Repeat Transrectal Ultrasound Biopsies with Additional Targeted Cores According to Results of Functional Prostate MRI Detects High-risk Prostate Cancer in Patients with Previous Negative Biopsy and Increased PSA – A Pilot Study

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Abstract. Background/Aim: Patients with previous negative transrectal ultrasound-guided biopsy (TRUS-GB) and persistently increased prostate-specific antigen (PSA) value represent a great diagnostic problem. Magnetic resonance imaging (MRI)-guided biopsy demonstrates high prostate cancer detection rates in these patients if functional MRI is suspicious for prostate cancer. However, MRI-guided biopsy is not commonly available and features considerable technical requirements. This was a pilot study to investigate if a standard repeat TRUS-GB, with additional targeted cores to suspicious lesions on functional MRI, can achieve similar detection rates as compared to MRI-guided biopsy. Patients and Methods: 3 Tesla functional MRI was performed in 58 patients with ≥1 previous negative biopsy, persistently increased PSA ≥4 ng/ml and unsuspicious digital rectal examination. Suspicious lesions were marked on a localization map to enable their finding on TRUS. Random TRUS-GB with additional targeted cores according to the functional MRI findings were performed in patients with ≥1 suspicious lesion. Results: In 37.9% (22/58), functional MRI demonstrated suspicious findings. Out of these 22 patients, 16 underwent TRUS-GB with additional targeted cores. Prostate cancer was diagnosed in 68.8% (11/16). Eight out of these 11 patients subsequently underwent radical prostatectomy and all tumors fulfilled criteria for high-risk prostate cancer. With a median follow-up of 49.1 weeks neither significant PSA increase nor prostate cancer was detected in patients with normal functional MRI findings. Conclusion: Our approach enables excellent detection rates of clinically significant prostate cancer in patients with ≥1 previous negative biopsy and persistently increased PSA levels. Due to the current disadvantages of MRI-guided biopsy, our approach therefore represents an excellent alternative to MRI-guided biopsy.

Random biopsies of the prostate by transrectal ultrasound (TRUS) represent the gold-standard of prostate cancer (PCa) detection (1). However, after an initial negative prostate biopsy, many men present with persistently elevated prostate-specific antigen (PSA) levels (2). This is due to the low positive predictive value of PSA, accounting for a high proportion of unnecessary biopsies (3-5). On the other hand, the negative predictive value of a TRUS-guided biopsy (TRUS-GB) is 36%-89% (6). PCa can be found in up to 34% of cases by repeated biopsy, sometimes using the saturation biopsy technique (7). Because a high proportion of tumors in repeat biopsies are of clinical significance (8), patients with an initially negative biopsy remain a great diagnostic problem. Secondly, random biopsies represent an undirected biopsy technique not satisfying the heterogeneous and multifocal growth patterns of PCa. This disadvantage is confirmed by low concordance between biopsy and prostatectomy Gleason score (9).

Multiparametric functional MRI (fMRI) of the prostate combining T2-weighted imaging with diffusion-weighted imaging (DWI) and perfusion imaging has been extensively investigated in recent years. The strengths of this technique lie in a high sensitivity, particularly for detection of high-grade carcinomas (10). With these reported results in mind, a direct MRI-guided biopsy (MRI-GB) of suspicious lesions seems to be the next logical step. In recent years, several groups have reported first results of MRI-GB. MRI-GB is
feasible and PCa detection rates of up to 59% have been reported (11-15). But MRI-GB is not commonly available and is associated with other disadvantages as compared to TRUS-GB. The biopsy device has to be MR compatible and is expensive. Furthermore, MRI-GB is probably associated with higher patient discomfort. The procedure is usually performed in a prone position with a duration for one biopsy session in the range of 34-80 minutes (13).

MRI-GB is not currently available in our department. Therefore, in patients with at least one previous negative biopsy, increased PSA and suspicious fMRI, we performed repeat TRUS-GB with additional targeted cores. Suspicious lesions were previously marked on a localization map to help their location on TRUS. By combining the advantages of TRUS and diagnostic fMRI, we wanted to demonstrate that our approach can achieve similar detection rates, but without considerable technical requirements associated with pure MRI-GB. Concurrently, we wanted to avoid unnecessary repeat biopsy in patients with normal fMRI findings. Here we report on results of this pilot study.

