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MRI-TRUS fusion guided prostate biopsy – initial experience and assessment of the role of contralateral lobe systematic biopsy

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Abstract

Aims: To present our initial experience and results of MRI-TRUS fusion guided prostate biopsy and assess the role of contralateral lobe systematic biopsy. **Material and method:** A number of 119 patients with clinical or biochemical suspicion for prostate cancer (PCa) were included. All patients harbored at least one PIRADS score ≥ 3 lesion and underwent MRI-TRUS fusion guided biopsy, as well as a concurrent systematic biopsy. The biopsy was performed by the same operator, using a rigid registration software system. **Results:** The mean age of the patients was 62.2 years. The mean pre-biopsy PSA was 9.15 ng/dl. The diagnosis rate of MRI-TRUS fusion guided biopsy was 47% for overall PCa and 29.4% for clinically significant (cs) PCa. A higher PIRADS score was significantly associated with the presence of overall and csPCa. MRI-TRUS fusion guided biopsy had a higher percentage of positive biopsy cores (51% vs 29%), higher likelihood of csPCa (OR 5.36, p=0.008) and upgrading (14.8%) in comparison with systematic biopsy but missed 6.7% csPCa. The contralateral lobe systematic biopsy could have been avoided without losing the PCa diagnosis all patients with PIRADS score 5, both in initial and repeat biopsy setting. Anterior and transitional lesions were more likely to be diagnosed only by targeted cores. **Conclusion:** MRI-TRUS guided prostate biopsy improves the detection of PCa, but systematic biopsy is still essential. In selected cases (PIRADS 5), contralateral lobe systematic biopsy can safely be avoided. Pre-biopsy mpMRI might reduce the number of biopsy sessions in patients with anterior and transitional lesions.

Keywords: image-guided biopsy; magnetic resonance imaging; prostate cancer

Introduction

The prostate is one of the few organs for which, in cases where the presence of cancer is suspected, the biopsy is done in a nearly blind manner [1]. The systematic biopsy is performed according to the recommendations of the European Association of Urology (EAU) Guidelines [2], with transrectal ultrasound (TRUS) guidance, either by transrectal or transperineal approach. A number of 10-12 biopsy cores are usually obtained using a predefined scheme to sample the whole gland [2].

TRUS allows for prostate and zonal anatomy identification and biopsy guidance towards the peripheral area but has a low accuracy for the diagnosis of prostate cancer (PCa), due its heterogenous appearance [3,4]. Less than half of the lesions visible on TRUS are confirmed as malignant at pathological assessment [5]. Therefore,

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the systematic TRUS-guided prostate biopsy associates a high rate of underdiagnosis of aggressive PCa, but also overdiagnosis of indolent PCa [6].

As a result, multiparametric magnetic resonance imaging (mpMRI) has become the new standard imaging evaluation for the initial diagnosis of PCa [7], ensuring a detection rate as high as 93% for Gleason score >7 PCa [8], albeit for the time being the EAU Guidelines recommend its use only in the setting of a prior negative prostate biopsy and persistent suspicion of PCa [2].

Due to the possibility of the identification of PCa, mpMRI is an important tool for performing targeted biopsies from visible abnormal areas inside the prostate. Three techniques have been developed in order to assist a targeted prostate biopsy [9]: cognitive, in-bore and MRI-TRUS fusion guided. Cognitive MRI-guided biopsy involves that the operator mentally superimposes the lesion seen on mpMRI onto the ultrasound examination, whereas in-bore guided biopsy allows for exact needle positioning and biopsy inside the MRI gantry during sequential scans. The MRI-TRUS fusion guided biopsy employs a software which overlaps the contouring of the lesion from the MRI images onto the ultrasound in real-time, thus allowing a targeted biopsy [10].

Recently published, the results of the PRECISION trial demonstrate the superiority of MRI-targeted biopsy in comparison with standard TRUS-guided for the diagnosis of clinically significant (cs)PCa (38% vs 26%, respectively, p=0.005) even in the setting of first biopsy [11]. Moreover, in-bore guided prostate biopsy has shown a superior PCa detection rate in comparison with cognitive biopsy, but a similar diagnostic yield with MRI-TRUS fusion guided biopsy [12]. Current literature does not show a clear superiority of one technique over the other [2]. The long duration and high costs of procedure, but also the need for magnetic field compatible devices hamper the use of in-bore MRI guided biopsy [13]. On the other hand, MRI-TRUS fusion guided prostate biopsy combines the advantages of TRUS and MRI, by ensuring increased patient comfort, lower costs, as well as real-time lesion visualization and guidance of the biopsy [14].

