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MRI/TRUS fusion vs. systematic biopsy: intra-patient comparison of diagnostic accuracy for prostate cancer using PI-RADS v2

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Abstract

Objective To evaluate the efficacy of multiparametric magnetic resonance/transrectal ultrasound fusion (MRI/TRUS fusion) biopsy versus systematic biopsy and its association with PI-RADS v2 categories in patients with suspected prostate cancer.

Materials and methods 122 patients undergoing both MRI/TRUS fusion and systematic biopsy, with suspicion of prostate cancer, with suspicious findings on MRI based on PI-RADS v2, were included between April 2016 and March 2017. Comparison of tumor detection rates using each technique and combined techniques was performed for all lesions as well as those that are traditionally difficult to access (i.e., anterior lesions).

Results Prostate cancer was detected in 83/122 patients (68%) with 74.6% clinically significant lesions (Gleason 3 + 4 or greater). There was a statistically significant difference in presence of clinically significant prostate cancer in PI-RADS v2 categories of 3, 4, and 5 (20%, 52% and 77%, respectively, $p < 0.001$). Fusion biopsy was positive in a significantly higher percentage of patients versus systematic biopsy (56% versus 48%, respectively, $p < 0.05$). The fusion biopsy alone was positive in 20%. Of 34 patients with anterior lesions on MRI, 44% were detected only by fusion biopsy, with a joint yield of 71%. In patients with previous negative systematic biopsies, 48.7% lesions were found by fusion biopsy with 20.5% being exclusively positive by this method. The percentage of positive cores for fusion biopsies was significantly higher than for systematic biopsies (26% vs. 12.3%, $p < 0.001$).

Conclusion The incorporation of MRI/TRUS fusion biopsy significantly improves the detection rate of prostate cancer versus systematic biopsy, particularly for anterior lesions.

Keywords Prostate cancer · Prostate MRI · PI-RADS · MRI/TRUS fusion

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Introduction

Prostate cancer is currently the second leading cause of death from cancer in men in United States [1], with an estimated mortality rate in 2012 of 21,4 per 100,000 men [2], while its incidence is estimated in 131,5 per 100,00 men [1]. The discrepancy between incidence and mortality is because many of these cancers are of low malignant potential, with some series showing up to 92% of the lesions confined to the prostate at the time of diagnosis, with a 5-year survival rate of 99% [2]. For the diagnosis of prostate cancer, there are multiple predictive models and nomograms that combine prostate specific antigen (PSA), digital rectal examination (DRE) and transrectal ultrasound (TRUS)-guided biopsies; however, each has limitations [3, 4]. For the detection of prostate cancer, PSA has a sensitivity of 78–100% and specificity of 6–66% [5], while the sensitivity and specificity of the DRE is 37% and 91% respectively [6]. The TRUS-guided biopsy consists of sampling of the apex, mid-gland and base of the prostate, generally taking two samples at each location per side for a total of 12 cores. This has shown to have high error rates in the classification of the lesions, with 25–42% of lesions downgraded and 14% of lesions upgraded when compared with prostatectomy specimens [7]. Other series show that TRUS-guided biopsy fails to find the most aggressive component in 30 to 50% of cases when compared with the final operative pathology [7], and that TRUS-guided biopsy adequately risk stratifies only 16% of patients [8]. This risk stratification error is observed in practice with rates of up to 30% of tumors that increase in grade in a subsequent systematic TRUS-guided biopsy, which probably occurs due to an inadequate investigation in the initial biopsy and not due to actual tumor progression [9, 10].

The traditional TRUS-guided approach has focused on the peripheral zone of the prostate [11], in which between 70 and 80% of the lesions originate. However, 20–30% of lesions originate in the central and transition zones, which are potentially under-represented at TRUS-guided biopsy [12]; in some series, this can be the cause of up to 47% of false negatives [13]. Other studies have shown that in patients diagnosed with confirmed prostate cancer with prior negative biopsies, the foci of cancer were located in the anterior central or transition zone in 47–57% of the cases [12, 14, 15]. In an attempt to improve the performance of TRUS-guided biopsy performance, other strategies have been designed, such as saturation biopsies and transperineal biopsies, which have been shown to increase detection rate by 18–34%, albeit at the expense of increasing morbidity with a higher number of cores [15].

