Accuracy of Diagnosis with Non-contrast Magnetic Resonance Imaging/Transrectal Ultrasound Fusion-Guided Transperineal Prostate Biopsy

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Objective: We evaluated the efficacy of non-contrast magnetic resonance imaging (MRI)/transrectal ultrasound (TRUS) fusion-guided transperineal biopsy for the detection of prostatic carcinoma.

Methods: Between November 2013 and June 2015, eighty-three men, who presented to the Department of Urology with a clinically suspicious prostatic cancer, underwent non-contrast MRI/TRUS fusion biopsy (FB) (BioJet®; D&K Technologies, Kanalweg, Germany) and 16-core systematic biopsy (SB). All biopsies were taken through a transperineal template. In 27 patients, the Gleason scores of biopsy specimens were compared to those of radical prostatectomy specimens.

Results: The median patient age was 69 years (IQR 67-73) and the median Prostate Specific Antigen (PSA) level was 6.6 ng/ml (IQR 5.2-8.9). Fifty-three patients were diagnosed with prostate cancer (PCa) (64%) by biopsy. The per-core cancer detection rate (CDR) was found to be higher for FB than for SB (32.5 vs 13.3%; p<0.0001). Although not statistically significant, the CDR for clinically significant PCa was numerically higher for FB than for SB (65.1 vs 58.0%; p=0.309). The Gleason scores of prostatectomy specimens were assessed to be higher than those of biopsy specimens in 44% of the cases in the FB group and in 37% of those in the SB group.

Conclusion: Our study adds to the literature which supports the potential role of non-contrast MRI/TRUS fusion-guided transperineal biopsy in the detection of PCa, with a significantly higher per-core CDR compared with SB.

Key words: prostate cancer (PCa), ultrasound fusion-guided biopsy, transperineal biopsy, non-contrast MRI

Introduction

The prevalence of PCa is expected to increase worldwide, with the growing aging population and widespread screening programs for this disease. Since the 1980s, TRUS-guided biopsy has been the standard method for obtaining tissue for histological diagnosis, but its limitations are increasingly being recognized1-4, including imprecise sampling and frequent diagnosis of clinically insignificant PCa5.

There is now an emerging role for MRI/US fusion technology in improving diagnostic accuracy for clinically relevant PCa6-10. Multiparametric MRI (mpMRI) enables visualization and stratification of many PCas and, when fused with real-time ultrasound (US), can help guide the biopsy needle towards suspicious lesions of interest5,11-13. While MRI/US fusion platforms or systems vary (with each having its own advantages and disadvantages)14, promising clinical application is largely limited due to the toxicity of agents used to enhance image contrast15.

In this study, we examined the efficacy and usefulness of non-contrast MRI/TRUS fusion biopsy (FB) with non-contrast MRI in the diagnosis of PCa.
Materials and Methods

From November 2013 to June 2015, 83 consecutive patients with suspected PCa noted using non-contrast MRI, who additionally had PSA levels less than 20 ng/ml, received an FB and a standard-of-care 16-core systematic biopsy (SB). All patients provided a written informed consent to enrollment in the study. Our institutional review board approved the study (No. 13-089). All MRI examinations were performed at 1.5 Tesla using a pelvic phased array coil, including T2 weighted imaging (T2WI) and diffusion weighted imaging (DWI) with apparent diffusion co-efficient (ADC) mapping. Selection of patients for FB and SB was based on lesion imaging and interpretation by radiologists, without the use of any scoring systems. All biopsies were conducted within 2 months post-MRI and under general anesthesia utilizing a transperineal approach. FB was performed using the BioJet® system (D&K Technologies, Kanalweg, Germany) and the ARIETTA 70® ultrasound system (Hitachi Aloka Medical Ltd., Japan) combined with a TRUS-targeted transperineal biopsy platform. The volume of the target tumor was calculated based on the tumor diameter measured on MRI T2WI images. For comparison purposes, 16-core random biopsies were performed by one experienced urologist (detailed method was based on the report of Sakamoto et al.16). Histopathological parameters in all SB and FB were analyzed. The pathological findings of prostatectomy specimens of 27 patients taken within 3 months of the biopsy with no preoperative hormonal therapy were compared to their respective FB and SB specimens. The location of the target tumor on the MRI image (T2WI, axial section) in FB and the positive cores of cancer were identified in 16 regions in SB, and each was compared with the position of PCa in the axial section of surgical specimens. Also, Gleason score was compared between each biopsy cores and surgical specimens. Univariate analysis was performed to identify clinical and pathological factors predictive of PCa. These included age, PSA levels, prior biopsy frequency, abnormal findings in digital rectal examination, tumor volume, and prostate volume. Clinically significant cancers are defined by at least three positive biopsy cores, a Gleason score >3+4, and at least 50% of cancer per core. Statistical analyses were performed using SAS 9.2 (SAS Institute, NC, USA), and p-value less than 0.05 was considered statistically significant.

