PIRADS Score 3: to Biopsy or Not to Biopsy?

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Abstract

Introduction and Objectives. Prostate Imaging Reporting and Data System (PIRADS) was developed in order to standardize the reporting of mpMRI and to establish clear guidelines for the characterization of suspect lesions in the prostate. By assigning a score from 1 to 5, the PIRADS shows the probability of every lesion to harbor clinically significant prostate cancer (PCa). Despite clear recommendations in case of PIRADS Score 1/2 or 4/5 lesions, it does not exist a consensus regarding PIRADS 3 areas.

Materials and Methods. We performed a retrospective analysis of the patients who presented to our department between January 2017 and January 2019 with the clinical or biochemical suspicion of PCa and harbored PIRADS 3 lesions. Our study included 37 patients. In all patients a 1-3 core MRI-TRUS Fusion targeted biopsy was performed along with the 12 core standard systematic biopsy.

Results. The mean age of the patients was 62.9 years (±5.8 years), the mean PSA was 7.38 ng/ml (±5.19 ng/ml) and the mean prostate volume was 62.2 g (±23.2 g). Overall cancer diagnosis rate was 27%, whereas clinically significant PCa was present in 8.1% of the cases. All lesions located in the TZ were confirmed as benign. All patients with Gleason group III PCa were confirmed both on systematic and targeted biopsy. MRI-TRUS fusion biopsy showed the possibility to reduce the overdiagnosis of indolent PCa by 50%, but missed one patient with Gleason group II PCa.

Conclusions. The overall and csPCa detection rate in patients with PIRADS 3 lesions is low. Performing only MRI-TRUS fusion targeted cores leads to an accurate diagnosis of aggressive PCa in these patients and can reduce the overdiagnosis of indolent disease by 50%. Further methods are needed in order to refine the indication for biopsy in patients who harbor PIRADS 3 lesions.

Key-words: multiparametric MRI, PIRADS 3, targeted biopsy, FUSION biopsy

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Introduction and Objectives

Prostate cancer screening represents one of the current hot topics in urology and intense research is performed in order to improve the diagnosis of prostate malignancies. At the present moment there are two main factors limiting the accuracy of prostate cancer diagnosis: the screening modality and the way to perform the prostate biopsy.

For PCa screening digital rectal examination is still recommended, but has poor accuracy for low volume or transitional zone PCa and most of the patients harbor locally advanced PCa at diagnosis.[1] A huge step forward was done in the late 1980s when the PCa screening based on prostate specific antigen (PSA) was introduced and resulted in a three fold lower incidence of metastatic PCa at presentation.[2] However, due to being a prostate specific marker, PSA is influenced by numerous factors[3] and a high rate of false positive PSA results was observed.[4] Other parameters such as PSA doubling time, PSA velocity, free PSA ratio, PSA density, or markers such as PCA3 were evaluated in order to increase the specificity of PSA, but showed poor performance in improving PCa diagnosis or the high costs limited their use on large scale.[5]

Prostate biopsy is the only invasive diagnostic procedure which is performed in a “blind” manner, based on a sectorial scheme of prostate. The randomized transrectal ultrasound guided biopsy has low cancer detection rates, varying between 20%-40% and high rates of false negative results,[6] with up to 40% of repeated biopsy confirming the presence of PCa. Repeated biopsies expose the patients to higher risks such as hemorrhage and sepsis.[7]

According to the European Association of Urology, multiparametric Magnetic Resonance Imaging (mpMRI) may be used as a tool both for PCa screening and to guide the prostate biopsy.[8] In 2012, it was introduced Prostate Imaging Reporting and Data System v1 which showed a high accuracy for PCa diagnosis but had several limitations due to high inter-reader variability.[9] In 2015 a joint committee of American College of Radiology (ACR) and European Society of Urogenital Radiology (ESUR) published Prostate Imaging Reporting and Data System v2 (PI-RADSv2) with the aim to improve the standardization, interpretation and reporting of mpMRI examination.(PIRADSv2).[10] PI-RADS v2 assesses each lesion in a category from 1 to 5 which correlates with the presence of a clinically significant cancer (PIRADS 1: very low, clinically significant cancer is unlikely to be present; PIRADS 5: very high, clinically significant cancer is highly likely to be present).[10] In patients with a PI-RADS Score of 1 or 2 lesion, the urologist may safely defer the biopsy, because of the high negative predictive value (NPV)[11], while a score of 4 or 5 suggests a high probability of malignancy thus the biopsy is considered imperative.[12]

The limitation of PIRADS v2 is represented by the lack of a consensus of how PIRADS 3 lesions should be approached. PCa incidence in case of PIRADS 3 lesions varies a lot among studies, from 5% to 35%.[13] Follow-up of indeterminate lesions may lead to undertreatment by postponing the curative surgical treatment, while the biopsy may expose patient to an invasive evaluation with its risks and patient’s discomfort. The aim of our study was to evaluate the prostate cancer diagnosis rate of MRI-TRUS fusion biopsy in PI-RADS v2 score 3 lesions in order to refine the indication for prostate biopsy in such setting.

