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Erstveröffentlichung in / First published in:

Urologia Internationalis. 2019, 102(1), S. 20 – 26 [Zugriff am: 23.01.2020]. Karger. ISSN 1423-0399.

DOI: https://doi.org/10.1159/000492495

Original Paper

Urologia Internationalis

Urol Int 2019;102:20–26
DOI: 10.1159/000492495

Received: July 5, 2018
Accepted: July 27, 2018
Published online: August 27, 2018

Evaluation of Transperineal Magnetic Resonance Imaging/Ultrasound-Fusion Biopsy Compared to Transrectal Systematic Biopsy in the Prediction of Tumour Aggressiveness in Patients with Previously Negative Biopsy

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Keywords

Magnetic resonance imaging/Ultrasound-fusion biopsy · Prostate cancer · Multiparametric magnetic resonance imaging · Systematic biopsy · Previous negative biopsy · Prostatectomy · Prediction

Abstract

Objectives: We compared the transperineal MRI/ultrasound-fusion biopsy (fusPbx) to transrectal systematic biopsy (sysPbx) in patients with previously negative biopsy and investigated the prediction of tumour aggressiveness with regard to radical prostatectomy (RP) specimen. ***Material and Methods:*** A total of 710 patients underwent multiparametric magnetic resonance imaging (mpMRI), which was evaluated in accordance with Prostate Imaging Reporting and Data System (PI-RADS). The maximum PI-RADS (maxPI-RADS) was defined as the highest PI-RADS of all lesions detected in mpMRI. In case of proven prostate cancer (PCa) and performed RP, tumour grading of the biopsy specimen was compared to that of the RP. Significant PCa (csPCa) was defined according to Epstein criteria. ***Results:*** Overall, scPCa was detected in 40% of patients. The detection rate of scPCa was 33% for fusPbx and 25% for sysPbx alone ($p < 0.005$). Patients with a maxPI-RADS ≥3 and a prostate specific antigen (PSA)-density ≥0.2 ng/mL^2 harboured more csPCa than those with a PSA-density <0.2 ng/mL^2 (41% [33/81] vs. 20% [48/248]; $p < 0.001$). Compared to the RP specimen ($n = 140$), the concordance of tumour grading was 48% ($\gamma = 0.57$), 36% ($\gamma = 0.31$) and 54% ($\gamma = 0.6$) in fusPbx, sysPbx and comPbx, respectively. ***Conclusions:*** The combination of fusPbx and sysPbx outperforms both biopsy modalities in patients with re-biopsy. Additionally, the PSA-density may represent a predictor for csPCa in patients with maxPI-RADS ≥3.

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Introduction

In the last decade, multiparametric magnetic resonance imaging (mpMRI) of the prostate has become an established diagnostic tool for prostate cancer (PCa) [1, 2]. Targeted biopsy of tumour-suspicious lesions in mpMRI has been demonstrated as a promising method for PCa detection [3–6]. Moreover, it has been shown that targeted biopsy detects significantly more high-risk PCa than systematic biopsy (sysPbx) alone [3–6]. As a consequence, most of the current guidelines recommend mpMRI and consecutive targeted biopsy in patients in whom suspicion of PCa remained after a negative biopsy [7–10]. Previous studies have reported the benefit of MRI/ultrasound-fusion biopsy (fusPbx) in higher detection rates for clinically significant PCa (csPCa) in both biopsy-naïve patients and patients with previously negative prostate biopsy [4–6, 11–15].

In addition, fusPbx has shown a higher concordance of tumour grading compared to that of the radical prostatectomy (RP) specimen [16–19]. Therefore, fusPbx represents a more accurate tool in terms of prediction of tumour aggressiveness.

The aim of this study was to assess the value of mpMRI by comparing targeted fusPbx with sysPbx and the combination of both biopsy modalities (comPbx) in patients with previously negative biopsy. Additionally, in patients with proven PCa undergoing RP, we compared the tumour grading of the biopsy to that of the RP specimen.