Results

Values representing the median age, BMI, serum PSA level, prostate volume and targeted tumor volume (median with IQRs) for the entire study population were 69 (64-73) yrs, 24.5 (24.4, 22.7-26.2) kg/m², 6.6 (5.2-8.9) ng/ml, 32.7 (23.3-44.5) ml, and 0.56 (0.27-1.36) ml, respectively.

Eighteen patients had 1 or 2 prior biopsies (Table-1). The per-patient CDR was 51.8% (n=43/83) for FB and 60.2% (n=50/83) for SB. The corresponding rates per biopsy core were 32.5% (n=90/277) for FB and 13.3% (n=176/1,328) for SB (p<0.0001 Pearson’s Chi-squared test; Figure-1). The

<table>
<thead>
<tr>
<th>Table-1 Patient characteristics</th>
<th>Median (n=83)</th>
<th>IQR</th>
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</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>69</td>
<td>64-73</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>6.6</td>
<td>5.2-8.9</td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>32.7</td>
<td>23.3-44.5</td>
</tr>
<tr>
<td>Target tumor volume (ml)</td>
<td>0.56</td>
<td>0.27-1.36</td>
</tr>
<tr>
<td>Number of target biopsy cores per patient</td>
<td>3</td>
<td>3-3</td>
</tr>
<tr>
<td>DRE-positive</td>
<td>27 (33%)</td>
<td></td>
</tr>
<tr>
<td>TRUS-positive</td>
<td>37 (45%)</td>
<td></td>
</tr>
<tr>
<td>Number of prior biopsies</td>
<td>0</td>
<td>65</td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

PSA: prostate-specific antigen, DRE: digital rectal examination, TRUS: transrectal ultrasound
respective rates of patients with Gleason scores of \(\leq 3+3, 3+4, 4+3, \text{ and } \geq 4+4\) were 44\% (n=19/43), 21\% (n=9/43), 12\% (n=5/43) and 23\% (n=10/43) for FB, and 50\% (n=25/50), 16\% (n=8/50), 20\% (n=10/50) and 14\% (n=7/50) for SB. Clinically significant cancer was detected in 65\% (n=28/43) of patients by FB and in 58\% (n=29/50) by SB (p = 0.48 Pearson’s Chi-squared test) (Figure-2). In a univariate analysis, PSA (p=0.006) and prostate volume (p<0.001) were assessed to be significant predictive factors of PCa.

Only 1 patient was assessed to have clinically significant cancer in the SB group. When compared with the prostatectomy specimens, the Gleason scores of prostatectomy specimens were assessed to be higher than those of biopsy specimens in 44\% of the cases in the FB group and in 37\% in the SB group (Table-2).

**Discussion**

Current standardized prostate biopsies conducted following PSA examination have been widely used as a global standard due to their versatility, but various problems have been indicated. Wright *et al.* reported that in their study, the limited sensitivity of SB anterior apical cancer in particular caused 17\% of such cancers to remain overlooked\(^1\). Clinically insignificant cancer detection is another problem associated with SB. In a randomized study by Draisma *et al.*, overdetection of clinically low risk cancer varied from 24\~57\% \(^3\), leading to unnecessary complications due to treatment and degradation of quality of life\(^18\). Meanwhile, Bjurlin *et al.* reported false negatives associated with SB, with up to 30\% of clinically significant cancer cases missed using the systematic biopsy method\(^19\). MRI plays an important role in solving these problems. The National Comprehensive Cancer Network (NCCN), European Association of Urology (EAU), and European Society of Urogenital Radiology (ESUR) guidelines recommend MRI for patients with elevated PSA or a negative result in a previous biopsy with a PSA which persists and rises. MRI, and mpMRI in particular, reduces overdetection and overtreatment of clinically insignificant PCa and facilitates early detection of significant cancer\(^5\). Multiparametric MRI consists of T2WI, DWI, dynamic contrast enhanced imaging (DCE), and/or magnetic resonance spectroscopic imaging (MRSI). There are two representative evaluation methods of these images: PIRADS and Likert scales. There have been numerous reports on prostate targeted biopsy using these methods in recent years. In-bore MRI guided biopsies, cognitive fusion, and MRI/US software–based image–fusion techniques were compared by Moore CM *et al.*, and a higher DR of clinically significant cancer was indicated using all of these techniques\(^20\). Many platform types were used for MRI/US fusion biopsies with these
methods, as in our present report.\(^6\)\(^9\)\(^{10}\)

