The role of MRI/TRUS fusion biopsy in the diagnosis of clinically significant prostate cancer

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Abstract

Background: The aim of this work is to evaluate the detection rate of magnetic resonance imaging/transrectal ultrasound (MRI/TRUS) fusion-guided biopsy for clinically significant prostate cancers (Cs PCas), with particular interest in biopsy-naive patients and patients in active surveillance. MRI-targeted biopsy improves cancer detection rate (DR) in patients with prior negative biopsies; the current literature focuses on biopsy naive patients. We also evaluated the pathologic concordance between biopsies and surgical specimens.

Methods: MRI/TRUS fusion-guided biopsies were performed between February 2016 and February 2019. Patients with previous negative biopsies, biopsy-naive or in active surveillance (AS) were included. Cs PCas were defined through Epstein's criteria.

Results: A total of 416 men were enrolled. The overall DRs and Cs PCa DRs were 49% and 34.3%, respectively. Cs PCas were 17.2%, 44.9% and 73.4%, respectively for PI-RADS 3, 4 or 5. Among biopsy-naive patients, 34.8% were found to have a Cs PCa, while a 43.6% tumour upgrading was achieved in men with a low risk of PCa. In patients who underwent radical prostatectomy (RP), the concordance between biopsy Gleason score (GS) (bGS) and pathological GS (pGS) was 90.8%.

Conclusion: Our study highlights the role of MRI/TRUS fusion prostate biopsy in the detection of PCa in patients with previous negative biopsies focusing on Cs PCa diagnosis. The MRI/TRUS fusion biopsy is also emerging as a diagnostic tool in biopsy-naïve patients and deserves a fundamental role in AS protocols. A greater concordance between bGS and pGS can be achieved with targeted biopsies.

Keywords: fusion biopsy, multiparametric MRI, PIRADS, prostate cancer

Introduction

The transrectal ultrasound (TRUS)-guided biopsy is still considered the gold standard for the diagnosis of prostate cancer in men with an elevation of the serum prostate-specific antigen (PSA) level and/or suspect digital rectal examination (DRE).[1,2] The cancer detection rate (DR) for this technique in the literature ranges between 33% and 57%.[1] A significant underdetection of Cs PCas has been described for standard biopsy; missing 50–80% of cases.[1,2] The best approach to patients with a persistent clinical suspicion of prostate cancer after a prior negative biopsy still represents a matter of debate for urologists. Multiparametric magnetic resonance imaging (mp-MRI) nowadays plays an increasingly important role in these patients.[1–3] According to the 2019 European Association of Urology (EAU) guidelines, an mp-MRI evaluation should be recommended in all patients with clinical suspicion of prostate cancer regardless of previous negative systematic biopsy.[4] The MRI-targeted biopsy should be performed for findings with a Prostate Imaging Reporting and Data System (PI-RADS)

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score ≥3.[4,5] Several studies report how an MRI-targeted biopsy approach improves the cancer DR over 12-core random biopsies, and strongly reduces the number of clinically insignificant prostate cancers diagnosed. There are currently three techniques for the MRI-targeted biopsy: cognitive registration, software-assisted fusion registration and in-bore biopsy.[6,7,8] With the software-assisted fusion registration, also known as MRI/TRUS fusion-guided biopsy, the prostate and suspicious lesions are contoured on mp-MRI images. The MRI images are then fused with real-time ultrasound images, so that the TRUS probe can be used to guide the needle.[7,9] Several different fusion platforms, registered by the Food and Drug Administration (FDA), are currently available. Greater precision and lower operator-dependence represent some of the main advantages of this technique.[7,9] The best MRI-targeted biopsy technique is still a matter of debate in the literature. However, some authors have concluded that the MRI/TRUS fusion-guided biopsy is much more accurate and cost-effective than visual registration and in-bore biopsy.[10,11] The aim of our study is to evaluate the role of the MRI/TRUS fusion biopsy in the diagnosis of clinically significant prostate cancer, stratifying the DR for PI-RADS score. The study also focuses on the DR of clinically significant prostate cancers (Cs PCas) in biopsy-naive patients and in patients in active surveillance (AS) protocols. In addition, we evaluated the concordance of the pathological results achieved with radical prostatectomy (RP) and targeted biopsy. We also performed an analysis of literature data for the biopsy systems currently available in order to provide a general overview (Table 1).