Patients and Methods

Recruitment and Study Endpoints

Patients with suspected PCa due to elevated prostate specific antigen (PSA) level (≥4.0 ng/mL) and/or abnormal digital-rectal examination and at least one previously negative prostate biopsy were included. Patients with mpMRI, without evaluation of lesions according to START criteria [20–22], were excluded.

This study was approved by the Institutional Review Board of the Technische Universität Dresden (Votes: EK53022014).

Patients underwent transperineal fusPbx combined with transrectal sysPbx. The primary endpoint was the proportion of patients diagnosed with csPCa, defined according to Epstein criteria (presence of Gleason Score [GS] ≥7 [3 + 4] or a GS 6 [3 + 3] with a cancer core involvement ≥50% or ≥3 positive cores) in at least one of both biopsy modalities.

Investigations of Multiparametric MRI

Prostate mpMRIs were performed on 3-Tesla MR-systems by Siemens (Siemens Medical Solutions, Erlangen, Germany) without the use of endorectal-coils. MpMRI protocols included T2-weighted images in axial and coronal orientations, T1-weighted images, diffusion-weighted images, dynamic contrast-enhanced imaging, and contrast-enhanced T1-weighted images in transverse orientation. The total mpMRI acquisition time was approximately 30 min. The evaluation of mpMRI-data was performed by 2 uro-radiologists with an experience of 10 and 8 years in evaluating prostate mpMRI.

Tumour-suspicious lesions were evaluated by the Prostate Imaging Reporting and Data System (PI-RADS) classifications v1 and v2 [20–22]. The maximum PI-RADS (maxPI-RADS) in mpMRI was defined as the lesion with the highest PI-RADS of all lesions per patient. Analysis of detection rates in lesions detected in mpMRI was performed on both patient-based (maxPI-RADS) and lesion-based (all lesions in mpMRI of all patients) levels.

Prostate Biopsy and Histopathological Examination

The BioJet-System (d&k Technologies, Barum, Germany) was used for fusPbx, as described previously [23]. Briefly, fusPbx was performed in a transperineal approach while taking at least 2 cores per lesion depending on the size of the lesion. Due to a better targeting of lesions located in the anterior zone of the prostate, the transperineal approach was chosen for targeted biopsy. Lesions classified as PI-RADS ≥2 were biopsied in a targeted fashion. Subsequently, every patient underwent a conventional, transrectal 12-core sysPbx. The procedure was performed under general anaesthesia (larynx mask) or under sedation. Both biopsy modalities were performed by the same urologist. The detection rate of PCa in fusPbx and sysPbx were compared. The concordance, up- and downgrading of GS in PCa detected in fusPbx and sysPbx compared to the GS of RP specimen were analysed. Tumour aggressiveness was expressed by GS. The pathological stage was determined according to the 2010 TNM classification.

Statistical Analysis

Data were analysed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Categorical data are presented as absolute and relative frequencies. Continuous variables are described as means, complemented by median and range. The Student *t* test and the χ^2 test were applied to determine differences between continuous and categorical variables. The McNemar test was used to compare the detection rate of fusPbx with sysPbx and comPbx. A p value < 0.05 was considered as statistically significant. Uni- and multivariate logistic regression analyses were used to evaluate the prediction of csPCa in prostate biopsy stratified to age, number of previous biopsies, PSA, PSA-density, prostate volume, number of lesions, localisation of lesions, maxPI-RADS ≥3 and maxPI-RADS ≥4. The Goodman-Kruskal-gamma (γ) statistic was used as a measure of correlation between the tumour grading of the biopsy and RP specimen. A $\gamma = 1$ indicates a concordance of 100%.

