ORIGINAL ARTICLE

Multiparametric magnetic resonance imaging predicts the presence of prostate cancer in patients with negative prostate biopsy

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Abstract

Objective: To assess the ability of multiparametric prostate magnetic resonance imaging (mpMRI) to detect prostate cancer in patients with prior negative transrectal prostate biopsy (TPB).

Materials and methods: mpMRI (TSE-T2-w, DWI and DCE sequences) was performed on 1.5 T (Magnetom Avanto; Siemens Healthcare Solutions) in 150 patients suspicious of prostate cancer and with negative TPB. European Society of Urogenital Radiology (ESUR) criteria were used (score 1: clinically significant disease is highly unlikely to be present; score 2: clinically significant cancer is unlikely to be present; score 3: clinically significant cancer is equivocal; score 4: clinically significant cancer is likely to be present; score 5: clinically significant cancer is highly likely to be present). PSA measurement (total and free), digital rectal examination (DRE), transrectal ultrasound (TRU) and a second TPB (at least 14 cylinders) were performed in all patients. Variables were submitted for independent blind analysis. The accuracy of each test was measured. Stepwise selection model for prediction of prostate cancer in second TPB was developed.

Results: Mean age was 66.2 ± 5 years (51–77), mean PSA 11.3 ± 9.6 ng/mL (0.9–75) and mean prostate volume 82.2 ± 42 (20–250) cc. DRE was suspicious in 11 (7.3%) patients. The mean number of cylinders per patient sampled in second TRB was 17.6 ± 2.7(14–22). Second TRB was positive in 28 patients (18.7%). mpMRI was positive (score 3–5) in 102 (68%), test

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Introduction

Prostate cancer is the second most frequently diagnosed malignancy in men and the sixth leading cause of cancer death worldwide. The confirmation diagnosis is performed by means of the histopathological study, usually by means of transrectal ultrasound-guided prostate biopsy (TRUS) practiced by elevated PSA or before finding DRE suspicious for malignancy. In any case, both the risks and benefits of performing this biopsy must be taken into account, as well as the age and comorbidty of the patient. There is no consensus on the ideal final number of samples to be obtained, but it has been found that obtaining a minimum of 8 prostate cylinders and a maximum of 12 rises up the detection rate of cancer in up to 20–33% of cases.

We also know that TRUS is not infallible and that due to different factors it may fail in the diagnosis of prostate malignancy. One of these factors is the one that refers to the technique of performing the biopsy, which tends to be carried out on the same prostate areas repeatedly, resulting in a detection rate that does not exceed 25%. Another factor involved considers that, according to studies on radical prostatectomy specimens, 25–33% of prostate cancers are distributed along the anterior prostate. This figure rises to 57% when transperineal saturation biopsy guided by grid is used. Moreover, prostate malignancy is often diagnosed...
in patients with previous negative TRUS and persistence of elevated PSA.6

There is no doubt that techniques to better detect and characterize prostate tumors are needed. Computed tomography showed unsatisfactory results.7 The multiparametric study using magnetic resonance imaging (mpMRI) associates turbo spin echo (TSE) with the usual T2-weighted (T2-w) for morphological sequences in a functional study based on diffusion-weighted sequences (DWI) and a postcontrast dynamic perfusion study (DCE).8 It enables a high rate of detection of clinically significant prostate tumors with volume >0.5 mL, even located in the most anterior regions of the prostate gland.9 It has also obtained promising results for assessing the extraglandular extension and other parameters of tumor extension in patients with prostate cancer.10

Our work has a two-fold objective. On the one hand, it aims to evaluate the diagnostic accuracy of the multiparametric study to detect prostate cancer in patients who underwent TPB for suspected neoplasia due to elevated PSA, which was negative, and compare it with the accuracy of the findings of the DRE and derivatives of the PSA (PSA velocity, % free/total PSA, and PSA density). Secondly, a univariate and multivariate model is considered to predict in these patients the presence of prostate cancer, given the data on clinical examination, PSA and derivatives, transrectal ultrasonography, and findings in mpMRI.

Materials and method

Patients

We designed a prospective study conducted in 150 patients with suspected prostate cancer due to elevated PSA > 4 ng/mL who had previously undergone TPB and whose result was negative for malignancy. All patients consented to participate in the study, so 3–6 months after the biopsy they underwent DRE, analysis of PSA and its derivatives, mpMRI, including T2-w, DWI and DCE, as well as transrectal ultrasound with new prostate biopsy taking of, at least, 14 cylinders.