Multiparametric magnetic resonance imaging (mpMRI) of prostate is currently the most accurate imaging technique for the diagnosis of prostate cancer and local staging [16–20], with studies that have shown sensitivity of 74–81%, specificity of 84–88% and accuracy of 83% [21, 22]. Hu et al. observed a reclassification rate of 27% of patients with suspicious MRI findings based on pathology from subsequent biopsies [23]. Multiple methods have been devised to integrate information from mpMRI into the performance of prostate biopsies, specifically MRI-TRUS fusion biopsies [24]. The MRI-TRUS fusion biopsy combines the improved diagnostic accuracy of mpMRI for lesion detection and characterization [25] with the cost-effectiveness and familiarity of the TRUS-guided platform for urologists [8]. In these, the ultrasound is connected to a device that receives and fuses the mpMRI images of the prostate with the transrectal US images. The lesions denoted on mpMRI are superimposed on the display of the ultrasound unit and allows guided biopsy. On average, the procedure lasts 20 min, which varies according to the operator's experience and the number of biopsies to be taken in the session [8].

In the Siddiqui et al. series, fusion biopsies had sensitivity of 77%, and specificity of 68% with accuracy of 73% [26]. In addition, in the Portalez et al. series, the cores obtained by MRI-TRUS fusion were seven times more likely to be positive than those obtained by systematic biopsy [27]. In the Pinto et al. series, a positive rate of 21% versus 12% was reported in MRI-TRUS fusion and systematic biopsy, respectively [28]. The purpose of this study is to evaluate the efficacy of MRI/TRUS fusion biopsy versus systematic biopsy and its association with PI-RADS v2 categories in patients with suspected prostate cancer.

Materials and methods

This retrospective study was approved by our Institutional Review Board, who approved a waiver for informed consent.

Patient selection

A total of 122 patients with suspected prostate cancer, either due to elevation of the PSA and/or abnormal DRE, and who presented an abnormal MRI according to the Prostate Imaging Reporting and Data System v2 (PI-RADS v2) [29] (scores 3–5) underwent prostate biopsy by TRUS/MRI fusion and systematic biopsy at our institution between April 2016 and March 2017 (Fig. 1).

MRI performance and interpretation

All patients were evaluated in our center with mpMRI with a 3 T scanner (Skyra, Siemens Medical, Erlangen, Germany) using a phased array coil and utilizing MRI technical parameters as defined in PI-RADS v2 [29]. Specifically, acquired images included: thin-section (3 mm section thickness) turbo

