

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

Filippo Russo*, Daniele Regge*, Enrico Armando*, Valentina Giannini*, Anna Vignati*, Simone Mazzetti*, Matteo Manfredi[†], Enrico Bollito[‡], Loredana Correale[§] and Francesco Porphiglia[†]

*Department of Radiology, Candiolo Cancer Institute – FPO, IRCCS, Candiolo Torino, [†]Division of Urology, Department of Clinical and Biological Science, Azienda Ospedaliero-Universitaria San Luigi Gonzaga, Orbassano, [‡]Division of Pathology, Department of Clinical and Biological Science, Azienda Ospedaliero-Universitaria San Luigi Gonzaga, Orbassano, and [§]im3D S.p.A. Medical Imaging Lab, Torino, Italy

Objective

To evaluate the sensitivity of multiparametric magnetic resonance imaging (mp-MRI) for detecting prostate cancer foci, including the largest (index) lesions.

Patients and Methods

In all, 115 patients with biopsy confirmed prostate cancer underwent mp-MRI before radical prostatectomy. A single expert radiologist recorded all prostate cancer foci including the index lesion ‘blinded’ to the pathologist’s biopsy report. Stained whole-mount histological sections were used as the reference standard. All lesions were contoured by an experienced uropathologist who assessed their volume and pathological Gleason score. All lesions with a volume of >0.5 mL and/or pathological Gleason score of >6 were defined as clinically significant prostate cancer. Multivariate analysis was used to ascertain the characteristics of lesions identified by MRI.

Results

In all, 104 of 115 index lesions were correctly diagnosed by mp-MRI (sensitivity 90.4%; 95% confidence interval [CI]

83.5–95.1%), including 98/105 clinically significant index lesions (93.3%; 95% CI 86.8–97.3%), among which three of three lesions had a volume of <0.5 mL and Gleason score of >6. Overall, mp-MRI detected 131/206 lesions including 13 of 68 ‘insignificant’ prostate cancers. The multivariate logistic regression modelling showed that pathological Gleason score (odds ratio [OR] 11.7, 95% CI 2.3–59.8; $P = 0.003$) and lesion volume (OR 4.24, 95% CI 1.3–14.7; $P = 0.022$) were independently associated with the detection of index lesions at MRI.

Conclusions

This study shows that mp-MRI has a high sensitivity for detecting clinically significant prostate cancer index lesions, while having disappointing results for the detection of small-volume, low Gleason score prostate cancer foci. Thus, mp-MRI could be used to stratify patients according to risk, allowing better treatment selection.

Keywords

prostatic neoplasm, magnetic resonance imaging, diagnostic imaging

Introduction

Prostate cancer is the most common malignancy in males and the second cause of cancer-related death in industrialised countries [1]. In 2012, the total incidence and mortality of prostate cancer in 40 European countries was estimated at 417 000 and 92 000 cases, respectively [1]. According to most widely used guidelines, high circulating

levels of PSA and/or a suspicious DRE are indications for prostate biopsy, on which pathological evaluation is performed [2]. PSA levels, clinical stage, and biopsy Gleason score at diagnosis, classify patients as at low, intermediate and high risk of clinical progression [3]. Radical prostatectomy (RP) or radiotherapy is the ‘gold standard’ for patients with intermediate–high risk prostate cancer; in low-risk cases active surveillance is considered a reasonable

option. However, both PSA measurements and TRUS-guided biopsies have limitations affecting their ability to reliably detect prostate cancer. Indeed, $\approx 15\%$ of men with normal PSA levels (≤ 4.0 ng/mL) have prostate cancer [4]. Conversely, conditions other than prostate cancer, such as prostatitis and lower urinary infections, can give rise to elevated PSA levels. As about two-thirds of men with elevated PSA levels (>4 ng/mL) will not have prostate cancer [5], using this method as a screening test can cause potential harms, e.g. additional medical visits, side-effects of prostate biopsies, anxiety, and over diagnosis leading to overtreatment with its associated side-effects (bowel urgency, urinary leakage, erectile dysfunction). Also, 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 $\approx 40\%$ of prostate cancer cases will be under-staged as low risk [7,8]. Consequently, alternative options to radical treatment, such as active surveillance, focal therapies, and chemoprevention can be inappropriately chosen, thus failing to control disease progression. The evidence to date is insufficient to support the use of novel markers (e.g. prostate cancer antigen 3 [PCA3], -2pro-PSA isoform and the serine protease transmembrane protease, serine 2 [TMPRSS2]-erythroblast transformation-specific-related gene (*ERG*) translocation, etc.) in clinical practice [9,10].

