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ORIGINAL ARTICLE

Prospective nonrandomized study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy to magnetic resonance imaging with subsequent MRI-guided biopsy in biopsy-naïve patients

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ABSTRACT

BACKGROUND: To evaluate the diagnostic efficacy in cancer prostate (PCa) of Multiparametric prostate magnetic resonance imaging (mp-MRI) targeted biopsy compared to standard systematic transrectal ultrasound-guided biopsy (TRUSGB) in biopsy-naïve patients.

METHODS: A total of 168 biopsy-naïve men with clinical suspicion of PCa due to elevated PSA levels and/or an abnormal digital rectal examination were consecutively enrolled from July 2011 to July 2014. All patients underwent TRUSGB. Patients with equivocal (Pi-rads 3) or suspicious lesion (Pi-rads 4-5), were additionally biopsied using two cores, by the same operator (cognitive technique).

RESULTS: Among the 168 cases, mp-MRI was equivocal for PCa (Pi-rads 3) in 46 subjects (27.4%) and suspicious (Pi-rads 4, 5) in 40 cases (23.8%). Of the 69 patients with PCa, standard TRUSGB showed Gleason ≥7 in 75% of patients with Pirads 3 and 77.8% in cases with Pirads 4-5 on mp-MRI. Among the 40 patients with Pi-rads 4-5 lesion on the MRI, cognitive mp-MRI-guided biopsy (MRCGB) detected a higher number of cases of PCa with a Gleason score equal or superior to 7 (90%) with a higher negative predictive value (97.5%) than cases with Pi-rads 3 lesion or subjects with TRUSGB alone.

CONCLUSIONS: mp-MRI followed by selective biopsy seems to be a valuable tool to improve the diagnosis of intermediate and high risk PCa compared to standard TRUSGB.

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Key words: Prostatic neoplasms - Biopsy - Magnetic resonance imaging.

Prostate cancer (PCa) is the most common male malignancy and the second cause of male cancer-related death.[1] The current approach to PCa-diagnosis involves digital rectal examination (DRE), prostate-specific antigen (PSA) testing and transrectal ultrasound-guided biopsy (TRUSGB) and has several limitations.[2] DRE is operator-dependent and mostly detects

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larger tumors located in the posterior peripheral zone of the gland. PSA is a non-specific marker; nonetheless, several large PSA screening trials have shown reduction in the risk of death from PCa,[3, 4] while others have concluded otherwise, reporting no appreciable effectiveness in reducing PCa death rate.[5] Also, the benefits of PSA-driven testing are associated with the diagnosis of many indolent tumors, for which radical treatment leads to an adverse impact on quality of life without altering survival.[6, 7] The overdiagnosis and overtreatment of PCa has caused various professional organizations to review their PSA screening guidelines, potentially reversing recent declines in disease-specific mortality.[8, 9] Another approach to minimize overtreatment would be to reduce the diagnosis of low-risk PCa tumors.[10-12] Transrectal ultrasound-guided biopsy (TRUSGB) has been the cornerstone of PCa diagnostics but is not devoid of shortcomings. Urologists use PSA followed by systematic TRUSGB, and this diagnostic pathway finds many indolent tumors. TRUSGB also causes difficulties in managing patients with high PSA values and benign biopsies. Moreover, sampling errors make some cancers requiring definitive treatment undetectable in the first TRUSGB session. Optimal management of PCa requires accurate and safe diagnosis and staging. Current imaging-based diagnostic techniques are intimately involved in PCa-diagnosis and treatment. Multiparametric prostate magnetic resonance imaging (mp-MRI), which involves T2-weighted sequences, diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) evaluation, has shown to enhance diagnostic accuracy of clinically significant prostate cancer detection.[13-15] In the past, spectroscopic imaging also showed some value in pre-biopsy e examination.[16] Nowadays, mp-MRI allows for more specific sampling methods for targeted biopsies of mp-MRI suspicious lesions using mp-MRI/TRUS fusion biopsy. Only a few studies have highlighted clearly the role of mp-MRI in men with elevated PSA without prior biopsy; still, prostate cancer could be found in up to 41% of patients who underwent mp-MRI-guided biopsy, with a diagnosis of clinically significant cancer in 87% of cases.[17] Cognitive targeting is the most widely used option for mp-MRI targeted biopsies.[18] With this approach, the physician reviews all mp-MRI images and cognitively registers the suspected lesion location onto ultrasound volume of the prostate before performing the biopsy.[18] The aim of this study was to evaluate the diagnostic efficacy of cognitive mp-MRI-guided biopsy (MRCGB) compared to standard systematic TRUSGB in biopsy-naïve patients.