Study protocol

At baseline, the DRE was classified as suspicious/not suspicious for cancer. The new PSA determination (total and free) was compared in each patient with the previous value, thus calculating the PSA velocity, and determining in each case the free/total fraction. All patients agreed to perform the multiparametric prostate study through a system of magnetic resonance imaging with a magnetic field strength of 1.5 T (Magnetom Avanto; Siemens Healthcare Solutions) and endorectal probe (Medrad) along with a surface pelvic antenna and parallel image acquisition (iPAT factor 2; 200 mm FoV). The prostate morphology was obtained by T2-w TSE sequence in 3 parallel and orthogonal planes to the main prostatic axis (TR/TE/FA: 4000/95/139°, with 3-mm slice thickness and 460 × 152 matrix). For the diffusion sequence (DWI), an EPI sequence with fat suppression (TR/TE/FA: 3400 ms/79 ms/90°, 340 mm FoV, PAT2, 135 × 192 matrix, and b factor: 50, 550, 1000) was used. Finally, for dynamic perfusion (DCE), a 3D gradient-echo sequence (VIBE) T1 weighted with parameters (TR/TE/FA: 6.3 ms/2.5 ms/10°, 430-mm FoV, PAT2, 106 × 192 matrix) was used.

Subsequently, we conducted a second extended TPB in all cases with periprostatic infiltration of local anesthetic, analyzing the histological outcome blindly to the aforementioned variables. The prostate volume was assessed by transrectal ultrasound performed during TPB, making it possible to calculate the PSA density. In a database, age, PSA value, % free/total PSA, PSA velocity, PSA density, prostate volume, suspicious at touch (yes/no), and suspicious in mpMRI according to gradient 1–5 (1: quite possibly benign, 2: possibly benign, 3: doubtful, 4: possibly malignant, and 5: quite possibly evil), following radiological criteria of the European Society of Urogenital Radiologists, focused on the combination of T2-w, DWI, and DCE.11 For analysis, studies categorized as 3–5 were considered positive and negative if they were defined as 1–2.

Statistical method

Descriptive analysis of the series and the variables analyzed was conducted. Study of diagnostic accuracy (sensitivity, specificity, NPV, and PPV) was performed to screen for prostate cancer considering globally the findings of the multiparametric study (positive 'categories 3–5' and negative 'categories 1–2') and the individual findings in each of the analyzed studies including T2-w, DWI, DCE ('suspected yes' positive, and 'suspected no' negative), DRE findings ('suspected yes' positive, and 'suspected no' negative), PSA velocity (>0.75 ng/mL positive and <0.75 ng/mL negative), % free/total (<15% positive and >15% negative), and PSA density (>0.15 ng/mL/cc positive and <0.15 negative). ROC curve analysis and area under the curve (AUC) were performed for each of the variables.

Finally, a predictive model for prostate cancer in these patients was proposed. First, a univariate model in which all variables that discriminate the presence or absence of cancer, defining odds ratio (OR) with 95% confidence interval (CI) for each of them, was established. We identified as variables likely to be predictive those showing a limit of significance <0.1. These variables were included in the multivariate model by stepwise selection of variables. The OR and 95% CI were defined to predict cancer in the second TPB, pointing as independent variables those with p < 0.05 value.

Results

The mean age ± standard deviation was 66.2 ± 5 (51–77) years and the mean PSA 11.3 ± 9.6 (0.9–75) ng/mL. The DRE was suspicious for malignancy in 11 (7.3%) cases. The mean prostate volume was 82.2 ± 42 (20–250) cc by transrectal ultrasound. Nine (6%) cases showed sonographic findings compatible with presence of prostate malignancy in this examination. The findings obtained in the mpMRI were suspicious of malignancy in 10 (6.7%) cases for the sequence T2-w, 76 (50.7%) cases for DW, and 17 (11.3%) for DCE.