According to recent guidelines, the use of MRI is currently limited to men with clinical suspicion of prostate cancer that have already had one or more negative prostate biopsies [11] and in the staging of locally advanced disease [2]. In the near future, multiparametric MRI (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 Gleason score tumours, it has limitations in identifying the smaller prostate cancer foci, which are very common, as the disease is frequently multifocal [15,16]. Recent advances in the understanding of prostate cancer support the theory that disease progression and metastatisation are driven by the largest tumour 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 multi-reader study of a small group of patients, Rosenkrantz et al. [22] reported a sensitivity and positive predictive value (PPV) of 75.9% and 82.6%, respectively, for detecting 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 the present study was to assess the sensitivity of mp-MRI for detecting index prostate cancer lesions using whole-mount histological sections as the

reference standard. Lesion characteristics were also evaluated by multivariate analysis.

Patients and Methods

Between April 2010 and November 2012, 143 consecutive men with prostate cancer diagnosed by TRUS-guided core biopsy were sent to our Institution from the same tertiary care centre for 1.5-T mp-MRI evaluations. All patients were candidates for RP based on systematic TRUS biopsy, PSA values and clinical parameters. The mp-MRI was performed at ≥ 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 in the study signed informed consent forms.

MRI Protocol

The MRI studies were performed with a 1.5-T scanner (Signa Excite HD; GE Healthcare, Milwaukee, IL, USA) using a four-channel phased array coil combined with an endorectal coil (Medrad, Indianola, PA, USA). Routinely, just before the beginning of the examination 20 mg butylscopolamine bromide (Buscopan, Boehringer Ingelheim, Germany) was injected (i.m.) to reduce bowel movements. First, T2-weighted (T2W) images were taken to assess prostate morphology, using the following protocol: slice-thickness, 3 mm; field of view (FOV), 16×16 cm; number of excitations (NEX), 2; acquisition matrix, 384×288 ; repetition time (TR)/echo time (TE) ratio 3020/85, 3620/90 and 3960/110 in the axial, coronal and sagittal plain, respectively. Second, a T1 fast spin-echo axial sequence was taken to assess for areas of haemorrhage within the prostate using the following protocol: slice-thickness, 3 mm; FOV 16×16 cm; NEX, 2; acquisition matrix 320×256 ; TR/TE 580/min. Three diffusion-weighted (DW) image sequences were then obtained using axial echo planar imaging (EPI) sequences as follows: slice-thickness, 3 mm; FOV 16×16 cm, matrix 128×128 , NEX 6; TR/TE 7 000/min; *b*-values of 0–600, 0–1 000, 0–1 400 s/mm^2 . Finally, dynamic contrast-enhanced (DCE)-MRI was performed using an axial fast spoiled gradient-recalled-echo (FSPGR) sequence with a temporal resolution of 13 s, after i.v. power injection of gadobutrol (Gadovist; Bayer Pharma AG, Berlin, Germany) at 2 mL/s, followed by a saline solution flush. The following scanning parameters were used for image acquisition: slice thickness, 3 mm; FOV 20×20 cm; matrix, 224×192 ; 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) with specialised software for image processing for both DW and DCE-MRI images (Functool v 4.5.3 and 7.4.01d, GE Healthcare). A single experienced radiologist (F.R.), interpreting >500 prostate mp-MRI studies per year, analysed all the mp-MRI examinations that met the inclusion criteria, to identify prostate cancer foci. The reader was informed that the patients had prostate cancer detected by biopsy but was unaware of the pathologist's biopsy report, i.e. its location.

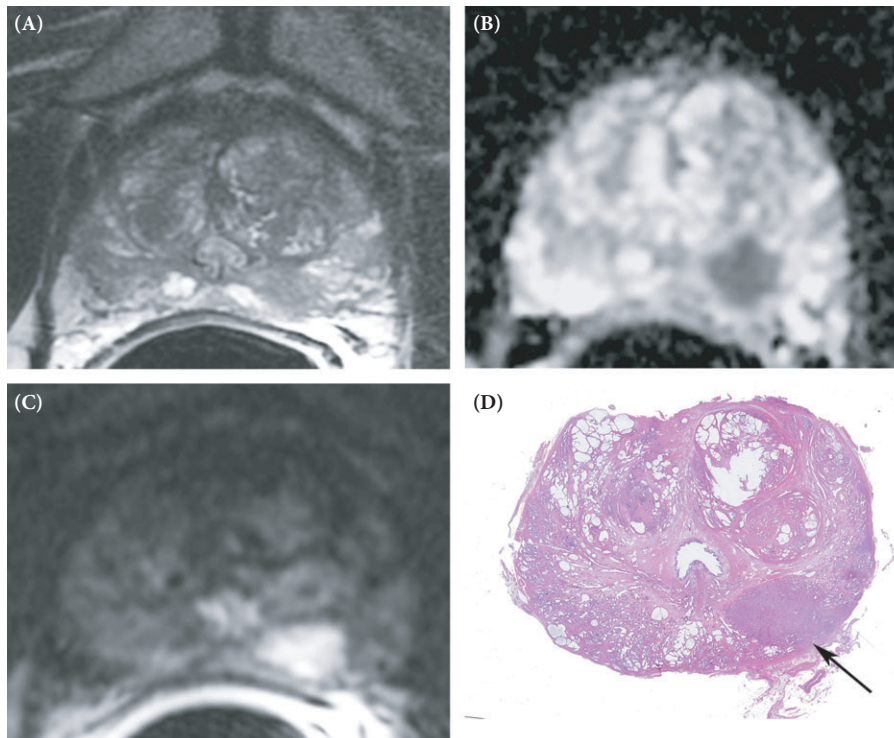
The following were considered suspicious signs for prostate cancer in the peripheral zone (PZ): a round, oval or plaque-like area of low signal intensity on T2W sequences; presence of extracapsular extension signs [24], i.e. hypointense focus bulging the contour of the prostate or crossing the prostatic capsule with gross extension in the periprostatic fat, asymmetry of the neurovascular bundle. Focal areas of reduced Apparent Diffusion Coefficient (ADC): $<1.1 \times 10^{-3} \text{ mm}^2/\text{s}$ corresponding or not to a hyperintense signal on the DW imaging with a b-value of $1\,400 \text{ s}/\text{mm}^2$ were considered as foci suspicious for cancer [25,26] (Fig. 1). The ADC maps were computed on the DW imaging