Materials and methods

Men with clinical suspicion of PCa because of elevated PSA levels and/or an abnormal DRE were consecutively enrolled from July 2011 to July 2014 (Hospital Universitario Infanta Sofía, Madrid, Spain). All subjects underwent mp-MRI prostate scans at 1.5 tesla (1.5T) and TRUSGB. All mp-MRI images were scored independently by two readers (with 10 and 15 years' experience, respectively) using the validated Prostate Imaging Reporting and Data System (Pi-rads).[19] Subjects with normal MRI scans (Pi-rads 1, 2) underwent TRUSGB only, based on the Vienna Nomogram (Table I). Each equivocal (Pi-rads 3) or suspicious (Pi-rads 4-5) lesion was additionally biopsied using 2 cores. All biopsy specimens were evaluated by three qualified urogenital pathologists.

Magnetic resonance imaging technique

Before radiological examination, all patients received one 10 mg dose of scopolamine butylbromide (Buscopan®) intramuscularly to minimize intestinal peristalsis. Scans were acquired using a 1.5 T MRI (Achieva, Philips

TABLE I.—*Vienna nomogram.*

Prostate volume (mL)	Age (y)			
	<50	51-60	61-70	>70
0-30	8	8	8	6
31-40	12	10	8	6
41-50	14	12	10	8
51-60	16	14	12	10
61-70	18	16	14	12
>70	18	18	16	14

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HealthCare, Best, The Netherlands) apparatus with a surface coil. The procedure targeted prostate and seminal vesicles. Maximum gradient intensity was 80 m/m Pan (speed: 200 m/s). As per standard protocol, diffusion weighted images (DWI) were also obtained. The standard image acquisition study involves a sagittal-weighted T2 turbo spin-echo (TSE) sequence and an axial-weighted T1 gradient echo (GE) acquisition sequence, with different angles of magnetization. Diffusion-weighted images were obtained using echo-planar imaging (EPI) fast sequences. All images were exported to a computer for analysis (Intel Quad Core, 8 GB traRAM).

Biopsy technique

All patients underwent transrectal ultrasound-guided biopsy (TRUSGB) of the prostate. All were prescribed prophylactic antibiotics (ciprofloxacin 500 mg every 12 h for three days, starting the day before biopsy) and received a fleet enema 12 hours and 2 hours before the procedure. Patients were placed in either the lithotomy or fetal position, depending on preferences of individual urologists. The transducer probe was covered with a condom and placed in the rectum. Biopsies were performed under local anesthesia (10 cc of 2% mepivacaine) by any of the seven urologists in the department (>15 years' experience withg TRUSGB), using an 18-gauge automated spring-loaded biopsy gun providing 22-mm-long tissue cores and an ultrasound Siemens® probe.

All patients underwent TRUSGB and those with Pi-rads 3-4-5 were additionally biopsied by the same operator (2 cores, cognitive technique), each sample pair was placed in a cassette with spongy pad and put in a container with formalin.

To correlate the puncture area with the location of suspicious lesions on mp-MRI, a 16-section standardized Emberton diagram of the prostate was used (Figure 1).

All urologists performing the procedures were trained in MRCGB and in the use of the radiology scheme; additionally, all cases were discussed with radiologists expert in this field.

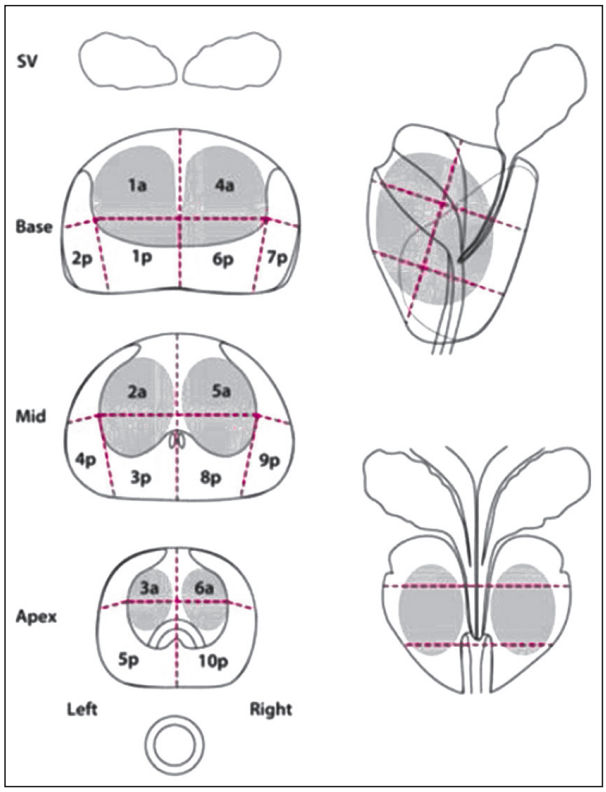

Figure 1.—Diagram of the 16 sections of the standard magnetic resonance image of the prostate, according to the outline Emerton modified, divided as follows: Basal area: anterior: 1a and 4a; posterior: 2p, 7p and 1p-6p; medial area: anterior: 2a and 5a, posterior: 4p, 3p, 8p, 9p; apical area: anterior: 3a and 6a; posterior: 5p and 10p.