The second TPB obtained an average of 17.6 ± 2.7 (14–22) cylinders per case. 14 cylinders were analyzed in 38 (25.3%) patients, 15–16 in 28 (28.7%), 17–18 in 4 (2.7%), and 20 or more cylinders in 80 (53.3%). The histopathological
study was positive for adenocarcinoma in 28 (18.7%) patients. In the remaining 122 (81.3%), the histological diagnosis was: inflammation in 38 (31.1%), atrophy in 1 (0.8%), atrophy and inflammation in 36 (29.5%), ASAP or PIN in 9 (7.4%), and unchanged in 38 (31.2%). The Gleason score of the positive biopsies was ≥6 in 15 (53.6%) cases, 7 in 6 (21.4%) cases, and ≥8 in 7 (25%) cases. 20 patients (71.4% of diagnoses of malignancy) subsequently underwent radical prostatectomy, 16 (79%) being a pT2 stage, and 4 (21%) a pT3 stage.

The gradient of results of the multiparametric study in 5 categories is associated ($\chi^2$, $p=0.0085$) to likelihood of developing cancer in TPB (Table 1). Following the criteria of the European Society of Urogenital Radiology, the mpMRI was considered positive in 102 (68%) patients, if categories 3–5 with a simultaneous evaluation of T2-w, DW, and DCE are grouped (Fig. 1). The sensitivity of this test is 92.9%, the specificity 37.7%, the NPV 95.8%, and the PPV 25.5% (Table 2). The ABC defining the accuracy of the multiparametric study to predict the presence of cancer was 0.77 mpMRI (Fig. 2).

Regularly, the prediction of cancer in the second TPB is usually based on the findings of the DRE and the evolution of the PSA isomorphic compounds. In this series, the DRE was considered positive in 11 (16.5%) patients, the test sensitivity resulting in 3.6% and the specificity 92.6%. The PSAV was considered positive in 100 (35.3%) patients, 82.1% sensitivity and 36.9% specificity; the free/total PSA ratio in 53 (35.3%) patients, 50% sensitivity, and 68% specificity, and PSAD in 62 (41.3%) patients, 53.6% sensitivity, and 61.5% specificity. For these variables, the ABC was significantly lower than that of mpMRI: free/total PSA fraction 0.59; PSAD 0.56; PSAV 0.54, and DRE 0.5.

The findings obtained in each sequence of the MRI were suspicious of malignancy and, therefore, were considered positive in 10 (6.7%) patients for T2-w (3.6% sensitivity and 92.6% specificity), 76 (50.7%) cases for DWI (60.7% sensitivity, and 51.6% specificity), and 17 (11.3%) cases for DCE (17.9% sensitivity, 91% specificity). Table 2 also shows the different NPV and PPV for each test.

Table 1  Probability of developing cancer in the second TPB (malignant pathology) according to results of the multiparametric study.

<table>
<thead>
<tr>
<th>Pathological anatomy</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>19(100%)</td>
<td>27 (93.1%)</td>
<td>33 (91.7%)</td>
<td>27 (71.1%)</td>
<td>16 (57.1%)</td>
<td>122 (81.3%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>0 (0%)</td>
<td>2 (6.9%)</td>
<td>3 (8.3%)</td>
<td>11 (28.9%)</td>
<td>12 (42.9%)</td>
<td>28 (18.7%)</td>
</tr>
</tbody>
</table>

$\chi^2$, $p=0.0085$.

Figure 1  Multiparametric study using magnetic resonance imaging of the prostate with simultaneous evaluation of T2-w (A), DW (B), and DCE (C).