sequence with a b-value of $1\,000 \text{ s}/\text{mm}^2$, using a monoexponential model, and the mean ADC value was, evaluated on a selected region of interest, 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 seen on T2W sequences that may correspond to a hyperintense area on DW imaging. 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 imaging and DW imaging, was considered negative for prostate cancer.

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

Fig. 1 A 59-year-old man with a positive biopsy for adenocarcinoma in the left PZ with a biopsy Gleason score of 3 + 3 in one of 12 samples. The axial T2W image (A) shows a very inhomogeneous PZ signal intensity with a nodular hypointense area identifiable in the posterior left PZ (arrow). The axial 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 (pathological Gleason score of 4 + 5) with a volume of 2.59 mL (arrow).



provided by the European Society of Urogenital Radiology (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

Whole-mount histological sections resected from the RP specimens were used as the reference standards. In detail, the prostate was cut into 3-mm thick sections; slices were obtained perpendicular to the rear gland surface, with the same inclination as that of the axial T2W images. Conversely, the bases and the apices were sectioned longitudinally. Then, 5- μ m sections were taken from each thick slice and stained with haematoxylin and eosin. All samples were then assessed for cancer foci by the same experienced uropathologist (E.B). The lesion volume was obtained by summing the area involved by the tumour on each contiguous slide. The pathologist also assessed the pathological Gleason score for each focus and in multifocal cases he recorded which of the foci the index lesion was. The index lesion was defined as the largest tumour focus within the prostate gland [17]; clinically significant prostate cancer was defined as a tumour of >0.5 mL and/or pathological Gleason score >6; consequently, prostate cancer foci with a volume <0.5 mL and a Gleason score <6 were defined as clinically insignificant [29]. All malignant lesions were then contoured with a marker and each section was scanned for comparison with MRI findings. To finalise the reference standard a second experienced radiologist (E.A.) matched each lesion detected by the pathologist with the MRI findings. When the sections and axial T2W images were not perfectly overlapped, usually due to the modified prostate shape following fixation in formaldehyde, the pathologist and second radiologist used TZ adenoma nodules as landmarks to better identify the lesions on the MRI images. Lesions that did not match were classified as false findings on MRI.

Statistical Analysis

In the present study a patient was defined 'true positive' (TP) when at least one pathologically confirmed prostate cancer lesion was detected by MRI and as a FN when the MRI did not detect a pathologically confirmed cancer within the prostate gland. Accordingly, per-patient sensitivity was defined as the number of TP findings over the total number of positive patients. The false positive (FP) rate and PPV were not computed in the per-patient analysis, as all patients had TRUS-biopsy confirmed prostate cancer. Per-lesion

analysis was performed considering both only index lesions and all prostate cancer lesions. In the per-index lesion assessment a patient was classified as TP when the MRI-defined index lesion exactly matched the equivalent finding at full-mount pathology, as FN when no lesions were detected by MRI, and as FP when the MRI-identified index lesion did not exactly match with the full-mount pathology defined index lesion. The 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 Gleason score and size thresholds, and different prostate cancer locations (i.e. PZ vs TZ). Accordingly, a prostate cancer 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 methods used to assess the relationship between pathological Gleason score and other patient characteristics. Multivariate analysis was used to ascertain the characteristics of lesions identified by MRI and is also reported in the Appendix. All statistical analysis was performed by using R software (version 2.15.2). Significance was assigned for a $P < 0.05$, when appropriate.