Statistical analysis

Data were collected prospectively in the Access database® (Office 2013) created for this study. Analysis of variance (ANOVA) and a χ^2 Test were used for categorical and quantitative variables, respectively. Comparisons between mp-MRI and TRUSGB were based on sensitivity, specificity, negative predictive values (NPV) and positive predictive values (PPV). All tests were two-sided and the alpha risk was set at 5%. Statistical analysis was performed using IBM SPSS® Statistics (version 20).

Results

A total of 168 biopsy-naive men were enrolled in our study. The average age of patients was 61.4 years (±7.6) and total PSA average was

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8.3 ng/mL (±6.1). Average prostate volume was 48.9 mL (±6.7). mp-MRI for PCa was equivocal (Pi-rads 3) in 46 subjects (27.4%) and suspicious (Pi-rads 4, 5) in 40 subjects s (23.8%).

All MRI lesions underwent biopsy, the mean number of lesions biopsied per patient being 2.4 and 2.7 in Pi-rads 3 and Pi-rads 4-5, respectively (Table II). Of the 168 patients evaluated, 69 (41.1%) were positive for PCa. The overall cancer detection rate was 35.7%, 28.6% and 41.1% in TRUSGB, MRCGB and combination technique, respectively, whereas the clinical significant cancer detection rate was 55%, 62.5% and 59.4%, respectively (Table III).

Both in MRCGB could detect a higher percentage of clinically significant tumors than TRUSGB (88.9% *vs.* 75% and 90% *vs.* 70.8%, respectively) in both patients with Pi-rads 3 findings and those with Pi-rads 4-5 findings.

MRCGB also showed higher sensivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) than TRUSGB and had higher diagnostic performances in Pi-rads 4-5 lesions than in Pi-rads 3 lesions (Tables IV, V). No major complications were reported after the procedure.

Discussion

In our study, MRCGB had better performance than TRUSGB in terms of clinically significant cancer detection rate, sensivity, speci-

TABLE II.—*Patient demographics.*

	Total		PI-RADS 1-2		PI-RADS 3		PI-RADS 4-5		P value
	N.	%	N.	%	N.	%	N.	%	
Total: 168			82	48.8	46	27.4	40	23.8	
Age (years)									
Mean (SD)	61.4 (7.6)		62 (5.2)		60 (7.6)		63.8 (8.2)		
<60 years	65	38.7	39	47.6	22	47.8	12	30	
≥60	103	61.3	43	52.4	24	52.2	28	70	
PSA ng/mL									
Mean (SD)	8.3 (6.1)		8.7 (7.3)		8.3 (6.1)		9.4 (7.5)		0.1
0-3.9	8	4.8	3	3.6	6	13	2	5	
4-9.9	124	73.8	68	83	34	74	25	62.5	
≥10	36	21.4	11	13.4	6	13	13	32.5	
Prostate vol (mL)									
Mean (SD)	48.9 (6.7)		50.3 (5.2)		49.5 (4.7)		51.2 (3.5)		0.1
Clinical stage									
T1	137	81.5	137	72	37	80.4	31	77.5	0.1
T2	28	16.7	28	9	8	17.4	9	22.5	
T3	3	1.8	3	1	1	2.2	0	0	
MRI lesions per patient, N.									
Mean (SD)			1.8 (1.6)		2.4 (1.1)		2.7 (1.6)		

TABLE III.—*Analysis of cancer detection by transrectal ultrasound biopsy, magnetic resonance-guided biopsy, and combined modality histology.*

	TRUSGB		MRGB		*Combined	
	N.	%	N.	%	N.	%
Benign	108	64.3				
Low risk cancer (Gleason grade 3+3)	27	45	18	37.5	28	40.6
Intermediate/high risk cancer (Gleason grade)						
3+4	9		10		12	
3+5	1		7		8	
4+3	9	55	10	62.5	16	59.4
4+4	13		1		3	
4+5	1		2		2	
Cancer detection	60	35.7	48	28.6	69	41.1

*The combined histology is determined from the highest cancer risk found with either TRUSGB or MRGB.