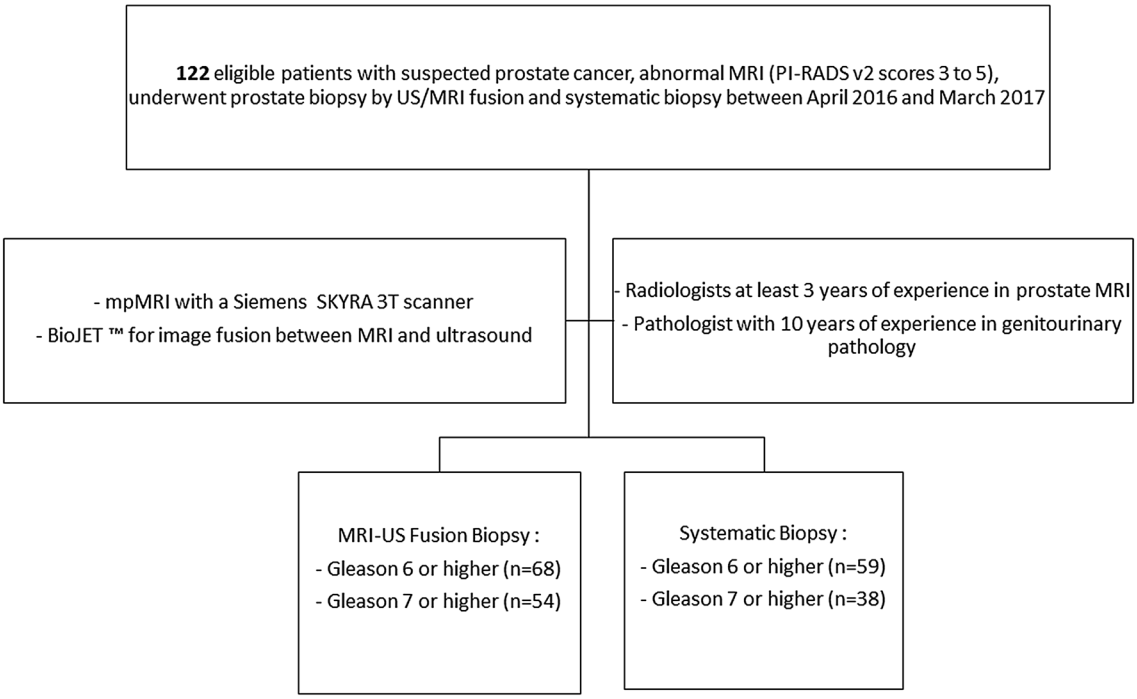

Fig. 1 Flowchart of inclusion criteria of the final patient cohort

spin echo T2-weighted images in the coronal, axial and sagittal planes; diffusion weighted images (DWI) using multiple *b* values (50, 500, 1000 s/mm^2) with calculation of apparent diffusion coefficient (ADC) maps and a high *b* value imaging ($b = 1400$ s/mm^2); and dynamic contrast-enhanced MR images (DCE-MRI) obtained after administration of a weight-based dose of gadolinium based extracellular MR agent, gadobutrol (Bayer Pharma AG, Wayne, NJ) with temporal resolution of 9 s for a total of 3 min. All exams were interpreted by radiologists with at least 3 years of experience in prostate MRI. In all cases, the number of suspicious lesions was reported and the score was made according to PI-RADS v2 criteria.

Fusion and systematic biopsy technique

BioJET™ (DK Technologies GmbH, Barum, Germany) was used to perform image fusion between MRI and ultrasound, and the MRI-TRUS-guided biopsy. Using this system, a radiologist with 6 years of experience, marked the area of the suspicious lesion using this computer software. Using this user input, the system then fuses the MR images with those of ultrasound, and targeted core biopsies are taken from each suspicious lesion. A total of 6 cores were taken from each lesion as per institutional practice. For the systematic biopsy, 13 cores were taken from each patient using an extended sextant methodology as per institutional practice.

Pathologic analysis

All samples were analyzed by the same pathologist, with 10 years of experience, who described in their report: the total number of samples for systematic and MRI-TRUS fusion biopsies, the number of positive samples using each of the techniques and their respective Gleason score. Positive result was considered a Gleason score of 6 or higher and clinically significant prostate cancer was defined as Gleason 3 + 4 or higher, consistent with PI-RADS v2. In cases of patients who underwent subsequent radical prostatectomy, the surgical specimens were evaluated by the same pathologist to minimize inter-reader variability.

Statistical analysis

The patient data were tabulated. The demographic data, the result of the mpMRI, and the result of the systematic and fusion biopsies were recorded along with the number of samples taken using each biopsy technique, and surgical pathologic analysis from the radical prostatectomy. The statistical analysis was performed with Stata 12® (STATA Corp), performing univariate analyzes with measures of central tendency and dispersion, analysis with χ^2 test for the comparison of performance of systematic biopsies and fusion. Additional subset analysis was performed in the subgroups of patients who had lesions located in the anterior transition zone, central zone and anterior PZ based on the mpMRI, as well as in the subgroup

of patients with history of negative previous biopsies. The rate of positive cores for each of the techniques was compared. Statistical significance was defined as p value of <0.05. 95% confidence intervals were estimated when deemed feasible.