Materials and methods

We retrospectively evaluated all patients who underwent the MRI/TRUS fusion biopsy in our institution between February 2016 and February 2019. The criteria for submitting patients to mp-MRI were those suggested by the EAU guidelines.[4] All patients with at least one PI-RADS 3 or higher lesion were enrolled in our study and underwent targeted biopsy of the lesions. Biopsies were performed using the BioJet system (DK Technologies). The procedure is performed in an outpatient setting under local anaesthesia with transperineal approach. Patients were required to have oral antibiotic prophylaxis with ciprofloxacin (500 mg). At least three biopsy cores from each lesion were taken. In addition, a systematic 12-core biopsy was performed in biopsy-naive patients, patients in AS and patients with a prior negative biopsy performed more than 6 months before. Cs PCas were defined through the Epstein's criteria [Gleason score (GS) ≥ 7, >2 positive cores, PSA density >0.15 and bilateral cancer].[27] Clinical and pathological data of patients enrolled in our trial have been reported, including age, serum PSA level and free/total (F/T) PSA ratio, biopsy history, location of lesion(s), lesion(s) size, PI-RADS score, number of biopsy cores and histological results of each lesion. A lesion-based analysis was performed to define overall and stratified by PI-RADS score detection rates. Finally, the anatomopathological results of patients who underwent subsequent RP have been reported to evaluate the concordance between biopsies and surgical specimens.

Results

A total of 416 patients were enrolled during the study period. The median age was 65.5 ± 6.85 years (range 52–83) and the median PSA was 8.3 ± 2.9 ng/ml.

Of the 416 patients, 236 (56.7%) had a previous negative systematic biopsy, 108 (26%) underwent their first biopsy, 39 (9.4%) had a previous atypical small acinar proliferation (ASAP) or high grade prostatic intraepithelial neoplasia (HG-PIN) diagnosis, whereas 33 (7.9%) had a low-risk prostate cancer on AS. In total, 510 prostate lesions were biopsied. Most of the patients 336 (81.3%) included in our study had only one region of interest (ROI), 62 patients (14.9%) had two targets and only 16 (3.8%) had three suspicious lesions detected through mp-MRI. According to the mp-MRI results, the median lesion diameter was 11.8 ± 4.2 mm. The distribution of the PI-RADS score was: 261 lesions (51.2%) PI-RADS 3, 185 (36.3%) PI-RADS 4 and 64 (12.5%) PI-RADS 5. For each patient, a median of 6.3 ± 4.5 overall biopsy cores and 5.5 ± 2.2 targeted biopsy cores was taken. The patients' characteristics are detailed in Table 2. The overall DR was 49% (250/510 lesions). Cs PCa, as defined by Epstein's criteria, was diagnosed in 34.3% of the cases (175/510 lesions). Furthermore, we evaluated the relationship between the PI-RADS score and the DR of the fusion biopsy. The overall PI-RADS 3 DR was 33.7% (88 lesions), the PI-RADS 4 DR was 58.4% (108 lesions), whereas in patients with PI-RADS 5 the PCa was detected in 84.4% of the cases (54 lesions).

Table 1. Most significant characteristics and results of the published studies about MRI/TRUS fusion-guided biopsy.