Results

Demographic and Pathological Characteristic of the Study Group

We enrolled 141 of the 143 patients, as two (1%) were excluded because they were undergoing hormonal therapy at the time of the mp-MRI. 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 RP (25/141, 18%) or because the prostate cancer foci were not found on the excised prostate (1/141, 0.7%) (Fig. 2). Patient characteristics and clinical information are reported in Table 1.

Fig. 2 Study selection flow chart.

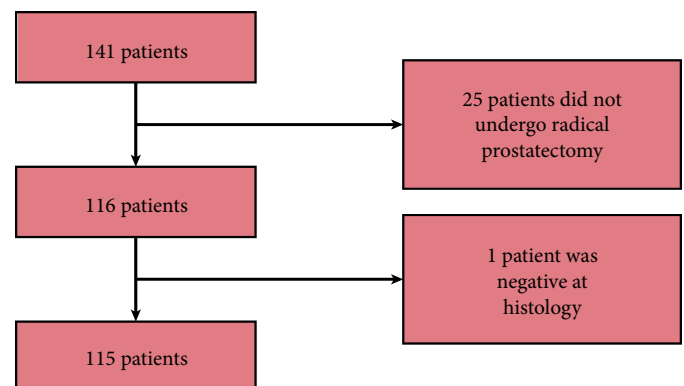


Table 1 The patients' demographic and clinical characteristics.

Variable	Value
No. of patients included in study	115
Median (interquartile range)	
Age, years	64 (60–69)
PSA level, ng/mL	6.24 (4.97–8.82)
Previous TRUS-guided biopsy sessions, <i>n</i>	1 (1–1)
Time between biopsy and MRI, days	85 (55–111)
Time between MRI and surgery, days	26 (8–55)
Prostate volume, mL	42.61 (35.87–57.03)

Overall, the pathologist identified 206 cancer foci of which 138 (67%) were clinically significant lesions. Of the latter, 122 (88%) were located in the PZ and 16 (12%) in the TZ. The median volumes of lesions according to pathological Gleason score and prostate location are reported in Table 2. Lesions distribution was as follows: one prostate cancer focus was detected in 55/115 patients (48%), two in 39 (34%), three in 13 (11%), four in six (5%), while five lesions were identified in the last two patients (2%). Multifocal disease was therefore present in 52% of patients. In this RP cohort, 157 of 206 lesions (76.2%) had a pathological Gleason score of 3 + 3 or 3 + 4 and 176 foci (85.4%) were located in the PZ. The mean (median; range) tumour volume was 1.3 (0.74; 0.001–20.51) mL. The 115 index lesions included: 102 lesions (88.7%) with a volume of >0.5 mL, three lesions (2.6%) with a volume of <0.5 mL but with a pathological Gleason score >6, and 10 clinically insignificant lesions (8.7%), i.e. with a volume <0.5 mL and a Gleason score ≤6 mL. Pathological Gleason Score 3 + 3 index tumours had a significant lower median

volume than those with Gleason score 3 + 4, 4 + 3 and ≥8 (All $P < 0.001$). In all, 34 of the 115 index lesions were pathological stage T3 (24 cases were T3a and 10 were T3b); the remaining 81 index lesions were pT2.

Per-Patient Analysis

The mp-MRI detected at least one prostate cancer foci in 106 of 115 patients, yielding an overall sensitivity of 92.2% (95% CI 85.7–96.4%). None of the FN patients had lesions with a pathological Gleason score of ≥4 + 3. Four of the nine FN patients had clinically insignificant lesions and one had two prostate cancer foci of which the largest was in the TZ (size 1.26 mL; pathological Gleason score 3 + 4). The remaining four patients had Gleason score 3 + 3 (two) and 3 + 4 (two) clinically significant prostate cancer foci.

Per-index Lesion Analysis

The 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 pathological Gleason score. The mp-MRI detected all index lesions with pathological Gleason score of 4 + 3 (22 lesions) and ≥8 (15). The mp-MRI also detected 55 of the 59 index lesions with a 3 + 4 pathological Gleason score (sensitivity of 93.2%; 95% CI 83.5–98.1%). None of the missed lesions was stage T3. As there were two FP findings, the PPV for index lesions was 98%.

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

Prostate regions	Number of lesions (median volume, mL)			
	Gleason score ≤6	Gleason score 3 + 4	Gleason score 4 + 3	Gleason score ≥8
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.

	Sensitivity, % (<i>n/N</i>)				
	Gleason score ≤6	Gleason score 3 + 4	Gleason score 4 + 3	Gleason score ≥8	Total
Index lesions (<i>n</i> = 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 (<i>n</i> = 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 Gleason score ≥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)

NA, not applicable because no cases were found.