Results

Patients' Characteristics and Detection Rates of csPCa in fusPbx and sysPbx

A total of 1,115 patients underwent comPbx at our institution from January 2013 to April 2017. Of which, 767 patients with previously negative prostate biopsy and fur-

ther suspicion of PCa underwent repeat biopsy. Fifty-seven patients were excluded due to incomplete mpMRI data. Therefore, 710 patients were included in this study. Patients' characteristics are depicted in Table 1. In comPbx, the overall PCa detection rate was 48% (338/710), whereby csPCa was detected in 40% (282/710). FusPbx detected more PCa of any GS than sysPbx (39% [275/710] vs. 32% [225/710]; $p < 0.005$). Moreover, fusPbx detected more csPCa than sysPbx (33% [234/710] vs. 25% [176/710]; $p < 0.005$). ComPbx outperforms fusPbx and sysPbx in the detection of csPCa (40 vs. 33% [$p < 0.005$] and vs. 25% [$p < 0.005$], respectively). Regarding the missing rates of csPCa, fusPbx alone would have missed 17% (48/282) whereas sysPbx alone would have missed 38% (106/282).

Evaluation of mpMRI

Regarding all mpMRI lesions detected in all included patients, 1,282 lesions were detected. CsPCa was found in 5% (13/239), 15% (78/523), 29% (107/369) and 62% (93/151) of lesions classified as PI-RADS 2, 3, 4 and 5, respectively.

Regarding the maxPI-RADS, detection rate for csPCa was 14% (11/81), 28% (70/248), 43% (110/257) and 74% (91/124) in patients presenting maxPI-RADS2, maxPI-RADS3, maxPI-RADS4 and maxPI-RADS5, respectively.

In patients with maxPI-RADS2 ($n = 81$), csPCa was detected in 12% ($n = 11$) by sysPbx and in 7% ($n = 6$) by fusPbx ($p = 0.219$), respectively. Only in 1 patient with maxPI-RADS2, csPCa was detected by fusPbx alone. Patients presenting a maxPI-RADS ≥4 showed a higher detection rate of csPCa than patients presenting a maxPI-RADS ≤3 (53 [201/381] vs. 25% [81/329]; $p < 0.001$). Regarding the localisation of lesions harbouring csPCa ($n = 291$), 41% ($n = 121$), 29% ($n = 84$) and 30% ($n = 86$) were located in the peripheral, central and anterior zone of the prostate, respectively.

Prediction of csPCa

In multivariate analysis, the strongest independent predictors for csPCa in comPbx and fusPbx were a high PSA value and density, a higher age, a small prostate, the evidence of at least one PI-RADS ≥4 lesion and an anteriorly located lesion. The localisation and grade of suspicion of the lesion did not predict csPCa in sysPbx (Table 2).

Patients with maxPI-RADS ≤3 ($n = 329$) and a PSA density ≥0.2 ng/mL^2 harboured more csPCa than those with a PSA density <0.2 ng/mL^2 (41% [33/81] vs. 20% [48/248]; $p < 0.001$). Table 3 represents detection rates of csPCa stratified to the PSA density and maxPI-RADS.

Table 1. Patients' demographics, findings on mpMRI and histopathology of prostate biopsy cores

Parameter	Value
Age, years, median (IQR)	67 (61–72)
Number of previous prostate biopsies, median (IQR)	1 (1–2)
Number of patients with previous negative fusPbx combined with sysPbx, *n* (%)	38 (5)
PSA, ng/mL, median (IQR)	8.8 (6.3–12.9)
PSA density, ng/mL^2, median (IQR)	0.15 (0.08–0.28)
Suspicious findings in DRE, *n* (%)	83 (12)
Prostate volume, mL, median (IQR)	50.0 (35.0–69.5)
Overall biopsy cores per patient, *n*, median (IQR)	19 (17–21)
Targeted biopsy cores per patient, *n*, median (IQR)	7 (5–9)
Systematic biopsy cores per patient, *n*, median (IQR)	12 (12–12)
Ratio of positive cores to total cores in targeted biopsy per patient, %, mean ± SEM	7±0.5
Ratio of positive cores to total cores in systematic biopsy per patient, %, mean ± SEM	18±1
Number of lesions/patient, *n*, median (IQR)	2 (1–2)
MRI before prostate biopsy, n	
Total number of lesions	1,282
PI-RADS of lesion, *n*	
2	239
3	523
4	369
5	151
maxPI-RADS, *n* (%)	
2	81 (11)
3	248 (35)
4	257 (36)
5	124 (18)
Histological findings (n) *in combined prostate biopsy*	
Gleason score of biopsy (combination of targeted and systematic biopsy), *n*	
No tumour	372
3 + 3 = 6 (clinically significant 3 + 3 = 6[#])	76 (20)
3 + 4 = 7	161
4 + 3 = 7	42
≥8	59

[#] Gleason score 3 + 3 = 6 and ≥50% tumour involvement or ≥ 3 cores positive.