Study	Fusion platform	Definition for Cs PCa	Sample size, n	Overall DR	DR Cs PCa	DR PI-RADS 3 (Cs PCa)	DR PI-RADS 4 (Cs PCa)	DR PI-RADS 5 (Cs PCa)
Rastinehad *et al.*[12]	UroNav	Epstein criteria	105	50.5%	44.8%	NR	NR	NR
Wysock *et al.*[13]	Artemis	GS ⩾3+4	125	32%	20.3%	NR	NR	NR
Sonn *et al.*[7]	Artemis	Cancer core length ⩾4 mm or GS ⩾3+4	105	34%	25%	NR	NR	NR
Shoji *et al.*[14]	BioJet	Cancer core length ⩾4 mm or GS ⩾3+4	20	31.8%	NR	13.3%	33.3%	88.9%
Junker *et al.*[15]	Logiq 9	NR	50	46%	NR	28.6%	54.3%	100%
Borkowetz *et al.*[16]	BioJet	Epstein criteria	263	44.1%	35.7%	24.2%	41.6%	
Mozer *et al.*[17]	UroStation	Cancer core length ⩾4 mm or GS ⩾3+4	152	53.9%	43.4%	NR	NR	NR
Siddiqui *et al.*[2]	UroNav	NR	1003	46%	37.5%	NR	NR	NR
Oberlin *et al.*[9]	NR	GS ⩾3+4	81	48.1%	28.6%	NR	NR	NR
Cash *et al.*[18]	Aplio 500, HiVision Preirus	Cancer core length ⩾4 mm or GS ⩾3+4	408	56%	NR	26% (16.8%)	62% (46.1%)	89% (84.7%)
Filson *et al.*[19]	Artemis	GS ⩾3+4	1042	43.6%	27.8%	NR (16%)	NR (33%)	NR (69%)
Borkowetz *et al.*[20]	BioJet	GS ⩾3+4	625	43%	34%	20% (12%)	33% (27%)	70% (61%)
Tan *et al.*[21]	UroNav	GS ⩾3+4	115	35.7%	30.4%	21.4% (15.7%)	52.9% (47.1%)	72.7% (72.7%)
Hansen *et al.*[22]	Biopsee	GS ⩾3+4	487	51.1%	30.6%	43.7% (19.5%)	58% (32%)	(82.6%) (70.4%)
Osses *et al.*[23]	NR	GS ⩾3+4	664	64.5%	40.6%	10.3% (3.5%)	77.3% (45.2%)	88.9% (66.7%)
Boesen *et al.*[5]	HI-RVS-system	Epstein criteria	206	33.8%	26.4%	22.2%	62.7%	94.1%
Porpiglia *et al.*[24]	BioJet	Epstein criteria	212	60.5%	56.8%	12.5% (12.5%)	80% (75%)	87.5% (81.3%)
Hofbauer *et al.*[25]	Aplio i900, HiVision Preirus	GS ⩾3+4	704	63%	45%	39% (23%)	72% (49%)	91% (77%)
Kasivisvanathan *et al.*[3]	BioJet, UroNav, UroStation, Esaote, Aplio 500, Artemis, BiopSee	GS ⩾3+4	252	47%	38%	34% (12%)	69% (60%)	94% (83%)
Pepe *et al.*[26]	Logiq E9, Arietta 70	Epstein criteria	NR	72%	61.3%	NR	48.4% (44%)	
Our results	BioJet	Epstein criteria	510	49%	34.3%	33.7% (17.2%)	58.4% (44.9%)	84.4% (73.4%)

Cs PCa, clinically significant prostate cancer; DR, detection rate; GS, Gleason score; MRI/TRUS, magnetic resonance imaging/transrectal ultrasound; NCCN, National Comprehensive Cancer Network; NR, not reported; PI-RADS, prostate imaging reporting and data system.

Table 2. Clinical characteristics of patients and lesions.