The UroNav\(^{\text{®}}\) (Invivo, Gainesville, FL) tracks the location of the TRUS probe using electromagnetic sensors to follow real-time motion, enabling the operator to perform freehand biopsy. The CDR was 45.9% by FB and 46.7% by SB, but FB diagnosed 30% more high-risk cancers compared with SB (37.5% vs 26%, \(p<0.001\)\(^{21}\)\(^{22}\)).

The Artemis\(^{\text{®}}\) (Eigen, grass Valley Calif) can rebuild the TRUS 2D-images into a 3D-model on screen. The robotic arm which stabilizes the TRUS probe can track the location of both TB and SB\(^{23}\).

Wysock \textit{et al.} reported that FB detected 75.0% of all clinically significant cancers and 86.4% of Gleason sum \(\geq 7\) cancers detected on SB. And among 172 targets, fusion biopsy detected 55 (32.0%) cancers and 35 (20.3%) Gleason sum \(\geq 7\) cancers compared with 46 (26.7%) and 26 (15.1%), respectively, using visual targeting\(^{24}\).

The Urostation\(^{\text{®}}\) (Koelis, La Tronche, France) uses real-time 3D TRUS. It initially fuses mpMRI images to TRUS images, and after biopsies, tracks and logs the position of each core into the 3D prostate model. Ukimura \textit{et al.} reported the

\begin{table}[h]
\centering
\begin{tabular}{l|c|c|c|c|c}
\hline
\multicolumn{1}{c|}{\textbf{GS of biopsies}} & \textbf{FB} & \textbf{SB} & \hline
\textbf{GS of radical prostatectomy} & \textbf{\(\leq 6\)} & \textbf{3+4} & \textbf{4+3} & \textbf{\(\geq 8\)} & \textbf{\(\geq 8\)} \\
\hline
\textbf{\(\leq 6\)} & 4 & 7 & 1 & 1 & 1 \\
\textbf{3+4} & 1 & 0 & 3 & 0 & 0 \\
\textbf{4+3} & 0 & 0 & 1 & 0 & 0 \\
\textbf{\(\geq 8\)} & 0 & 0 & 4 & 2 & 0 \\
\hline
\textbf{\(\leq 6\)} & 6 & 5 & 4 & 0 & 0 \\
\textbf{3+4} & 0 & 1 & 1 & 0 & 0 \\
\textbf{4+3} & 0 & 1 & 3 & 0 & 0 \\
\textbf{\(\geq 8\)} & 0 & 0 & 2 & 2 & 0 \\
\hline
\end{tabular}
\caption{Comparison of Gleason score between preoperative biopsy and prostatectomy specimens}
\end{table}

GS: Gleason score, FB: fusion biopsy, SB: systematic biopsy

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Case of a 67-year-old man with elevated PSA and no prior biopsy}
\end{figure}

\begin{itemize}
\item[A:] T2WI shows low signal intensity area in the left lobe transition zone.
\item[B:] The MRI/TRUS fusion platform overlays the outline of the contour of the prostate (green line) and the target lesion (red line).
\item[C:] The 3D-TRUS image documenting the location of target lesion and each biopsy.
\item[D:] Axial-view TRUS of the prostate. The dots indicate SB puncture points. Gleason score of TB was 4+3. No cancer was detected in SB.
\item[E:] Photograph of the prostatectomy specimen. Gleason score was 4+3.
\end{itemize}
accuracy of this system using prostate models, with all biopsies (100%) successfully hitting the target lesion for hypoechoic lesions, and 84% hitting the lesion for isoechoic lesions. The CDRs of FB and SB were 55.0% and 43.3%, and the Negative Predictive Values of SB and FB were 94% and 85%, respectively.

