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Original Article

Added value of randomised biopsy to multiparametric magnetic resonance imaging-targeted biopsy of the prostate in a contemporary cohort

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Objective

To assess the added value of concurrent systematic randomised ultrasonography-guided biopsy (SBx) to multiparametric magnetic resonance imaging (mpMRI)-targeted biopsy and the additional rate of overdiagnosis of clinically insignificant prostate cancer (ciPCa) by SBx in a large contemporary, real-world cohort.

Patients and Methods

A total of 1552 patients with positive mpMRI and consecutive mpMRI-targeted biopsy and SBx were enrolled. Added value and the rate of overdiagnosis by SBx was evaluated. Primary outcome: added value of SBx, defined as detection rate of clinically significant PCa (csPCa; International Society of Urological Pathology [ISUP] Grade ≥2) by SBx, while mpMRI-targeted biopsy was negative or showed ciPCa (ISUP Grade 1). Secondary outcome: rate of overdiagnosis by SBx, defined as detection of ciPCa in patients with negative mpMRI-targeted biopsy and PSA level of <10 ng/mL.

Results

Detection rate of csPCa by mpMRI-targeted biopsy and/or SBx was 753/1552 (49%). Added value of SBx was 145/944 (15%). Rate of overdiagnosis by SBx was 146/656 (22%). Added value of SBx did not change when comparing patients with previous prostate biopsy and biopsy naïve patients. In multivariable analysis, a Prostate Imaging-Reporting and Data System (PI-RADS) 4 index lesion (odds ratio [OR] 3.19, 95% confidence interval [CI] 1.66–6.78; $P = 0.001$), a PI-RADS 5 index lesion (OR 2.89, 95% CI 1.39–6.46; $P = 0.006$) and age (OR 1.05, 95% CI 1.03–1.08; $P < 0.001$) were independently associated with added value of SBx.

Conclusions

In our real-world analysis, we saw a significant impact on added value and added rate of overdiagnosis by SBx. Subgroup analysis showed no significant decrease of added value in any evaluated risk group. Therefore, we do not endorse omitting concurrent SBx to mpMRI-guided biopsy of the prostate.

Keywords

prostate cancer, multiparametric magnetic resonance imaging-targeted biopsy, systematic randomised biopsy, added value, overdiagnosis

Introduction

Multiparametric MRI (mpMRI) emerged as a new cornerstone in the diagnostic pathway of prostate cancer. The European Association of Urology (EAU) recommends performing an mpMRI before prostate biopsy by a strength rating of 'strong' [1]. Studies showed that mpMRI-ultrasonography (US) fusion-guided biopsy increases the detection rate of clinically significant prostate cancer (csPCa; defined as grading by the International Society of Urological Pathology [ISUP] Grade >1) compared to systematic randomised US-guided biopsy (SBx) [2,3]. Also, it reduces the diagnosis of clinically insignificant PCa (ciPCa) and therefore reduces overdiagnosis [2,3]. However, studies showed that, highest detection rates are gained with the combination of mpMRI-US fusion-guided biopsy and SBx [3,4].

In efforts to safely omit SBx studies established nomograms, expressing the risk of missing csPCa [5,6]. These nomograms do not play a role in clinical practice to date. The EAU guideline recommends omitting SBx in patients with prior negative biopsy [1]. However, omission of SBx inevitably leads to missing out on PCa invisible on mpMRI. By comparing preoperative mpMRI to the whole-mount specimen after radical prostatectomy of 588 patients, Johnson et al. [7] found that mpMRI detected 45% (95% CI 42–47%) of all cancer lesions and 65% (95% CI 61–69%) of clinically significant cancer lesions, respectively. The mpMRI missed at least one clinically significant PCa lesion in every third patient [7]. Data on the role of SBx in trials outside of centres with high experience in assessment of mpMRI are sparse. Studies show worse inter-reader agreement and reproducibility in radiological institutes with moderate experience in mpMRI interpretation compared to high-volume centres [8,9]. A large meta-analysis by the EAU Guideline Panel summarising 48 studies with 9613 patients showed a median (interquartile range [IQR]) negative predictive value of 88.1% (85.7–92.3%) for csPCa. The authors concluded that a main limitation of the use of mpMRI today is a significant variability of technical protocols, mpMRI interpretation and inter-reader reproducibility throughout the evaluated studies [10].

In conclusion, SBx offers the advantage of detection of csPCa, while mpMRI-targeted biopsy is negative (added value by SBx), while simultaneously harbouring the danger of unnecessary detection of ciPCa (overdiagnosis by SBx). We aimed to evaluate added value as well as rate of overdiagnosis of ciPCa in our prospectively maintained database of patients undergoing mpMRI-US fusion-guided biopsy and SBx at the outpatient clinic of our department. Patients' mpMRI had been assessed by a group of 111 radiology offices, resulting in a heterogenous mix of mpMRI expertise.

