

Diagnostic Performance of Multiparametric Magnetic Resonance Imaging and Fusion Targeted Biopsy to Detect Significant Prostate Cancer

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Abstract. *Background/Aim:* Multiparametric magnetic resonance imaging combined with ultrasound-fusion-targeted biopsy of the prostate intends to increase diagnostic precision, which has to be clarified. *Patients and Methods:* We performed multiparametric magnetic resonance imaging followed by ultrasound-fusion-guided perineal biopsy in 99 male patients with elevated prostate-specific-antigen and previous negative standard biopsy-procedures. *Results:* In 33/99 patients (33%) no malignancy could be confirmed by histopathology. Low-grade carcinomas (Gleason-Score 6+7a) were found in 42/66 (64%) and high-grade carcinomas (Gleason-Score $\geq 7b$) in 24/66 (36%) men. A high-grade carcinoma corresponded to PI-RADS 4 or 5 (suspected malignancy) in 21/24 cases, which accounted for a sensitivity of 88% and negative-predictive-value of 85% ($p=0.002$). Differentiation between high-/low-grade carcinomas (Gleason-Score $\leq 7a$ vs. $\geq 7b$) by means of PI-RADS related to a sensitivity of 88% and a negative-predictive-value of 70% ($p=0.74$). *Conclusion:* The results support the view that multiparametric magnetic resonance

imaging/ultrasound-fusion-guided biopsy promotes considerably higher detection rates of clinically relevant prostate malignancies than do conventional diagnostic procedures. With regard to differentiation between high- and low-grade carcinomas, no significant difference was demonstrated.

Diagnosis of prostate cancer is still based on non-specific screening methods, such as prostate-specific antigen (PSA) plasma levels and digital rectal examination. Currently, diagnosis is confirmed by core biopsy guided by transrectal ultrasound (US) guidance, but this may result in failure of carcinoma detection in 20-30% of cases, or undergrading/underestimation of tumor aggressivity, respectively (1-3). A major clinical concern is elevated or rising PSA after negative random core prostate biopsy (4). Further diagnostic steps include alternative tumor markers, such as PCA3, repeated or saturation biopsy and prostatic imaging. For elevated PSA with prior negative biopsies, current guidelines recommend multiparametric magnetic resonance imaging (mpMRI) as superior to other diagnostic tools (1, 5-7). This MRI modification selectively combines T2-weighted MRI features with dynamic contrast enhanced (DCE) and diffusion weighted imaging (DWI).

For clinical communication and data exchange purposes, the prostate imaging reporting and data system (PI-RADS/PR) version No. 1 has been introduced in 2012 (8). Within this system, point values are applied for each lesion and method that are summarized and transformed into a 5 digit sum score, ranging between PR 1 in case of a presumed benign, and PR 5 in case of a presumed malignant pathology.

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The introduction of the PR system certainly boosted clinical usage and acceptance of mpMRI, providing a considerable gain in diagnostic precision along an enhanced interreader reliability (9). Recently, in collaboration of ESUR and ACR, an actualized version 2 of the PR system has been presented that is optimized for sensitivity and traceability patterns. This system mainly combines the advantages of T2-weighted and DWI imaging, while MRS is spared and DCE is utilized exclusively for classification of PR 3 lesions in the peripheral zone (10).

The undisputed focus of MRI imaging in cancer diagnostics is detection of clinically relevant malignant tumors, with avoidance of over-diagnosis of non-significant lesions (1, 11, 12). Technical fusion of MRI and ultrasound-guided biopsy allows for targeted cancer identification without the need of a second MRI procedure, thus promoting better localization of tumor tissue (13).

This study intends to quantify the diagnostic precision of prostate cancer detection in patients with increased PSA and prior negative core biopsy, by use of mpMRI and PR with subsequent US-fusion-guided biopsy. Furthermore, we demonstrate that the results of this approach is predictive of defining the histological aggressivity of the underlying tumor.

Patients and Methods

Inclusion criteria consisted of all patients of a single urological practice seen between January 2015 and January 2016, with a history of elevated PSA (≥ 4.0 , depending on age) and one or more prior negative biopsies within the previous 6-24 months. Patients with a history of specific cancer pretreatment, surgical intervention, or inconspicuous PSA plasma levels were excluded.

In all patients that met criteria, MRI was performed using a 3.0 Tesla scanner (General Electric, 3.0T HDxt, MI, USA) and a body phased-array coil. Radiologic evaluation was performed according to the PR version No. 1. Although the updated PR version No. 2 was available in the second half of 2015, we did not change the version for evaluation reason (to compare data).