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TABLE IV.—*Statistical Performance characteristic of transrectal ultrasound-guided biopsy and magnetic resonance-guided biopsy.*

	TRUSGB	MRCGB
Sensitivity (95% CI)	91.8 (90-95)	94.2 (92-98)
Specificity (95% CI)	65.5 (63-69)	68.1 (66-72)
Positive Predictive Value (95% CI)	52.3 (50-56)	57 (55-61)
Negative Predictive Value (95% CI)	95.1 (93-98)	96.3 (94-100)
LR +*	2.95	2.67
LR -*	0.08	0.12

*LR: likelihood ratio.

TABLE V.—*Statistical Performance characteristic of magnetic resonance-guided biopsy in subjects with PI-RADS 3 and 4-5.*

	PI-RADS 3	PI-RADS 4-5
Sensitivity (95% CI)	33.3 (14-61)	83.3 (55-95)
Specificity (95% CI)	60.7 (51.69)	72 (63-80)
Positive Predictive Value (95% CI)	8.7 (3-20)	25 (12-40)
Negative Predictive Value (95% CI)	89 (80-94)	97.5 (91-99)
LR +*	0.85	2.97

*LR: likelihood ratio.

ficity, PPV and NPV. Moreover, MRCGB had a higher clinically significant cancer detection rate than any of the combination techniques.

Our findings are consistent with literature. In fact the combination of PCa by mp-MRI and histological examination of biopsy or prostatectomy specimens has shown an excellent sensitivity in identifying malignant tumors of the prostate with a Gleason Score >7.[20-23]

The European Association of Urology (EAU) clinical guidelines place a special emphasis on TRUSGB; however, this technique alone does not appear to be sufficient for PCa detection since lesions exhibit different patterns in the TRUS grayscale. This is reflected in the low sensitivity of detection of PCa foci when using TRUSGB alone.[24]

mp-MRI is becoming the most important tool for urologists in the diagnosis, treatment and monitoring of prostate cancer,[17] helping to identify PCa foci to which transrectal ultrasound-guided biopsy should be targeted.[25] This notwithstanding, a more recent randomized prospective blinded controlled trial has shown that the overall PCa detection rate and the clinically significant cancer detection rate were similar between mp-RMI transrectal ultrasound fusion targeted biopsy and TRUSGB alone.[26]

mp-MRI is also able to identify tumors in the anterior portion of the prostate, which are not normally detected in standard prostate biopsy.[27, 28] Some multicenter studies comparing systematic prostate biopsy with mp-MRI guided biopsy have found that the latter achieves a significantly higher positivity rate in PCa diagnosis,[29-31] suggesting that mp-MRI could be improve patient management, since it helps to identify potentially malignant lesions with clinical significance without unnecessary biopsies.[32, 33] Moreover, in men with negative DRE results and PSA levels <15 ng/mL without prior biopsy, mp-MRI allows urologists to detect a greater number of clinical significant cancers than standard biopsy.[34]

According to published literature, mp-MRI guided biopsy has a detection rate comparable to that of TRUSGB using fewer specimens, suggesting that traditional TRUSGB could be replaced by 2-core mp-MRI-guided biopsy for detection of clinically significant prostate cancers.[35] Our findings are likewise encouraging, since they demonstrate a high rate of positive significant tumours in patients with Pi-rads 3 and Pi-rads 4-5 (88.9% and 90%, respectively; estimated NPV of 89% and 97.5%, respectively).

Limitations of the study

The main limitation of this study is related to the method for transposing mp-MRI images to TRUSGB, since we employed the cognitive technique, whereas other studies in literature used fusion devices. Although our findings are supported by extant literature, further confirmation is required for clinical standardization. In addition, cost-benefit studies of mp-MRI performance before biopsy have not yet been conducted.[36]

Error margins in biopsy samples should also be taken into account. mp-MRI fusion studies

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showed that in patients with high risk lesions, mp-MRI-guided biopsy consistently detects more clinically significant tumors than standard prostate biopsy.[37] Another point to be considered is that biopsies were not carried out always by the same specialist. Using a surface coil also have been a limitation, due to the overall quality of the images; however, a surface coil with 1.5T RMI did not pose any problems in other studies.[18] Finally, we used PI-rads v1, not v2, which was published when our study was already in progress. This could explain some of our results, even though, as highlighted in a recent paper, both versions are characterized by high diagnostic accuracy for detection of PCa.[38]

Despite these limitations, our study proves that: 1) mp-MRI could be a valid support for guided biopsy in patients with suspected PCa; and 2) in case of Pi-rads 4-5 lesions, the possibility of clinically significant PCa is relevant.

Conclusions

MRCGB appears to be a more valuable tool for the diagnosis of intermediate- and high-risk PCa than standard TRUSGB

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