Cognitive Versus Software Fusion for MRI-targeted Biopsy: Experience Before and After Implementation of Fusion

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OBJECTIVE
To compare the diagnostic performance of the 2 most common approaches of magnetic resonance imaging targeted biopsy (TB)—cognitive registration targeted biopsy (COG-TB) and software fusion targeted biopsy (FUS-TB)—we assessed our institutional experience with both methods. TB has emerged to complement systematic template biopsy (SB) in prostate cancer (PCa) diagnosis; however, which magnetic resonance imaging targeting methodology is diagnostically better remains unclear.

MATERIALS AND METHODS
A total of 510 patients underwent TB at our institution before and after the adoption of fusion software with the UroNav platform (Invivo Corporation, Gainsville, FL). All patients had concurrent 12-core SB. We compared rates of clinically significant PCa detection, and rates of upstaging and missed diagnosis in reference to SB among patients who received COG-TB and patients who received FUS-TB. We also compared both COG-TB and FUS-TB results to their paired SB results.

RESULTS
The rates of upstaging or missing clinically significant PCa with FUS-TB (in reference to SB) was not significantly different from COG-TB (\(P = 0.172\)), nor was the risk of missing clinically significant PCa different between FUS-TB vs COG-TB on logistic regression (Odds ratio = 0.55, \(P = 0.106\)). No significant difference in biopsy outcomes was observed between FUS-TB and COG-TB (\(P = 0.171\)). We did find significant differences between FUS-TB and SB and between COG-TB and SB, with SB finding more clinically insignificant PCa (\(P < 0.001\) and \(P = 0.04\)).

CONCLUSION
In our institutional experience, no significant difference was observed between the diagnostic ability of COG-TB vs FUS-TB for detecting clinically significant PCa. Greater evidence demonstrating an advantage of FUS-TB over COG-TB would be required for clear recommendations in favor of FUS-TB.

The role of multiparametric magnetic resonance imaging (MRI) in the diagnosis of prostate cancer (PCa) continues to advance. Higher field strength 3 Tesla magnets, which provide improved image quality are increasingly available in clinical practice. The performance and interpretation of prostate MRI has been standardized with the adoption of the Prostate Imaging-Reporting and Data System (PI-RADS), now in its second iteration, at many institutions. These advancements ensure that the use of MRI to guide prostate biopsy will continue to evolve as an integral component of prostate cancer management. Systematic template biopsy (SB) performed with transrectal ultrasound remains standard of care for diagnosis of PCa. However compared to SB, MRI targeted biopsy (TB) offers improved ability to diagnose clinically significant cancer while not over-diagnosing clinically insignificant cancer. TB Gleason grade is also more representative of the ultimate radical prostatectomy pathology. Furthermore, TB is more efficient; per core, a higher rate of cancer is detected compared to SB.

As TB advances, it remains unclear which MRI targeting methodology is best for the assessment of suspicious
lesions. Currently, 3 methods of variable complexity are used. (1) In-bore biopsy represents perhaps the most intensive approach where biopsy is performed simultaneously with MRI to ensure biopsy needles are placed accurately in regions of suspicion. This process is time intensive, expensive, and currently not widely utilized. (2) Fusion software targeted biopsy (FUS-TB) represents a more common alternative where prior MRI imaging is fused with ultrasound via specialized software equipment to provide real-time information about biopsy location. (3) Finally, cognitive targeted biopsy (COG-TB) represents the simplest TB approach. The practitioner views MRI images of suspicious prostate lesions to visually estimate where the needle should be placed. Needle placement is then targeted to the estimated lesion location during transrectal ultrasound guided biopsy without additional technological guidance.

Two prospective trials and a meta-analysis have shown a similar ability between COG-TB and FUS-TB for PCa diagnosis. There has been some evidence suggesting improved overall PCa diagnosis with FUS-TB compared to COG-TB, but the same research did not show significantly different detection rates for clinically significant PCa. Evidence also suggests that FUS-TB outperforms COG-TB for smaller lesions and that FUS-TB allows more accurate placement of biopsy needles with respect to a targeted lesion. Intuitively, since FUS-TB incorporates visual feedback on needle location with respect to computed MRI lesion location, consensus statements suggest FUS-TB allows more accurate needle placement in difficult lesions and is less reliant on user expertise than COG-TB. These perceived advantages have not yet proven to be clinically meaningful.

