DIAGNOSTIC VALUE OF COGNITIVE-REGISTRATION MULTIPARAMETRIC MAGNETIC RESONANCE GUIDED BIOPSY FOR THE DETECTION OF PROSTATE CANCER AFTER INITIAL NEGATIVE BIOPSY

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SUMMARY – The aim of this prospective clinical study was to determine the detection rate of prostate cancers by multiparametric magnetic resonance and transrectal ultrasound (mpMRI-TRUS) cognitive fusion biopsies in patients with a previously negative TRUS-guided biopsy. Between 1 October 2016 and 1 July 2017, in 101 consecutive patients with elevated antigen (PSA) and/or positive digital rectal examination and after a negative first TRUS biopsy, a second, repeated prostate biopsy was performed. In 24 patients, cognitive fusion mpMRI-TRUS biopsy of the prostate with 8-10 system cores and 1-3 target biopsies was performed, in line with the European Association of Urology guidelines. In 77 patients, only a classic, repeated TRUS guided biopsy was performed. In patients with mpMRI, the detection rate according to PIRADS-v2 reporting system was: PIRADS 1, n = 0; PIRADS 2, n = 0; PIRADS 3, n = 0; PIRADS 4, n = 6/8 (75%); and PIRADS 5, n = 2/3 (67%). In the group of patients with MR-TRUS cognitive fusion biopsy, the prostate cancer detection rate was 8/24 (33%), while in the control group the detection rate was 12/77 (16%), which was statistically significant (t test, p = 0.037, CI 95% is 0.01 to 0.37). Patients with PIRADS ≤ 3 (54%) could have avoided the biopsy.

Key words: Prostate cancer; Multiparametric magnetic resonance; Biopsy

Introduction

Current prostate cancer diagnostic pathway in men who present with elevated serum prostate specific antigen (PSA) and/or suspicious digital rectal examination (DRE) findings offers transrectal ultrasound guided biopsy (TRUS-biopsy)1.

Unlike many other solid tumors for which image-guided biopsy is common, prostate cancer has tradi-
may improve diagnostic accuracy for higher-risk tumors\(^5\). Traditionally, pelvic MRI has been used for treatment planning and monitoring with locoregional staging of a biopsy proven prostate cancer. However, physiologic and functional sequences (diffusion weighted imaging [DWI], dynamic contrast enhanced imaging [DCE] and MR spectroscopy) have now been added to traditional sequences (T1 and T2 weighted images) to create current state of the art multiparametric MRI (mpMRI). The newfound ability to target suspicious areas of the prostate during biopsy has decreased the likelihood of missing clinically significant disease. This fusion of MRI images and real-time ultrasonography (US) can be performed cognitively by a surgeon or can be digitally overlaid on live US with the assistance of external platforms.

There is some evidence that mpMRI tends to detect higher risk disease and systematically overlooks low-risk disease, which makes it attractive as a potential triage test\(^6\). Contemporary mpMRI fusion biopsy trials included a concurrent standard systemic biopsy and targeted biopsies. Although the place of mpMRI in the diagnostic pathway of prostate cancer is still being studied, some authors are suggesting that it should be done prior to any biopsy of the prostate\(^7\). Despite this fact, current European Association of Urology guidelines suggest that mpMRI should be used prior to a repeated TRUS biopsy where clinical suspicion of prostate cancer persists in spite of previous negative biopsy\(^1\). The European Society of Urogenital Radiology (ESUR) prostate imaging reporting and data system (PI-RADS) standardizes reporting of multiparametric prostate MRI\(^8\). An institutional learning curve for an MRI/ultrasound (US) fusion biopsy program is very diverse and one should be aware of the overall importance of experience for radiologists' performance in prostate MRI interpretation, which has been well characterized and established\(^9\).

The purpose of this study was to determine whether the application of magnetic resonance–ultrasound (MR–US) fusion biopsy results in improved detection of PCA compared to repeat conventional biopsy in patients with previous negative systematic TRUS-guided biopsy and persistently elevated/rising prostate-specific antigen (PSA) levels.

