Detection of prostate cancer index lesions with multiparametric magnetic resonance imaging (mp-MRI) using whole-mount histological sections as the reference standard

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Detection of prostate cancer index lesions with multiparametric MRI (mp-MRI) using whole-mount histological sections as the reference standard.

Abstract

Objectives: To evaluate the sensitivity of mp-MRI for prostate cancer (PCa) foci, including index lesions.

Materials and methods: 115 patients with ultrasound biopsy confirmed PCa underwent mp-MRI, and radical prostatectomy. A single expert radiologist recorded all PCa foci including the largest (index) lesion blinded to pathologist's biopsy report. The reference standard was 5 μm microsections obtained from 3mm thick whole mount histological sections. All lesions were contoured by an experienced uropathologist who assessed their volume and pathological Gleason Score (pGS). PCas with volume>0.5 cc and/or pGS>6 were defined as clinically significant. Multivariate analysis to describe the characteristics of lesions identified by MRI was performed. The study received approval by the local ethical board and was conducted according to the principles of the Helsinki Declaration.

Results: Mp-MRI correctly diagnosed 104/115 index lesions (sensitivity=90.4%; 95% CI 83.5%-95.1%), including 98/105 clinically significant index lesions (93.3%; 95% CI=86.8%-97.3%) among which 3/3 lesions with volume<0.5 cc and pGS>6. Overall mp-MRI detected 131/206 lesions including 13 of 68 insignificant PCa. The multivariate logistic regression modeling showed that pGS value (ORs, 11.7; 95% CI: 2.3-59.8; P=0.003) and lesion volume (ORs, 4.24; 95% CI: 1.3-14.7; P=0.022) were independently associated to detection of index lesion at MRI.

Conclusions: This study shows that mp-MRI has a high sensitivity in the detection of clinically significant PCa index lesions, while it has disappointing results in the detection of small volume low pGS prostate cancer foci. Mp-MRI may be used to stratify patients according to risk, allowing better treatment selection.

Keywords: Prostatic neoplasm, Magnetic Resonance Imaging, Diagnostic Imaging.

Introduction

Prostate cancer (PCa) is the most common malignancy in males and the second cause of cancer related death in industrialized countries [1]. In 2012 the total incidence and mortality of PCa in the 40 European countries were estimated at 417.000 and 92.000 cases respectively [1]. According to the most widely used guidelines, high circulating levels of Prostate Specific Antigen (PSA) and/or a suspicious digital rectal examination provide indication for acquisition of multiple prostate biopsies, on which pathological evaluation is performed [2]. PSA levels, clinical stage and biopsy Gleason score (GS) at diagnosis classify patients in low, intermediate and high risk of clinical progression [3]. Radical prostatectomy or radiotherapy are the gold standard for intermediate-high risk patients; in low risk cases active surveillance is considered a reasonable option. However both PSA test and trans-rectal ultrasound (TRUS) guided biopsies have limitations that affect their ability in reliably detecting PCa. Indeed, around 15% of men with normal PSA values (measured as ≤4.0 ng/ml) have PCa [4]. On the other hand conditions other than PCa, such as prostatitis and lower urinary infections, can give rise to elevated levels of PSA. Since about two-thirds of men with elevated PSA levels (measured as > 4 ng/ml) will not have PCa [5], using this method as a screening test can cause potential harms: additional medical visits, side effects of prostate biopsies, anxiety, and overdiagnosis leading to overtreatment with its associated side effects (bowel urgency, urinary leakage, erectile dysfunction). Besides, prostate biopsies are affected by sampling limitation. Even

when adopting extended schemes, up to 30% of TRUS guided biopsies will give false negative (FN) results [6] and about 40% PCa cases will be under-staged as low risk [7,8]. As a consequence, alternative options to radical treatment, such as active surveillance, focal therapies and chemoprevention can be inappropriately chosen, failing to contrast disease progression. Current evidence is to date insufficient to support the use of novel markers (e.g. PCA3, -2pro-PSA isoform and the TMPRSS2–ERG translocation, etc.) in clinical practice [9, 10].

According to recent guidelines, the use of Magnetic Resonance Imaging (MRI) is currently limited to men with clinical suspicion of PCa that have already performed one or more rounds of prostate biopsies with a negative result [11] and in staging of locally advanced disease [2]. In the near future, mp-MRI could be used to select PSA positive men for biopsy reducing the number of unnecessary procedures, intervention related risks and costs [12-14]. However, while MRI is accurate in detecting large and/or high GS tumours, it has limitations in identifying the smaller PCa foci, which are very common, being that the disease is frequently multifocal [15,16]. Recent advances in the comprehension of PCa support the theory that disease progression and metastatization are driven by the largest tumor focus, the index lesion [17-21]. According to this theory therapeutic decision-making could be heavily influenced by the clinical relevance of index lesions, which therefore need to be accurately assessed. In a multireader study on a small group of patients Rosenkrantz et al. [22] report sensitivity and PPV of 75.9% and 82.6 % respectively, for the detection of index lesions. In view of the increasing clinical importance of index lesions these data need to be verified on larger surgically confirmed series.