IQR, interquartile range; SEM, standard error of the mean; PSA, prostate specific antigen.

Comparison of Biopsy Specimen with Prostatectomy Specimen

Around 41% (140/338) of patients with proven PCa underwent RP whereby 26% (37/140) presented an unfavourable pathological tumour stage (≥pT3). Five patients (4%) presented lymph node metastasis (pN1). In these patients,

Table 2. Multivariate logistic regressions analysis for the determination of predictors for the detection of significant prostate cancer in the combination of fusion biopsy and systematic biopsy (comPbx), fusion biopsy alone (fusPbx) and systematic biopsy alone (sysPbx)

Co-variate	Comparison	ComPbx		FusPbx		SysPbx	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, years, median 67a	≥ vs. < median	**2.0 (1.4–2.9)**	**<0.005**	**1.6 (1.1–2.3)**	**0.017**	**1.8 (1.2–2.5)**	**0.002**
Number of previous biopsies	> vs. ≤1 biopsy	–	–	–	–	**0.5 (0.37–0.8)**	**0.002**
PSA, median 8.8 ng/mL	≥ vs. < median	**2.4 (1.6–3.5)**	**<0.005**	**2.4 (1.6–3.7)**	**<0.005**	**1.8 (1.2–2.8)**	**0.009**
PSA density	≥ vs. <0.2 ng/mL^2	**1.8 (1.2–2.8)**	**0.005**	**1.6 (1.03–2.5)**	**0.036**	1.6 (0.9–2.4)	0.454
Prostate volume, median 50 mL	≥ vs. < median	**0.3 (0.2–0.5)**	**<0.005**	**0.3 (0.2–0.5)**	**<0.005**	**0.5 (0.3–0.7)**	**<0.005**
Number of lesions	> vs. ≤1 lesion	**0.62 (0.4–0.9)**	**0.011**	0.7 (0.5–1.01)	0.057	**0.5 (0.4–0.7)**	**0.002**
Localisation of lesions	Anterior zone vs. peripheral and central	**1.9 (1.2–2.8)**	**0.004**	**2.5 (1.6–3.7)**	**<0.005**	–	–
MaxPI-RADS ≥3	≥3 vs. ≤2	**2.4 (1.2–5.1)**	**0.018**	**2.9 (1.2–7.3)**	**0.023**	1.6 (0.8–3.6)	0.188
MaxPI-RADS ≥4	≥4 vs. ≤3	**1.9 (1.3–2.9)**	**0.001**	**2.5 (1.6–3.8)**	**<0.005**	2.3 (0.8–1.9)	0.255

If the co-variate was not statistically significant in univariate analysis, it was not considered for multivariate analysis. Significant parameters are depicted in bold. PSA, prostate specific antigen.

Table 3. Detection rates and accuracy for clinically significant PCa in patients with PSA density ≥0.2 vs. <0.2 ng/mL^2 stratified to the maxPI-RADS