Materials and Methods

We performed a retrospective evaluation of all the patients who presented in the urology department at the Municipal Hospital Cluj-Napoca between July 2017 - January 2019 with the suspicion of PCa based on elevated PSA (> 4 ng/ml) or abnormal digital rectal examination. We included only the patients who were evaluated by mpMRI, presented a PIRADS 3 lesion and were biopsied in a MRI-TRUS Fusion manner. The final number of patients part of the current analysis was 37. The MRI-TRUS Fusion biopsy was performed by the one experienced urologist (more than 150 biopsies). Local anesthesia was performed by endorectal instillation of lidocaine gel. The Arietta 70a System (Hitachi, Japan) with endfire endorectal probe C41V1 2-10 mHz and RVS software with rigid registration were used to perform all the prostate biopsy. One to three biopsies were obtained for each lesion. Also, a 12 core systematic biopsy was performed in all patients. Three experienced pathologists reviewed the biopsies.

The statistical analysis was performed using Medcalc v.12.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org). Chi-square test was used for the correlation between categorical variables, and ANOVA for the correlation between categorical and continuous variables. P<0.05 was considered statistically significant.

Results

Patient characteristics

The mean age of the patients was 62.9 years (±5.8
years), the mean PSA was 7.38 ng/ml (±5.19 ng/ml) and the mean prostate volume of the patients included in our study was 62.2 g (±23.2 g). Eight patients had a history of prior biopsies, of whom 6 (75%) had one and 2 patients underwent 2 or more prostate biopsies due to persistent clinical or biochemical suspicion for PCa.

In 75% of cases, there was a single suspicious lesion identified on pre-biopsy MRI, whereas in 21.6% of the patients there were two abnormal areas. Two patients harbored a number of 3 suspicious lesions. The maximum dimension of the lesion was 11.1 mm (± 3.3 mm). The details describing the location of the lesions are summarized in Table 1.

The mean number of total biopsy cores was 15 (min 14 – max 16) and the mean number of targeted cores was 3 (min 2 – max 4).

**Detection of PCa**

Overall PCa detection rate was 27% (10 cases) and clinically significant disease was found in 8.1% of the cases (3 patients). Atypical small acinar proliferation was present in 8.1% of the cases, whereas 64.9% of cases had benign prostate hyperplasia. Seventy percent of the patients diagnosed with PCa had Gleason grade group I tumors, whereas Gleason score higher than 7 (3+4) was identified in 30% of the cases. Two patients harbored Gleason group III PCa. The presence of PCa was not correlated with the number of lesions seen on MRI (p=0.7) nor with their location at the base, middle or apex of the prostate (p=0.4). All the suspicious areas located in the transitional zone were confirmed as benign.

A comparison between PCa and benign pathology patients is summarized in Table 2. Although patients with PCa seem to be older and have smaller prostates, no statistically significant difference was identified between these two groups.

**Discussions**

Our cancer detection rate in case of PIRADS 3 lesions was similar to the one reported in a similar retrospective analysis by Kim et al (24%) who also performed MRI-TRUS fusion biopsy. Better results were observed in larger retrospective cohorts published by Kaufmann et al (33%)[16] and Venderink et al (35%)[13], but in both studies the targeted biopsy was performed inside the MRI gantry. It is well known that the targeted biopsy significantly outperforms the systematic biopsy[17]. Moreover there are also differences in the performance of the various types of targeted biopsy, in-bore MRI targeted biopsy showing higher CDR compared to MRI-TRUS Fusion biopsy, even though the difference

<table>
<thead>
<tr>
<th>Prostate lobe location</th>
<th>Malignant</th>
<th>Benign</th>
<th>p</th>
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<tbody>
<tr>
<td>Left lobe</td>
<td>32.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right lobe</td>
<td>48.6%</td>
<td></td>
<td></td>
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<tr>
<td>Bilateral</td>
<td>18.9%</td>
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**Table 1. Detailed location of the suspicious lesions on mpMRI**

The mean number of positive biopsy cores in patients diagnosed with PCa was 3 (min 1 – max 7) and the mean number of positive targeted biopsy cores was 1 (min 0 – max 3) (Table 3).

<table>
<thead>
<tr>
<th>No of positive biopsy cores/ total (%)</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of positive biopsy cores/ systematic (%)</td>
<td>3 (24.5%)</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>No of positive biopsy cores/ targeted (%)</td>
<td>1 (22.4%)</td>
<td>0</td>
<td>6</td>
</tr>
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**Table 2. Comparison of clinical parameters between malignant and benign result of MRI-TRUS fusion prostate biopsy**

**Table 3. Summarization of the mean number of positive biopsy cores**

Lymphovascular invasion or extracapsular extension were identified in none of cases included in our study.