The main aim of this study was to assess the sensitivity of mp-MRI in the detection of index PCa lesions using whole-mount histological sections as the reference standard. Lesion characteristics were also evaluated by multivariate analysis.

Materials and methods

Patient population

Between April 2010 and November 2012 143 consecutive males with PCa diagnosed by TRUS guided core biopsy were sent to our Institution from the same tertiary care centre to perform 1.5 T multiparamentric-MRI (mp-MRI). All patients were candidates to radical surgery based on systematic TRUS biopsy, PSA values and clinical parameters. Mp-MRI was performed at least 6 weeks after biopsy to reduce artefacts of blood pooling within the gland. Hormonal therapy at the time of the mp-MRI examination was a condition for exclusion from the study.

The study received approval by the local ethical board and was conducted according to the principles of the Helsinki Declaration. Participants into the study signed informed consent forms.

MRI protocol

MRI studies were performed with a 1.5-T scanner (Signa Excite HD, GE Healthcare, Milwakee, Illinois, USA) using a 4–channels phased array coil combined with an endorectal coil (Medrad, Indianola, Pa). Intramuscular injection of 20 mg butylscopolamine bromide (Buscopan, Bohringer Ingelheim, Germany) was performed routinely just before the beginning of the examination to reduce bowel movements. First, T2w images were obtained to assess prostate morphology, using the following protocol: slice-thickness, 3 mm; FOV, 16 x 16 cm; NEX, 2; acquisition matrix, 384x288; TR/TE ratio 3020/85, 3620/90 and 3960/110 in the axial, coronal and sagittal plain respectively. Second, a T1 fast spin-echo (SE) axial sequence was performed to assess for areas of haemorrhage within the prostate using the following protocol: slice-thickness, 3 mm; FOV 16 x 16 cm; NEX, 2; acquisition matrix 320x256; TR/TE 580/min. Three DWI sequences were then obtained using axial EPI sequences as follows: slice-thickness, 3 mm; FOV 16 x 16 cm, matrix 128 x 128, NEX 6; TR/TE 7000/min; b-values of 0-600, 0-1000, 0-1400 s/mm^2. Finally DCE-MRI was performed using an axial FSPGR sequence with a temporal resolution of 13 sec, following

intravenous power injection of gadobutrol (Gadovist, Bayer Pharma AG, Berlin) at the rate of 2 ml/sec, followed by a saline solution flush. The following scanning parameters were used for image acquisition: slice thickness, 3mm; FOV 20 x 20 cm; matrix, 224x192; NEX, 0.5; TR/TE, ~3.5/min. The DCE-MRI sequence was repeated 26 times. Overall imaging parameters satisfied the minimal scanning requirements of the recently published european consensus statement [23].

Image analysis

All images were sent to a dedicated workstation (Advantage Windows 4.3 or 4.4, GE Healthcare, Milwakee, Ill) with specialized software for image processing for both DW and DCE-MRI images (Functool v 4.5.3 and 7.4.01d, GE Healthcare, Milwakee, Ill). A single experienced radiologist (F.R.), interpreting > 500 prostate mp-MRI studies per year, analysed all mp-MRI examinations, that met the inclusion criteria, to identify PCa foci. The reader was informed that the patients had PCa detected by biopsy but was blinded to pathologist's biopsy report, i.e., its location.

The following were considered suspicious signs for PCa in the peripheral zone (PZ): a round, oval or plaque-like area of low signal intensity on T2w sequences; presence of extracapsular extension signs [24], i.e. hypointense focus bulging the contour of the prostate or crossing the prostatic capsule with gross extension in the periprostatic fat, asymmetry of the neurovascular bundle. Focal areas of reduced Apparent Diffusion Coefficient (ADC: $<1.1 \times 10^{-3}$ mm²/s) corresponding or not to hyperintense signal on the DWI images with b-value of 1400 s/mm² were considered suspicious for cancer foci [225,26] (Figure 1). The ADC maps were computed on the DWI sequence with a b-value of 1000 s/mm², using a monoexponential model, and the mean ADC value was, evaluated on a selected ROI, drawn in order to encompass as much of the inner aspect of the lesion as possible without contacting the edges.