**Materials and Methods**

This prospective study was conducted in the period from 1 October 2016 until 1 July 2017 and included 101 male patients with elevated PSA and/or positive DRE, and a previous negative TRUS biopsy. Before the second, repeated prostate biopsy all patients were divided into two groups according to their urologist’s preference. In the first group, 24 patients underwent previous multiparametric magnetic resonance imaging (mpMRI), followed by cognitive fusion biopsy of the prostate with 8-10 systematic biopsy cores and 1-3 targeted biopsy cores according to mpMRI findings, in line with the European Association of Urology guidelines. In the second group, 77 patients underwent only a classic, repeated TRUS biopsy without prior image processing. mpMRI was performed at least 6 weeks after the first biopsy. The detection of suspected lesions was labeled and graded according to Prostate Imaging Reporting and Data System, version 2 (PI-RADSv-2).

All MRI examinations were performed on a 1.5T system Siemens MR ESPREE with the body and endorectal coil placed in the lateral decubitus position of the patient. The endorectal coil was filled with air. T2 weighted images were performed in sagittal, coronal and transversal planes with the 200 mm x 200 mm field–of–view (FOV), 3 mm slice thickness, repetition time (TR) of 4000–4130 ms and echo time (TE) of 105 ms. Diffusion-weighted sequences were performed with the standard b values of 0 s/mm\(^2\), 500 s/ mm\(^2\), 1000 s/mm\(^2\) and 1500 s/mm\(^2\). Dynamic sequences consisted of precontrast T1W image turbo spin echo (TSE) and 36 postcontrast T1W vibe images with 3.6 mm slice thickness and 260 mm x 260 mm FOV. The delay between the first and the second postcontrast image was 10 seconds. The dynamic phase of MR imaging ended with T1W TSE, 3 mm slice thickness, 200 mm x 200 mm FOV. In the final phase, after the removal of the endorectal coil, 3D coronal T2W images were made with thin layers of 1.1 mm slice thickness.

Two radiologists reviewed the images together and classified the lesions according to the PI-RADS classification system.

Conventional systematic biopsy of detectable lesions was performed in patients without mpMRI. A median of 10–cores on TRUS biopsy and 13\(^{10-13}\) cores on a fusion biopsy was obtained. Patients were classified into the groups with mpMRI or without mpMRI, according to the ordering urologist’s preferences. The study was approved by the Ethics Committee of Sestre milosrdnice University Hospital Center, and each patient signed an informed consent.
Statistics

Stata v.11 software (StataCorp, College Station, TX, USA) was used for statistical analysis. The mean values of continuous variables were expressed by arithmetic mean and standard deviation for normally distributed variables, and by median and range for unequally distributed variables. Nominal indicators were shown by frequency distribution according to groups and share. T test was used to determine differences between two independent samples for normally distributed variables, while Mann-Whitney test was used for variables that do not follow normal distribution. The level of significance was set at p<0.05.

Results

In the examined population of 101 patients, the median age was 66.8 ± 6.9 (51-79) years, PSA was 11.8 ± 7.7 (1.8-55.86), the number of biopsies was 10.6 ± 110-13, and the mean interval between the first negative biopsy and the repeated biopsy was 39.9 ± 32.2 (range 0-180) months. Study population demographics are shown in Table 1. Table 2 shows demographics of each study group. Median PSA level was 10.35 ± 7.9 (1-72) ng/ml and median age was 63.42 ± 6.8 years in the group of patients undergoing mpMRI cognitive TRUS biopsies, while in the classical TRUS biopsy group median PSA was 12.1 ± 7.6 ng/ml (4.4-59.9), and median age was 67.0 ± 6.8 (53-86) years. There was no difference between the groups in PSA levels (p = 0.35, 95% CI -2.0 to 5.5) or in the number of positive biopsies (p = 0.41, 95% CI -0.27 to 0.67).

Cancer detection rate according to PIRADS V2 in patients with detected lesion on mpMRI was: PIRADS 1, n = 0; PIRADS 2, n = 0; PIRADS 3, n = 0; PIRADS 4, n = 6/8 (75%); and PIRADS 5, n = 2/3 (67%), as shown in Table 3. Prostate cancer detection rate in the MR-TRUS cognitive fusion biopsy group was 8/24 (33%), while in the control group the detection rate was 12/77 (16%), which appeared to be significantly different (t test; p = 0.037, CI 95% is 0.01 to 0.37) (Table 4). Prostate cancer detection rate for patients with PIRADS 4 and 5 is 8/11, which makes...
73% of the biopsied men with this finding on mpMRI, and the difference in detection rate is even more significant when compared to the standard TRUS biopsy, p < 0.001 (95% CI 0.42 to 0.90) (Table 5). In this scenario, 13/24 patients with PIRADS ≤ 3 (54%) could have avoided biopsy.