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

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

All three clinically significant index lesions with a volume of <0.5 mL (0.14, 0.33 and 0.41 mL) but with a pathological Gleason score >6 (respectively 4 + 3, 4 + 3, 3 + 4) were identified by mp-MRI (Fig. 5). Also, mp-MRI correctly identified six of 10 clinically insignificant index lesions, i.e. with a volume of <0.5 mL and a pathological Gleason score ≤6.

According to multivariate analysis, two index lesions characteristics were independently associated with detection at MRI: lesion volume (odds ratio [OR] 4.24, 95% CI 1.3–14.7; $P = 0.022$) and pathological Gleason score. The odds of detecting an index lesion with pathological Gleason score >6 was 11.7 (95% CI 2.3–59.8; $P = 0.003$) times that of a lesion with a Gleason score ≤6. No other variables were statistically significant, i.e. patient age, prostate weight, prostate volume, PSA scores, or areas of prostatitis.

Overall Per-lesion Analysis

The mp-MRI detected 131 of the 206 prostate cancer foci, yielding an overall per-lesion sensitivity of 63.6% (95% CI 56.6–70.2%) (Table 4). The 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 prostate cancer 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

Fig. 3 A 63-year-old man with a positive biopsy for adenocarcinoma in the left PZ with biopsy Gleason scores of 3 + 3 and 3 + 4 in two of 12 samples. The axial T2W image (A) shows an inhomogeneous PZ signal with a faint hypointense area in the 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 T1 curve (not shown in the figure). The final MRI report was negative for prostate cancer foci. Pathology (D) depicted an adenocarcinoma (arrows) corresponding to the index lesion with a volume of 2.18 mL and a pathological Gleason score of 3 + 4 with a pattern 4 of 20%.

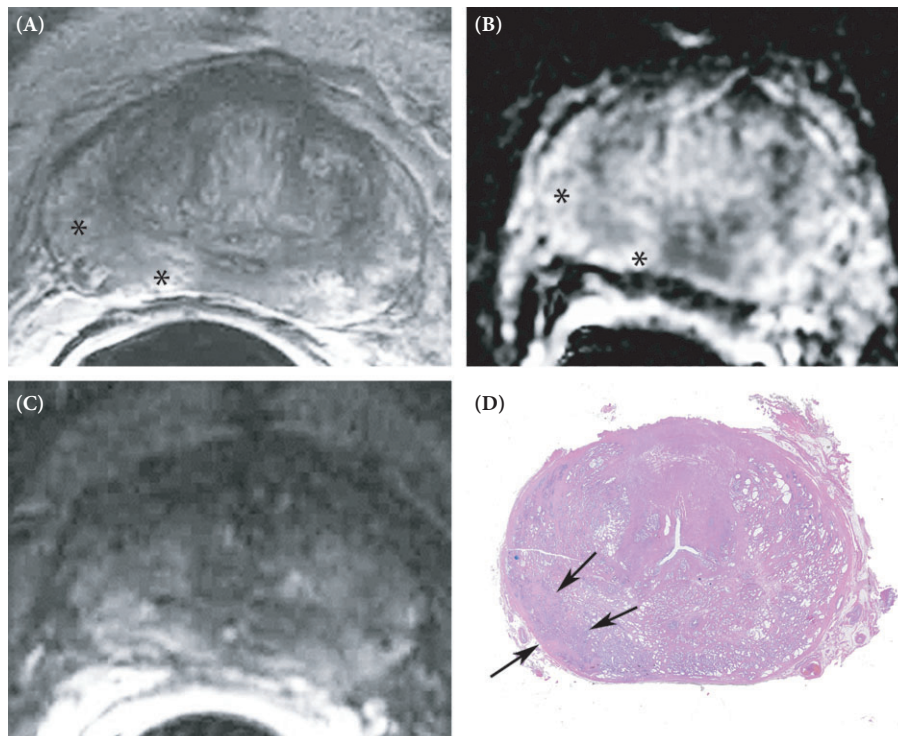
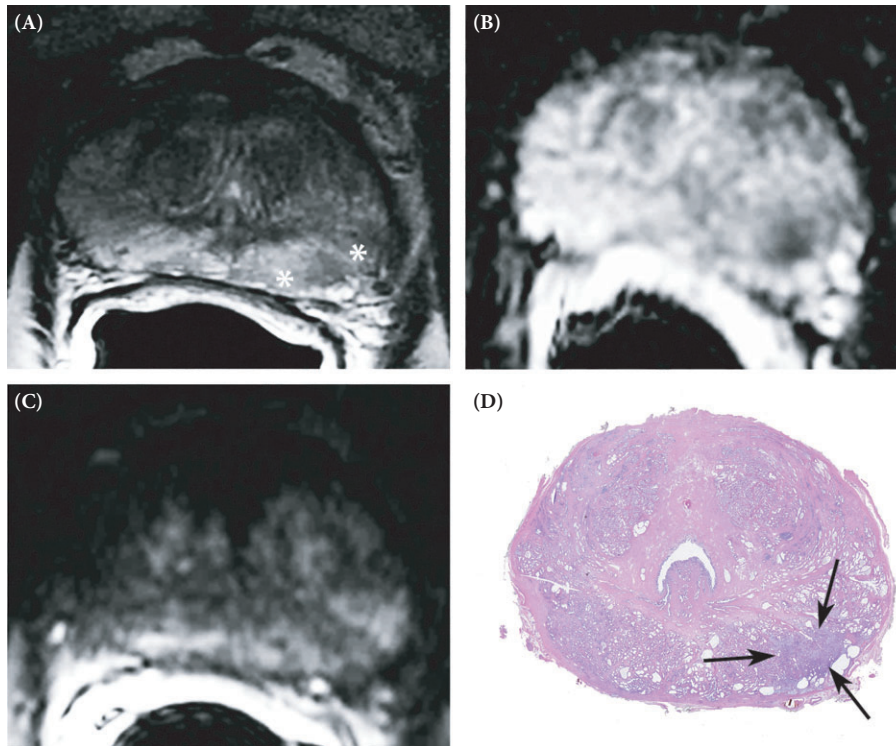