Given the high accuracy of mpMRI and MRI-TRUS fusion guided prostate biopsy for the detection of csPCa, the importance of concurrent systematic biopsy has been questioned, as it may increase the diagnosis rate of indolent PCa, as well as the morbidity of the procedure [15].

The objective of the current study was to present our initial experience and results of MRI-TRUS fusion guided prostate biopsy. A secondary objective of our study was to assess the role of concurrent contralateral lobe systematic biopsy.

Material and methods

We conducted a prospective cohort study in which we included a number of 119 patients who presented to our department for the clinical or biochemical suspicion of PCa and harbored at least a Prostate Imaging Reporting and Data System (PIRADS) score ≥3 lesion seen on pre-biopsy mpMRI. The criteria for the indication of mpMRI prior to first biopsy were as follows: patients age below 70 years and PSA below 15 ng/ml. For patients in repeat biopsy setting no maximum cut-off value was used for age or PSA in order to select the patients who underwent MRI prior to targeted biopsy, as these patients have a clear indication for imaging assessment according to the EAU Guidelines [2].

The mpMRI were performed using a 1.5T system (MAGNETOM Aera®; Siemens Healthcare, Erlangen, Germany) coupled with a 16-channel phased-array body coil (Siemens Healthcare). On the evening prior to the examination the patients self-administered a bowel preparation solution (FORTRANS®, 1 liter reconstituted solution for each 20 kg of body mass). Prior to the MRI examination, drotaverin was administered i.v. (No-Spa, 40 mg/2ml). The following non-contrast sequences were acquired: axial T2WI, sagittal T2WI, coronal T2WI, axial T1WI, axial diffusion-weighted imaging (DWI), (Table I). An unenhanced axial T1 VIBE sequence acquisition was performed and was followed by additional axial T1 VIBE scans after contrast administration. Diffusion-weighted MRI was performed with measured b values of 50, 400, 800, 1000, 1500 and the image software automatically calculated apparent diffusion coefficient maps (ADC). Afterwards, the contrast agent gadobutrol (Gadovist® 1.0; Bayer Schering Pharma AG, Berlin, Germany) was administered employing the free-hand technique, using a dose of 0.1 mmol/kg−1. Dynamic contrast enhanced axial 3D T1WI were immediately acquired after contrast administration. The MRI studies were reviewed by 2 experienced radiologists (more than 5 years of experience) using the PIRADS v2 system and the corresponding anatomic division diagram to illustrate the location of the lesion [16]. The radiologists were aware of the clinical information of all patients.

The MRI-TRUS fusion guided biopsy was performed by the same operator (urologist) in an outpatient setting, using local anaesthesia with lidocaine gel instilled endorectally, by transrectal approach, with the patient positioned in left lateral decubitus. Prior to this study, the urologist had performed 30 MRI-TRUS fusion guided prostate biopsies and more than 150 TRUS-guided systematic biopsies. All biopsies were performed using the Arietta 70a system (Hitachi, Japan) with endfire endorec-

Table I. Multiparametric MRI examination specifications

Pulse sequence	Plane	TR (ms)	TE (ms)	Flip angle (degrees)	Slice thickness (mm)	Matrix size	Field of view (mm)	Time
T2 TSE	Sagittal	4960	73	161	3	256x320	220	3m5s
T2 TSE	Coronal	7430	108	160	3	298x320	200	4m36s
T2 TSE	Axial	4330	84	156	3	266x320	200	4m56s
T1 TSE	Axial	587	22	177	3	266x320	200	3m6s
DWI	Axial	4700	77		3	112x112	200	6m41s
T1 VIBE fat sat	Axial	4.46	1.72	12	3	154x192	260	8s precontrast acquisition and 3m22s postcontrast evaluation