All patients underwent a stereotactic, image fusion-guided biopsy of the prostate. The procedure was performed in short-term anesthesia, using the BiopSee® device (MedCom, Inc., Darmstadt, Germany). Prior to tissue sampling, MRI data was transferred to the computing unit of the biopsy device and recorded. Suspicious sites of malignancy were tagged and electronically fused with 3D transrectal ultrasound images obtained previously. Once the images were fused, at minimum two experienced urologists (KT, KL, TS) performed the biopsy using a transperineal approach. First, targeted biopsies of suspicious lesions were obtained (maximum of 4 samples per lesion), followed by a standard core random sampling (total max. 15 samples).

Biopsy specimens were histopathologically evaluated according to the Gleason System (2014 ISUP criteria), and were stratified into low-grade (Gleason-Score $\leq 3+4=7a$) and high-grade (Gleason-Score $\geq 4+3=7b$), malignancies respectively (14). In cases of confirmed malignancy, we additionally assessed the clinical T stage (according to the TNM classification system), in addition to a total risk estimate based on ESUR criteria (8) as follows:

Table I. Baseline characteristics and patient outcomes.

Age	66.5±7.3 years (49-80 years)		
PSA (ng/ml) (n=99)	9.8±7.8 (3.0-70.0)		
PSA-category (n=99)			
I (≤ 5 ng/ml)	21 (21.2%)		
II (6-<10 ng/ml)	54 (54.5%)		
III (10-20 ng/ml)	19 (19.2%)		
IV (>20 ng/ml)	5 (5.1%)		
mpMRI PI-RADS (n=99)			
1	3 (3.0%)		
2	3 (3.0%)		
3	21 (21.2%)		
4	27 (27.3%)		
5	45 (45.5%)		
T-classification (n=66)			
T1c	60 (90.9%)		
T2c	6 (9.1%)		
Low risk	13 (19.7%)		
Intermediate risk	40 (60.6%)		
High risk	13 (19.7%)		
Gleason-Score (GS) result of fusion guided biopsy	Total (n=99)	GS ≥ 6 (n=66)	Grading
<6	33 (33.3%)	-	-
6	13 (13.1%)	13 (19.7%)	Low-grade
7a	29 (29.3%)	29 (43.9%)	42 (63.7%)
7b	15 (15.2%)	15 (22.7%)	High-grade
8	4 (4.0%)	4 (6.1%)	24 (36.3%)
9	5 (5.1%)	5 (7.6%)	

- Low Risk: PSA < 10 ng/ml, cT1-2a, Gleason ≤ 6
- Intermediate Risk: PSA 10-20 ng/ml, cT2b/c, Gleason 7a/b
- High Risk: PSA >20 ng/ml, >cT2c, Gleason 8-10

Clinically significant cancer was defined as Gleason-Score (GS) $\geq 7b$. Descriptive statistics, intercept correlations between PR, categorical data and underlying risk factors were assessed by semiquantitative approaches based on calculation of Spearman's correlation coefficient. Test performance metrics (sensitivity, specificity, negative/positive predictive value) were calculated using Chi-square- and Fisher's exact test.

Results

A total of 99 patients were included, with a mean age of 66 years (48-80). All patients had at least one prior negative standard core biopsy, and none had undergone pretreatment of prostate carcinoma at any time. The mean baseline PSA plasma level was 9.8±7.8 ng/ml (Table I).

MpMRI results indicated that 6 patients (6%) had presumed benign disease (PR 1+2), 21 patients (21%) had equivocal diagnostic findings (PR 3), and the majority of patients (n=72, 73%) displayed diagnostic findings suggestive for malignancy