In this study, we compare our institutional experience with COG-TB and FUS-TB in the diagnosis of clinically significant PCa.

MATERIALS AND METHODS

Subjects
With Institutional Review Board approval, we reviewed our prospectively maintained prostate MRI database from January 2011 to December 2016. We identified 510 patients who underwent MRI with identification of a suspicious lesion prior to TB. Patients received COG-TB until December 2014 (n = 162) when fusion software was adopted, and subsequent patients received FUS-TB (n = 348). All patients also received a concurrent 12-core SB.

MRI and Biopsy Technique
Our techniques for prostate MRI, FUS-TB, and COG-TB have been published previously. Briefly, all patients underwent 3 Tesla multiparametric MRI on Siemens Trio or Skyra (Siemens, Munich, Germany) with surface pelvic phased-array coils. All MRI were read as part of the clinical workflow of the abdominal radiology section at our institution by fellowship-trained attending radiologists supervising residents and fellows.

PI-RADS version 1 was implemented at our institution in September 2014, followed by PI-RADS version 2 in February 2015. Although there are differences between the earlier and current scoring systems, recent studies have shown excellent inter-reader agreement for both scoring systems. Our institutional prostate MRI reporting methodology used prior to implementation of PI-RADS has been described in the past. Briefly, a binary (yes/no) system was used for each of the following parameters: T2 hypointensity, diffusion restriction on diffusion-weighted imaging, and dynamic contrast enhancement washout kinetics. MRI suspicious regions were then described as a triple match (suspicious on all 3 of the above parameters) or double match. Internal review of our prior institutional MRI reporting methodology has found that triple-match MRI suspicious regions correlate to PI-RADS classification 4 or 5 (61.4% rate of PCa for triple parametric match and 67.4% rate of PCa for PI-RADS 4 or 5 at our institution, P = 0.40. Double-match, triple-match, and PI-RADS 3+ lesions were targeted on TB.

COG-TB was performed using the TargetScan system for ultrasound guidance (TargetScan, Best Nomos, Pittsburgh, PA) with MRI reports and images immediately displayed nearby. FUS-TB was performed with the UroNav biopsy platform (Invivo Corporation, Gainsville, FL) which provides a software overlay of live ultrasound to stored MRI registered with T2-weighted images with elastic deformation. All patients receiving TB also underwent a 12-core transrectal ultrasound biopsy in the same session.

Statistical Analysis

Cohort demographics and characteristics comparisons were made using the chi-square test of independence for categorical variables and Wilcoxon rank-sum test for continuous variables.

The highest-grade pathology from all cores was recorded for each biopsy technique (TB and SB). In comparing “missed,” “upstaged,” and “equivalent,” diagnoses rates between FUS-TB and COG-TB, we defined a “missed” biopsy as finding Gleason 6 or no PCa on TB while finding Gleason 7+ on SB. Similarly, an “upstaged” biopsy was defined as Gleason 7+ on TB while finding Gleason 6 or no PCa on SB. “Equivalency” was achieved when both TB and SB were Gleason 6 and/or no PCa, or when both were Gleason 7+. In essence, we used SB as the reference state and classified by TB concordance with SB.

Multivariable logistic regression modeling was used to compare the likelihood of FUS-TB vs COG-TB missing clinically significant PCa that was found on SB, while controlling for patient age, prostate-specific antigen (PSA), and prostate volume.

McNemar–Bowker test was used to evaluate TB vs paired SB in 3 × 3 contingency tables of no PCa, Gleason 6, and Gleason 7+ biopsy results. Further evaluation of TB vs paired SB was performed for individual groupings with 2 × 2 McNemar’s tests with continuity corrections.

RESULTS

Patient characteristics were overall similar between the 2 groups (Table 1). Significant differences were found between our 2 cohorts of patients in race and family history of PCa. More African-Americans and more patients without a family history of PCa underwent prostate biopsy in the FUS-TB cohort (P = 0.027 & 0.037).

No significant differences were observed between FUS-TB consistency with SB and COG-TB consistency with SB; meaning, the rates of missed, upstaged, and equivalent biopsy results were not significantly different (P = 0.172; Table 2). FUS-TB and COG-TB were equivalent to SB in 85.1% and 82.1% of
cases, respectively, whereas FUS-TB and COG-TB resulted in upstaging to clinically significant PCAs from SB diagnosis in 8.0% and 9.5% of cases. The rate of missed cancer with respect to SB was 5.5% in FUS-TB and 9.9% in COG-TB.