TR = repetition time; TE = echo time; TSE = turbo-spin echo; DWI = diffusion weighted imaging; VIBE = spoiled 3D generic gradient echo; ms = miliseconds

tal probe C41V1 2-10 mHz, RVS software and rigid registration, using sagittal and axial T2WImpMRI sequences. The biopsy was performed in the sagittal TRUS plane (fig 1). A number of 1-3 biopsies/lesion along with 12 systematic cores were obtained in all patients. The suspicious areas were biopsied at the beginning of the procedure in order to avoid errors of registration due to prostate swelling. The systematic biopsy was performed by the same operator as MRI-TRUS fusion biopsy, being aware of the MRI results. All biopsies were reviewed by the same 2 experienced pathologists. Any prostate cancer with a Gleason score ≥7(3+4)/ ISUP (International Society of Urological Pathology) grade 2 was considered a clinically significant disease.

All patients signed the informed consent according to the World Medical Association Declaration of Helsinki, revised in 2000. The study was approved by the local Ethical Committee.

Statistical analysis

The statistical analysis was performed using Medcalc v.12.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org). The difference between two means was analyzed by the Independent Sample T-test. Chi-square test was used for the correlation between categorical variables, and ANOVA for the correlation between categorical and continuous variables. The diagnostic accuracy was assessed by Receiver Operating Curve (ROC) analysis and expressed using sensitivity (Se), specificity (Sp) and area under the curve (AUC). $p<0.05$ was considered statistically significant.

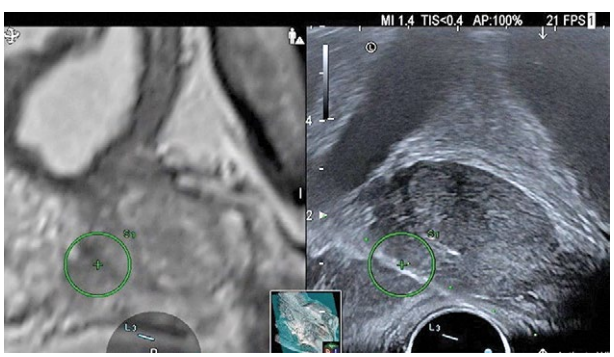

Fig 1. A 60-year-old patient with a PSA of 5.8 ng/ml and a PIRADS score 3 lesion at the base of the right prostate lobe. An MRI-TRUS fusion biopsy was performed and confirmed the diagnosis of PCa Gleason score 7(3+4), with 1/2 and 4/12 positive targeted and systematic cores, respectively.

Results

Study group

The mean age of the patients was 62.2 years (range: 46-78 years) and the mean pre-biopsy PSA was 9.15 ng/dl (range: 1.8-70 ng/dl). Fourteen patients (16.8%) had a history of at least one negative prostate biopsy. Twenty-nine (24.3%) patients had multiple lesions (≥2) on mpMRI. The mean number of total biopsy cores was 14 (range: 13-16) and the mean number of targeted cores was 2 (range: 1-4).

Characteristics of PCa patients

Prostate cancer was diagnosed in 47% of cases (55 patients) whereas atypical small acinar proliferation/ high-grade intraepithelial neoplasia (ASAP/HGPIN) were present in 6.8% of patients. Clinically significant disease was identified in 29.4% of all patients included in the study.

The presence of multiple lesions on MRI was not correlated with a higher rate of overall or csPCa diagnosis ($p=0.7$ and $p=0.4$, respectively).

The PIRADS score was significantly associated with the presence of PCa, $p<0.0001$, with an AUC of 0.805 (95% CI: 0.71 – 0.87, $p<0.01$) for the detection of overall PCa in lesions with PIRADS score 4 and 5. If PIRADS 4 would have been used as a cut-off for selecting patients for biopsy, in 29 cases a prostate biopsy could have been avoided ($p<0.0001$).

Clinically significant disease was present in 35 (64.8%) of the patients diagnosed with PCa and was cor-

related with a higher PIRADS score, p=0.02 (Table II). The presence of a PIRADS score 5 lesion had a Se of 57.14%, Sp 90.5% and AUC of 0.738 (95% CI: 0.64-0.81) for the presence of csPCa, p<0.0001.

MRI-TRUS fusion guided vs systematic prostate biopsy

Of the patients with PCa (n=55), 35.8% were diagnosed only on systematic cores, 7.5% only on MRI-TRUS fusion guided biopsy cores, whereas 56.6% had both systematic and targeted positive cores.

