Diagnostic pathway of the biopsy-naïve patient suspected for prostate cancer: Real-life scenario when multiparametric Magnetic Resonance Imaging is not centralized

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Received 10 September 2020; accepted 7 December 2020
Available online 9 January 2021

KEYWORDS
Prostate cancer; mpMRI; Fusion; Prostate biopsy; PIRADS

Summary
Introduction. — We aimed to compare the pathway including multi-parametric Magnetic Resonance Imaging (mpMRI) versus the one without mpMRI in detection of prostate cancer (PCa) when mpMRI is not centralized.

Materials. — January 2019-March 2020: prospective data collection of trans-perineal prostate biopsies. Group A: biopsy-naïve patients who underwent mpMRI (at any institution) versus Group B: patients who did not. Within Group A, patients were stratified into those with negative mpMRI (mpMRI−, PIRADS v2.1 = 1-3, with PSA density < 0.15 if PIRADS 3) who underwent standard biopsy (SB), versus those with positive mpMRI (mpMRI+, when PIRADS 3−5, with PSA density > 0.15 if PIRADS 3) who underwent cognitive fusion biopsy.
Introduction

The European Association of Urology (EAU) guidelines for diagnostic evaluation of prostate cancer (PCa) recommends an individualized risk-adapted strategy for the early detection, seeking to reduce the risk of over-diagnosis [1].

In the routine scenario, serum prostate specific antigen (PSA) and digital rectal examination (DRE) are irreplaceable diagnostic tools. Trans-rectal ultrasound (TRUS) is not reliable in PCa detection. As such, within the standard TRUS-guided biopsy setting, there is no significant added value of targeted biopsies on suspicious lesions at TRUS [2, 3], even if promising studies are being published about micro-ultrasound guided biopsy [4].

Results. — Two hundred and eighty one biopsies were analyzed. 153 patients underwent mpMRI (Group A). 98 mpMRI+ underwent fusion biopsy; 55 mpMRI- underwent SB. 128 Group B patients underwent SB. Overall PCa detection rate was 52.3% vs. 48.4% (Group A vs. B, P=0.5). Non-clinically-significant PCa was detected in 7.8 vs. 13.3% (Group A vs. B, P=0.1). Among the 98 mpMRI+ Group A patients only 2 had non clinically-significant disease. In 55 mpMRI- patients who underwent SB, 10 (18.2%) had clinically-significant PCa. Prostate volume predicted detection of PCa. In Group B, age and PSA predicted PCa. Sensitivity of mpMRI was 75.0% for all PCa, 85.3% for clinically-significant PCa.

Conclusion. — Higher detection of PCa and lower detection of non-clinically-significant PCa favored mpMRI pathway. A consistent number of clinically-significant PCa was diagnosed after a mpMRI+. Thus, in real-life scenario, mpMRI does not obviate indication to biopsy when mpMRI is not centralized.

Level of evidence. — 3.

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With the implementation of the PIRADS v.2, improvements have been undoubtedly observed in the accuracy of mpMRI and MRI-guided biopsies, but lack of centralization of mpMRI could lead to low performance of the pathway including such prostate imaging [9–13].

To contribute to this field, we sought to perform an internal evaluation comparing the two diagnostic pathways of the patient with suspicious PCa: one including mpMRI versus the standard. Specifically for the purpose of the study, our analysis was conducted on cases undergoing prostate biopsy at our institution, but had mpMRIs performed at any institution.

The aim of the study was to compare the outcomes of the diagnostic pathway including mpMRI versus the one without mpMRI, for either all PCAs or clinically-significant PCAs, and to look for eventual predictors of detection of all PCAs and clinically-significant PCAs when mpMRI is not centralized.

Materials and methods
From January 2019, to March 2020, data of all prostate biopsies performed at our Institution were prospectively collected. All patients had signed an informed consent before the procedure. The study was performed in accordance with the Declaration of Helsinki.

A critical evaluation of the dataset was performed. For the purpose of the study, patients were stratified into two groups. Patients who did undergo mpMRI represented Group A; patients who did not, represented Group B. Notably, within Group A, patients had undergone mpMRI either at our Institution or elsewhere. Group B composed of patients referred for standard prostate biopsy to our Institution by general urologists from the territory. Only biopsy-naïve patients and patients with negative DRE were considered. We excluded patients intaking 5-alfa reductase inhibitors at the time of biopsy and patients who previously underwent prostate surgeries.