Findings in the transition zone (TZ) were considered abnormal when a wedge-shape or elliptic ill-defined area of low signal intensity was observed on T2-w sequences that may correspond to a hyper-intense area on DW images. DCE-MRI was considered positive for tumour if an asymmetric nodular or plaque-like early intense contrast uptake was shown in either the PZ or TZ. Time intensity curves were considered pathological when type 3 and equivocal when of type 2 [27,28]. However, early contrast uptake on DCE-MRI with indefinite margins without corresponding suspicious findings on T2w and DWI, was considered negative for PCa.

In addition to these criteria the reader recorded on radiological report an overall impression for each suspected area to be probably or highly likely cancer and identified the larger lesion (i.e. index lesion) that was topographically recorded using the 16 prostatic region scheme provided by the ESUR guidelines [23].

To compare imaging with pathological data, PZ findings were classified as belonging to one of three axial levels - i.e. apex, mid-gland and base and to one of six additional regions – i.e. right anterior-lateral, right posterior-lateral and right posterior, left anterior-lateral, left posterior-lateral and left posterior. TZ findings were classified as being either on the right and/or left side.

Reference standard

The reference standard was represented by whole-mount histological sections obtained from the resected prostate specimens. In detail, the prostate was cut into 3 mm thick sections; slices were obtained perpendicular to the rear gland surface, with the same inclination of the axial T2w images. Conversely, the bases and the apexes were sectioned longitudinally. Five µm sections were obtained from each thick slice by means of a microtome and were coloured with hematoxylin eosin. All samples were then searched for cancer foci by the same experienced uropathologist (E.B). Lesion volume was obtained by summing the area involved by tumour on each contiguous slide. The

pathologist also assessed the pathological GS (pGS) for each focus and in multifocal cases he recorded which of the foci was the index lesion. Index lesion was defined as the largest tumour focus within the prostate gland [17]; clinically significant PCa was defined as a tumour with volume >0.5 cc and/or pGS >6; consequently PCa foci with a volume <0.5 cc and a pGS <6 were defined as clinically insignificant [29]. All malignant lesions were then contoured with a marker and each section was scanned for comparison with image findings. To finalize the reference standard a second experienced radiologist (E.A.) matched each lesion detected by the pathologist with MR findings. When pathological microslices and axial T2W images were not perfectly overlapped, usually due to modified prostate shape soaked by formaldehyde, pathologist and second radiologist used TZ adenoma nodules as landmarks in order to better identify the lesions on the MRI images. Non-matching lesions were classified as false findings of MRI.

Statistical analysis

In this study a patient was defined true positive (TP) when at least one pathologically confirmed PCa lesion was detected at MRI, and as a false negative (FN) when MRI did not detect cancer within the prostate gland. Accordingly, per-patient sensitivity was defined as the number of TP findings over the total number of positive patients. FP and PPV were not computed in the per-patient analysis, since all patients had TRUS biopsy confirmed PCa. Per-lesion analysis was performed considering both only index lesions and all PCa lesions. In per-index lesion assessment a patient was classified TP when the MRI defined index lesion exactly matched the equivalent finding at full mount pathology, as FN when no lesions were detected at MRI and as FP when the MRI identified index lesion did not exactly match with the full mount pathology defined index lesion. PPV was defined as the number of TPs over the total number of positive calls. Sensitivity and PPV were also assessed on a per-lesion basis considering different GS and size cut-offs, and different PCa locations (i.e. PZ versus TZ). Accordingly, a PCa lesion detected at MRI was considered a TP

if it exactly matched an equivalent finding at full mount pathology, a FP if it did not match with any histological finding and a FN when a pathologically confirmed lesion was not detected by MRI.

The appendix reports on the methodology used to assess relation between pGS and other patient characteristics. Multivariate analysis aimed at describing the characteristics of lesions identified by MRI is also reported in the appendix. All statistical analysis was performed by using R software (version 2.15.2). Significance was assigned for a P less than 0.05 when appropriate.

Results

Demographic and Pathological characteristic of the study group

We enrolled 141/143 patients sent to us by the same tertiary care centre; 2/143 (1%) were excluded because they underwent hormonal therapy at the time of mp-MRI exam. The final analysis included 115 (81.5%) patients; 26 patients were excluded because the reference standard was not available either because they did not undergo radical prostatectomy (25/141, 18%) or because the PCa foci was not found on the excised prostate (1/141, 0.7%) (figure 2). Patient characteristics and clinical information are reported in table 1.