Patients and Methods

Patients. Between May 2010 and June 2011, a total of 58 patients with at least one prior negative TRUS-GB, unsuspicious digital rectal examination (DRE), and persistently increased PSA values ≥4 ng/ml were submitted for a 3 Tesla fMRI examination in our radiological institute. Time to last TRUS-GB was at least six weeks. The patient’s PSA value and the number of previous negative TRUS-GBs were recorded. The study was approved by the local Ethics Committee and informed consent was obtained from all participants.

Functional magnetic resonance imaging. fMRI was performed with a 3 Tesla MR scanner (Magnetom Trio; Siemens Medical Systems, Erlangen, Germany) using a standard six-channel phased-array body-coil. The imaging protocol comprised T2-weighted images, T1-weighted images, DWI and perfusion imaging. Images were analyzed by two radiologists in consensus, taking into account the appearance of a lesion in T2-weighted images, and the diffusion and perfusion characteristics. T1-weighted images were used to exclude possible bleeding due to prior biopsy. Lesions were marked with arrows in the T2-weighted images. A printout of these images was attached to the written report, as well as printouts from perfusion images and a representative region of interest (ROI) measurement in the apparent diffusion coefficient (ADC) parameter image. To enable targeted biopsy by TRUS, suspicious lesions were marked on a localization map (Figure 2).

TRUS-GB with additional targeted cores. A repeat random biopsy with additional targeted cores according to the localization map was offered only to patients with suspicious fMRI. Our goal was to reduce unnecessary biopsies. Therefore, patients with nonsuspicious fMRI were monitored by further PSA evaluation. The biopsies were performed in a left lateral position or in a lithotomy position using a 7.5 MHz biplane and endfire transducer (Type 8818, BK Medical). Random biopsies were taken with an 18-gauge biopsy device (TruPath™; BostonScientific, Ratingen Germany). After completion of the random biopsies, 1-3 additional targeted cores were obtained from the suspicious lesions following the localization map (Figure 2).

Statistical analysis. The Kolmogorov-Smirnov test was used to assess the normal distribution of variables. The Mann-Whitney U-test was used for comparisons of non-normally distributed continuous variables and the Pearson chi-square test was used for comparisons of categorical variables.

Results

Patient characteristics and fMRI findings. We evaluated a total of 58 patients (median age 67.0 years) by fMRI who had previously undergone at least one (range 1-6) negative in-office biopsy with at least 10 cores each. The median PSA value at the time of fMRI examination was 9.30 ng/ml (range 4.6-108.0 ng/ml). A total of 22 out of these 58 patients (37.9%) had at least one suspicious fMRI lesion. The number of suspicious lesions was ranging from 1-3. The other 36 patients (62.1%) were assessed as having either benign prostatic hyperplasia (BPH) or prostatitis. With respect to patient characteristics, there were no statistically significant differences between patients with suspicious and those with normal fMRI findings (Table 1).

Number and location of suspicious lesions. A total of 35 lesions were suspicious for PCa in 22 patients. We analyzed the location of these lesions according to the zonal anatomy described by McNeal (16). Most lesions (n=18) were found in the peripheral zone. However, nearly one half of these lesions were located in ventral parts of the peripheral zone. The other lesions were found in the transition zone (n=17) or in anterior fibromuscular stroma (n=2). Two lesions overlapped more than one anatomical region.

Biopsy results. Of all 22 patients with suspicious fMRI findings, 16 underwent repeat TRUS-GB as described above. One patient declined TRUS-GB. Five patients were directly referred by their urologists to our Department of Radiology and they agreed to undergo in-office biopsy if the fMRI revealed a suspicious lesion.