On logistic regression, FUS-TB was not found to be a significant predictor of missing clinically significant PCa on TB while controlling for age, PSA, and prostate volume (Odds ratio (OR) 0.55, 95% confidence interval (CI) 0.27, 1.13, P = 0.106). Prostate volume was found to be a significant predictor of missing less clinically significant PCa on TB (OR 0.79, 95% CI 0.66, 0.95, P = 0.013; Table 3).

Results of 3 × 3 extended McNemar’s tests showed a near significant difference when comparing COG-TB and SB (P = 0.053) in a contingency table of no cancer, clinically insignificant cancer, and clinically significant cancer. Similarly, a significant difference was demonstrated between FUS-TB and paired SB (P = 0.006; Table 4). On further 2 × 2 McNemar’s tests, COG-TB was found to yield significantly less Gleason 6 disease than paired SB (22.8% vs 30.2%, P = 0.045). FUS-TB was also found to yield significantly less Gleason 6 disease than paired SB (14.4% vs 22.4%, P < 0.001). There was no significant difference between either TB method and SB in terms of detecting clinically significant PCAs (COG-TB vs SB, P = 0.58 and FUS-TB vs SB, P = 0.071).

Table 1. Demographics and characteristics of the 2 patient cohorts

<table>
<thead>
<tr>
<th></th>
<th>Cognitive (n = 162)</th>
<th>Fusion All (n = 348)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>63.9 (7.8)</td>
<td>65.0 (7.2)</td>
<td>0.129</td>
</tr>
<tr>
<td>Prostate-specific antigen (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.9 (7.8)</td>
<td>7.8 (7.8)</td>
<td>0.915</td>
</tr>
<tr>
<td>Prostate volume* (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>49.4 (21.4)</td>
<td>56.0 (29.1)</td>
<td>0.062</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/other</td>
<td>97.5%</td>
<td>92.2%</td>
<td>0.027</td>
</tr>
<tr>
<td>Black</td>
<td>2.5%</td>
<td>7.8%</td>
<td></td>
</tr>
<tr>
<td>Initial digital rectal examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>84.6%</td>
<td>81.9%</td>
<td>0.758</td>
</tr>
<tr>
<td>Abnormal</td>
<td>8.6%</td>
<td>10.1%</td>
<td></td>
</tr>
<tr>
<td>Not done/unknown</td>
<td>6.8%</td>
<td>8.0%</td>
<td></td>
</tr>
<tr>
<td>Family history of prostate cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>58.0%</td>
<td>67.5%</td>
<td>0.198</td>
</tr>
<tr>
<td>Yes</td>
<td>42.0%</td>
<td>32.5%</td>
<td></td>
</tr>
<tr>
<td>Previous biopsy results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>27.2%</td>
<td>36.2%</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>51.9%</td>
<td>45.4%</td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>18.5%</td>
<td>17.0%</td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td>2.5%</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td>Gleason—Nontargeted systematic template biopsy cores</td>
<td></td>
<td></td>
<td>0.050</td>
</tr>
<tr>
<td>0</td>
<td>40.7%</td>
<td>53.7%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>30.2%</td>
<td>22.4%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>21.0%</td>
<td>14.7%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3.7%</td>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>9 or 10</td>
<td>4.3%</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>Gleason—targeted biopsy cores</td>
<td></td>
<td></td>
<td>0.171</td>
</tr>
<tr>
<td>0</td>
<td>50.0%</td>
<td>57.8%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>22.8%</td>
<td>14.4%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>18.5%</td>
<td>20.1%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3.1%</td>
<td>3.4%</td>
<td></td>
</tr>
<tr>
<td>9 or 10</td>
<td>5.6%</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td>0.564</td>
</tr>
<tr>
<td>No</td>
<td>91.4%</td>
<td>92.2%</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8.6%</td>
<td>7.2%</td>
<td></td>
</tr>
</tbody>
</table>

*Eleven and 9 prostate volumes were not estimated in the cognitive registration targeted biopsy and software fusion targeted biopsy cohorts.