Figure 2  ROC curve for the multiparametric study by prostate resonance. Area under the curve (AUC) = 0.77.
Table 2  Accuracy of different diagnostic tests for the detection of prostate cancer in the second prostate biopsy in patients with previous negative biopsy.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>III/positive</th>
<th>III/negative</th>
<th>Healthy/negative</th>
<th>Healthy/positive</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRE</td>
<td>2</td>
<td>26</td>
<td>113</td>
<td>9</td>
<td>0.0714</td>
<td>0.9262</td>
<td>0.8129</td>
<td>0.1818</td>
</tr>
<tr>
<td>PSAV</td>
<td>23</td>
<td>5</td>
<td>45</td>
<td>77</td>
<td>0.8214</td>
<td>0.3689</td>
<td>0.9000</td>
<td>0.2300</td>
</tr>
<tr>
<td>Free/total PSA</td>
<td>14</td>
<td>14</td>
<td>83</td>
<td>39</td>
<td>0.5000</td>
<td>0.6803</td>
<td>0.8557</td>
<td>0.2642</td>
</tr>
<tr>
<td>PSAD</td>
<td>15</td>
<td>13</td>
<td>75</td>
<td>47</td>
<td>0.5357</td>
<td>0.6148</td>
<td>0.8523</td>
<td>0.2419</td>
</tr>
<tr>
<td>mpMRI</td>
<td>26</td>
<td>2</td>
<td>46</td>
<td>76</td>
<td>0.9286</td>
<td>0.3770</td>
<td>0.9583</td>
<td>0.2549</td>
</tr>
<tr>
<td>MRI T2-w</td>
<td>1</td>
<td>27</td>
<td>113</td>
<td>9</td>
<td>0.0357</td>
<td>0.9262</td>
<td>0.8071</td>
<td>0.1000</td>
</tr>
<tr>
<td>MRI DW</td>
<td>17</td>
<td>11</td>
<td>63</td>
<td>59</td>
<td>0.6071</td>
<td>0.5164</td>
<td>0.8514</td>
<td>0.2237</td>
</tr>
<tr>
<td>MRI DCE</td>
<td>5</td>
<td>23</td>
<td>111</td>
<td>11</td>
<td>0.1786</td>
<td>0.9098</td>
<td>0.8284</td>
<td>0.3125</td>
</tr>
</tbody>
</table>

PSAD: PSA density (≥0.15 ng/mL/cc positive and <0.15 ng/mL/cc negative); mpMRI: multiparameter study using MRI in gradient of 5 categories (1: very possibly benign, 2: possibly benign, 3: doubtful, 4: possibly malignant, and 5: very possibly malignant; "categories 3–5" positive and "categories 1–2" negative); MRI DCE: study by contrast resonance (‘suspected yes’, positive, and ‘suspected no’ negative); MRI DW: study using diffusion balanced sequence resonance (‘suspected yes’, positive, and ‘suspected no’ negative); Free/total PSA: % free PSA over the total (≤15% positive and >15% negative); DRE: digital rectal examination (‘suspected yes’, positive, and ‘suspected no’ negative); PSAV: PSA velocity (≥0.75 ng/mL positive and <0.75 ng/mL negative).

The univariate analysis revealed the following as predictors (p value >0.1) of cancer in second biopsy: PSAV (1.04 OR [95% CI, 0.99–1.08]; p = 0.065), free/total PSA (0.37 OR [95% CI, 0.13–1.05]; p = 0.06), transrectal ultrasound prostate volume (each cc) (0.98 OR [95% CI, 0.97–0.99]; p = 0.017), and mpMRI with gradient of 5 values (3–5 vs. 1–2) (7.87 OR [95% CI, 1.78–34.7]; p = 0.006). Table 3 also shows the values for the variables that showed no significance (PSAD, age of patients, and findings in DRE). The multivariate analysis included in the stepwise type selection model the variables revealed in the univariate analysis. Both mpMRI (7.41 OR [95% CI, 1.65–33.28]; p = 0.009) and prostate volume (0.31 OR [95% CI, 0.12–0.78]; p = 0.01) define cancer risk independently (Table 3). Prostate volume is an inverse factor, detecting cancer less likely in prostates with larger volume. The ABC of the proposed predictive model is 0.84 (Fig. 3). Fig. 4 shows the successive steps by which this model is constructed.

If the sample is stratified in patients with prostates with a volume <70 cc and is included in the PSAV model, free/total PSA, and mpMRI, the multiparametric study remains the only independent variable (4.75 OR [95% CI, 1.65–33.28]; p = 0.05). In prostates >70 cc, it is not possible to establish a predictive model because there are very few patients with positive biopsy for malignancy.

Discussion

In the last 2 decades, the determination of serum PSA has emerged as a fundamental tool of early and opportunistic diagnosis of prostate cancer. As a consequence of the gradual increase in its use, the increased number of patients showing maintained elevated PSA levels with a negative result for malignancy in TBP is noticeable. The usual management strategies of these patients include performing repeated biopsies with taking of 12–20 cylinders, saturation biopsy with sampling of prostate transition zone or even expectant management with periodic estimation of PSA.13,14 MRI is presented as the best method for directing biopsies and acting as a target for the detection of significant cancers.15 In addition, a follow-up through monitoring of