A mean of 10.6 cores (maximum 15) including the targeted cores were obtained from the 16 patients undergoing a biopsy in our Department. The procedure was well tolerated and no patient suffered from severe complications. In 11 out of these 16 patients, PCa was detected. On biopsy, eight tumors had a Gleason score ≥7. Five patients had negative biopsy results. Based on D’Amico criteria (17), five tumors fulfilled high-risk criteria. The remaining tumors were intermediate (n=3) or low risk carcinoma (n=3), respectively. We were able to find out the biopsy results of three out of the five patients who underwent in-office biopsy without the localization map from our radiologists. Only in one patient was cancer detected.
Pathological findings at prostatectomy. Of all 11 patients with newly diagnosed PCa, eight subsequently underwent radical prostatectomy. The other three patients were referred for radiotherapy or active surveillance. Definitive histopathology on radical prostatectomy revealed upgrading of Gleason score in three cases. All tumors fulfilled criteria for clinically significant PCa (Table II).

(Gleason score 9). Although repeat biopsy was not routinely conducted in patients with nonsuspicious fMRI, we obtained prostate tissue from 6 out of these 36 patients. These patients underwent transurethral resection of the prostate (TUR-P) or prostatic adenomectomy due to concomitant bladder outlet obstruction. In none of these patients was PCa detected. With a median follow-up of 49.1 weeks, neither significant PSA increase nor PCa was detected in the remaining 30 patients with normal fMRI findings.
Discussion

The detection rate of PCa in these preselected study subjects was 68.8%. This is a surprisingly high detection rate as compared to detection rates of 38%-59% reported for MRI-GB in populations similar to our own. Using a 3 Tesla MR scanner without an endorectal coil but with a phased-array body-coil, our approach was different from the one of other groups who performed MRI-GB after examination of the prostate with an endorectal coil in a 1.5 Tesla MR scanner (11-14). T2-weighted MR images at 3 Tesla (with phased-array coil) and 1.5 Tesla (with endorectal coil) in the evaluation of local staging accuracy for PCa have been shown to be equivalent with a trend towards a lower incidence of MR artifacts at 3 Tesla (18). To our knowledge, corresponding studies comparing the multiparametric MRI techniques at 3 Tesla (with phased-array coil) and 1.5 Tesla (with endorectal coil) do not exist. Therefore, the improved detection rate in this study is potentially a result of using an MRI scanner that operates at a higher field strength.

Table II. Characteristics of eight patients who underwent consecutive prostatectomy.

<table>
<thead>
<tr>
<th>Number of previous negative biopsies</th>
<th>PSA value (ng/ml)</th>
<th>Highest Gleason score biopsy</th>
<th>pTNM classification prostatectomy</th>
<th>Gleason score</th>
</tr>
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<tr>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>6</td>
<td>15.92</td>
<td>4+4=8</td>
<td>T2b N0 (0/17) R0</td>
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</tr>
<tr>
<td>1</td>
<td>7.26</td>
<td>3+3=6</td>
<td>T3a NX R1</td>
<td>3+4=7</td>
</tr>
<tr>
<td>1</td>
<td>14.2</td>
<td>4+4=8</td>
<td>T3b N0 (0/14) R0</td>
<td>4+4=8</td>
</tr>
<tr>
<td>1</td>
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<td>T2c NX R1</td>
<td>3+4=7</td>
</tr>
<tr>
<td>1</td>
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<td>3+4=7</td>
<td>T2c NX R0</td>
<td>3+4=7</td>
</tr>
<tr>
<td>1</td>
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<td>3+4=7</td>
<td>T2c NX R0</td>
<td>3+4=7</td>
</tr>
<tr>
<td>1</td>
<td>24.0</td>
<td>4+4=8</td>
<td>T2c N0 (0/17) R1</td>
<td>4+4=8</td>
</tr>
<tr>
<td>2</td>
<td>108</td>
<td>3+4=7</td>
<td>T3a N0 (0/10) R1</td>
<td>4+5=9</td>
</tr>
</tbody>
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For TRUS-GB it was shown that this technique remains operator dependent (19). All TRUS-GBs in this study were performed by well experienced urologists. MRI-GB of the prostate is not yet widespread and the transrectal approach
is not common for interventional radiologists. Consequently, we cannot exclude that the higher experience of urologists in obtaining biopsy cores from the prostate via the transrectal approach influenced the detection rate in this pilot study.