Table 2. Comparisons between cognitive registration targeted biopsy and software fusion targeted biopsy in respect to their agreement with concurrent systematic template biopsy (SB)

<table>
<thead>
<tr>
<th></th>
<th>Cognitive (n = 162)</th>
<th>Fusion (n = 348)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missed (targeted biopsy [TB] &lt; 7 &amp; SB ≥ 7)</td>
<td>9.9%</td>
<td>5.5%</td>
<td>0.172</td>
</tr>
<tr>
<td>Equivalent (TB &amp; SB ≥ 7 or TB &amp; SB &lt; 7)</td>
<td>82.1%</td>
<td>85.1%</td>
<td></td>
</tr>
<tr>
<td>Upstage (TB ≥ 7 &amp; SB &lt; 7)</td>
<td>8.0%</td>
<td>9.5%</td>
<td></td>
</tr>
</tbody>
</table>
less likely to detect PCa in larger prostates.21 Importantly, the literature, as previous reports demonstrate that SB is volumes in respect to SB. Our study words, TB performed better in patients with larger prostate missing clinically signi
ecreasing prostate size

DISCUSSION

Despite prospective trials by Wysock et al. and Puech et al., it remains unclear what MRI-TB methodology is best for detecting clinically significant PCAs.9,10 We found that although both COG-TB and FUS-TB differed from concurrent SB, there was no clear superiority of either TB methodology. Both COG-TB and FUS-TB upstaged and missed clinically significant PCa at similar rates compared to their matched SB; no significant difference was observed between the two, nor did FUS-TB significantly reduce the rate of missed biopsy on logistic regression when controlling for prostate size, PSA, and patient age. These results align with past studies that also found no significant differences in the ability of FUS-TB to detect clinically significant PCa compared to COG-TB.5,9,10,20

In support of TB generally, we did find that both COG-TB and FUS-TB detected significantly less clinically insignificant PCa than paired SB. There was not a significant difference between either TB method or its paired SB in detecting clinically significant PCa. This work affirms past research showing that the major benefit of both COG-TB and FUS-TB is the reduction in the detection of clinically insignificant PCa when compared to SB.5

Interestingly, on multivariate analysis we found that increasing prostate size was associated with reduced odds of TB missing clinically significant PCa found on SB. In other words, TB performed better in patients with larger prostate volumes in respect to SB. Our study finding is supported by the literature, as previous reports demonstrate that SB is less likely to detect PCa in larger prostates.21 Importantly, for patients with larger prostate volumes, MRI and subsequent TB (regardless of method) may significantly improve the detection of clinically significant PCa.

The differences that were observed between FUS-TB and SB were more pronounced than between COG-TB and SB. This may reflect a larger sample size in FUS-TB (348 patients vs 162 patients) but may also represent a trend towards improved diagnostic performance in FUS-TB. As there was a trend toward increased upstaging and decreased missed clinically significant PCas with FUS-TB, our study may have been underpowered to demonstrate a statistically significant difference between FUS-TB and COG-TB. The previously mentioned prospective trials of Wysock and Puech also showed non-significant trends in improved diagnostic performance with FUS-TB vs COG-TB but were also suggested by their authors to be likely underpowered to detect any true difference (125 and 68 patients respectively).9,10 Still, given the lack of statistically significant differences observed between FUS-TB and COG-TB across multiple studies, any true difference is likely not very pronounced.

The optimal biopsy technique would detect 100% of clinically significant PCa while simultaneously reducing the detection of clinically insignificant PCa. The exact constellation of SB and TB to optimize diagnostic performance should be evaluated in further research. It has been suggested that COG-TB and FUS-TB perform better in different lesions, with FUS-TB performing better for small and transitional zone lesions and COG-TB performing better in the prostate base.9,20 The comparative performance of FUS-TB and COG-TB in lesions of varying size and location is relevant but beyond the scope of this work.