Table 3  Univariate analysis and multivariate predictors of cancer in second biopsy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
<td>0.97–1.14</td>
<td>0.23</td>
</tr>
<tr>
<td>Suspicious digital rectal exam</td>
<td>1.04</td>
<td>0.21–5.08</td>
<td>0.97</td>
</tr>
<tr>
<td>Prostate volume</td>
<td>0.98</td>
<td>0.97–0.99</td>
<td>0.017</td>
</tr>
<tr>
<td>PSA density</td>
<td>1.7</td>
<td>0.74–3.94</td>
<td>0.21</td>
</tr>
<tr>
<td>% free/total PSA</td>
<td>0.37</td>
<td>0.13–1.05</td>
<td>0.06</td>
</tr>
<tr>
<td>PSA velocity</td>
<td>1.04</td>
<td>0.99–1.08</td>
<td>0.06</td>
</tr>
<tr>
<td>mpMRI</td>
<td>7.87</td>
<td>1.78–34.7</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Multivariate study

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mpMRI</td>
<td>7.41</td>
<td>1.65–33.28</td>
<td>0.009</td>
</tr>
<tr>
<td>Prostate volume</td>
<td>0.31</td>
<td>0.12–0.78</td>
<td>0.01</td>
</tr>
</tbody>
</table>

mpMRI: multiparameter study using MRI in gradient of 5 categories (1: very possibly benign, 2: possibly benign, 3: doubtful, 4: possibly malignant, and 5: very possibly malignant; "categories 3–5" positive and "categories 1–2" negative).
strategy for diagnostic management of prostate cancer. One of the difficulties for the routine use of this technology has to do with its rapid development, which brings forth new generations of equipment simultaneously with the publication of results.\textsuperscript{16}

Our study with mpMRI includes the use of T2-w, DWI, and DCE sequences. The study by spectroscopy (MRS) was excluded following the recommendations and protocols indicated by the European Society of Urological Radiology, which does not include such sequences given the limited conclusive results obtained by this test.\textsuperscript{12,17} On the other hand, it is known that the combination of the T2-w, DWI, and DCE sequences significantly improves the results obtained in the detection of cancer,\textsuperscript{18} showing higher sensitivity and specificity than the usual T2-w sequences in isolation.\textsuperscript{10}

The images obtained by MRI-T2-w sequences provide the best available description of prostatic areas by imaging, allowing for both cancer detection and location and staging.\textsuperscript{19} Prostate cancer is typically shown in T2-w sequences as contour foci roughly defined of low signal intensity. Sequences with dynamic contrast perfusion (DCE), employing the administration of gadolinium contrast, allow for excellent assessment of tumor vascularity. DCE sequences in combination with T2-w and DW assess the prostate gland much more accurately than that obtained with each of the sequences in isolation. Probably, the clearest indication of the DCE sequence is its application to assess biochemical relapse after curative treatment.\textsuperscript{20}

Several studies have shown optimal results for detection of the disease with mpMRI around 59–61%.\textsuperscript{21} Lee et al. described a prospective randomized study of 87 patients with rising PSA and previous negative prostate biopsy, identifying in 94.2% of cases mpMRI suspicious lesions, often localized lesions in prostatic areas not accessible to conventional TPB.\textsuperscript{22} The use of biopsies directed to those areas that were suspicious for malignancy in mpMRI significantly improves the detection rate of cancer.\textsuperscript{3}

The results obtained with image fusion techniques using resonance and endorectal ultrasound could be even more promising. In the study by Pinto et al., the TPB with 12 cylinders taken using image fusion achieved a detection rate of low-medium risk of disease of 20.6%, compared with 11% obtained with conventional ultrasound-guided TPB. The difference was even more pronounced in patients with high-risk disease, in which the detection rate increased from 29.9 to 53.8%.\textsuperscript{23}

In conclusion, the mpMRI prostate study is, in our experience, the best tool for predicting cancer in patients with previous negative prostate biopsy for malignancy and is more reliable in prostates of smaller volume. We are aware that these results must be treated with caution, due to the serious economic implications of their indiscriminate application. On the other hand, we need to improve diagnostic discrimination, but most particularly in clinically significant disease. It is also necessary to conduct multicenter prospective studies to corroborate the data obtained as well as the reproducibility of the technique between professionals from different institutions. However, at present, we can consider that the mpMRI prostate study may become established as a key element in the investigation of patients with suspected prostate cancer and negative transrectal biopsy.
Funding

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Conflict of interest

The authors declare that they have no conflict of interest.

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