Parameter	Value
Age (years), median ± SD (min; max)	65.5 ± 6.85 (52; 83)
PSA (ng/ml), median ± SD	8.3 ± 2.9
Repeat biopsy, *n* (%)	308 (74%)
Prior negative biopsy, *n*	236
Prior diagnosis of ASAP or HG-PIN, *n*	39
On active surveillance, *n*	33
First biopsy, *n* (%)	108 (26%)
Total number of targeted lesions, *n* (%)	510 (100%)
PI-RADS 3, *n* (%)	261 (51.2%)
PI-RADS 4, *n* (%)	185 (36.3%)
PI-RADS 5, *n* (%)	64 (12.5%)
Maximum diameter of lesions (mm), median ± SD	11.8 ± 4.2
Overall biopsy cores, median ± SD	6.3 ± 4.5
Targeted biopsy cores, median ± SD	5.5 ± 2.2

ASAP, atypical small acinar proliferation; HG-PIN, *high-grade* prostatic intraepithelial neoplasia; PI-RADS, prostate imaging reporting and data system; PSA, prostate-specific antigen; SD, standard deviation.

Cs PCas were found to be 17.2% (45 cases), 44.9% (83 cases) and 73.4% (47 cases), respectively, for PI-RADS 3, 4 or 5. For each PI-RADS score, the overall and Cs PCa detection rates are described in Table 3. The GS distribution of prostate cancer was as follows: 54.4% (136/250) were classified as GS 3+3, 16.4% (41/250) as 3+4, 13.2% (33/250) as 4+3, 9.6% (24/250) as 4+4, 4% (10/250) as 4+5 and 2.4% (6/250) as 5+4. The relationship between the GS and the PI-RADS classification is shown in Table 3.

In addition, an analysis of the 108 patients with no history of prior biopsy was carried out. The overall DR in biopsy-naïve patients was 54.1% (73/135 lesions), while 34.8% (47/135 lesions) showed evidence of clinically significant PCas. If only a systematic biopsy was performed, 36 cases (49.3%) of prostate cancer would have been missed. The targeted biopsy missed only seven PCa (9.6%), all classified as GS 3+3.

The overall and significant PCa DR in patients undergoing their first biopsy are described in Table 4. A total of 33 patients in AS protocol were enrolled. PCa was detected in 76.9% of cases (30/39 lesions). Of the 30 cancer cases, 12 (40%) were diagnosed by both systematic and fusion biopsy. The standard 12-core approach missed 14 prostate cancers (46.7%), whereas targeted biopsy missed only 4 PCa (13.3%). In patients in the AS cohort, our data show that an mp-MRI evaluation and a subsequent MRI-targeted biopsy result in a 43.6% (17/39 lesions) tumour upgrading from low-risk indolent disease to significant PCa, needing an active treatment. A laparoscopic RP was performed in 98 patients with diagnosis of clinically significant prostate cancer. From the RP specimen analysis, it results that tumour was confined within the prostate (pT2) in 43.9% (43) of patients, whereas 56.1% (55) of patients had locally advanced disease. Among these, 15 patients had positive lymph nodes (pN1). The pathological GS distribution was as follows: 31.6% (31/98) of the cases were classified as 3+3, 18.4% (18/98) as 3+4, 23.5% (23/98) as 4+3, 18.4% (18/98) as 4+4, 6.1% (6/98) as 4+5 and 2% (2/98) as 5+4. The anatomopathological results of surgical specimens revealed that 89 patients had the same GS as revealed by MRI/TRUS fusion-guided biopsy. The concordance between biopsy GS (bGS) and pathological (pGS) was therefore 90.8%. In four patients, the cancer was upgraded on final pathology (in one case from 3+3 to 3+4 and in three cases from 3+4 to 4+3), and in five cases cancer was downgraded (in three cases from 3+4 to 3+3 and in two cases from 4+3 to 3+4).

Discussion
TRUS-guided biopsy has been considered for many years as the gold standard in the diagnosis of PCa, but it is known that this approach may result in a high risk of false-negative results and is affected by a low DR of clinically significant PCa. The procedure is also related to complications such as infections, sepsis and bleeding that could prolong hospitalisation and increase healthcare costs. The introduction of mp-MRI for the detection of suspicious lesions has nowadays revolutionised the way in which PCa is managed. With

Table 3. Detection rates related to PI-RADS score and pathologic results.