This study is not without limitations. More benign biopsies were observed on SB in our FUS-TB group (53.7%) vs our COG-TB group (40.7%) which was near significant (P = 0.050). This may partially reflect

### Table 3. Logistic regression model of the odds of targeted biopsy missing clinically significant prostate cancer that was found on systematic template biopsy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Lower</th>
<th>95% Upper</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Software fusion targeted biopsy vs cognitive registration targeted biopsy</td>
<td>0.55</td>
<td>0.27</td>
<td>1.13</td>
<td>0.106</td>
</tr>
<tr>
<td>Age (continuous, 1 yr),</td>
<td>1.03</td>
<td>0.98</td>
<td>1.08</td>
<td>0.227</td>
</tr>
<tr>
<td>Prostate-specific antigen (continuous, 1 ng/ml)</td>
<td>0.99</td>
<td>0.93</td>
<td>1.05</td>
<td>0.629</td>
</tr>
<tr>
<td>Prostate volume (continuous, 10 g)</td>
<td>0.79</td>
<td>0.66</td>
<td>0.95</td>
<td>0.013</td>
</tr>
</tbody>
</table>

### Table 4. Cross tabulations representing biopsy results from patients undergoing targeted biopsy and systematic template biopsy (SB). All results reported are the highest pathology acquired from each method for each patient

<table>
<thead>
<tr>
<th>Concurrent cognitive registration targeted biopsy &amp; SB (n = 162)</th>
<th>0</th>
<th>6</th>
<th>≥7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive registration biops SB</td>
<td>81 (50%)</td>
<td>37 (22.8%)</td>
<td>44 (27.2%)</td>
</tr>
<tr>
<td>SB</td>
<td>66 (40.7%)</td>
<td>49 (30.2%)</td>
<td>47 (29%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concurrent software fusion targeted biopsy &amp; SB (n = 348)</th>
<th>0</th>
<th>6</th>
<th>≥7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Software fusion targeted biopsy SB</td>
<td>201 (57.8%)</td>
<td>50 (14.4%)</td>
<td>97 (27.9%)</td>
</tr>
<tr>
<td>SB</td>
<td>187 (53.7%)</td>
<td>78 (22.4%)</td>
<td>83 (23.9%)</td>
</tr>
</tbody>
</table>
differences in biopsy approach as COG-TB patients received SB with TargetScan while FUS-TB patients received free-handed SB and later template guidance from UroNav. However, since SB was approached mostly similarly in both cohorts, these differences in SB results more likely suggest cohort differences in who received biopsy at our institution in the COG-TB and FUS-TB eras.

Significant differences in racial makeup and positive family history of PCa were also found between the cohorts. Additionally, as PI-RADS and then PI-RADS 2 were adopted, there may have been differences in the diagnostic performance of MRI at our institution affecting targeted biopsy performance. In this study, we have included patients that had MRI lesions identified before PI-RADS, with PI-RADS v1, and with PI-RADS v2. This adds variability to our study but allows for our large sample size. Future comparisons of COG-TB and FUS-TB should account for lesion characteristic such as size, location, and PI-RADS score.

Both COG-TB and FUS-TB have been suggested to have significant learning curves. Especially, in targeting small lesions COG-TB may require greater expertise. In this study, COG-TB was performed by academic urologists with significant experience. This study does not address the learning curves of COG-TB and FUS-TB although experience certainly affects the performance of both modalities.

Although the comparisons made in this study are retrospective, they represent the largest comparison between COG-TB and FUS-TB to date. These results reflect clinical outcomes seen in day-to-day practice at our institution. In this work, we supplement the results of existing prospective trials with our comparatively large sample size and unique dataset representing coinciding TB and SB. By comparing 2 eras of TB at our institution in a before and after quasi-experimental study design, we ensure that the confounding effects of patient factors are somewhat minimized; when a patient was biopsy was the sole deciding factor in which TB methodology was used.

Since prostate MRI has until recently been a tool of the major academic centers, urologists must ask what resources are necessary to effectively and safely implement MRI TB in their practice. Although COG-TB may have a larger learning curve, the similar performance of COG-TB and FUS-TB at our center suggests both are reasonable approaches. Indeed, both COG-TB and FUS-TB provided similar benefits over SB in reduced detection of clinically insignificant PCa.

**CONCLUSION**

We found no significant difference in the diagnosis of clinically significant PCa between COG-TB and FUS-TB among a large cohort of patients at our institution. This experience aligns with the current consensus statement by the American Urological Association and the Society of Abdominal Radiology Consensus Statement that supports COG-TB as a viable alternative to FUS-TB. Our results suggest COG-TB and FUS-TB are both reasonable approaches to MRI targeted prostate biopsy.

**References**