Overall the pathologist identified a total of 206 cancer foci of whom 138 (67%) were clinically significant lesions. Of the latter, 122 (88%) were located in the PZ and 16 (12%) in the TZ. Median volumes of lesions according to pGS and prostate location are reported in table 2. Lesions distribution was as follows: one PCa focus was detected in 55 of the 115 patients (48%), two in 39 (34%), 3 in 13 (11%), 4 in 6 (5%) while 5 lesions were identified in the last 2 patients (2%). Multifocal disease was therefore present in 52% of patients. In this surgical cohort 157 of 206 lesions (76.2%) had a pGS of 3+3 or 3+4 and 176 foci (85.4%) were located in the PZ. Average mour volume was 1.3 cc (range 0.001 – 20.51 cc; median 0.74 cc). The 115 index lesions included: 102 lesions (88.7%) with a volume > 0.5 cc, 3 lesions (2.6%) with a volume < 0.5 cc but with a pGS >6 and 10 clinically insignificant lesions (8.7%), i.e. with a volume < 0.5 cc and a pGS

≤6 cc. pGS 3+3 index tumours had a significant lower median volume than pGS 3+4 ($p<0.001$), 4+3 ($p<0.0001$) and ≥8 ($p<0.001$). Thirty-four of the 115 index lesions were pathological stage T3 (24 cases were T3a and 10 T3b); the remaining 81 index lesions were pT2.

Per-patient analysis

Mp-MRI detected at least one PCa foci in 106 of 115 patients, yielding an overall sensitivity of 2.2% (95% CI 85.7%-96.4%). None of the FN patients had lesions with a pGS of 4+3 or higher. Four of the 9 FN patients had clinically insignificant lesions and one had two prostate cancer foci of whom the largest in the TZ (size=1.26 cc; pGS=3+4). The remaining 4 patients had 3+3 (n=2) and 3+4 (n=2) clinically significant PCa foci.

Per-index lesion analysis

Mp-MRI identified 104 of the 115 index lesions (sensitivity of 90.4%; 95% CI 83.5%-95.1%) including 98 of the 105 clinically significant index lesions (sensitivity of 93.3%; 95% CI 86.8%-97.3%). Table 3 reports the per-index lesion sensitivity of mp-MRI according to pGS. Mp-MRI detected all index lesions with pGS of 4+3 (n=22) and pGS ≥ 8 (n=15). Mp-MRI also detected 55 of the 59 index lesions with a 3+4 pGS (sensitivity of 93.2%; 95% CI 83.5%-98.1%). None of the missed lesions was stage T3. Since there were 2 FP findings, the PPV for index lesions was 98%.

Among the 7 clinically significant index lesions missed at mp-MRI, 6 were located in the PZ. Three of the 6 lesions (50%) were pGS 3+4 with pattern 4 respectively of 10% in one and 20% in the last two cases; the 3 remaining cases were pGS 3+3. The index lesion of one of the 3 above reported patients with a pGS 3+4 had a volume of 2.18 cc and a percentage of pattern 4 of 20% (Figure 3); this was the only case with a secondary, more aggressive lesion, but with a smaller volume (1.85 cc and a pGS of 4+3); the latter was correctly diagnosed at mp-MRI (Figure 4). In this case the missed lesion did not change the therapeutic approach.

The only missed index lesion located in the TZ had a GS of 3+4 with pattern 4 of 25%.

All 3 clinically significant index lesions with a volume < 0.5 cc (0.14, 0.33 and 0.41 cc) but with a pGS > 6 (respectively 4+3, 4+3, 3+4) were identified by mp-MRI (Figure 5). Also, mp-MRI correctly identified 6 of 10 (60%) clinically insignificant index lesions – i.e. with a volume < 0.5 cc and a pGS ≤ 6.

According to multivariate analysis, two index lesions characteristics were independently associated to detection at MRI: lesion volume (ORs, 4.24; 95% CI: 1.3-14.7; P=0.022), and pGS. The odds of detecting a index-lesion with pGS>6 were 11.7 (95% CI: 2.3-59.8; P=0.003) times of a lesion with pGS≤6. No other variables showed (i.e., patient age, prostate weight, prostate volume, PSA scores, areas of prostatitis) the 0.05 significance.

Overall per-lesion analysis

Mp-MRI detected 131 of the 206 PCa foci, yielding an overall per-lesion sensitivity of 63.6% (95% CI 56.6%-70.2%) (Table 4). Mp-MRI correctly identified 118 of the 138 clinically significant cancer foci (sensitivity = 85.5%; 95% CI 78.5%-90.9%) including 107 of the 122 PZ lesions (sensitivity = 87.7%; 95% CI 80.5%-93.0%) and 11 of the 16 TZ lesions (sensitivity = 68.8%; 95% CI 41.3%-89.0%). Sensitivity for clinically insignificant PCa lesions was 19.1% (13 of 68; 95% CI 10.6%-30.5%).