Fig. 4 The same case shown in Fig. 3. The axial T2W image (A) shows a left PZ nodular area of decreased signal intensity (asterisks) corresponding to a low ADC value (B). DCE-MRI (C) shows only a slight early contrast enhancement. Pathology (D) confirmed an adenocarcinoma (arrows) with a volume of 1.85 mL and a pathological Gleason score of 4 + 3.



that the detection rate of MRI increased with increasing Gleason score: the odds of detecting a lesion with pathological Gleason score >6 was 3.2 (95% CI 1.2–8.5) times that of a lesion with a Gleason score ≤ 6 . In addition, lesions in the PZ 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; $P < 0.001$).

The mp-MRI erroneously identified as cancer five prostate areas in an equivalent number of patients, leading to a PPV of 96%. In four of the five cases, the FP findings belonged to patients with at least one other significant prostate cancer correctly identified at MRI and confirmed at histopathology. Four of the five FPs were areas of atrophy or prostatitis.

Discussion

In the present single-centre cohort study, 90.4% of prostate cancer index lesions were identified by mp-MRI. The sensitivity was 93.3% when considering only clinically significant index lesions, which were the vast majority. Interestingly, MRI detected 83.3% of TZ index lesions, all 4 + 3 and ≥ 8 Gleason score index lesions, and all stage T3 cancers. As expected, high-grade and/or large index lesions

were more easily detected at mp-MRI. Conversely, the sensitivity was 63.6% for lesions of any size and pathological Gleason score, with a PPV of 96%. In the present study, the good detection results for index and for clinically significant lesions were counterbalanced 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 the present study, Rosenkrantz et al. [22] using 3-T equipment reported an average sensitivity for index lesions of 60.2% and a PPV of 65.3% when considering an exact match with histopathological specimens, while the sensitivity and PPV rose to 75.9% and 82.6% respectively with an approximate match. In addition, a recent article by Le et al. [31] examined the performance of mp-MRI for detecting prostate cancers confirmed on whole-mount pathology in 122 patients, reporting an overall sensitivity of 47% and sensitivity for the index lesion of 80%. Due to the many 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 by Le et al. [31] is due to their different definition of ‘index lesion’, which they defined as the lesion with the highest Gleason grade, while in the present study the ‘index lesion’ was defined as the lesion

Fig. 5 A 64-year-old man positive for a left PZ adenocarcinoma in one of 20 samples (biopsy Gleason score 3 + 3) with a PSA level of 13 ng/mL at diagnosis. The axial T2W image (A) shows a small hypointense area in the 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 mL with a pathological Gleason score of 4 + 3) (arrows).