The protocol used at our Institution in the typical patient suspected for PCAs, is based on the indication to perform prostate biopsy after two consecutive PSA elevations above 4 ng/ml.

mpMRI was suggested in all patients counselled at our Institution. In patients who did not undergo mpMRI, this was discussed with the urologist, after accounting for appropriateness and eventual contraindications. Within Group A, according to the findings of the mpMRI, patients were further stratified into those with negative mpMRI who underwent standard biopsy, versus those with positive mpMRI who underwent cognitive fusion biopsy.

At our Institution, mpMRI was performed on a 1.5 Tesla scanner (Magnetom Aera, Siemens, Munich, Germany) with a 30-channel surface coil, by two radiologists experienced in the urogenital field. According to PIRADS v 2.1 guidelines [14], the following sequences were used: Axial T2 Turbo Spin Echo (ST: 3.5 mm—TR: 3180—TE: 163), T2 Isoluminetic 3D Axial (ST: 0—TR: 1200—TE: 146), sagittal T2 Turbo Spin Echo (ST: 3.5 mm—TR: 4900—TE: 100), diffusion-weighted imaging (DWI) spin-echo echo-planar sequence with different values of b (0, 50, 400, 1500 s/mm2) and associated apparent diffusion coefficient (ADC) map, axial fat-sat T1 volumetric interpolated breath-hold examination (ST: 3.5 mm—TR: 6.26—TE: 2.39) before and after administration of contrast medium (Gadoteric Acid 0.2 ml/kg injected at 2 ml/sec), T1 fat saturation dynamic sequences were acquired to monitor tissue enhancement (ST: 3.5 mm—TR 5—TE 1.4), with acquisition intervals every 6 seconds. Eventually, every lesion detected was labeled according to the PI-RADS score v 2.1. No information about the protocol used and the experience of the radiologist reading the mpMRI were available for mpMRI performed at external institutions.

Negative mpMRI (mpMRI−) was considered when PIRADS v 2.1 = 1–3, with PSA density <0.15 in case of PIRADS v 2.1 = 3; positive mpMRI (mpMRI+) was considered when PIRADS v 2.1 3–5, with PSA density ≥0.15 in case of PIRADS v 2.1 = 3 [15,16].

When mpMRI was positive for a suspicious lesion, the biopsy was performed under ultrasound guidance (Esaote MyLab 9, Esaote, Genova, Italy) and fused in a cognitive way, together with a 12-cores standard biopsy. Two cores were targeted on the index lesion as previously suggested [17].

All biopsies, either standard or cognitive fusion, were performed by three experienced urologists (hundreds of biopsy procedures performed) under local anesthesia via a trans-perineal approach. Final pathology analysis was performed by one dedicated uro-pathologist. Clinically-significant PCa was defined according to the Standards of Reporting for MRI-targeted Biopsy Studies (START) criteria for fusion biopsy (biopsy Gleason Score 3+4 or maximum cancer core length ≥ 5 mm) [18,19] and the updated Epstein criteria for standard biopsy [20].

Statistical analysis
A dedicated database was used to record the data of all patients who underwent the procedure. Collected data included:
• patient’s data;
• prostate’s data;
• mpMRI data (when performed);
• biopsy procedure data (standard vs. fusion);
• final pathology data.

The chi-square test was used to compare categorical variables. For continuous variables with normal distribution, differences between means were compared by the Student’s t-test. The Mann–Whitney U test was used otherwise. Diagnostic tests were used: sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to assess the quality of the tests. 2-sided tests with a level of significance of 5% were used. Univariate/multivariate analyses were used to look for predictors of PCAs and clinically-significant PCAs within the Groups. Statistical analyses were carried out by using SPSS Software, version 20.0, SPSS Inc., Chicago, IL, USA).

Results
As of March 31st, 2020, a total of 422 biopsies were recorded in our institutional database. After accounting for inclusion/exclusion criteria, a total of 281 biopsies were included in the present study. A hundred fifty-three patients underwent mpMRI and were included in Group A. Within Group
Figure 1. Study flow chart. DRE: Digital Rectal Examination; 5-ARI: 5-alpha reductase inhibitors; mpMRI: multi-parametric Magnetic Resonance Imaging; mpMRI+: positive mpMRI; mpMRI−: negative mpMRI.

A, 98 patients who had mpMRI+ underwent fusion-biopsy, whilst the 55 patients who had mpMRI− underwent standard biopsy. Group B included the 128 patients who did not undergo mpMRI thus undergoing standard biopsy. The study flow chart is reported in Fig. 1.

Baseline characteristics of grouped patients are summarized in Table 1.