Results

Our final study population included 122 patients with a median age of 63 years (IQR 54–70) and median PSA of 5.8 ng/dL (IQR 4–8.6). Prostate cancer was detected in 83/122 patients (68%). Of these, 39/122 (32%) had previous negative biopsies and 34/122 (28%) had lesions in anterior TZ, anterior PZ or central zone. Based on the mpMRI, 30/122 (25%) were classified as PI-RADS 3, 61/122 (50%) as PI-RADS 4, and 31/122 (25%) as PI-RADS 5.

There were positive results for prostate cancer Gleason 6 or higher in 59/122 (48%) patients in the systematic biopsies, and in 68/122 (56%) in the fusion biopsies ($p=0.049$). Utilizing both methods of biopsy in conjunction, the presence of cancer was demonstrated in 83/122 patients (68%). From this group of patients, a clinically significant lesion (Gleason 3 + 4 or higher), independent of the biopsy modality, was demonstrated in 62/83 patients (74.7%). 54/83 (65%) patients were positive by fusion and 38/83 (46%) by systematic, a statistically significant difference ($p<0.001$). Low grade Gleason 6 prostate cancer was found in 21/83 patients.

When evaluating by method of performing the biopsy either by fusion, systematic or both in patients in whom cancer was demonstrated, the biopsy was positive in both methods in 44/83 patients (53%), fusion biopsy only in 24/83 cases (29%), and by systematic sampling only in 15/83 patients (18%) (Table 1).

Patients with previous negative biopsies

In this series, 39/122 (32%) patients had previous negative systematic biopsies. Of these, 23/39 (59%) patients had positive biopsies in the current study using MRI-TRUS fusion and/or systematic biopsy. In 8/39 patients (20.5%), positive results were found only using MRI-TRUS fusion biopsy, 4/39 patients (10.3%) only in systematic sampling, and in 11/39 cases (28.2%) positive results were obtained in both.

In total, 48.7% of patients had neoplastic foci found with MRI-TRUS fusion biopsy alone or with both systems, 38.5% of patient had neoplastic foci found with systematic biopsy alone or both, without achieving a statistically significant difference ($p=0.13$).

Patients with difficult to access lesions for routine biopsy

In 34/122 (28%) patients, the mpMRI showed lesions in the anterior transition zone (25/34), anterior PZ (4/34) or in the central zone (5/34), (Fig. 2). Of this group, positive biopsy was obtained in 15/34 patients (44%) only by fusion, 1/34 patient (3%) only in systematic biopsy, 8/34 patients (24%) in both methods, and in 10/34 patients (29%) in neither. In total, the approaches mediated with fusion biopsies detected lesions in 68% of these patients and those involving systematic biopsies in 27% ($p<0.001$), with a joint yield of 71%.

Results by core samples

A total of 2318 samples were made, of which 1586 were made by systematic sampling, 13 cores per patient, with 12.3% of positive core samples. 732 samples were recorded

Table 1 Patients demographics and results by method of biopsy

Variables	All	Fusion biopsy US/MRI	Systematic biopsy	p value
Patients (n)	122			
Age [median years (IQR)]	63 (IQR 54–70)			
PSA [median ng/ml (IQR)]	5.8 (IQR 4–8.6)			
Positive result Gleason 6 or higher	83 (68%)s	68 (56%)	59 (48%)	0.049*
Clinically significant lesion Gleason 7 or higher	62/83 (74.7%)	54/83 (65%)	38/83 (46%)	<0.001*
Patients with negative prior biopsies:	39/122 (32%)			
Positive Gleason 6 or higher	23/39 (59%)	19/39 (48,7%)	15/38 (38,5%)	0.13
Patients with difficult access lesions:	34/122 (28%)			
Positive Gleason 6 or higher	24/34 (70,5%)	23/34 (68%)	9/34 (27%)	<0.001*
Core samples [n]	2597	946	1651	
Positive Gleason 6 or higher	394/2318 (17%)	190/732 (26%)	195/1586 (12.3%)	<0.001*