The relationship between detection at MRI and lesion features is shown in Table 5 and in the appendix. There was evidence that detection of MRI increased with increasing of pGS: the odds of detection of a lesion with pGS>6 were 3.2 (95% CI: 1.2-8.5) times of a lesion with pGS≤6. In addition, lesions in the peripheral zone of the prostate were more likely to be detected than those in central zone (OR, 5.4; 95% CI: 1.1-24.0; P=0.036). Finally, there was evidence of improved detection with increasing lesion volume (OR, 7.1; 95% CI: 2.4-23.7; P<0.001).

Mp-MRI erroneously identified as cancer 5 prostate areas in an equivalent number of patients, leading to a PPV of 96%. In 4 out of the 5 cases, FP findings belonged to patients with at least one other significant PCa, correctly identified at MRI and confirmed at histopathology. Four of the 5

FPs were areas of atrophy or prostatitis.

Discussion

In this single centre cohort study 90.4% prostate cancer index lesions were identified with mp-MRI. Sensitivity was 93.3% considering only clinically significant index lesions, which were the vast majority. Interestingly MRI detected 83.3% TZ index lesions, all 4+3 and ≥8 GS index lesions and all stage T3 cancers. As expected, high grade and/or large index lesions were more easily detected at mp-MRI. Conversely, sensitivity was 63.6% for lesions of any size and pGS, with a PPV of 96%. In this study the good detection results for index and for clinically significant lesions was off-balanced by the very low sensitivity of mp-MRI for clinically insignificant lesions (19.1%). Similarly, other Authors have reported poor sensitivity for low volume lesions [30]. In contrast with the results of this study, Rosenkrantz et al. [22] using 3T equipment, reported an average sensitivity for index lesions of 60.2% and a PPV of 65.3% considering an exact match with histopatological specimens; the sensitivity and PPV rose at 75.9% and 82.6% with an approximate match. In addition, a recent article by Le et al [31] examined the performance of mp-MRI in the detection of PCas confirmed on whole-mount pathology in 122 patients, reporting an overall sensitivity of 47% and a sensitivity for the index lesion of 80%. Due to the high number of missed index lesions they highlighted the continuous need for systematic biopsy despite increasing enthusiasm for image-guided biopsy and possible avoidance of biopsy with MRI screening. In our opinion, the lower sensitivity reported in Le et al. is due to their different definition of index lesion. For Le et al. [31] the index lesion was the tumour with the highest Gleason grade while in the present article the index lesion was defined as the lesion with the largest volume, assessed on the pathological specimen [17]. In their series 14% of smaller secondary lesions had a higher GS with respect to the largest tumour, while we observed only one such case (0.9%). The importance of using the tumour volume to define the index lesion was supported by the results of our multivariate analysis.

The ability of mp-MRI to detect index lesions and the very low sensitivity of the test for clinically insignificant lesions observed in this study are a good premise to bring forward a paradigmatic shift in the PSA based diagnostic workflow of subjects with suspicion of prostate cancer. According to epidemiological data and new insights in tumour biology it seems now quite plausible that localized prostate cancer should be reclassified, as argued by Ahmed et al. [32] "into two subtypes — one that can be safely ignored, or better, not diagnosed and another that, if left untreated, would compromise either quality or quantity of life". Ruling out clinically insignificant cancer should limit the number of patients undergoing radical treatments with their related complications, reduce patient anxiety for having cancer and limit the costs derived from overtreatment. In this study we have shown that state-of-art prostate MRI accurately detects dominant tumours while insignificant secondary lesions are missed in a large proportion of patients. We report a sensitivity of more than 90% for dominant lesions, which are the main drivers of cancer progression [17-20]. If our results will be confirmed in larger studies, mp-MRI could be safely proposed as a triage test in subjects with increased PSA blood levels to select patients for TRUS biopsy. A randomized trial comparing cost-efficacy of the traditional diagnostic workflow to that of the MRI mediated pathway would probably represent the best methodological approach to define the role of imaging in localized prostate cancer diagnosis. Patients with a negative MRI study would have to undergo surveillance to detect false negatives, yielding information on NPV and specificity. This study did not include patients with a negative TRUS biopsy or those that did not perform biopsy.

