Negative predictive value for cancer in patients with "gray-zone" PSA level and prior negative biopsy: preliminary results with multiparametric 3.0T magnetic resonance

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Purpose

Background

- Recent technical development and increasing availability are extending indications for Magnetic Resonance Imaging (MRI) from tumor local staging to several clinical scenarios, including early cancer detection and surveillance in patients with persistently elevated PSA level [1].
- To our knowledge, little is known [2-3] about the role for MRI in evaluating patients with prostatic specific antigen (PSA) level in the so called "gray zone" (2.5-10 ng/mL) and repeated negative biopsies [4].
- No consensus exists about the timing and method of surveillance in "gray zone" patients, who may harbour cancer in up to 33% of cases [4]. Kubota et al. [2] showed that a combination of T2-weighted imaging findings and PSA density has the potential to reduce the workload of biopsies, while Kumar et al. [3] showed that Magnetic Resonance Spectroscopic Imaging (MRSI) has a negative predictive value of 100% for prostate cancer.

Purpose

To estimate the negative predictive value of multiparametric MRI at 3.0T in excluding cancer in patients with "gray zone" PSA levels and prior negative biopsies.
Methods and Materials

Patients population

• Included were patients under clinical surveillance for PSA level ranging from 2.5 to 10.0 ng/mL [4], PSA velocity less than 0.75 ng/mL/year, and negative digital rectal examination (DRE), who performed a post-biopsy MRI over the period July 2010-May 2011. Excluded were seven patients with contraindications to MRI, who refused or did not perform post-MRI biopsy, or presented intraglandular haemorrhage on T1-weighted imaging.

• Study population was represented by 26 subjects (age 51-74 y-o, median 64.0 y-o), showing last dosage PSA level between 2.52 and 9.74 ng/mL (median 5.95 ng/mL). Patients had previously undergone at least one transrectal ultrasonography (TRUS)-guided biopsy 2 to 35 months before MRI. All biopsies were negative for cancer.

MRI protocol

Examinations were performed on a 3.0T magnet (Achieva, Philips Medical Systems, Best, the Netherlands), by using two 2-channels high-resolution loop coils placed to cover the perineum. Before the examination the rectum was emptied from stool and air by performing a rectal enema and inserting a rectal catheter, respectively. Hyoscine butylbromide (Buscopan®, Boehringer Ingelheim,Germany) was administered i.m. as antiperistaltic agent (10 mg).

Mean acquisition parameters are reported in Table 1 on page .

Image analysis

• Images were analyzed by two expert radiologists in consensus, on a dedicated workstation (Philips Medical Systems, Best, The Netherlands).

• The gland was divided into eight regions, as shown in Fig. 1 on page 5. The scheme was used to record any prostate abnormality, separately for each of the following image sets: TSE T2-weighted, DW imaging, 3D PRESS MRSI, and dynamic study.

• Criteria for lesion detection were: (i) circumscribed, round-ellipsoid or ill-defined low-signal intensity area both in peripheral or transitional zone on T2-weighted images; (ii) focal low-signal intensity area in the Apparent Diffusion Coefficient (ADC)-map obtained with DW imaging, corresponding to an ADC lower than 0.9 x 10-3 mm²/sec [5]; (iii) at least one voxel showing a choline+creatine/citrate ratio 2 or more standard deviation above the mean healthy value [6], assessed on a per-patient basis as the mean of choline+creatine/citrate ratios of the voxels without MRI abnormalities; (iv) an
Intensity-time curve of areas with suspected enhancement showing a rapid contrast wash-in and wash-out as compared to the healthy tissue, at visual interpretation of the dynamic study. Spectroscopic postprocessing was performed off-line with the in-built application (SpectroView, Philips Medical Systems, Best, The Netherlands). Mean value of the choline+creatine/citrate ratio resulted of 0.57±0.19 in healthy voxels. Intensity-time curves were built by placing one region of interest (ROI) both on suspected foci and controlateral healthy glandular tissue.

**Gold standard**

- Histology after TRUS-guided biopsy (average biopsy-MRI interval was 1.46 months).
- The same regional scheme of MRI report was used to perform biopsy (Fig. 1 on page 5). For ethical reasons, urologists were informed about the location of suspicious findings on MRI, in order to obtain additional cores from those regions. All patients underwent a minimum of 8 core sampling.