PI-RADS score	Total lesions, *n* (%)	All PCa, *n* (%)	Cs PCa, *n* (%)
3	261 (51.2%)	88 (33.7%)	45 (17.2%)
4	185 (36.3%)	108 (58.4%)	83 (44.9%)
5	64 (12.5%)	54 (84.4%)	47 (73.4%)
Overall	510 (100%)	250 (49%)	175 (34.3%)
PI-RADS score	**GS 3+3**	**GS 3+4**	**GS 4+3**
3	73	11	4
4	50	23	19
5	13	7	10
Overall, *n*° (%)	136 (54.4%)	41 (16.4%)	33 (13.2%)

Cs PCa, clinically significant prostate cancer; GS, Gleason score; PCa, prostate cancer; PI-RADS, prostate imaging reporting and data system.

Table 4. Overall and Cs PCa detection rates, related to PI-RADS score, in biopsy-naïve patients and in patients on AS.

	PI-RADS score	Total lesions, *n*° (%)	No cancer detected, *n*° (%)	All PCa, *n*° (%)			Cs PCa, *n*° (%)
				TBx + SBx	TBx	SBx	
Biopsy-naïve patients	3	69 (51.1%)	44 (63.8%)	9	13	3	11 (15.9%)
	4	50 (37%)	17 (34%)	14	15	4	23 (46%)
	5	16 (11.9%)	1 (6.2%)	7	8	–	13 (81.2%)
	Overall, *n*° (%)	135 (100%)	62 (45.9%)	73 (54.1%)			47 (34.8%)
Patients on active surveillance	3	15 (38.5%)	5 (33.3%)	4	4	2	3 (20%)
	4	19 (48.7%)	4 (21%)	6	8	1	10 (52.6%)
	5	5 (12.8%)	–	2	2	1	4 (80%)
	Overall, *n*° (%)	39 (100%)	9 (23.1%)	30 (76.9%)			17 (43.6%)

AS, active surveillance; Cs PCa, clinically significant prostate cancer; PCa, prostate cancer; PI-RADS, prostate imaging reporting and data system; SBx, standard biopsy; TBx, targeted biopsy.

a transperineal approach, which reduces sepsis risk and leads to a better approach to the anterior zone, we obtained an overall DR for PCa of 49% and a Cs PCa DR of 34.3%; values comparable with the current available literature.[2,4,16,19,20,23] Borkowetz *et al.*, adopting the same system, reported an overall and Cs PCa DR of 43% and 34%, respectively.[20] In another study involving 487 patients with a previous negative biopsy, Hansen *et al.* showed a DR of 51.1% and 30.6%, respectively, for PCa and Cs PCa.[22] The MRI/TRUS fusion biopsy can overcome the main limitations of TRUS-guided random biopsy. When compared with random biopsy, targeted biopsy increases the DR of CS PCas, particularly if the anatomical location of cancer is in the transition zone or in the anterior fibromuscular stroma. MRI/TRUS fusion biopsy also reduces

the detection of clinically insignificant cancers, therefore preventing overtreatment.[4,5,16,23] The diagnostic accuracy of the MRI and subsequent fusion biopsy does not allow the prostate standard biopsy to be avoided: if the targeted and systematic biopsies are used in conjunction, they enable the detection of a greater number of PCa cases.[19] This is why the EAU guidelines recommend that both systematic and targeted cores are performed.[4]

Our study confirms that the likelihood of diagnosing Cs PCas correlates with the PI-RADS score. A Cs PCa DR of 17.2%, 44.9% and 73.4% for PI-RADS 3, 4 and 5 lesions, respectively, has been achieved. This is in line with data recently published in literature, according to which the most significant predictive factor for the diagnosis of PCas through targeted biopsy is the ROI grade.[4,5,18–20,25] In the analysis performed by Cash *et al.* on 408 patients with prior negative biopsies, the Cs PCa detection rate was 16.8%, 46.1% and 84.7%, respectively, for PI-RADS score 3, 4 and 5.[18] Based on the data above, the EAU guidelines strongly recommend the use of mp-MRI in men with previously negative biopsies and persistent clinical suspicion of cancer.[4]