We further analyzed the significance of detected cancers (Fig. 1) and found that most cancers were significant according to standard Epstein’s criteria. Specifically, the only patient in whose case insignificant cancer was detected: Gleason score 6 (3+3) in 1 core with <10% of cancer underwent radical prostatectomy which revealed pT2N0M0 cancer of upgraded Gleason score 7(3+4).

Discussion

Low specificity of the PSA test and low sensitivity of TRUS-guided systematic biopsy have resulted in a high number of patients diagnosed with elevated PSA levels and negative TRUS-guided systematic biopsy results. Persistent suspicion of prostate cancer leaves neither the patient nor his urologist at peace after the first negative set of biopsies. This can result in tremendous anxiety for the patient and increased risk of delayed diagnoses. In the present study of men with a prior negative biopsy and persistently elevated PSA levels, we found that MR–US fusion biopsy yielded a 33% cancer detection rate and outperformed standard TRUS guided repeated biopsy. Recent developments in MRI technology led to a potential of prostate cancer imaging that was not previously available. Although MRI protocols and guided-biopsy methods vary, there is a growing body of evidence that mpMRI fusion biopsies should be utilized in the scenario of repeated prostate biopsies1,10,11. Repeat conventional biopsy yields a decreasing cancer rate with each subsequent biopsy session. In the European Prostate Cancer

Table 3. Prostate cancer detection rates according to assigned PIRADS v2

<table>
<thead>
<tr>
<th>PIRADS</th>
<th>No. of patients</th>
<th>No. of detected cancers</th>
<th>% cancer detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>6</td>
<td>75%</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>2</td>
<td>67%</td>
</tr>
</tbody>
</table>

PI-RADS, Prostate Imaging Reporting and Data System

Table 4. Comparison of prostate cancer detection rate between TRUS guided and mpMRI cognitive guided biopsies

<table>
<thead>
<tr>
<th>No. of cancers detected</th>
<th>Detection rate</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRUS</td>
<td>12/77 (16%)</td>
<td>-0.01</td>
<td>p=0.037*</td>
</tr>
<tr>
<td>mpMRI</td>
<td>8/24 (33%)</td>
<td>-0.37</td>
<td></td>
</tr>
</tbody>
</table>

mpMR, multiparametric magnetic resonance; TRUS, transrectal ultrasound

Table 5. Comparison of prostate cancer detection rate between TRUS guided and mpMRI cognitive guided biopsies in patients with PIRADS 4 and 5

<table>
<thead>
<tr>
<th>Number of cancers</th>
<th>Detection rate</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRUS</td>
<td>12/77 (16%)</td>
<td>0.42 to 0.90</td>
<td>p&lt;0.001*</td>
</tr>
<tr>
<td>PIRADS 4,5</td>
<td>8/11 (73%)</td>
<td>0.90</td>
<td></td>
</tr>
</tbody>
</table>

mpMR, multiparametric magnetic resonance; TRUS, transrectal ultrasound; PI-RADS, Prostate Imaging Reporting and Data System

Fig. 1. Distribution of significant and insignificant prostate cancers according to Epstein’s criteria in PIRADS 4 and 5 groups.

PI-RADS, Prostate Imaging Reporting and Data System, INSIG-insignificant cancer, SIG-significant cancer
Detection study, the first repeat eight-core TRUS biopsy was positive in 10% of men, while the second repeat biopsy revealed cancer in only 4% of cases. Thus, the 33% PCA detection rate with fusion biopsy in the present study exceeds the historical detection rates obtained by conventional biopsy.