**Data analysis**

- Analysis was performed on a per patient and per-region basis.
- MRI positive findings were defined as the presence of a suspicious lesion in at least one prostate region and two image sets (TSE T2-weighted and DW imaging and/or MRSI and/or dynamic study; alternatively, DW imaging and/or MRSI and/or dynamic study, even without any evidence on T2-weighted images).
- Patients were considered true-positive cases (TP) if MRI correctly detected at least one cancer in the same region assessed by biopsy; true-negative cases (TN) if neither MRI or biopsy found cancer; false-positive cases (FP) if MRI detected at least one suspected cancer in case of negative biopsies; false-negative cases (FN) if MRI detected no cancer in case of positive biopsy. Regions were considered TP or TN if MRI and biopsy agreed for the presence or absence of cancer; FP if MRI detected a cancer not confirmed by biopsy; FN if MRI failed to detect a biopsy-proven cancer.
- The negative predictive value (NPV), sensitivity, specificity, positive predictive value (PPV), and accuracy, together with the 95% C.I were calculated.
Table 1: Acquisition parameters of the study. MRSI was performed by using a multivoxel Point Resolved Spectroscopy (PRESS) acquisition with 3D chemical-shift imaging (CSI) over the whole glandular volume. Each spectrum (1024 complex points) was obtained with spectral width of 2000 Hz. Second order shimming was used to maximize magnetic field homogeneity. Mean full width at half maximum (FWHM) of the water peak was 8.96 ppm (range 5-20). Pre- and post-contrast dynamic study was performed by using a volumetric Fast Field Echo (FFE) T1-weighted sequence with high temporal resolution, repeated sequentially over 5 minutes (40 acquisitions, without a delay among them). Gadobentate dimeglumine (MultiHance®, Bracco, Milan, Italy) was used as contrast agent, injected at a rate of 2 mL/sec, followed by a flush of 30 mL of saline solution at the same injection rate.

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Fig. 1: In order to match MRI findings with ultrasound-guided biopsy ones, the prostate was divided in eight standardized regions as represented in the figure.
Results

Biopsy results

- Per-patient lesion distribution is summarized in Fig. 2 on page 9 and Table 2 on page 9. A total of 328 biopsy samples were obtained on 26 study subjects (per-patient range and mean of 8-24 and 12.6 cores, respectively). Patients received one per-region sampling in seven cases, and a mean of 1.79 per-region samplings in the remaining 19 cases. Overall, fourteen patients showed 33 lesions on 36 prostate regions (3 lesions in 3 patients were included in two adjacent regions). Per-patient number of lesions were 1-6 (range) and 2.5 (mean). Of these lesions, 11 were cancers (11/33; 33.3%), with a Gleason score of 3+3 in 4 cases, 3+4 in 6 cases, 4+5 in 1 case. Cancers were located in the peripheral zone in 10 cases and in the transitional zone in 1 cases. Remaining lesions were assessed as high-risk lesions [7], i.e. high grade prostatic intraepithelial neoplasia (HGPIN) in 13 cases (13/33; 39.4%), and atypical small-acinar proliferation (ASAP) in 9 cases (9/33; 27.3%). These lesions were found in the glandular peripheral zone.

- Of two patients with both cancer and ASAP, biopsy found 2 cancers and 4 ASAP in one case, and 4 cancers and 1 ASAP in the remaining one. Of two patients with both cancer and HGPIN, biopsy found 2 cancers and 1 HGPIN in one case, and 1 cancer and 4 HGPIN in the remaining one (Table 2 on page 9). On a per-patient basis, cancer prevalence was 5/26 (19.2%), and HGPIN+ASAP prevalence was 13/26 (50.0%) (including cases with co-existing cancer). Two patients with cancer (1 patient with multifocal cancer and 1 patient with cancer and multifocal HGPIN) and one patient with multifocal HGPIN alone underwent radical prostatectomy. Surgical specimens analysis confirmed the number and localization of lesions.

MRI and cancer detection

- MRSI examination was excluded from the analysis in seven patients due to low spectra quality (2/7 patients had cancer). Spectra were assessed as showing low quality because of contamination by insufficiently suppressed water or lipid and/or the presence of unresolvable metabolite peaks (peak area-to-noise ratios lower than 5:1) [8]. One additional patients did not undergo the dynamic study because of low glomerular filtration rate, i.e. increased risk for systemic nephrogenic fibrosis.

- MRI performance on a per-patient and per-region basis is summarized in Fig. 2 on page 9. MRI detected 5/11 cancers on 5 patients, distributed on 6 prostate regions (one cancer was observed across two adjacent regions, as confirmed by biopsy) (Fig. 3 on page 10). Of these cancers, four were in the peripheral zone, and 1 in the transitional zone. Lesions
ranged from 5 to 13 mm in diameter, with a mean of 10.2±2.6 mm. The remaining 6 tumors (on 6 regions) were missed by MRI. All visible cancers were detected on TSE T2-weighted imaging as focal hypointense foci, in association with abnormalities on DWI and/or MRSI and/or dynamic study. MRI findings are summarized in Table 3 on page 11.