### Biopsy Procedures Data

Overall, the detection rate for all PCa within the 153 Group A patients was 52.3% (80 patients).

In 12 patients (7.8%), non-clinically-significant PCa was detected.

Among the subgroup of 98 patients who had mpMRI+, 60 patients were diagnosed with PCa (61.2%). Among them, only 2 patients had non-clinically-significant PCa (2.0%).

Concerning the 55 mpMRI− patients who underwent standard biopsy, 20 were diagnosed with PCa (36.4%). Among them, 10 patients (18.2%) had clinically-significant PCa.

Among the 128 Group B patients who underwent standard biopsy as well, 62 were diagnosed with PCa (48.4%). Seventeen patients (13.3%) were diagnosed with a non-clinically-significant PCa. Fig. 2 details the biopsy results.

<table>
<thead>
<tr>
<th>Patients’ baseline characteristics.</th>
<th>Group A</th>
<th>Group B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agea, years</td>
<td>68.0 (13.2)</td>
<td>68.9 (13.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
<td>7.1 (7.3)</td>
<td>6.7 (7.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>PVol, mL</td>
<td>51 (19)</td>
<td>47 (21)</td>
<td>0.1</td>
</tr>
<tr>
<td>PSAD, ng/mL²</td>
<td>0.13 (0.09)</td>
<td>0.15 (0.18)</td>
<td>0.2</td>
</tr>
<tr>
<td>Qmax, mL/sec</td>
<td>12.4 (6.5)</td>
<td>12.6 (7.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>PVR, mL</td>
<td>25 (29)</td>
<td>32 (43)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

PSA: Prostate Specific Antigen; PVol: Prostate Volume; PSAD: PSA Density; Qmax: Urinary Maximum Flow; PVR: Post-Voiding Residual Volume.

a Reported as mean (Standard Deviation).

Figure 2. Bar chart detailing the biopsy results. PCa: Prostate Cancer; cs-PCa: clinically-significant PCa; mpMRI: multi-parametric Magnetic Resonance Imaging; mpMRI+: positive mpMRI; mpMRI−: negative mpMRI.
Table 2  Multivariate analysis results.

A. All Prostate Cancers

<table>
<thead>
<tr>
<th>mpMRI+</th>
<th>beta</th>
<th>SE</th>
<th>95% C.I. for beta</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.22</td>
<td>0.11</td>
<td>−0.00 to 0.44</td>
<td>0.055</td>
</tr>
<tr>
<td>PSA</td>
<td>0.03</td>
<td>0.11</td>
<td>−0.20 to 0.25</td>
<td>0.8</td>
</tr>
<tr>
<td>PVol no</td>
<td>−0.30</td>
<td>0.12</td>
<td>−0.54 to −0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>no. cores</td>
<td>0.11</td>
<td>0.12</td>
<td>−0.11 to 0.35</td>
<td>0.3</td>
</tr>
<tr>
<td>mpMRI−</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>−0.03</td>
<td>0.16</td>
<td>−0.36 to 0.30</td>
<td>0.8</td>
</tr>
<tr>
<td>PSA</td>
<td>0.09</td>
<td>0.18</td>
<td>−0.27 to 0.46</td>
<td>0.6</td>
</tr>
<tr>
<td>PVol no</td>
<td>−0.13</td>
<td>0.18</td>
<td>−0.50 to 0.23</td>
<td>0.5</td>
</tr>
<tr>
<td>no. cores</td>
<td>−0.14</td>
<td>0.17</td>
<td>−0.47 to 0.20</td>
<td>0.4</td>
</tr>
<tr>
<td>mpMRI no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.22</td>
<td>0.09</td>
<td>0.03 to 0.41</td>
<td>0.02</td>
</tr>
<tr>
<td>PSA</td>
<td>0.25</td>
<td>0.09</td>
<td>0.06 to 0.45</td>
<td>0.006</td>
</tr>
<tr>
<td>PVol no</td>
<td>−0.10</td>
<td>0.09</td>
<td>−0.29 to 0.08</td>
<td>0.3</td>
</tr>
<tr>
<td>no. cores</td>
<td>0.03</td>
<td>0.09</td>
<td>−0.15 to 0.22</td>
<td>0.7</td>
</tr>
</tbody>
</table>