The presence of an anterior or transitional zone lesion was significantly correlated with PCa diagnosis only on targeted biopsy cores in all patients (p=0.02).

Patients in the repeat biopsy setting showed a higher percentage of lesions located in the anterior and transitional areas in comparison with patients at initial biopsy and a higher exclusive diagnosis yield by MRI-TRUS fusion biopsy (25% vs 4.4%, Table III).

The overall percentage of positive biopsy cores (PBC) of the total number, systematic and targeted cores was 32%, 29% and 51%, respectively (p=0.0012).

More than half of the patients (57.9%, n=19) diagnosed only on systematic cores harbored clinically insignificant PCa, as well as 4 patients diagnosed exclusively on MRI-TRUS fusion biopsy cores. Performing concurrent systematic biopsy led to an absolute difference of 12.1% more clinically insignificant PCa patients diagnosed in comparison with MRI-TRUS fusion guided prostate biopsy (32.7% vs 20.6%).

A csPCa was 5 times more likely to be diagnosed by MRI-TRUS fusion guided biopsy cores than systematic biopsy (OR 5.36, p=0.008) (Table IV). In 14.8% of cases (n=55) an upgrading to a higher Gleason score was found by MRI-TRUS fusion guided cores, in comparison with 11.1% by systematic biopsies. A number of 8/119 patients (6.7%) harbored csPCa but had negative MRI-TRUS

Table II. Diagnostic yield of MRI-TRUS fusion biopsy for overall and clinically significant prostate cancer depending on PIRADS score

	PCa patients/all patients with the same PIRADS score x 100	**csPCa patients/all patients with the same PIRADS score x 100**	**NPV for csPCa**
PIRADS 3	17.1	5.7	55.4
PIRADS 4	52.2	27.7	64.5
PIRADS 5	92.6	74.1	81.7

All results are expressed in percentages. cs = clinically significant; PCa = prostate cancer; PIRADS = prostate imaging reporting and data system; NPV = negative predictive value

Table III. Comparison of prostate cancer diagnosis rates between initial and repeat biopsy setting

		Initial biopsy setting	**Repeat biopsy setting**	**p**
PIRADS score	3	33.3	26.3	
	4	41.1	52.6	0.6
	5	25.6	21.1	
mpMRI lesion location	Base	15.9	25	0.09
	Midgland	49.2	33.3	
	Apex	19	0	
	Transitional	12.7	25	
	Anterior	3.2	16.7	
Overall PCa diagnosis rate		48.5	40	0.6
csPCa diagnosis rate		30	25	0.6
PCa diagnosis only on targeted cores		4.4	25	**0.04**
PCa diagnosis only on systematic cores		35.6	37.5	0.9
PCa diagnosis both on systematic and targeted cores		60	37.5	0.2
ISUP grade	1	34.8	37.5	0.6
	2	47.8	37.5	
	3	13	12.5	
	4	2.2	12.5	
	5	2.2	-	
Percentage of patients in whom the contralateral lobe biopsy did not change the management		93.5	83.3	0.4

All results are expressed in percentages. cs = clinically significant; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; ISUP = International Society of Urological Pathology; PIRADS = prostate imaging reporting and data system

Table IV. Diagnostic yield of MRI-TRUS fusion and systematic biopsy with regards to International Society of Urological Pathology grading (ISUP)

ISUP grade	Diagnostic yield of MRI-TRUS fusion biopsy	Diagnostic yield of systematic biopsy
1	22.9	34
2	57.1	46
3	14.3	14
4	2.9	4
5	2.9	2

All results are expressed in percentages.

fusion biopsy, in comparison with 1.6% (2/119 cases) csPCa with negative systematic biopsy, thus showing a higher sensitivity for the systematic biopsy.

Positive targeted biopsy cores had a higher percentage of mean PCa tissue length (55%, range:10-100%) and maximum PCa tissue length (68.7%, range: 0%-100%) in comparison with positive systematic biopsy cores - 47.2% (range: 7-94%) and 63% (range: 0%-100%), respectively, p=0.1.