- Patients were assessed as FN and FP in 0 and 13 cases, respectively. In particular, MRI detected 8 suspected cancers in 8 patients (8/26; 30.7%) without correspondence at biopsy (range of dimensions 7-19 mm, mean 11.1±0.02 mm), that showed a variable combination of epithelial hyperplasia, fibrosis/atrophy and inflammation in the involved regions (Fig. 4 on page 12). Of these patients, four presented high-risk lesions in different prostatic regions (2 HGPIN and 2 ASAP, respectively). Remaining FP patients (5/26; 19.2%) showed 3 HGPIN alone in 3 cases (dimensions mean 12.5 mm), and 2 ASAP alone in 2 case (8 mm in diameter each). Overall, five out of 22 high-risk lesions were detected by MRI (22.7%), corresponding to the aforementioned FP lesions. On a per-patient basis, MRI showed a NPV of 100% (95% C.I. 84.0-100%) in cancer detection. In particular, 8/26 patients (30.8%) showed no lesions both at MRI and biopsy. Sensitivity, specificity, PPV and accuracy values are reported in Table 4 on page 13.
Fig. 2: Flow-chart illustrating the results of biopsy and MRI on 26 patients of the study, both on per-patient and per region basis. *One cancer was found across two adjacent prostatic regions. ** Two high-grade lesions were found in two adjacent prostatic regions each.

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<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>Number of patients</th>
<th>Number of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer alone</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HGPIN alone</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>ASAP alone</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Cancer + ASAP</td>
<td>2</td>
<td>11 (6 cancers + 5 ASAP)</td>
</tr>
<tr>
<td>Cancer + HGPIN</td>
<td>2</td>
<td>8 (3 cancers + 5 HGPIN)</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 2: Distribution on a per-patient basis of 33 lesions found at prostate biopsy on 14/26 patients, i.e. on 36/208 prostate regions (3 lesions were found across two adjacent regions in 3 patients). Overall, 5 patients had 11 cancers (alone or in association with high-risk lesions), while 9 patients had high-risk lesions only (see also Fig. 1). HGPIN = high grade prostatic intraepithelial neoplasia; ASAP = atypical small acinar proliferation.

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Fig. 3: MRI true-positive case of cancer in a 61 yo patient with prostatic specific antigen (PSA) level of 3.9 ng/mL and previous negative biopsies. MRI showed a focal ill-defined area in the right peripheral base, showing hypointensity on axial high-resolution Turbo Spin Echo T2 weighted imaging (arrow in A) and restricted diffusivity on the echo-planar Diffusion weighted image at b-value of 1200 sec/mm² (arrow in B) and Apparent Diffusion Coefficient map (arrow in C). Same lesion presented a rapid wash-in after i.v. contrast medium injection on axial Fast Field Echo T1-weighted image (arrow in D). Based on these findings, the lesion was assessed as a cancer. Transrectal-guided biopsy confirmed the presence of a prostate adenocarcinoma (Gleason Score 4+4).

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Table 3: MRI findings at each images set, on a per-region basis. The correspondence with biopsy results is shown in the columns reporting the number of true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) regions. DWI = Diffusion-weighted Imaging; MRSI = Magnetic Resonance Spectroscopic Imaging.

<table>
<thead>
<tr>
<th>Number of suspected regions</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSE T2w</td>
<td>21</td>
<td>6</td>
<td>181</td>
<td>15</td>
</tr>
<tr>
<td>DWI</td>
<td>18</td>
<td>4</td>
<td>182</td>
<td>14</td>
</tr>
<tr>
<td>MRSI*</td>
<td>6</td>
<td>1</td>
<td>137</td>
<td>5</td>
</tr>
<tr>
<td>Dynamic study**</td>
<td>16</td>
<td>5</td>
<td>170</td>
<td>11</td>
</tr>
</tbody>
</table>

* 7 patients excluded due to low spectra quality
** 1 patient excluded because of renal function impairment
Fig. 4: False-positive case of cancer in a 63 yo patient (PSA of 4.93 ng/mL). MRI showed focal, round hypointensity on axial (A) and coronal (B) Turbo Spin Echo T2-weighted images in the left central adenoma region (arrows), corresponding to restricted water diffusion on axial ADC map (C) (arrows). The area presented a normal spectrum (D). However, the dynamic study showed a rapid wash-in/wash-out curve (not shown). Lesion was assessed as a cancer. According to biopsy results, the lesion corresponded to a mix of epithelial hyperplasia and glandular atrophy.
Table 4: Diagnostic performance of MRI in detecting cancer and high grade lesions, both on a per-patient (overall performance) and per-region basis (stratified for each sequence). Overall performance of MRI on a per-region basis corresponds to that of TSE DWI = Diffusion-weighted Imaging; MRSI = Magnetic Resonance Spectroscopic Imaging.