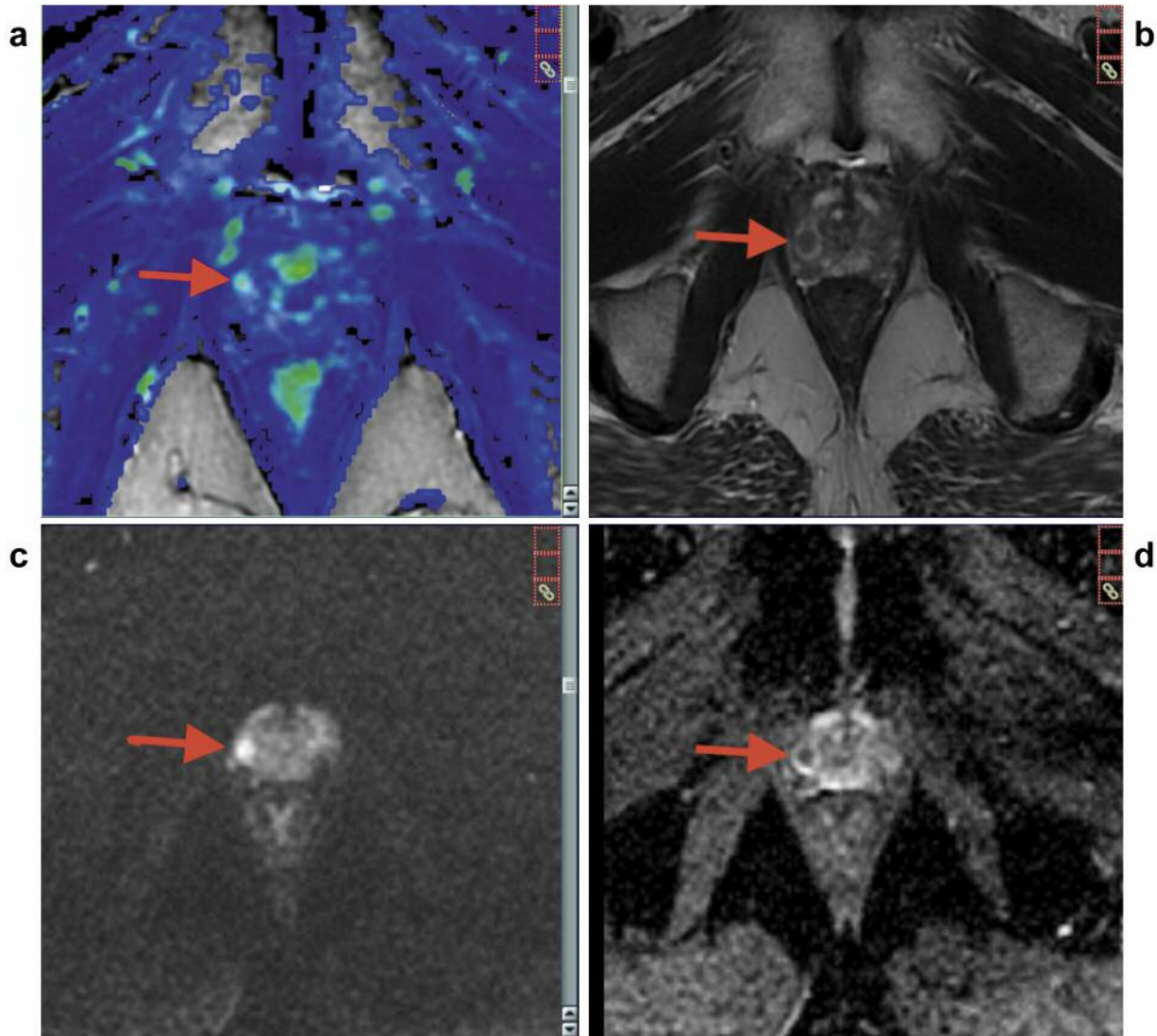


Figure 1. Prostate mpMRI from patient (PR 5) with biopsy confirmed high-grade carcinoma ($GS \geq 7b$). The conspicuous lesion, seen in the peripheral zone of the prostate gland, shows an asymmetric hyperperfusion on DCE (a), a low signal intensity focus on axial T2-weighted imaging (b), a focus of high signal on DWI (c) and a focal area of reduced ADC (d).

(PR 4+5) (Figure 1 and Table I). Due to continuously rising PSA-levels, all 27 patients with PR <4 also underwent biopsy.

Histopathological examination following targeted stereotactic biopsy revealed no signs of malignancy in specimens of 33 patients (33%) (Table II). The respective changes in these patients detected by mpMRI were prostatitis or benign prostate hyperplasia, confirmed by histopathology.

Of the 66 remaining patients, prostate cancer was diagnosed in the suspicious regions. These were classified according to the GS, which yielded a low-grade carcinoma (GS 6, 7a) in 42 cases (64%), and a high-grade carcinoma ($GS \geq 7b$) in 24 cases (36%). The distribution of GS 6-9 is shown in Table I.

When using clinical staging, GS, and PSA for risk stratification, 13 patients (20%) were considered low risk, 40 (61%) intermediate and 13 (20%) high risk (Table I).