Several studies examined the utility of mpMRI in the diagnosis of prostate cancer. Siddiqui et al. reported that targeted biopsy diagnosed 30% more high-risk cancers versus standard biopsy (173 vs. 122 cases, P < .001) and 17% fewer low-risk cancers (213 vs. 258 cases, P < .001). Oberlin reported a 16% improvement in cancer detection of MR fusion biopsy versus conventional TRUS biopsy. The detection of clinically significant cancer was 24% higher with MRI-US fusion–targeted biopsy compared to conventional TRUS biopsy. These findings reinforced the results of the American National Cancer Institute that mpMRI has the potential to increase the detection of high-risk prostate cancer and decrease the detection of low-risk prostate cancer. Our study is consistent with similar reports in literature which show the potential for MRI-guided biopsy to improve the detection of prostate cancer compared to TRUS biopsy. Furthermore, all the cancers detected appeared to be clinically significant.

This study has several limitations. First, it is a relatively small, prospective case study. Patients were referred to mpMRI according to their doctor’s preferences, which could affect the results both positively and negatively, while a randomized trial comparing men undergoing conventional versus fusion biopsy would provide level 1 evidence. Second, it remains possible that some clinically significant cancers are missed on MR-US fusion biopsy, so the false-negative rate is unknown. Finally, all biopsies were performed by a single urologist, and all MRIs were interpreted by an experienced uroradiologist. Less experienced urologists and radiologists might not achieve the same diagnostic yield.

Conclusions

A diagnostic dilemma in patients who have a prior negative biopsy and persistent suspicion of PCA can, in part, be solved with more precision and accuracy by using mpMRI. When a suspicious lesion is found on mpMRI, there is demonstrated improvement in clinically significant cancer detection compared to TRUS biopsy. It is of particular importance that the visualization of the tumor allows for better sampling of difficult to reach tumors in the anterior and apex of the prostate. Additionally, mpMRI prior to repeated biopsy could be used to reduce unnecessary prostate biopsies in some patients. Nevertheless, while the advances in MRI fusion biopsy technology are promising and represent an exciting area of research, urologists should be mindful of potential limitations of mpMRI cognitive fusion biopsy. The performance of mpMRI relies on the ability of mpMRI to identify clinically significant cancer, but also on the operator dependent reading and interpretation, as well as diagnostic accuracy of biopsy itself.

References


DIJAGNOSTIČKI ZNAČAJ BIOPSIJE PROSTATE VOĐENE KOGNITIVNOM FUZIJOM 
MULTIPARAMETRIJSKE MAGNETNE REZONANCE I TRANSEKTALNOG ULTRAZVUKA 
(mpMRI-TRUS) KOD BOLESNIKA S PRETHODNO NEGATIVNOM TRUS VOĐENOM BIOPSIJOM


U ovoj prospektivnoj kliničkoj studiji cilj je odrediti stopu detekcije raka prostate biopsije vođene kognitivnom fuzijom multiparametrijske magnetske rezonance i transrektalnog ultrazvuka (mpMRI-TRUS) kod bolesnika s prethodno negativnom TRUS vođenom biopsijom. U razdoblju od 1. 10. 2016. do 1. 7. 2017. kod 101 uzastopnog bolesnika s povišenim prostata specifičnim antigenom (PSA) i/ili pozitivnim digitorektalnim pregledom, a nakon negativne prve TRUS biopsije je učinjena druga, ponovljena biopsija prostate. Kod 24 bolesnika učinjena je, u skladu sa Smjernicama Europskog urološkog društva, prethodna mpMRI i potom kognitivna fuzijska biopsija prostate s 8-10 sistemskih cilindara i 1-3 ciljane biopsije prema mpMRI nalazu. Kod 77 bolesnika je učinjena samo klasniča, ponovljena TRUS biopsija bez prethodne slikovne obrade. Kod bolesnika s mpMRI, stopa detekcije raka prema PIRADS-v2 je PIRADS 1, n = 0; PIRADS 2, n = 0; PIRADS 3, n = 0; PIRADS 4, n = 6/8 (75%) i PIRADS 5, n = 2/3 (67%). U skupini bolesnika s MP-TRUS kognitivnom fuzijskom biopsijom stopa detekcije raka prostate je 8/24 (33%), dok je u kontrolnoj skupini stopa detekcije 12/77 (16%), što se pokazalo statistički značajnom razlikom (t test; p=0.037, CI 95% je 0.01 to 0.37). Bolesnici s PIRADS ≤ 3 (54%) su mogli izbjeći biopsiju.

Ključne riječi: Rak prostate; Magnetna rezonancija; Biopsija prostate