B. Clinically-Significant Prostate Cancers

<table>
<thead>
<tr>
<th>mpMRI+</th>
<th>beta</th>
<th>SE</th>
<th>95% C.I. for beta</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.09</td>
<td>0.15</td>
<td>−0.22 to 0.40</td>
<td>0.6</td>
</tr>
<tr>
<td>PSA</td>
<td>0.02</td>
<td>0.16</td>
<td>−0.30 to 0.33</td>
<td>0.9</td>
</tr>
<tr>
<td>PVol no</td>
<td>−0.17</td>
<td>0.15</td>
<td>−0.48 to 0.15</td>
<td>0.3</td>
</tr>
<tr>
<td>no. cores</td>
<td>0.07</td>
<td>0.16</td>
<td>−0.24 to 0.39</td>
<td>0.6</td>
</tr>
<tr>
<td>mpMRI−</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.09</td>
<td>0.25</td>
<td>−0.45 to 0.64</td>
<td>0.7</td>
</tr>
<tr>
<td>PSA</td>
<td>0.25</td>
<td>0.28</td>
<td>−0.35 to 0.85</td>
<td>0.4</td>
</tr>
<tr>
<td>PVol no</td>
<td>−0.43</td>
<td>0.26</td>
<td>−0.98 to 0.12</td>
<td>0.1</td>
</tr>
<tr>
<td>no. cores</td>
<td>0.32</td>
<td>0.23</td>
<td>0.11 to 0.73</td>
<td>0.08</td>
</tr>
<tr>
<td>mpMRI no</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.11</td>
<td>0.14</td>
<td>−0.17 to 0.40</td>
<td>0.4</td>
</tr>
<tr>
<td>PSA</td>
<td>0.21</td>
<td>0.14</td>
<td>−0.07 to 0.50</td>
<td>0.1</td>
</tr>
<tr>
<td>PVol no</td>
<td>0.02</td>
<td>0.14</td>
<td>−0.26 to 0.31</td>
<td>0.9</td>
</tr>
<tr>
<td>no. cores</td>
<td>0.10</td>
<td>0.14</td>
<td>−0.18 to 0.39</td>
<td>0.5</td>
</tr>
</tbody>
</table>

mpMRI: multi-parametric Magnetic Resonance Imaging; SE: Standard Error; C.I.: Confidence Interval; PSA: Prostate Specific Antigen; PVol: Prostate Volume.

Supplementary Table 1 details biopsy results stratified by PIRADS group category within Group A.

At multivariate regression analysis, prostate volume (PVol) was found to be independent predictor of detection of PCa (beta = 0.30, 95% C.I. for beta = 0.54: −0.07, P = 0.01) among mpMRI+ patients.

In mpMRI-patients, regression analysis failed to find any significant predictor. Finally, age and PSA were found to be independent predictors of detection of PCa among patients who did not undergo mpMRI (Age: beta 0.22, 95% C.I. for beta 0.03: 0.41, P = 0.02; PSA: beta 0.25, 95% C.I. for beta 0.06: 0.45, P = 0.006). As concerning clinically-significant PCa, regression analysis did not show any significant predictor (Table 2).

Considering diagnosis of all PCa, within patients who underwent mpMRI, the sensitivity of the mpMRI was 75.0% in our series (true positives were 60 out of the 80 positive biopsies).

Specificity was 47.9% (35 true negatives out of 73 negative biopsies). False positives were 38 out of a total of 98 patients who had positive mpMRI (38.8%), while false negatives were 20 out of 55 patients who had negative mpMRI (36.4%) (PPV = 61.2%, NPV = 63.6%).

When considering the ability to detect clinically-significant PCa, sensitivity improved to 85.3%, whilst specificity was 52.9%. A PPV of 59.2% and a NPV of 81.8% were obtained at this re-analysis (Fig. 3).

Discussion

In our analysis of 281 biopsy procedures, we found an overall detection rate of PCa equal to 52.3% in patients who underwent mpMRI versus 48.4% in patients who did not (P = 0.5). A lower number of non-clinically-significant PCa was detected when mpMRI was performed (7.8% vs. 13.3% Group A vs. B,
respectively), although the difference was not statistically significant \(P=0.1\).

Notably, among the 98 patients who had a positive mpMRI within Group A, only 2 patients had non-clinically-significant disease (2.0%), confirming previous studies reporting a higher proportion of men diagnosed with clinically-significant PCa among those undergoing mpMRI-based fusion biopsy vs. those assigned to TRUS-guided random biopsy [21].

PVol was found as an independent predictor for detection of PCa among patients with positive mpMRI, whilst no significant predictors of diagnosing PCa were found in patients with negative mpMRI. In patients who did not undergo mpMRI, age and PSA were confirmed to be predictors of diagnosis of PCa.