PSA-density, ng/mL^2	ComPbx				FusPbx				SysPbx			
	<0.2	≥0.2	*p* value	accuracy	<0.2	≥0.2	*p* value	accuracy	<0.2	≥0.2	*p* value	accuracy
MaxPI-RADS 2 (*n* = 81), % (*n*)	11 (7/61)	20 (4/20)	0.334	0.72	7 (4/61)	10 (2/20)	0.610	0.73	10 (6/61)	20 (4/20)	0.230	0.73
MaxPI-RADS 3 (*n* = 248), % (*n*)	22 (41/187)	48 (29/61)	<0.005	0.71	16 (30/187)	31 (19/61)	0.010	0.71	14 (27/187)	36 (22/61)	<0.005	0.73
MaxPI-RADS 4 (*n* = 257), % (*n*)	29 (45/155)	64 (65/102)	<0.005	0.68	23 (36/155)	57 (58/102)	<0.005	0.69	20 (30/155)	32 (33/102)	0.018	0.61
MaxPI-RADS 5 (*n* = 124), % (*n*)	53 (25/47)	86 (66/77)	<0.005	0.71	47 (22/47)	83 (64/77)	<0.005	0.71	32 (15/47)	51 (39/77)	0.41	0.57

PSA, prostate specific antigen.

the mpMRI did not show evidence of lymph node metastasis; 6% (*n* = 9), 60% (*n* = 83), 26% (*n* = 36) and 8% (*n* = 11) of patients demonstrated a GS 6, GS 7 (3 + 4), GS 7 (4 + 3) and GS ≥8 PCa, respectively. In 1 patient, the GS could not be defined due to neoadjuvant androgen deprivation therapy. Clinically, no patient presented distant metastasis at the time of diagnosis. Concordance on GS between biopsy and RP specimen was 48% (*n* = 67), 36% (*n* = 50) and 54% (*n* = 75) in fusPbx, sysPbx and comPbx, respectively. Upgrading on GS between biopsy and RP specimen occurred in 36% (*n* = 50), 51% (*n* = 72) and 25% (*n* = 35) in fusPbx, sysPbx and comPbx, respectively. Gamma correlation for the detection of any PCa was γ = 0.60 for comPbx, γ = 0.57 for fusPbx alone and γ = 0.31 for sysPbx alone.

Discussion

We demonstrated that fusPbx detected significantly more PCa of any GS and especially csPCa than sysPbx in patients with previously negative prostate biopsy and further suspicion of PCa. More important, fusPbx seems to be a better predictor than sysPbx for the final tumour grading in the RP specimen. Especially, the latter is essential for counselling patients for further treatment options. Moreover, a PSA density ≥0.2 ng/mL^2 seems to be predictive for csPCa in patients presenting lesions classified as maxPI-RADS ≤3, suggesting that PSA density may represent a predictor for csPCa in this subgroup of patients.

Previous studies reported that the suspicion level of lesions described in mpMRI was positively associated with the detection rate of csPCa [3, 4, 24]. An enhancement of diagnostic accuracy of mpMRI for the detection of high-risk PCa was demonstrated in biopsy-naïve patients [11]. Moreover, the superiority of fusPbx versus sysPbx was shown in a recently published prospective trial evaluating mpMRI and targeted biopsy alone in case of suspicious lesions versus sysPbx alone without the integration of mpMRI [12]. As expected, patients presenting PI-RADS ≥4 lesions showed a higher detection rate of csPCa than patients presenting PI-RADS ≤3 lesions in our cohort. Additionally, multivariate analysis demonstrated that the presence of maxPI-RADS ≥4 was an independent predictor for csPCa in comPbx and fusPbx, but not for sysPbx.

Regarding missing rates of csPCa, our study revealed that fusPbx alone would have missed 17% whereas sysPbx alone would have missed 38%. Other studies showed that sysPbx alone would still detect an important number of intermediate and high-risk PCa either in the case of a negative mpMRI or one that was missed in targeted biopsy [25, 26]. Filson et al. [27] also reported that csPCa would be missed in up to 12% if systematic biopsies were not performed in patients without tumour-suspicious lesions in mpMRI, demonstrating that fusPbx cannot still replace sysPbx. As shown in recent studies [21, 28, 29], it is still important to consider clinical factors in the decision for further biopsies in patients with previously negative biopsy beside the mpMRI. In the current study, multivariate analysis showed that beside the evidence of a highly suspicious and anteriorly located lesion in mpMRI, clinical factors like a higher age, higher PSA levels and PSA density are associated with the detection of csPCa.