Patients and Methods

We retrospectively reviewed our prospectively maintained database of patients undergoing mpMRI-targeted biopsy and SBx of the prostate at the outpatient clinic of the Department of Urology at LMU Klinikum in Munich, Germany. Between March 2015 to August 2022, a total of 1552 consecutive patients underwent mpMRI-targeted biopsy and SBx at our department and were considered for analysis. Findings are reported based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for cohort studies [11]. A csPCa was defined as ISUP Grade ≥2, while a ciPCa was defined as ISUP Grade 1.

Added value of SBx was defined as:

- Detection of csPCa by SBx.
- The mpMRI-targeted biopsy showed ciPCa or no evidence of PCa.

Overdiagnosis by SBx was defined as:

- Detection of ciPCa by SBx.
- The mpMRI-targeted biopsy showed no evidence of PCa.
- Patient had a serum PSA level of <10 ng/mL.

Patients were referred for prostate biopsy by either their office urologist or by the outpatient clinic of the Department of Urology of the Ludwig-Maximilian-University of Munich, Germany.

Patients underwent mpMRI at our institution or by a heterogeneous group of radiology offices, including university hospitals, peripheral clinics, private practices, and radiology departments in foreign countries, respectively. Overall, biopsy was performed using mpMRI from 111 different radiology offices. Secondary review of the mpMRI before biopsy was not performed. MpMRI of recruited patients must have been assessed according to current Prostate Imaging-Reporting and Data System (PI-RADS) guidelines according to the radiology report. The mpMRI-targeted biopsy and SBx were conducted by a group of 10 urologists, with an experience of ≥100 procedures/year. According to current guidelines, biopsy was conducted as an mpMRI-targeted biopsy followed by a SBx [1,12]. In 1531/1552 (99%) patients, the SBx comprised of six cores from the left and right prostate lobe (base, mid and apex, 12 cores in total), following comprehensive reviews and national guidelines [12,13]. In very select patients (21/1552 [1.4%]), SBx was reduced to three cores from the left and right prostate lobe (base, mid and apex, six cores in total) due to largely infiltrating index lesions. Fusion of mpMRI and US was performed using plane wise fusion. The axial T2-weighted mpMRI-sequence was used for image fusion. The mpMRI and US fusion was achieved by software in every patient. The software used for fusion was the Philips PercuNav (Medical Systems, Bothell, WA, USA). The mpMRI-targeted biopsy was performed on up to three mpMRI lesions and three biopsy cores per lesion were obtained. In patients with more than one mpMRI target, the lesion with the highest PI-RADS score was considered as the index lesion. The following clinical parameters were evaluated: patient's age (years), total PSA level (ng/mL), history of prior prostate biopsy, result of the DRE, PI-RADS classification of mpMRI-lesions, and histopathology of biopsy cores according to ISUP grading.

All continuous variables were summarised as median with IQR, while all categorical variables were presented as absolute numbers with proportions. We compared the continuous variables using the Mann–Whitney *U*-test and the categorical variables using the chi-squared test. A multivariable logistic regression analysis was performed to assess the effect of clinicopathological parameters (age, PSA, pre-biopsy, and PI-RADS score) on the added value of SBx and on the overdiagnosis of SBx. For all outcomes, we estimated odds ratios (ORs) with 95% CIs. The statistical calculations were

undertaken with the R statistical software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria), GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA), and the software MedCalc version 20 (MedCalc, Ostend, Belgium). A two-sided $P < 0.05$ was considered statistically significant. This study was approved by the local Ethics Committee (#22-0318).

Results

Demographics and Subgroup Analysis

Patient demographics and clinical subgroup analysis are shown in Table 1. In total, 1552 patients underwent mpMRI-targeted biopsy and SBx at the outpatient clinic of the Department of Urology at LMU Klinikum in Munich, Germany, and were included in the final analysis. The median (IQR) age of patients was 68 (62–74) years. The median (IQR) PSA level was 8.05 (5.7–12.04) ng/mL. The median (IQR) PSA density was 0.17 (0.11–0.26) ng/mL/mL. The detection rate of PCa was 1175/1552 (76%). The detection rate of csPCa, defined as ISUP Grade ≥2, was 753/1552 (49%). The detection rate of csPCa by mpMRI-targeted biopsy was 608/1552 (39%). In all, 1179/1552 (76%) patients presented with one mpMRI target, 330/1552 (21%) presented with two mpMRI targets, and 43/1552 (2.8%) presented with three mpMRI targets. The detection rate of ciPCa, defined as ISUP Grade 1, by mpMRI-targeted biopsy was 285/1552 (18%). A total of 145/944 (15%) patients showed an added value of SBx, meaning detection of csPCa by SBx, while mpMRI-targeted biopsy showed ciPCa or no evidence of PCa. In all, 146/656 (22%) patients were over diagnosed by SBx, meaning detection of ciPCa, while mpMRI-targeted biopsy showed no evidence of PCa and the PSA level was <10 ng/mL.