In 91.9% of cases with MRI unilateral lesion (n=89 patients), PCa diagnosis would have been correctly identified if the systematic biopsy would have been performed only on the ipsilateral prostate lobe. A single patient with csPCa would have been missed if contralateral systematic biopsy would not have been performed. The contralateral lobe biopsy could have been avoided without losing the PCa diagnosis in 75%, 88.2% and 100% of patients with PIRADS score 3, 4 and 5, respectively. In PIRADS score 5 lesions, the possibility of avoiding in all cases the contralateral lobe systematic biopsy was independent of the initial or repeat biopsy setting.

Discussions

The results of our study confirm the already known importance of mpMRI and MRI-TRUS fusion guided prostate biopsy for the diagnosis of PCa. Similar overall and csPCa diagnosis rates have been reported by several centers [17-19]. A higher PIRADS score is significantly correlated with the presence of clinically significant disease. Performing MRI-TRUS fusion biopsy ensures a higher percentage of positive biopsy cores, higher cancer tissue length and a higher probability for diagnosing aggressive PCa, even from the beginning of the learning curve, as confirmed also by the systematic review of Wegelin et al [12]. In our study, the presence of multiple lesions on mpMRI was not predictive for overall or csPCa detection, similar to the conclusion of Patel et al [20].

Adding targeted cores to the systematic biopsy up to a median total of 14 cores does not result in higher pain or discomfort as reported by Robins et al in a group of 170 patients who underwent prostate biopsy [21].

One issue that merits further discussion is the type of registration employed during MRI-TRUS fusion biopsy which may account for errors of targeting. Rigid registration systems overlap the MRI and TRUS volumes, without taking into consideration a possible prostate deformation and lesion displacement [22], whereas elastic registration systems compensate for the deformation of the prostate due to patient positioning, endorectal coil or TRUS probe insertion [23]. A systematic review performed by Venderink et al [24] on 10 studies including a total of 3916 patients concluded that elastic registration has a higher csPCa detection rate (34.59%) in comparison with rigid registration (25.19%), albeit the difference is not statistically significant (p=0.83), possibly due to cognitive compensation of deformation performed by the operator. In our experience, using a rigid registration system for MRI-TRUS fusion guided prostate biopsy ensured a csPCa detection rate of 29.4%.

Although it associated a higher rate of indolent PCa, the systematic biopsy upgraded in our study only 11% of cases to a higher Gleason score. One possible explanation for the high cancer diagnosis accuracy of systematic biopsy in our study is that the operator was not blinded to the mpMRI results, so the location of the standard cores might have been biased by the information, thus representing a limitation of the current study. A percentage of 6.7% of csPCa patients were missed by MRI-TRUS fusion biopsy, but other authors reported a rate as high as 18.6% of csPCa missed by targeted biopsy [25], thus supporting the role of concurrent systematic biopsy. Furthermore, Borkowetz et al [26] assessed the concordance between the Gleason score of MRI-TRUS fusion biopsy and prostatectomy specimen and concluded that the combination of targeted and systematic cores ensures the highest accuracy (63% MRI-TRUS fusion vs 54% systematic vs 75% combination).

In order to decrease the diagnosis of indolent PCa, the role of contralateral prostate lobe biopsy has been investigated. Lepor et al [15] showed that avoidance of con-

tralateral biopsy associates a rate of 18.6% of less indolent PCa diagnosed and 4% missed csPCa, so in selected cases targeted plus ipsilateral systematic biopsy might be sufficient for an accurate diagnosis. Our results confirm that for lesions with PIRADS score of 5, contralateral biopsy could be safely avoided both in the initial and repeat biopsy setting.

The location of the lesion is also important when performing prostate biopsy. The systematic cores sample the most posterior and peripheral part of the prostate, whereas lesions located anteriorly might be missed [27]. Offering the possibility to visualize the lesion, MRI-TRUS fusion biopsy is significantly correlated with exclusive targeted cores diagnosis in all patients, irrespective of initial or repeat biopsy setting, as shown in our group. As a result, employment of mpMRI before the first biopsy might reduce the number of sequential negative biopsies usually performed in patients with anterior lesions in order to confirm the PCa diagnosis [28]. In the present study, patients with a history of previous negative biopsy had a higher probability of an anterior located lesion and MRI-TRUS fusion targeted cores showed a higher diagnostic yield in these cases (25% repeat biopsy vs 4% initial biopsy setting, p=0.04).