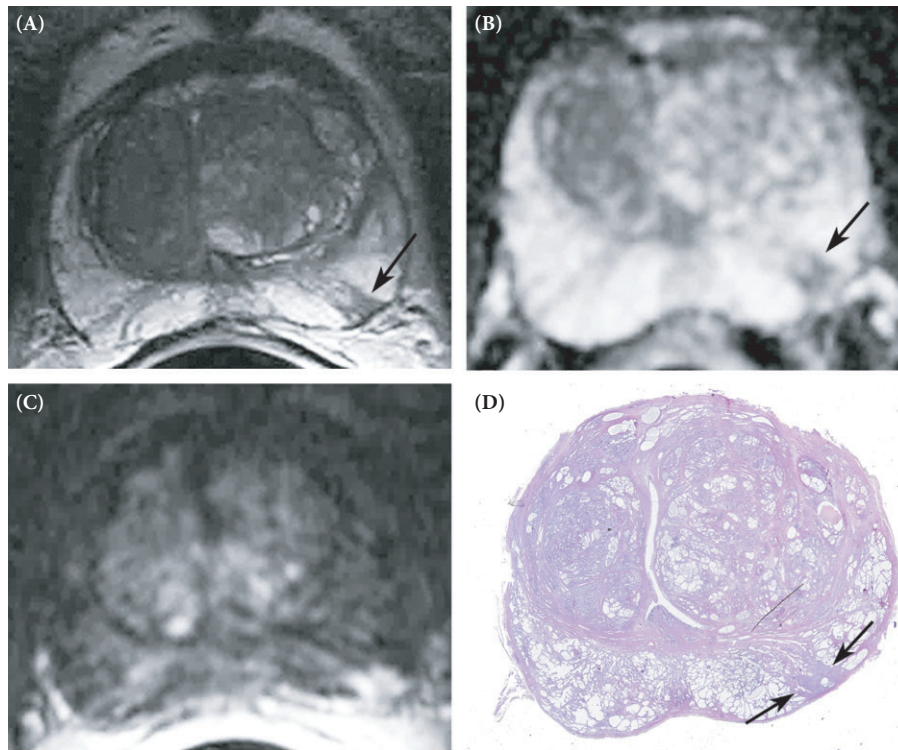


Table 4 Sensitivity of mp-MRI for all prostate cancer lesions and for clinically significant lesions; data are stratified according to Gleason score and prostate region.

	Sensitivity, % (n/N)				Total
	Gleason score ≤6	Gleason score 3 + 4	Gleason score 4 + 3	Gleason score ≥8	
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 mL or ≤0.5 mL and Gleason score ≥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)

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.

with the largest volume at pathology [17]. In their series [31], 14% of smaller secondary lesions had higher Gleason scores than the largest lesion, while in the present study there was 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 seen in the present study are a good premise to bring forward a paradigmatic shift in the PSA-based diagnostic workflow of

men with suspicion of prostate cancer. According to epidemiological data and new insights in tumour biology, it seems now quite plausible that localised 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'. Excluding clinically insignificant cancer should limit the number of patients undergoing radical treatments with their related complications, reduce patient anxiety of having cancer, and

Table 5 Results of multivariate logistic regression model (containing all of explanatory variables in Table S1, full model). Data are the odds of a lesion being correctly detected at MRI either for a 1-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).

Variable	OR (95% CI)	P
Patient age	0.98 (0.92–1.05)	0.682
Prostate volume	0.9 (0.85–1.06)	0.459
Prostate weight	1.0 (0.99–1.05)	0.144
Gleason score		
≤6	1.0	
>6	3.2 (1.2–8.5)	0.017
Lesion volume	7.1 (2.4–23.7)	<0.001
T stage		
T2	1.0	
T3	3.44 (0.15–70.5)	0.339
PSA level	0.93 (0.80–1.09)	0.378
Prostate area		
Central	1.0	
Peripheral	5.4 (1.1–24.0)	0.036

limit the costs resulting from overtreatment. In the present 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 >90% for dominant lesions, which are the main drivers of cancer progression [17–20]. If our present results are confirmed in larger studies, mp-MRI could be safely proposed as a triage test in men with increased PSA levels to select patients for TRUS biopsy. A randomised trial comparing the cost-effectiveness of the traditional diagnostic workflow to that of the MRI-mediated pathway would probably represent the best methodological approach to define the role of MRI in localised prostate cancer diagnosis. Patients with a negative MRI study would have to undergo surveillance to detect FNAs, yielding information on negative predictive value and specificity. The present study did not include patients with a negative TRUS biopsy or those that did not have a biopsy.

The quality of the reference standard is a major strength of the present study. The pathologist and a second radiologist in consensus contoured all detectable cancer foci on the 5- μ m whole-mount histological sections and on the corresponding axial T2W slices, to allow an exact match between MRI and the RP specimens. In most previous work, the reference standard for imaging was TRUS biopsy, which does not allow exact tumour matching and may underestimate Gleason score by up to 46% [8].

There are some potential limitations to the present study. First, interobserver variability was not assessed as only one experienced reader took part in the study, reporting on all MRI examinations. However, the main aim of the present study was to measure the sensitivity of mp-MRI in detecting localised prostate carcinoma in day-to-day practice. Reader variability will be addressed in an on-going multi-reader 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 a finding with a lower confidence threshold than if he had been unaware of this. Due to the trial design, this could not be avoided. However, in our opinion, the proposed workflow did not affect reading performance 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 MRI of the prostate gland should be preferably performed at 3 T. While it is probable that better MRI quality is obtained using high field intensity due to the higher signal to noise ratio, 3.0-T MRI is still affected by susceptibility artefacts and more meticulous tuning is required to obtain homogeneous fields required for high-definition imaging [33]. Debate on whether prostate MRI still requires endorectal coils is on-going. Recently, Turkbey et al. [34] reported higher sensitivity of dual-coil prostate MRI compared with non-endorectal coil MRI for detecting cancer foci. Finally, results of clinical trials, including ours, do not convincingly lean in favour of high-field MRI.