US ultrasound, *MRI* magnetic resonance imaging

The units of measurement are in brackets. Continuous variables are reported as mean. Categorical variables are summarized with frequency counts and percentages from total (in parenthesis)

The asterisk (*) indicates significant difference between fusion biopsy and systematic biopsy

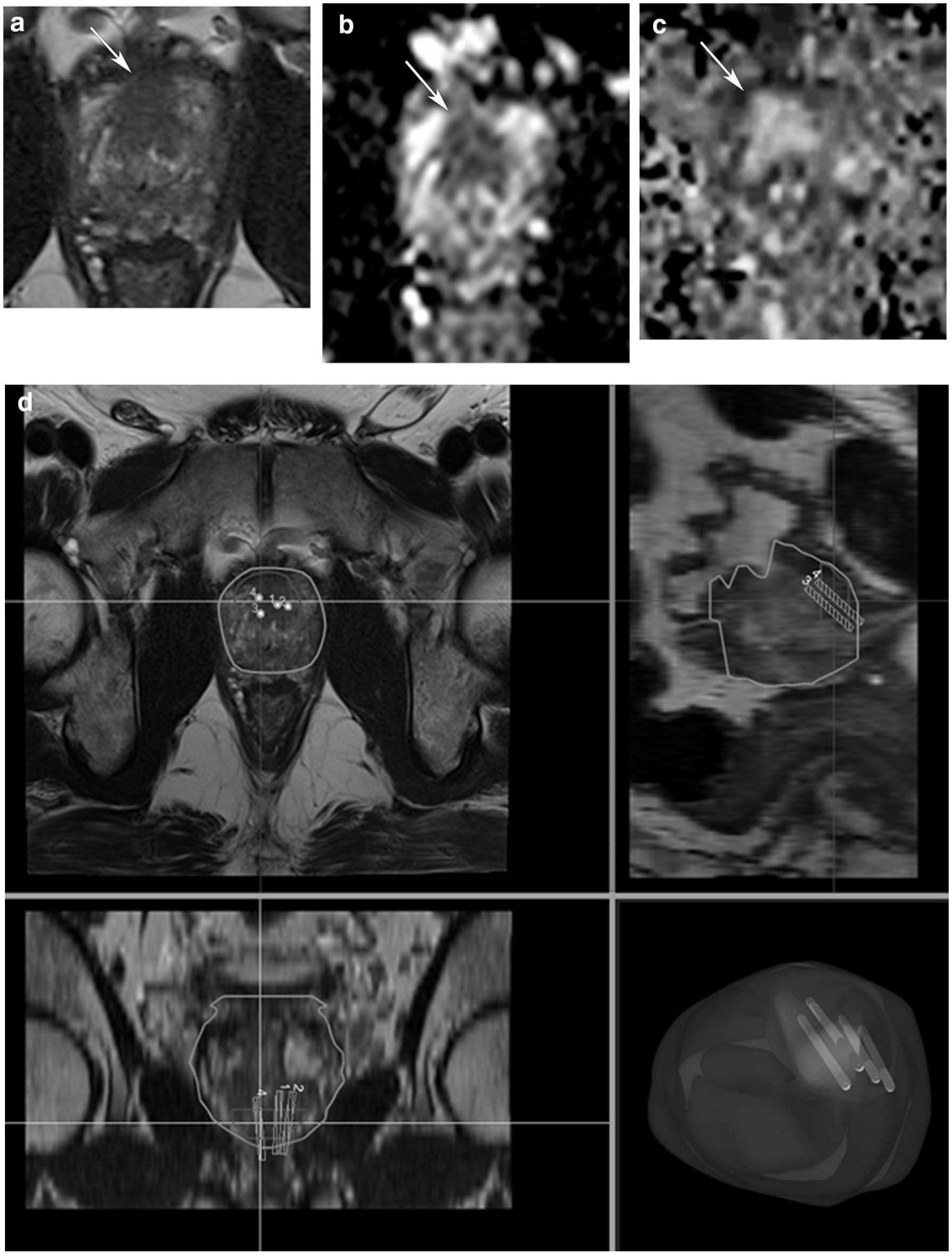

Fig. 2 A 51-year-old man with a rising elevated serum PSA level from 7 to 9 ng/mL (PSA density 0,16 ng/mL^2), prior TRUS biopsy with a negative result presents for mpMRI at 3 T. **a** Axial T2W image shows an anterior transitional zone (TZ) lesion with decreased T2W signal at the level of the apex (white arrow). **b** Axial ADC map and **c** axial high b value DWI ($b = 1400$ s/mm^2) demonstrates corresponding restricted diffusion (white arrow). These findings correspond to a suspicious PI-RADS 5 lesion. **d** BioJET™ software was used to perform image fusion and target the difficult access lesion during the fusion biopsy. The pathological results revealed a Gleason $4+3=7$ cancer in the anterior TZ at the apex

by fusion, 6 cores per lesion, with a positive biopsy rate of 26% ($p < 0.001$), with odds ratio (OR) for detection of lesions by fusion of 3.45 (95% CI 2.95–4.05).

PI-RADS v2-histology concordance

We also analyzed the concordance between the PI-RADS v2 score and the final result of the biopsies, showing the presence of prostate cancer in 36.7%, 72.1% and 90.3%, in PI-RADS v2 scores 3, 4 and 5 respectively. Of these patients, 74.6% (62/83 patients) showed clinically significant prostate cancer as defined by PI-RADS v2 (Gleason 3 + 4 or greater), with a statistically significant association between the proportion of clinically significant lesions for each category of PI-RADS v2 of 20% (6/30), 52% (32/61) and 77% (24/31) in scores 3, 4, and 5, respectively (p value < 0.001) (Fig. 3). Also 56/83 (67%) of clinically significant cancer was found in PI-RADS v2 scores 4 and 5 combined.