Suspicious lesions were located in all regions of the prostate, but were most commonly isolated to the peripheral zone (46/99) and transition zone (25/99) (Table III). Of the peripheral zone lesions, 34 cases (74%) were low-grade (GS 6+7a), while the remaining 12 cases (26%) were high-grade ($GS \geq 7b$). The corresponding distribution in the transitional zone was 22 (88%) low-grade and 3 (12%) high-grade lesions. Regarding PR, virtually all high-grade malignancies in the peripheral zone had been assessed correctly with PR 5,

Table II. Frequency distribution of Gleason-Score- and separate PI-RADS-categories

MRI	HISTO	Gleason-Score						
		<6	Low-grade carcinoma		High-grade carcinoma			
			6	7a	7b	8	9	
PI-RADS	Carcinoma (-)	1	2	0	0	1	0	0
		2	2	0	1	0	0	0
	Carcinoma (+)	3	13	1	5	1	1	0
		4	8	7	9	1	1	1
		5	8	5	14	12	2	4

Table III. PI-RADS Score in comparison with Gleason-Score (GS) considering lesions of the peripheral or transitional zone.

PI-RADS	Peripheral zone			Transitional zone		
	GS 6, 7a	GS ≥7b	Total	GS 6, 7a	GS ≥7b	Total
1	0	0	0	0	0	0
2	1 (100%)	0	1	2 (100%)	0	2
3	8 (100%)	0	8	7 (87.5%)	1 (12.5%)	8
4	11 (100%)	0	11	9 (100%)	0	9
5	14 (53.8%)	12 (46.2%)	26	4 (66.7%)	2 (33.3%)	6
total	34 (73.9%)	12 (26.1%)	46	22 (88.0%)	3 (12.0%)	25

whereas in the transitional zone 1 of 3 cases had been classified incorrectly with PR 3. MpMRI with US-fusion-guided biopsy demonstrated a sensitivity of 85% with a negative-predictive-value (NPV) of 63% ($p < 0.001$) to detect prostate cancer (GS 6-9) (Tables II and IV).

Among the 24 patients with high-grade carcinoma (GS ≥7b) mpMRI showed highly suspicious lesions (PR 4 or 5) in 21 cases (88%), which related to a sensitivity of 88% and a NPV of 85% ($p = 0.002$).

The proportion of corresponding results in mpMRI (PR 4-5), when a low-grade carcinoma had been detected, was 35/42 (83%) with a NPV of 71% ($p < 0.001$).

The overall sensitivity for mpMRI to differentiate between low- and high-grade lesion differentiation (GS ≤7a vs. ≥7b) via PR was 88%, with a NPV of 70% ($p = 0.74$; Fisher's exact test). The correlation analysis showed that GS also increased with increasing PR, but this relationship was not statistically significant ($R = 0.22$).

Discussion

Prostate cancer represents the most frequent cancer, and the third most common cause of cancer-related deaths in males in Germany (15), thus posing a considerable challenge in

morbidity and mortality handling in society. More than 60,000 patients are newly diagnosed per year, and 12,000 men will die of the disease. Considering increased life expectancy, and the fact that treatment is most effective when applied at very early states, early and precise diagnosis is essential.

However, screening for prostate cancer remains controversial. While PSA has a low sensitivity and specificity, DRE has a low PPV and a high inter-observer variability, resulting in overdiagnosing and overtreatment induced by false-positive findings. Similarly, studies have shown that TRUS-guided biopsy fails to detect cancer in about 20-30% of cases when present, and underdiagnoses the disease in about 25-40% of cases (2, 3, 16-18).

It has been shown that up to 40% of malignancies, initially classified low-risk by means of GS, were upstaged and the patients finally underwent prostatectomy (19). Given the fact that 70-80% of primary biopsies are negative, it remains unclear whether these are truly negative, or simply limitations of TRUS or PSA and DRE or both (20). The ultimate goal of prostate cancer screening will be to differentiate between clinically significant cancers requiring immediate intervention, and low-risk cancers that can be managed by watchful waiting as a preliminary approach.

Table IV. Diagnostic performance of mpMRI/US-fusion biopsy (Chi-square test¹, Fisher's exact test²).

Carcinoma-detection	Carcinoma (GS ≥ 6)	Low-Grade (GS 6+7a)	High-Grade (GS 7b+8+9)	High- vs. Low-Grade
Sensitivity	84.8%	83.3%	87.5%	87.5%
Specificity	51.5%	51.5%	51.5%	16.7%
PPV	77.8%	68.6%	56.8%	37.5%
NPV	63.0%	70.8%	85.0%	70.0%
Test-value	14.667 ¹	10.314 ¹	9.286 ¹	9.286 ²
p-Value	<0.001	<0.001	0.002	0.740

Recent advances in mpMRI have considerably expanded diagnostic options in prostate cancer management (21-23). This can be used to identify critical tissue alterations for biopsy purposes, thus supporting accurate grading and staging, *e.g.* by means of PR and GS, as shown in tables II, III and IV. In our study 73% of PR 4 or 5 alterations were identified by use of this approach, indicating that approximately 75% of patients displayed suspicious lesions despite previous negative core biopsies.