Moreover, Hansen et al. [3] suggested that the evidence of a negative or low-suspicious mpMRI (PI-RADS ≤3) associated with a PSA density ≤0.2 ng/mL^2 may omit an immediate repeat prostate biopsy in patients with a previously negative prostate biopsy. Moreover, Gomez Rivas et al. [30] suggested in a systematic review about the value of intermediate or equivocal lesions that the combination of mpMRI, clinical parameters, biomarkers and nomograms may allow a more accurate decision for or against a biopsy in these patients. Also in our cohort, especially patients with maxPI-RADS ≤3 and a PSA density ≥0.2 ng/mL^2 showed a higher detection rate of csPCa highlighting the importance of PSA density in the prediction of csPCa in this subgroup. However, the detection rate of csPCa in patients with maxPI-RADS ≤3 and PSA density <0.2 ng/mL^2 is still 20%. Consequently, we still recommend prostate biopsy in these patients. In this study, most of the lesions harbouring csPCa are located anteriorly or in the transition zone of the prostate and are not easily reached by sysPbx. Also, other study groups reported that anteriorly located tumours are frequently identified using MRI targeted biopsy [31].

Additionally, we showed that 57% of patients with maxPI-RADS of 4 and 26% of patients with maxPI-RADS of 5 did not harbour csPCa. Chelluri et al. demonstrated that most patients with mainly low- or intermediate-suspicious lesions on initial mpMRI and negative targeted biopsies presented in a follow-up targeted biopsy no PCa or low-grade PCa [32]. In contrast, Costa et al. [33] found that in patients with high-suspicious lesions in mpMRI and negative targeted biopsy, a high proportion of men harboured intermediate- or high-risk PCa in these lesions either in repeat targeted biopsy or in comparison to the RP specimen.

Our present findings demonstrated that comPbx is the most accurate predictor for final tumour grading in the RP specimen. Especially, fusPbx seems to majorly contribute to the prediction of tumour aggressiveness in comPbx in a repeat biopsy setting. Previous studies also demonstrated that fusPbx showed a better concordance of tumour grading in RP specimen than sysPbx. However, comPbx outperforms fusPbx and sysPbx alone [5, 16–19]. Based on these data, comPbx should be offered to patients with previous negative sysPbx. In case of a repeated negative comPbx and the presence of high-suspicious lesions in mpMRI or further PSA progress, a follow-up biopsy should be performed in a short interval. Patients with low-suspicious lesions and low PSA density should still undergo sysPbx.

Our study has several limitations. First, fusPbx and sysPbx were performed consecutively by the same urologist in an unblinded manner. Consequently, knowledge about the location of lesions in mpMRI could have influenced the operator in needle placement during sysPbx and could have resulted in a falsely high detection rate in sysPbx. Currently, data of the recently published PRECISION trial showed a superiority of fusPbx in biopsy-naïve patients [12]. Furthermore, prospective data are needed to clarify this issue in a re-biopsy cohort as well. Second, we did not perform a direct comparison of mpMRI and whole-mount prostatectomy specimen as previously described [17]. Data of this study are based only on the reported GS of biopsy and RP specimen; however, we performed the comparison in only 41% of patients with proven PCa. Lastly, we did not perform a standardised long-term follow-up assessment, especially in patients with negative repeat biopsy and higher suspicious levels in mpMRI. Recently published data have sug-

gested that negative targeted biopsies do not exclude csPCa in this subgroup of patients [33]. This should be considered in the further follow-up of these patients.

Conclusions

For men with previously negative biopsy, the combination of comPbx outperforms both biopsy modalities alone regarding the detection rate of csPCa and concordance of tumour grading compared to the RP specimen. However, the missing rate of csPCa in fusPbx is still high. Additionally, the PSA density may represent a predictor for csPCa in comPbx in patients with maxPI-RADS ≤3. Therefore, comPbx should still be recommended in patients with previously negative prostate biopsy and persisting suspicion of PCa.

Disclosure Statement

The authors declare that they have no conflict of interest.

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