Discussion

In this series, MRI-TRUS fusion biopsies provided a statistically significant advantage for detection of prostate cancer (Gleason 6 or more) in comparison with systematic biopsies. In addition, in 20% of patients, clinically significant lesions were found only on MRI-TRUS fusion biopsies and would have been missed using systematic biopsy alone. In addition, the combination of both techniques detected prostate cancer in 83 patients (68%), which is well above the 30–40% positivity reported for systematic sampling in the literature [30].

This study demonstrates that implementing sampling by MRI-TRUS fusion is an alternative to systematic biopsy alone that allows increased significantly improved diagnostic performance and tumor detection, 56% vs 48% ($p = 0.049$). When analyzing the histological results of the lesions found in each technique, we observed a tendency to find more clinically significant lesions using MRI-TRUS fusion biopsies, similar to findings from other investigators [26]. We do feel that a clear strength of our work is the rigid criteria used for fusion biopsy sampling of targets within the prostate. Much work has centered on the optimal number of core biopsies needed per target to optimize detection of prostate cancer [31, 32] and though there is no clear consensus as yet, recent work has suggested that taking only two cores of a target lesion can lead to missing nearly 25% of clinically significant prostate cancer that would have been diagnosed with a greater number of samples [33]. In this work, it was suggested that at least five cores through the MRI-identified target can lead to missing substantially fewer prostate cancers than two cores [33]. Our technique helps validate this as we take six cores