The BiopSee® (MedCom, Darmstadt, Germany) and the BioJet® (D&K Tech, Kanalweg, Germany) have similar systems which fuse the images of MRI and TRUS manually, designating the lesion site to be punctured on the system’s screen and puncturing through the hole on the template specified by the system. Using the BiopSee® platform, Kuru et al. compared TB and SB. Although the CDRs of PCAs were equal in both SB and TB (50.4% and 50.6% respectively), there was a difference in the CDR in favor of TB for clinically significant PCAs (41.1% for TB vs 38.0% for SB). Shoji et al. reported a comparison of transperineal FB and SB using the BioJet® platform; the CDRs of all PCAs were 58% in FB and 34% in SB. All reports used mpMRI for evaluation.

We used the BioJet® system in our present study, but unlike the reports of MRI/TRUS fusion biopsy incorporating the mpMRI evaluation methods of PIRADS or Likert, we used only non-contrast MRI. There were two reasons: the risk of exposure to the contrast agent and radiologist-based challenges. As the population ages, the proportion of elderly people among PCA patients inevitably increases. Potential renal dysfunction is anticipated in the elderly, discouraging use of a contrast agent in some cases. In addition, a trained radiologist is required for evaluation of PIRADS and the Likert scale, presenting a potential obstacle to expanded usage of FB. In our present report, we included patients simply based on the indication of a radiologist’s suspicion of PCAs. Although there are restrictions as shown below, the CDR was not low compared to reports by others (comparison of FB and SB CDR in each report is shown in Table-3). And considering the CDR per core, more effective biopsies could be performed with FB, resulting in a significant difference compared with SB. Although there were no differences between FB and SB in the total PCA DR, and in results of operative pathological specimens, clinically significant cancer tended to be detected more in FB than in SB.

Our present report has some limitations. One is the lack of procedural accuracy. The BioJet® system relies on the operator’s free-handed trace of both prostate and target lesion contours, using T2WI images. As reliable identification of the prostate gland outline in T2WI is difficult, the 3D model upon which it is based may be inaccurate. Another limitation is that our study design may facilitate selective biases, with a single institution and no blinding of operator (FB and SB were done by same urologist). Since the lesion location in MRI is stored by the operator when performing SB, the CDR might become higher than with ordinary SB. Finally, our study is limited by the small number of patients.

There is no conflict of interest associated with this report.

Conclusions

This is the first report focusing on non-contrast MRI/US-fusion biopsy. It can detect PCAs more effectively compared with SB and tends to detect clinically significant cancer more than SB. Our data show PCA detection results similar to those of other

Table-3 Comparison of FB and SB prostate CDR in each report

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>Platform/approach</th>
<th>Cancer detected rate per patient (%)</th>
<th>Cancer detected rate per core (%)</th>
<th>Clinically significant cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siddiqui et al.</td>
<td>1,003</td>
<td>UroNav®/TR</td>
<td>45.9</td>
<td>46.7</td>
<td>37.5</td>
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<td>Wysocki et al.</td>
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<td>Artemis®/TP</td>
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<td>55.2</td>
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<tr>
<td>Fiard et al.</td>
<td>30</td>
<td>Urostation®/TP</td>
<td>55</td>
<td>43</td>
<td>-</td>
</tr>
<tr>
<td>Kuru et al.</td>
<td>347</td>
<td>BiopSee®/TR</td>
<td>50.4</td>
<td>50.6</td>
<td>-</td>
</tr>
<tr>
<td>Shoji et al.</td>
<td>250</td>
<td>BioJet®/TP</td>
<td>58</td>
<td>34</td>
<td>42</td>
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<tr>
<td>Present report</td>
<td>83</td>
<td>BioJet®/TP</td>
<td>51.8</td>
<td>60.2</td>
<td>32.5</td>
</tr>
</tbody>
</table>

TR: trans rectal, TP: trans perineal

Author Number of patients Platform/approach Cancer detected rate per patient (%) Cancer detected rate per core (%) Clinically significant cancer (%) FB SB FB SB FB SB FB SB

Siddiqui et al. 1,003 UroNav®/TR 45.9 46.7 - - 37.5 26
Wysocki et al. 125 Artemis®/TP 40.3 55.2 16 5.7 63.6 41.8
Fiard et al. 30 Urostation®/TP 55 43 - - - -
Kuru et al. 347 BiopSee®/TR 50.4 50.6 - - 41.1 38
Shoji et al. 250 BioJet®/TP 58 34 42 8.3 55 25
Present report 83 BioJet®/TP 51.8 60.2 32.5 13.3 65.1 58

TR: trans rectal, TP: trans perineal
reports of FB using mpMRI. However, further research is needed into FB before it can gain recognition as the next standard detection method of PCa.

References