The role of mp-MRI in the diagnostic pathway of patients with no history of prior biopsy is still a matter of debate for urologists. Recent studies support the excellent performance of the mp-MRI and subsequent targeted biopsy in the detection of PCa in biopsy-naïve patients, when compared with TRUS-guided biopsy.[17,24,28,29] A clinical trial, recently performed on 212 biopsy-naïve patients, shows that the TRUS-guided biopsy provides a lower DR for both PCas (29.5% *versus* 50.5%) and Cs PCas (18.1% *versus* 43.9%).[29] The results of our study indicate that biopsy-naïve patients benefit from the use of mp-MRI as a preliminary test, with a DR of 54.1% for any cancer and 34.8% for Cs PCas. Moreover, 49.3% of the total number of prostate cancers would not have been detected through a standard systematic biopsy.

Although further confirmation is required, this data appears to confirm the potential role of mp-MRI as the primary diagnostic tool in naïve patients. A critical issue to consider when evaluating the implementation of the mp-MRI in biopsy-naïve patients is related to the economic resources that would be required if the MRI were used as the first step in patients with clinical suspicious of PCa. Nevertheless, recent analyses have shown that the mp-MRI for the initial detection of PCa appears to be cost-effective in comparison with repeated standard biopsy procedures.[17,24]

The mp-MRI is currently emerging as a significant diagnostic tool also in patients with a localised and low-risk prostate cancer on AS protocol (clinical T1c or T2a, PSA < 10 ng/ml, fewer than 2–3 positive cores with <50% cancer involvement of every positive core, GS 3+3). We regularly propose mp-MRI to these patients. In our study, the combined biopsy approach resulted in a rate of tumour upgrading of 43.6% from a low-risk disease to a significant PCa. A considerable number of upgraded cancers (9/17 lesions) were detected only by targeted cores. This result confirms recently published data.[30,31] In a review involving more than 1000 patients, Schoots *et al.* show that the combined biopsy approach of targeted and standard biopsies resulted in a 35% cancer upgrading.[30] According to the recently published EAU position paper, mp-MRI plays a significant role both at the time of initial diagnosis, in order to rule out significant PCas that were missed by the initial biopsy, and before the confirmatory biopsy. Therefore, MRI-targeted biopsy should be included in AS protocols in addition to systematic biopsy to minimise the risk of underestimating the extent and aggressiveness of prostate cancers.

Finally, prior to the introduction of MRI/TRUS fusion biopsy, a strong concordance between bGS and pGS could not be achieved. The present study demonstrated a good performance of the MRI/TRUS fusion biopsy in predicting pGS, therefore minimizing the risk of cancer up- or down-grading. For 90.8% of patients, the anatomopathological results of RP specimens agreed with those of targeted biopsy cores. The rate of underestimation and overestimation achieved was 4.1% and 5.1%, respectively. Similar results were obtained by Porpiglia *et al.*, according to which bGS and pGS concordance was 91.5%. GS up-grading and down-grading was 7.8% and 0.8% respectively, significantly lower than the rates achieved with the standard biopsy (39.3% and 6.8% respectively).[12]

Our study has some limitations: it was conducted in a single institution, without a single dedicated pathologist (DL) blinded to clinical information, prior interpretation and matched specimens.

In conclusion, we highlight the role of MRI/TRUS fusion prostate biopsy in the detection of clinically significant PCa in patients with previous negative biopsies, and confirm the increasing likelihood of diagnosing Cs PCa with the increasing of PI-RADS score. Although further studies are necessary, the MRI/TRUS fusion biopsy is emerging as a significant diagnostic tool in biopsy-naïve patients according to our results; we also believe this technique deserves an increasingly fundamental role in AS protocols. Moreover, a greater concordance between bGS and pGS can be achieved with targeted biopsies.

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