To measure the reliability of mpMRI, the criteria of clinical significance for PCa has to be taken into account [7].

As such, when considering detection of all PCa, the sensitivity of mpMRI was 75.0% in our database, with specificity being 47.9%, PPV 61.2% and NPV = 63.6%. These results sound below the average, but the reader should note that all Gleason scores 3 + 3, even if diagnosed in 1 core only, were named as PCa at this first analysis.

At re-evaluation considering detection of clinically-significant PCa only, sensitivity improved to 85.3% and specificity to 52.9%. Notably, NPV raised to 81.8%, suggesting that when mpMRI was negative, no cancer or non-clinically significant PCa was found at final pathology in the 82% of the cases. Such data are satisfactory, given the fact that we are unable to state the level of experience of the radiologists involved in the mpMRI considered. As such, as explained in the methodology of the study, mpMRI was not centralized. Notwithstanding this strong limitation, our data confirm the reliability of mpMRI in the detection of clinically-significant PCa. The NPV did not significantly differ to that published in the literature [22]. A systematic review and meta-analysis from the European Association of Urology prostate cancer guidelines panel reported a median mpMRI NPV equal to 82.4% (ranging between 69.0 and 92.4%) for all PCa and 88.1% (ranging between 85.7 and 92.3) for clinically-significant PCa [23].

In our analysis almost all PIRADS 3 lesions were considered as negative mpMRI (PSAD < 0.15 in 5 cases only). What is remarkable is that within patients who had negative mpMRI in our series, half of the patients diagnosed with PCa had a clinically-significant disease. This is in line with the data of the PICTURE study [24]. On the other hand, we admit we had only 10 PIRADS 1-2 lesions within the negative mpMRI group. In our analysis, the performance of mpMRI, particularly when negative, was inferior to that published from single-center analyses when only experienced radiologists were involved. In the prospective randomized trial by Porpiglia et al. comparing the two pathways focused in our study, detection rate of clinically-significant PCa in case of standard biopsy performed after a negative mpMRI was 3.8% only [25].

Our study is not devoid of limitations. Firstly, the relatively small sample size and selection bias of patients included. Although the EAU guidelines recommendations, the opportunity of mpMRI was not discussed in patients who were referred. Secondly, the technique used for fusion was "cognitive".

Software-based fusion could sound more precise in assessing the accuracy of mpMRI. Nevertheless, recent papers were unable to state the superiority of one approach over the challenger [26], thus, there is no definitive consensus about the best technique to be used.

On the other hand, we believe that the exclusion of non-biopsy-naïve patients, and/or patients with positive DRE, and/or patients who previously underwent prostate surgeries improved the quality of the analysis. The strength of the study is the prospective collection of granular data, and the provocative analysis of the real scenario when mpMRI is not centralized. As such, the purpose of our study was to check the performance of the pathway including mpMRI when mpMRI is performed at any Institution (without
information about the experience of the radiologist reading the mpMRI).

In summary, the results of our series are acceptable, but somewhat inferior to those of other large series published thus far.

A trend towards a higher detection of all PCa and a lower detection of non-clinically significant PCa was observed in the pathway including mpMRI, but many clinically-significant PCa were diagnosed after negative mpMRI.

It is a matter of debate whether patients with negative mpMRI of the prostate could obviate the need to perform a biopsy [27]. In the real-life scenario reported herein, biopsy must still be recommended after negative mpMRI in patients with clinical suspicion of PCa.

Since the obtained data, we started another prospective data collection to compare the pathways when mpMRI is performed only at our Institution and read by one experienced radiologist.

Among the inter-play among the factors influencing the accuracy of mpMRI in detecting clinically significant PCa, the experience of the radiologists involved represents the dominating factor [28].

In order to benefit from mpMRI in diagnosing PCa, it is necessary to develop expertise for both radiologists and urologists, joined in a multi-disciplinary team, by implementing the heterogeneity of the mpMRI considered herein, the unmeasurable considerable variability in PIRADS score assignment and the related detection of clinically-significant PCa yield across radiologists probably explained our results [7,29].

Conclusions

A higher detection of all PCa and a lower detection of non-clinically significant PCa was observed in the pathway including mpMRI, but many clinically-significant PCa were diagnosed after negative mpMRI. This reads that, in a real world scenario, where radiologists of highly variable skill level are grading prostate mpMRI, standard biopsy performs statistically equal to mpMRI followed by a fusion biopsy.

Acknowledgements

None.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.purol.2020.12.008.

References