The quality of the reference standard is a major strength of this study. The pathologist and a second radiologist in consensus contoured all detectable cancer foci on the 5 µm whole-mount histological sections and on the corresponding axial T2 weighed slices in order to allow an exact match between imaging and the prostatectomy specimens. In the majority of previous work the reference standard for imaging was TRUS biopsy, which does not allow exact tumour matching and may underestimate GS by up to 46% [8].

There are some potential limitations to this study. First, inter-observer variability was not assessed as only one experienced reader took part into the study, reporting all MRI exams. However, the main aim of this study was to measure the sensitivity of mp-MRI in detecting localized prostate carcinoma, in day-to-day practice. Reader variability will be addressed in an on-going multireader trial. Second, at the time of reporting the reader was aware that individuals recruited into the study all had a positive TRUS biopsy. In principle this could have strongly biased the interpreter, pushing him to report finding with a lower confidence threshold than if he had been in the dark. Due to trial design, this could not be avoided. However, in our opinion, the proposed workflow did not affect reading performances for the following reasons. First as reported above, lesion correspondence was obtained by exact match; lesions that were erroneously located in a different prostate sector were classified as false findings. Second, the criteria we chose to define a positive finding were not solely based on a subjective evaluation, but were supported by semi-quantitative and quantitative analysis. While this approach should guarantee a more reliable definition of disease, it could limit its applicability to MRI equipment produced by other companies.

Some authors argue that imaging of the prostate gland should be preferably performed at 3T. While it is probable that better image quality is obtained using high field intensity due to the higher SNR, 3.0 T MRI is still affected by susceptibility artefacts and more painstaking tuning is required to obtain homogeneous fields required for high definition imaging [33]. Debate on whether prostate MRI imaging still requires endorectal coils is still on-going. Recently, Turkbey et al. [34] report on the higher cancer sensitivity of dual-coil prostate MRI in comparison to nonendorectal coil MRI. Finally, results of clinical trials, including ours, do not convincingly lean in favour of high field imaging.

In conclusion, this study shows that mp-MRI has a high sensitivity in the detection of index lesions, that further increases with clinical significant index tumours and with the most aggressive tumours (GS >6) while it has disappointing results in the detection of small volume low GS prostate cancer

foci. Further evaluation will be needed to assess significance of a negative MRI scan and to compare patient acceptance and cost-efficacy of the conventional and newly proposed diagnostic workflows.

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Conflicts of Interest: None disclosed.

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FIGURES CAPTIONS

Figure 1: A 59-year-old man with a positive biopsy for adenocarcinoma in left PZ with bGS of 3+3 in 1/12 samples. Axial T2-weighted MR image (a) shows a very inhomogeneous PZ signal intensity with a nodular hypointense area identifiable in posterior left PZ (arrow). Axial apparent diffusion coefficient (ADC) map (b) shows a corresponding area of restricted diffusion; in the same location axial DCE-MRI (c) shows a nodular early intense contrast enhancement. Pathology (d) confirmed an aggressive adenocarcinoma (pGS of 4+5) with a volume of 2.59 cc (arrow).

Figure 2: Flow diagram of a cross-sectional study assessing the sensitivity of mp-MRI for prostate cancer detection.

Figure 3: A 63-years old man with a positive biopsy for adenocarcinoma in the left PZ with bGS of 3+3 and 3+4 in 2/12 samples. Axial T2-weighted image (a) shows an inhomogeneous PZ signal with a faint hypointense area in right PZ (asterisks) corresponding to a mildly reduced ADC value in the ADC map (b). DCE-MRI (c) shows absence of nodular early intense enhancement with a slightly diffuse enhancement and a type 2 T/I curve (not shown in the figure). The final MRI report was negative for PCa foci. Pathology (d) depicted an adenocarcinoma (arrows) corresponding to the index lesion with a volume of 2.18 cc and a GS 3+4 with pattern 4 of 20%

Figure 4: The same case illustrated in figure 3. Axial T2-w image (a) shows a left PZ nodular area of decreased signal intensity (asterisks) corresponding to a low ADC value (b). DCE-MRI (c) shows only a slight early contrast enhancement. Pathology (d) confirmed an adenocarcinoma (arrows) with a volume of 1.85 cc and a pGS of 4+3.

Figure 5: A 64 year-old man positive for left PZ adenocarcinoma in 1/20 samples (bGS 3+3) with PSA of 13 ng/ml at diagnosis. Axial T2-weighted image (a) shows a small hypointense area in left PZ (arrow), corresponding to a focal low ADC value (b). DCE-MRI (c) shows, in the same position, a focal early intense contrast enhancement. Pathology (d) confirmed a small volume aggressive adenocarcinoma (0.33 cc with pGS 4+3) (arrows).