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Conclusion

Considerations on the study protocol

- We used: (i) a multiparametric MRI protocol in evaluating the prostate, as suggested to increase diagnostic accuracy by combining different imaging information [9]; (ii) a 3.0 T system to enhance the potential of this "all-in-one" examination (in terms of higher signal-to-noise ratio of T2-weighted images, dynamic range of contrast enhancement, and spatial and spectral resolution of MRSI) [9-10].

- However, because of the difference in study goals, magnetic field strength and acquisition technique, it is difficult to compare MRI diagnostic performance we found with those of previous experiences on "gray zone" patients [2-3]. The diagnostic accuracy we found separately for T2-weighted imaging, DWI and dynamic study are comparable to those previously reported both on 3.0 [11] or 1.5T [12] systems. Very disappointing performance of MRS (10.0% of sensitivity and 16.7% of PPV) was probably related, at least in part, to limited available data, because of unsuccessful examination in two of five patients with cancer.

Study limitations

- The number of biopsy cores was not standardized, ranging from eight to 24 in our series, with a per-patient mean of about 13 cores. Thus, even if both peripheral and transitional zones were sampled, patients did not undergo extended and/or saturation biopsies, as recommended in cancer detection [13]. In addition, since referring urologists were aware of MRI lesions site, other prostate regions might have been undersampled as compared to the suspected ones. Potential MRI overestimation of TN patients may be expected accordingly (i.e., overestimation of the NPV). Institutional policy, ethical considerations, and the need to be less invasive as possible led to tailor the number of sampling to each patient, based on clinical history, PSA level, number of previous biopsies and patients compliance. Since the prevalence of cancer we found is comparable to previous experiences [2,12], potential overestimation of the NPV is probably limited, and does not affect the general trend of our results.

- We avoided the use of the endorectal coil based on: (i) the increase in signal-to-noise ratio provided by 3.0T MRI; (ii) well known limitations, i.e. invasiveness, costs, motion artifacts, and displacement of the prostate gland [14]. Despite our approach might have partially limited the gain of using ultra-high strength [9], the quality at 3.0T by using external surface coils has been proven to be at least comparable to that of a 1.5T study with the endorectal coil [15].

Main conclusions
The prevalence of cancer was relatively low (19.2%) in our series. This confirms that a diagnostic tool with high NPV is needed in order to avoid unnecessary biopsies in the majority "gray zone" patients [12].

NPV and sensitivity in detecting cancer were 100% on a per-patient basis, in agreement with previous results by Kumar et al. by using the endorectal coil and MRSI alone on a 1.5T system [3]. Despite MRI was unable to assess multicentricity (6/11 cancers missed), at least one cancer was detected in the 5/26 affected patients. MRI detected all clinically significant cancers of about 1 cm in diameter, i.e. all affected patients were properly addressed to biopsy (and to radical prostatectomy in 2 cases). From a complementary point of view, all patients without cancer (30.8%) were correctly assessed by MRI. A similar rate was estimated by Kubota et al. [2] when comparing cancer detection of MRI alone (with T2-weighted imaging) vs. MRI associated with the PSA density (50 of 185 patients; 27%). It is arguable MRI had the potential to avoid biopsy in about one-third of patients with PSA "gray zone" levels.

The number of FP cases was high in our series, both on a per-patient (n=13) and per-region (n=15) basis (by considering T2-weighted imaging). Accordingly, we obtained low specificity and PPV values (38.1 and 27.8%, respectively), in agreement with the general trend of literature and previous results on a similar population [3]. FP cancers corresponded to two type of biopsy findings: (i) areas of epithelial hyperplasia, fibrosis, atrophy or inflammation in 8 patients, i.e. to classical sources of differential diagnosis [11]; (ii) HGPIN or ASAP in remaining 5 patients. HGPIN and ASAP are associated with the presence of cancer in 22.0-24.1 and 78% of cases, respectively [7,16]. Consequently, we can assume that MRI had the potential to properly address to biopsy about another third of patients presenting cancer or high-risk lesions (HGPIN and ASAP).
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Personal Information

Thank you for the interest in this poster.

Do not hesitate to contact me for any question or comment.

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