In this study, only 30% of biopsies were negative, and most likely, other reasons (inflammatory disease and/or benign prostate hyperplasia) accounted for increased PSA levels. In the remaining 70% of our study population, prostate cancer was histologically-proven in the targeted lesions only, and not on random sampling. Stratification by tumor grade yielded 2/3 low-grade carcinoma (GS $\leq 7a$), *versus* 1/3 of patients high-grade carcinoma (GS $\geq 7b$), the latter requiring immediate intervention. While these results are in accordance to the results of other authors (24), it has to be noted that not every cancer will be detected by mpMRI. Recent studies (25, 26) indicate a false negative rate between 30% and 50%, however most of these are attributed to GS 6 lesions, and to a lesser extent GS 7 lesions. Sporadically however, even GS 8 malignancies were not seen. But, even if mpMRI fails to detect every tumor, the diagnosis of high-grade tumors seems to be improved by mpMRI (1, 27), as 88% of the patients in our series, diagnosed with high-grade carcinoma, were graded PR 4-5 in mpMRI, and were undetected in previous biopsies. In this study every high-grade carcinoma found in the peripheral zone was detected by mpMRI and classified with PR 4 or 5.

Ultimately, one of the most fundamental issues in prostate imaging is the ability of the modality to predict histological tumor grading on pathology. In this study malignancy, as confirmed by GS, was detected in 38% of patients with PR 3, in 70% with PR 4 and in 82% with PR 5. Interestingly however, 2 of 6 patients with PR 1 or 2 lesion were also found to harbour cancer, and one of these was even a high-grade tumor. Two out of three cases with PR 1-2 had no malignancy,

while 1/3 of cases were classified with GS 7a-7b. The probability of these 33% (1 patient each) was almost expectable in our collective. In our study, 3/21 high-grade lesions detected with PR 4-5 were GS 8 (14%) and 5/21 lesions were GS 9 (24%) (Tables II and IV).

In our study, we calculated a sensitivity of 88% for identification of high-grade carcinoma, with a NPV of 85%. These results are nearly in accordance with previously published data by Siddiqui *et al.*, who investigated the identifiability of \leq GS 7a and \geq GS 7b tumors as assessed by standard and fusion biopsy in 1,003 patients (13). The authors showed that use of fusion biopsy resulted in identification of 30% more high-risk and 17% less low-risk malignancies when compared to standard biopsy, with a NPV of 70% and 53%, respectively. Despite the significant benefits of using mpMRI, it is well understood that some clinically significant malignancies might not be detected in imaging (28-30). For this reason, it has been emphasized that supplementary samples should be obtained during the same procedure, and a combination of complementary biopsy methods could impose a new standard of prostate cancer detection (22, 28-33). In our study, cancer was detected within random biopsy in only two patients.

Conclusion

As imaging technologies improve, screening modalities and clinical surveillance patterns of prostate cancer change. Real-time tumor targeting, image fusion, and risk stratification, using highly specific scoring systems, impose a powerful diagnostic tool at the radiology/pathology interface, that will ultimately help to minimize unnecessary intervention and increase detection rates of clinically significant cancer.

In this study, we present the results from a single center series of 99 patients with increased PSA plasma levels and negative standard biopsy results undergoing mpMRI and US-fusion-guided biopsy to detect significant cancer of the prostate. In these selective cases, 67% were found to harbor malignancy.

In the present study, prostate carcinoma (GS 6-9) was discovered with a sensitivity of 85% and a NPV of 63% ($p < 0.001$), in patients with prior negative conventional biopsies. 24 High-grade carcinomas were identified, along with 42 low-grade lesions. Twenty-one of the high-grade carcinomas identified, corresponded directly with a PR 4-5 lesion on mpMRI, thus resulting in a sensitivity of 88% and a NPV of 85% ($p = 0.002$).

In addition, 35 of 42 patients (83%) with PR 4-5 lesion on mpMRI, were diagnosed as low-grade carcinoma-positive ($p < 0.001$). Malignancy rates as well as high-grade carcinomas were significantly associated with a high PR (4 and 5). Differentiation between high- and low-grade carcinomas (GS $\leq 7a$ vs. $\geq 7b$) by means of PR related to a sensitivity of 88% and a NPV of 70% ($p = 0.74$).

Our results support the view that the mpMRI/US-fusion biopsy promotes considerably higher detection rates of clinically relevant prostate malignancies than do conventional diagnostic procedures. With regard to the differentiation between high- and low-grade carcinomas, no statistical significance could be shown.

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