Appendix

Statistical analysis

Several secondary analyses were performed. First, the correlation between the pGS and clinical characteristics (e.g., lesion volume, prostate volume, PSA) were evaluated by performing a logistic regression. Two models were created, in which pGS was treated in two different ways. First, pGS was considered as a continuous measurement, then it wasdichotomized into ≤6 and >6. Only index lesions were included in this analysis.

A second analysis was performed to describe the characteristics of index lesions correctly identified at MRI. For this analysis, the binary response of variable of interest was the detection by MRI of an index lesion, coded as "detected" or "missed". Then, data were analyzed by using multivariate logistic regression analysis. For the purpose of this analysis, certain variables were continuous while others were collapsed into binary categories (table E1).

Finally, we performed the same analysis on a per-lesion level, i.e., characteristics of lesions correctly identified at MRI were compared to those of missed lesions by using multivariate logistic regression. The same variable of the per-index lesion analysis were used (table E1). In this analysis, the pGS value was treated in two different ways. First, the pGS score was considered as a continuous variable; ORs and 95% confidence intervals were calculated for this first model. Then, we build a model in which a dichotomized version of pGS value was used (i.e, pGS<=6 vs. pGS>6; see Table E1). ORs estimates for this second model were also calculated. Since the odds estimates changed slightly over the two models, only output of the model using the dichotomized version of pGS score was reported in the text and in table 5. Conversely, in the appendix results of both models were reported to demonstrate consistent estimation.

To assess the validity of the mixed effects analyses, we performed likelihood ratio tests comparing the models with fixed effects to the null models with only the random effects. We rejected results in which the model including fixed effects did not differ significantly from the null model. Data were

presented as odds ratios (ORs) and 95% confidence limits. The OR is interpreted as the ratio of the odds of detection for one group (e.g. T2 score) compared with the odds for another (e.g. T3).

All statistical analyses were performed by using software (R version 2.15.2 (2012-10-26). R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org. Significance was assigned for a P less than 0.05 when appropriate.

Correlation between the pGS and clinical characteristics

When GS was treated as a continuous variable, there was evidence of positive correlation between increasing index lesion volume and pGS: the estimated increase in pGS for a unit increase of index lesion volume was 0.12; 95% CI: 0.04-0.20; P<0.001. This finding was consistent when pGS was treated as a binary variable: each unit increase in index lesion volume increased the odds of having pGs>6 by 4.2 times (95% CI: 1.8-10.0; P<0.001). There was no evidence of a correlation between pGS and prostate volume (-0.06; 95% CI: -0.24-0.12; P=0.496).

Addendum to per- index lesion and per-lesion analysis

According to multivariate logistic regression analyses, two index lesions characteristics were independently associated to detection at MRI: pGS value (ORs, 11.7; 95% CI: 2.3-59.8; P=0.003) and lesion volume (ORs, 4.24; 95% CI: 1.3-14.7; P=0.022). No other variables (i.e., patient age, prostate weight, prostate volume, PSA scores, areas of prostate) showed the 0.05 significance. In the per lesion analysis, patient age (P=0.682), prostate weight (P=0.144) and prostate volume (P=0.459) did not significantly influenced detection at MRI. Also, there was no evidence that T3 cancer were more likely to be detected than T2 lesions (OR, 3.44; 95% CI: 0.15-70.5; P=0.339). However, there was evidence that detection of MRI increased with increasing of pGS. When pGS score was treated as a continuous variable, a unit increase in pGS score increased the odds of

detection by 2.4 times (95% CI: 1.1-5.3; P=0.035). This finding was consistent when pGS was treated as a binary variable: the odds of detection of a lesion with pGS>6 were 3.2 (95% CI: 1.2-8.5) of a lesion with pGS≤6. Lesions in the peripheral zone of the prostate were more likely to be detected than those in central zone (OR, 5.4; 95% CI: 1.1-24.0; P=0.036). Furthermore, there was evidence of improved detection with increasing lesion volume (OR, 7.1; 95% CI: 2.4-23.7; P<0.001). We did not observe a significant interaction between lesion detection and PSA values (P=0.378).

TABLES

Table 1. Patient demographic and clinical characteristics. (PSA = Prostate Specific Antigen. US = Ultrasound. MRI = Magnetic Resonance Imaging).