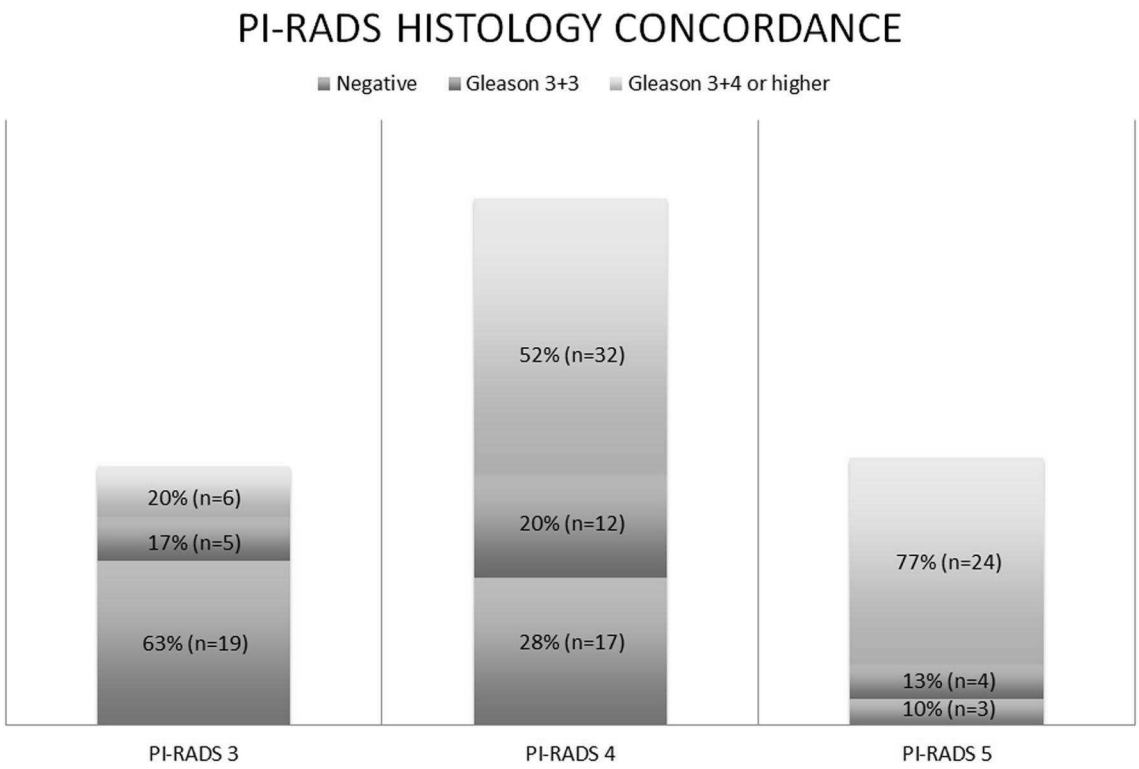

Fig. 3 Concordance between PI-RADS v2 category and histology. Note—Statistically significant association between the proportion of clinically significant lesions (Gleason 3 + 4 or higher) for each category of PI-RADS v2 (p value < 0.001)

through each identified target lesion, though of course, further work is needed to define the optimal number of targeted cores.

In the group of 39 patients with suspicion of prostate cancer and previous negative biopsies, 23/39 patients (59%) had a clinically significant neoplastic lesion in this series, with the fusion biopsy alone contributing to the positive biopsy finding in 8/23 (35%), again demonstrating the benefit of the technique in this group of patients.

