate sampling of
clinically significant prostate cancer in the
anterior prostate, enabling improved tumor
detection yield of lesions occult to routine
sectoral biopsy.

Conflict of interest disclosure
The authors declared no conflicts of interest.

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