The improved detection rate in our study may also be a result of the relatively low rate of patients with suspicious fMRI (37.9%). Weighting of the different multiparametric imaging techniques for rating lesions is not consistent. Franiel et al., for example, performed MRI-GB if an area was classified as suspicious on T2-weighted images, or if it was classified as inconclusive on T2-weighted images and as suspicious with at least one of the multiparametric MRI techniques (13). Unlike this, in our study, the images were analyzed by two radiologists in consensus and the different imaging techniques were equally weighted for rating lesions as suspicious or nonsuspicious, respectively. Unfortunately, the biopsy rate was not reported in those studies (11-14). Therefore, our reported biopsy rate cannot be compared to the one of MRI-GB studies.

With a detection rate of 11/16, our study demonstrates that targeted biopsy strategies based on fMRI findings are definitely superior to transrectal saturation biopsies which are usually performed in this situation (7). Concurrently, we were able to reduce the number of biopsy cores (mean=10.6, maximum=15) as compared to saturation schemes with an increased number of cores up to 40 and more (20). We commonly obtained 10-12 random biopsy cores according to the guidelines. However, in two cases, we restricted the number of targeted cores because fMRI findings were unequivocally suspicious for PCa. Thus, our reported mean number of obtained biopsy cores is distorted.

The location of the suspicious MRI lesions observed in this study confirms earlier results that a higher rate of cancer detection is identified in the anterior versus the posterior prostate on re-biopsy (21). For example, the patient with a PSA value of 108 ng/ml (Table II) had a ventrally located tumor. This probably explains two negative TRUS-GBs. Therefore, several authors prefer transperineal guided biopsy which provides reliable access to the entire prostate (21, 22). However, the transperineal approach has disadvantages, such as the need for general or regional anesthesia. Our data demonstrate that the ventral parts of the prostate can be sufficiently reached by TRUS.

With respect to the most commonly used criteria to define significant PCa (23), all patients who subsequently underwent radical prostatectomy had significant PCa. This emphasizes the high sensitivity of fMRI, especially for high-grade cancer.

Certainly, our study has several limitations. Firstly, this is a pilot study without a control group and the overall number of performed biopsies in our Department was relatively low (n=16). Therefore we cannot exclude a selection bias. But this was due to our conservative approach. Our goal was to avoid unnecessary overdiagnosis which is common in this critical population. Therefore we recommended PSA monitoring if fMRI was nonsuspicious. With a median follow-up of 49.1 weeks, none of these patients has had a significant increase of PSA value to date. Furthermore, in six patients undergoing TUR-P or adenomectomy, there was no evidence of PCa. Thus, the specificity of fMRI in this study population is high.

Secondly, most lesions seen on fMRI were not detectable on TRUS, or were vaguely perceptible at best. Therefore, there is not 100% certainty that the lesions were always detected; however, after biopsy, none of these patients were found to have PCa.

And Finally, this approach is still operator dependent. This is confirmed by the biopsy results of the three patients who underwent in-office biopsy at their office urologist: the detection rate was only one out of three.

The latter limitations could be overcome by novel ultrasound-based biopsy systems which integrate preinterventional fMRI by the means of TRUS/MRI fusion (24, 25).

Despite these limitations, our diagnostic yield can compete with MRI-GB and is superior to that of traditional saturation biopsy strategies. Therefore, it offers an excellent alternative when the MRI-GB technique is not available.

We believe that patient comfort is probably much higher with TRUS-GB and our pilot study has shown that the detection rate of TRUS-GB based on fMRI findings is equivalent to that of MRI-GB. In our opinion, our data therefore support a prospective randomized trial comparing pure MRI-GB with targeted ultrasound-guided biopsy techniques based on fMRI. Such a prospective randomized trial is now underway in our Department.

**Conclusion**

TRUS-GB with additional targeted cores from suspicious lesions in fMRI enables excellent detection rates of clinically significant PCa in patients with at least one previous negative biopsy and persistently increased PSA levels. The detection rate is equivalent to the one of pure MRI-GB, which is accompanied by several disadvantages such as costs, requirement of MR-compatible biopsy devices, limited patient comfort, and limited availability. Due to these disadvantages, our approach represents an excellent alternative to pure MRI-GB.

**References**