A number of studies aimed to compare the different types of targeted biopsy in terms of cancer diagnosis rates, but significant results are still awaited [29]. Probably the correct question is not which technique is best, but which technique is best for which patient.

As concluded by the PRECISION trial [11], any type of MRI targeted biopsy is superior to systematic TRUS for the detection of csPCa, thus at least cognitive prostate biopsy should be performed in all centers. This recommendation is indirectly supported also by our study, showing a high accuracy of systematic biopsy due to the bias caused by the lack of operator blinding to the prebiopsy mpMRI. If available, a more accurate targeted technique (MRI-TRUS fusion or in-bore) should be employed, as cognitive biopsy is hampered by operator's expertise and spatial cognition [10].

Wegelin et al [12] showed that MRI-TRUS fusion guided biopsy is similar with in-bore guided biopsy for the diagnosis of csPCa, but more recent studies support the superiority of in-bore guided biopsy in comparison with other types of targeting. Still, in-bore guided prostate biopsy is hampered by increased costs (due to the need of sequential scanning and magnetic field-compatible devices), a longer time of the procedure, increased patient discomfort and less availability [13]. Thus, taking into consideration the practical advantages of MRI-TRUS fusion systems in comparison with in-bore it is only logical to recommend MRI in-bore biopsy exclusively in cases in which MRI-TRUS fusion biopsy misses the target.

The dimension of the lesion is important due to the inherent needle placement error, which is the lowest in MRI in-bore biopsy (2.5 mm [30] vs 3.5mm for MRI-TRUS fusion with elastic registration [31]). Rigid registration might increase the needle placement error during MRI-TRUS fusion biopsy, thus lesions with a radius smaller than 5 mm would be better targeted by in-bore biopsy.

As shown by Porpiglia et al [32], MRI inhomogenous lesions suggest a Gleason score heterogeneity so they require the most exact targeting of the center of the lesion in order to have an accurate diagnosis of Gleason score. Therefore, if difficulty in the targeting of the lesion is predicted for MRI-TRUS fusion biopsy, MRI in-bore biopsy should be recommended.

Furthermore, Westhoff et al [31] showed that although elastic image registration ensures a more precise targeting in comparison with rigid registration during MRI-TRUS fusion biopsy, it still has a low accuracy for the diagnosis of lesions located at the base (vs transitional and anterior zones) and for small volume prostates (below 50 ml).

Therefore, MRI-TRUS fusion prostate biopsy should be performed in all cases, except patients with small prostates and small heterogenous basal lesions, who should be reserved for in-bore MRI biopsy.

Although mpMRI has significantly impacted the PCa diagnosis, its accuracy is still hampered by the lack of visibility of specific lesions. Cribriform pattern PCa is a very aggressive subtype of prostate adenocarcinoma, that is associated with poor prognosis and worse cancer-specific survival, but the accuracy of mpMRI for the detection of these lesions is low – 36% [33-35]. Truong et al assessed the performance of prostate biopsy in the detection of cribriform PCa and concluded that the combination of MRI-TRUS fusion and systematic prostate biopsy has the highest sensitivity for the diagnosis of this morphological subtype in comparison with either technique alone: 37.1% vs 28.6% for targeted biopsy and 20.7% for systematic [36]. Still, the accuracy is rather poor.

The relatively low number of patients, which might impair the statistical results and the availability of mpMRI information for the urologist who performed the systematic biopsy, leading to higher accuracy than standard, could be considered the limitations of the current study.

Conclusions

MRI-TRUS guided prostate biopsy improves the detection of PCa by a higher percentage of positive biopsy

cores, higher cancer tissue length and higher likelihood of csPCa detection, lower yield of indolent PCa and the possibility to diagnose anterior and transitional zone lesions, but systematic biopsy is still essential. An anterior or transitional lesion will most probably be diagnosed only by targeted biopsy cores. In highly selected cases (PIRADS 5), contralateral lobe systematic biopsy during MRI-TRUS fusion biopsy can safely be avoided both in an initial and repeat biopsy setting. In order to ensure the best results, clear indications for every MRI-targeting method for prostate biopsy should be established.

Conflict of interest: none

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