In our series, the increased diagnostic performance of MRI-TRUS fusion biopsies appears to be related to finding lesions in areas traditionally undersampled by systematic biopsy, specifically anterior transition zone, central zone and anterior peripheral zone. More specifically, of the 34 patients in whom suspicious lesions were reported in these locations on mpMRI, 24 had positive foci, of which 23 were positive on MRI-TRUS fusion. We feel that another strength of our study is the special attention paid to performance of fusion guided and systematic biopsies for anterior lesions as visualization of these lesions is a clear advantage that MRI provides. Our results help validate other studies such as that by Volkin et al. [34] which showed that for anterior lesions positive for prostate cancer, there was a statistically significant difference ($p = 0.001$) and improvement in detection of prostate cancer by fusion guided biopsies (40.3%) over systematic biopsies (25.7%). Our results confirm these findings and in fact, widen the performance gap between detection of anterior cancers with approaches mediated with fusion biopsies (68%) compared to those involving systematic biopsies (27%) ($p < 0.001$). We also feel that our results and the results of Volkin et al. are more reflective of current clinical practice than older studies which suggested that detection rates of anterior cancers by systematic biopsy could be as high as 54% [35]. Specifically, in our series, only 8/23 patients (34%) with anterior lesions were diagnosed on systematic biopsy at all and only 1/34 (3%) was diagnosed on systematic biopsy only. In contrast, the majority of these lesions were positive by fusion guided biopsy method only (15/24 patients, 63%).

The percentage of positive cores for fusion biopsies was 26% versus 12% for systematic biopsies, a difference that was statistically significant and similar to results from other series [36]. Maximizing the performance of biopsies at the expense of a smaller number of cores is an interesting alternative when compared with other strategies such as saturation biopsies, in which between 30 and 50 cores are taken with the associated risks involved. The percentage of positive biopsies was influenced by the PI-RADS score, 20% of clinically significant cancer in PI-RADS score 3 versus 52% and 77% in scores 4 and 5 respectively (statistically significant difference), which is expected and reinforces the concept of mpMRI is a good way to stratify the lesions that should be sampled [37]. Another strength of our work is the information that we provide on the positive biopsy rate of PI-RADS 3 lesions. In the era of MRI, many PI-RADS 3 lesions are not biopsied and work is underway to help understand which PI-RADS 3 lesions should be biopsied, based on other factors [38, 39] such as PSA density, etc. In our study, we show that 20% of PI-RADS 3 lesions demonstrate the presence of clinically significant cancer, which is consistent with some recent literature [38] and helps to validate what the rate of positive biopsy should be in this category.

There are limitations to our study that must be considered. First, we used PI-RADS v2.0 for lesion scoring as v2.1 had not been released at the time of study performance. Second, this is a retrospective study with a limited sample size from one institution. In addition, there is not a control group that underwent only systematic biopsies to quantify the additional benefit of fusion biopsy. That said, there is paired information available that confirms the ultimate utility of MRI-TRUS fusion, and that it could be used interchangeably with systematic biopsy [40]. Finally, a cost-effectiveness analysis of this modality and the evaluation of the degree of overdiagnosis of prostate cancer using this technique would be important future avenues for research.

Conclusion

The addition of MRI-TRUS fusion biopsies to systematic TRUS-guided biopsies increases the likelihood of identifying clinically significant prostate cancers. In this work, we confirm that this method is especially useful in patients with lesions that are difficult to access by a traditional systematic biopsy such as in the anterior transition zone, central zone and anterior peripheral zone and have demonstrated even higher differences between positive biopsy rates for these lesions between fusion and systematic biopsy than other studies.

In this series, biopsy sessions that combined systematic biopsy plus MRI-TRUS fusion of suspicious lesions in patients with suspicion of prostate cancer and previous negative biopsies detected clinically significant lesions in an important percentage of these patients.

The percentage of positive cores in MRI-TRUS fusion biopsies exceeds that of systematic biopsies, constituting an excellent alternative to increase the performance of biopsies at the expense of a reduced number of targeted cores. The PI-RADS v2 score is also associated with the probability of positivity of the lesions, demonstrating that imaging categorization improves the performance of the biopsies.

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Compliance with ethical standards

Conflict of interest Fernando González, MD, Andrés Labra, MD, Claudio Silva, MD, Gerhard Franz, MD, Rodrigo Pinochet, MD—none. Rajan T. Gupta, MD—Consultant, Invivo Corp.

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