No. of patients included in study	115
Patients median age [y] (1^{st}-3^{rd} quartile)	64 (60-69)
Median PSA [ng/ml] (1^{st}-3^{rd} quartile)	6.24 (4.97-8.82)
Median no. of previous transrectal US-guided biopsy sessions (1^{st}-3^{rd} quartile)	1 (1-1)
Median no. of days between biopsy and MRI (1^{st}-3^{rd} quartile)	85 (55-111)
Median no. of days between MRI and surgery (1^{st}-3^{rd} quartile)	26 (8-55)
Median prostate volume [cc] (1^{st}-3^{rd} quartile)	42.61 (35.87-57.03)

Table 2. Median volume of all lesions according to pathological Gleason score and location.

		Number of lesions (median volume, cc)			
		GS ≤6	**GS 3+4**	**GS 4+3**	**GS ≥8**
Prostate regions	**PZ**	64 (0.13)	74 (1.08)	22 (1.98)	16 (1.79)
	TZ	20 (0.42)	7 (2.26)	2 (1.66)	1 (6)
Total		84 (0.16)	81 (1.25)	24 (1.98)	17 (1.93)

Table 3. Per-index lesion sensitivity of mp-MRI according to pathological Gleason score and location. (Data are percentages, numerators indicates the number of detected lesions and denominators represents the total number of lesions. NA = not applicable because no cases were found. PZ = Peripheral Zone; TZ = Transitional Zone. GS = Gleason Score).

		Sensitivity (%)				
		GS ≤ 6	**GS 3+4**	**GS 4+3**	**GS ≥ 8**	**TOTAL**
Index lesions (n=115)	**PZ**	60 (9/15)	94.3 (50/53)	100 (21/21)	100 (14/14)	91.3 (94/103)
	TZ	75 (3/4)	83.3 (5/6)	100 (1/1)	100 (1/1)	83.3 (10/12)
	Total	63.1 (12/19)	93.2 (55/59)	100 (22/22)	100 (15/15)	90.4 (104/115)
Clinically significant index lesions (n=105)	**>0.5 ml**	66.6 (6/9)	93.1 (54/58)	100 (20/20)	100 (15/15)	93.1 (95/102)
	≤0.5 ml and GS≥7	NA	100 (1/1)	100 (2/2)	NA	100 (3/3)
	Total	66.6 (6/9)	93.2 (55/59)	100 (22/22)	100 (15/15)	93.3 (98/105)

Table 4. Mp-MRI sensitivity for all PCa lesions and for clinically significant lesions; data are stratified according to Gleason score and prostate region. (Data are percentages, numerators indicates the number of detected lesions and denominators represents the total number of lesions. PZ = Peripheral Zone; TZ = Transitional Zone. GS = Gleason score).

		Sensitivity (%)				
		GS ≤ 6	**GS 3+4**	**GS 4+3**	**GS ≥ 8**	**TOTAL**
All Lesions	**PZ**	28.1 (18/64)	85.1 (63/74)	100 (22/22)	93.7 (15/16)	67 (118/176)
	TZ	30 (6/20)	71.4 (5/7)	50 (1/2)	100 (1/1)	43.3 (13/30)

	TOTAL	28.6 (24/84)	83.9 (68/81)	95.8 (23/24)	94.1 (16/17)	63.6 (131/206)
Clinically Significant Lesions (>0.5 cc or ≤0.5 cc and GS≥7)	**PZ**	70 (7/10)	85.1 (63/74)	100 (22/22)	93.7 (15/16)	87.7 (107/122)
	TZ	66.6 (4/6)	71.4 (5/7)	50 (1/2)	100 (1/1)	68.8 (11/16)
	TOTAL	68.7 (11/16)	83.9 (68/81)	95.8 (23/24)	94.1 (16/17)	85.5 (118/138)

Table 5. Results of multivariate logistic regression model (containing all of explanatory variables in Table E1, full model). Data are the odds of a lesion being correctly detected at MRI either for one-unit increase in the explanatory variable (for variables on a continuous scale) or for each category relative to the odds of baseline category (for categorical explanatory variables). Data in parentheses are 95% confidence intervals.

Variable	**Odds Ratios**	**P Value**
Patient Age	0.98 (0.92-1.05)	0.682
Prostate Volume (cc)	0.9 (0.85-1.06)	0.459
Prostate Weight (g)	1.0 (0.99-1.05)	0.144
Gleason Score		
≤6	1.0	
>6	3.2 (1.2-8.5)	0.017
Lesion Volume (cc)	7.1 (2.4-23.7)	<0.001
Stage Prostate Cancer		
T2	1.0	
T3	3.44 (0.15-70.5)	0.339
PSA value (ng/mml)	0.93 (0.80-1.09)	0.378
Prostate Area		
Central	1.0	
Peripheral	5.4 (1.1-24.0)	0.036