None of the patients with PCa was diagnosed exclusively on targeted biopsy. In 40% of the cases the diagnosis was confirmed on both, systematic and targeted cores. MRI-TRUS fusion biopsy identified 2 out of 3 patients with csPCa, but missed the diagnosis of Gleason 6 (3+3) PCa in the other 5, who were confirmed on systematic cores. The most aggressive tumors (Gleason group III) were confirmed on targeted, as well as systematic biopsy. A single patient harbored csPCa and was missed by MRI-TRUS fusion guided biopsy.
was not statistically significant\textsuperscript{[18]}. On the other hand, in a prospective trial, Pokorny et al reported that only 15% of the PIRADS 3 lesions harbored PCa, in spite of performing in bore MRI targeted biopsy.\textsuperscript{[14]}

One possible reason for our relatively high CDR is that more than 75% of the lesions in our cohort were localized in the peripheral zone (PZ) and it is well that category 3 lesions situated in PZ are more likely to harbor PCa in comparison with those in the transitional zone (TZ)\textsuperscript{[15]}. Knowing that mpMRI performance in the diagnosis PCa in TZ is highly variable among studies, ranging from 66%-84\%\textsuperscript{[16],[20]}\textsuperscript{[20]}, other factors such as criteria location, shape, border, strong ADC restriction were observed to improve the diagnostic accuracy.\textsuperscript{[12]} Hansen et al suggested that factors such as wedge-shaped/geographical shape and strong restriction on ADC/DWI have a significantly higher positive prediction value for prostate cancer detection in case of PIRADS 3 lesions in TZ.\textsuperscript{[12]}

Another factor suggested as a criteria for the indication of prostate biopsy is the lesion volume, as lesions > 0.5 ml harbor more often clinically significant PCa.\textsuperscript{[21],[22]}

Despite that mpMRI inter-reader agreement was reported as good to excellent, high variability in characterizing lesions using PIRADS v2 was observed, especially in signal abnormality on DWI sequences\textsuperscript{[23]}, ADC map abnormality, DCE features for PZ lesions\textsuperscript{[24]}, and lesion texture and border in T2 for TZ lesions\textsuperscript{[24]}. As a result, Patel et al recommended caution in the interpretation of features with low inter-reader reliability.\textsuperscript{[23]}

Subsequently, Hansen et al recommends that the imaging of patients with equivocal lesions should be referred for a second opinion to an experienced uro-radiologist.\textsuperscript{[12]}

Apart from the imaging information, which may help the urologist in the diagnostic process, there are also biologic biomarkers that can be of help: PSA density (PSAD) and PCA3. It is well known that PSAD is a predictor factor for the biopsy result\textsuperscript{[25]}. In case of PIRADS 3 lesions, a cut-off value of 0.15 ng/ml for PSAD has shown a specificity and a sensitivity for PCa of 63%-70% and 70-79%, respectively.\textsuperscript{[15]} Also, Kundu et al observed a PSAD is a strong predictor for high Gleason Score and pathologic stage\textsuperscript{[26]}, while Epstein included it among the criteria for clinically significant PCa\textsuperscript{[27]}. Therefore up to 42% of the patients with a PIRADS 3 lesion and a PSAD < 0.15 ng/ml may safely avoid the biopsy\textsuperscript{[13]}. The negative predictive value of PSAD < 0.15 ng/ml for PCa presence along with a negative mpMRI is 79%-89% in biopsy naïve men, and 83-93% for men with previous biopsies.\textsuperscript{[28]}

Urinary PCA3 may also be helpful in the decision process, Fernstermaker et al reporting statistically significant association of PIRADS 2 and 3 lesions and PCA3 > 35 (p=0.04). In this way, more than 30% of biopsies may be avoided.\textsuperscript{[29]}

At the current moment there are several nomograms which can also be used in order to predict the presence of PCa and suggest the need of a prostate biopsy. Bjurlin et al analyzed a group of 389 men (age, PSA, PSAD, prostate volume) and established a nomogram for the prediction of GS ≥ 7 PCa in biopsy naïve men\textsuperscript{[30]}. Similarly, Niu et al reported that age, PIRADS v2 score and PSAD were independent predictors for csPCa in men with PSA 4-10 ng/ml, and published a nomogram which correlated positively with GS.\textsuperscript{[31]}

Conclusions

The overall and csPCa detection rate in patients with PIRADS 3 lesions is low. Transitional zone lesions are most probably benign and should defer the indication for biopsy. Further methods are needed in order to select the patients with PIRADS 3 lesions who should undergo prostate biopsy. Performing only MRI-TRUS fusion targeted cores leads to an accurate diagnosis of aggressive PCa in these patients and can reduce the overdiagnosis of indolent disease by 50%.

References


Clinical studies