In conclusion, the present study shows that mp-MRI has a high sensitivity for detecting index lesions, which further increases for clinically significant index tumours and for the most aggressive tumours (Gleason score >6), while it has disappointing results for detecting small-volume low Gleason score prostate cancer foci. Further evaluation will be needed to assess the significance of a negative MRI and to compare patient acceptance and cost-effectiveness of the conventional and newly proposed diagnostic workflows.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Correspondence: Valentina Giannini, Department of Radiology, Candiolo Cancer Institute – FPO, IRCCS, Strada Provinciale 142 Km 3,95, 10060 Candiolo, Torino, Italy.

e-mail: valentina.giannini@ircc.it

Abbreviations: ADC, Apparent Diffusion Coefficient; DCE, dynamic contrast-enhanced; DW, diffusion-weighted; FN, false negative; FOV, field of view; mp-MRI, multiparametric MRI; NEX, number of excitations; OR, odds ratio; PPV, positive predictive value; PZ, peripheral zone; RP, radical prostatectomy; T2W, T2-weighted; TE, echo time; TP, true positive; TR, repetition time; TZ, transition zone.

Appendix

Statistical Analysis

Several secondary analyses were performed. First, the correlation between the pathological Gleason score and clinical characteristics (e.g. lesion volume, prostate volume, PSA level) were evaluated by performing a logistic regression.

Two models were created, in which pathological Gleason score was treated in two different ways. First, pathological Gleason score was considered as a continuous measurement, then it was dichotomised 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 analysed by using multivariate logistic regression analysis. For the purpose of this analysis, certain variables were continuous while others were collapsed into binary categories (Table S1).

Finally, we performed the same analysis on a per-lesion level, i.e. characteristics of lesions correctly identified at MRI were compared with those of missed lesions by using multivariate logistic regression. The same variable of the per-index lesion analysis were used (Table S1). In this analysis, the pathological Gleason score was treated in two different ways. First, the pathological Gleason score was considered as a continuous variable; ORs and 95% CIs were calculated for this first model. Then, we built a model in which a dichotomised version of pathological Gleason score was used, i.e. pathological Gleason score ≤ 6 vs > 6 (Table S1). The ORs estimates for this second model were also calculated. As the odds estimates changed slightly over the two models, only the output of the model using the dichotomised version of pathological Gleason score value was reported in the text and in Table 5. Conversely, in the appendix results of both models are 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 ORs and 95% CIs. 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).

Correlation Between the Pathological Gleason Score and Clinical Characteristics

When pathological Gleason score was treated as a continuous variable, there was evidence of a positive correlation between increasing index lesion volume and Gleason score: the estimated increase in Gleason score 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 pathological Gleason score was treated as a binary variable: each unit increase in index lesion volume increased the odds of having a Gleason score > 6 by 4.2 times (95% CI 1.8–10.0; $P < 0.001$). There was no evidence of a correlation between pathological Gleason score and prostate volume (-0.06 , 95% CI -0.24 to 0.12 ; $P = 0.496$).

Per-index Lesion and Per-lesion Analysis

According to the multivariate logistic regression analyses, two index lesion characteristics were independently associated with detection at MRI: pathological Gleason score (OR 11.7, 95% CI 2.3–59.8; $P = 0.003$) and lesion volume (OR 4.24, 95% CI 1.3–14.7; $P = 0.022$). No other variables, e.g. patient age, prostate weight, prostate volume, PSA level, different areas of the prostate, were statistically significant. In the per-lesion analysis, patient age ($P = 0.682$), prostate weight ($P = 0.144$), and prostate volume ($P = 0.459$) did not significantly influence detection at MRI. Also, there was no evidence that T3 lesions were more likely to be detected than T2 (OR 3.44, 95% CI 0.15–70.5; $P = 0.339$). However, there was evidence that the detection rate of MRI increased with increasing pathological Gleason score. When pathological Gleason score was treated as a continuous variable, a unit increase in pathological Gleason score increased the odds of detection by 2.4 times (95% CI 1.1–5.3; $P = 0.035$). This finding was consistent when pathological Gleason score was treated as a binary variable: the odds of detection of a lesion with a pathological Gleason score of > 6 was 3.2 (95% CI 1.2–8.5) times that of a lesion with Gleason score of ≤ 6 . Lesions in the PZ 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; $P < 0.001$). There was no significant interaction between lesion detection and PSA levels ($P = 0.378$).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Patient and lesion characteristics used for multivariate analysis.