We aimed to evaluate the added value of SBx, as well as the rate of overdiagnosis by SBx, in clinical subgroups. Subgroups were categorised according to the preoperative clinical risk of harbouring csPCa. The added value of SBx in patients with a PI-RADS 3 index lesions was 12/179 (6.7%), in those with PI-RADS 4 index lesions it was 81/456 (18%), and in patients with PI-RADS 5 index lesions it was 40/203 (20%). Calculating a ratio of patients experiencing an added value of SBx divided by patients experiencing overdiagnosis, we calculated a ratio of 0.68 for the overall cohort. Regarding patients with PI-RADS 3 index lesions, we calculated a ratio of 0.29, for patients with PI-RADS 4 index lesions we calculated a ratio of 0.78, and for patients with PI-RADS 5 index lesions we calculated a ratio of 1. Regarding pre-biopsy status, added value and rate of overdiagnosis by SBx did not differ significantly comparing biopsy-naïve patients and patients with prior prostate biopsy. The calculated ratio of added value of SBx divided by overdiagnosis by SBx was 0.56 for patients with prior biopsy. For patients with a DRE suspicious of PCa (DRE positive) the added value of SBx was significantly higher compared to DRE-negative patients (31/96 [32%] vs 47/391 [12%]; $P < 0.001$). The calculated ratio of patients experiencing an added value of SBx divided by patients experiencing overdiagnosis by SBx was 1.4 for DRE-positive patients.

On further analysis of patients who were shown to have an added value of SBx, meaning detection of csPCa by SBx, while mpMRI-targeted biopsy showed ciPCa or no evidence of PCa, a median (IQR) of two (one–three) of the 12 cores of SBx showed csPCa. The location of csPCa-positive biopsies was in 108/283 positive biopsies (38%) in the apical zone, in 95/283 (34%) in the central zone, and in 80/283 (28%) in the basal zone of the prostate. After retrospective comparison of the location of the mpMRI target lesion, according to the radiology report, and the location of csPCa-positive cores, csPCa of 57/145 (39%) patients was detected in proximity to the target lesion by SBx.

A comparison of patients with and without an added value of SBx in patients diagnosed with csPCa (cancer prevalence group, $n = 753$) is shown in Table S1. For the cancer prevalence group, 145/753 (19%) patients diagnosed with csPCa were detected by SBx, while mpMRI-targeted biopsy was negative or showed ciPCa.

Multivariable Logistic Regression Analysis

The subgroups categorised according to the risk of harbouring csPCa were further analysed by multivariable logistic regression (Table 2). The DRE status was excluded from the analysis, because of insufficient data completeness in our cohort (808/1552 [52%]). In multivariable logistic regression, patient age was independently associated with an added value of SBx (OR 1.05, 95% CI 1.02–1.08; $P < 0.001$). Furthermore, a PI-RADS 4 index lesion (OR 3.19, 95% CI 1.66–6.78; $P = 0.001$) and a PI-RADS 5 index lesion (OR 2.89, 95% CI 1.39–6.46; $P = 0.006$) were independently associated with an added value of SBx.

Discussion

The addition of SBx to mpMRI-US fusion-guided biopsy represents advantages in terms of improvement in the overall detection rate and disadvantages in terms of overdiagnosis. Efforts are made to identify those patients in which SBx can safely be omitted, without affecting detection rate of csPCa. We therefore aimed to investigate the role of SBx in our prospectively maintained high-volume database working with a plethora of radiology offices with heterogenous mpMRI expertise. We conclude that the added value of SBx is substantial and not to be neglected in any analysed risk group.

The overall detection rate of csPCa of 49% in our real-world study is comparable to the detection rate of hallmark studies. In a large prospective study by Ahdoot et al. [3] evaluating

Table 1 Patient characteristics (A) and subgroup analysis (B) compared to the overall cohort.

(A)

Characteristics	Value
Number of patients, *n*	1552
Age, years, median (IQR)	68 (62–74)
PSA, ng/mL, median (IQR)	8.05 (5.7–12.04)
PSA density, ng/mL/mL, median (IQR)	0.17 (0.11–0.26)
Pre-biopsy, *n/N* (%)	472/1332 (35)
DRE positive, *n/N* (%)	304/808 (38)
Index lesion PI-RADS 3, *n/N* (%)	199/1394 (14)
Index lesion PI-RADS 4, *n/N* (%)	681/1394 (49)
Index lesion PI-RADS 5, *n/N* (%)	514/1394 (37)
Detection rate of PCa, *n/N* (%)	1175/1552 (76)
Detection rate of csPCa, *n/N* (%)	753/1552 (49)
Detection rate of csPCa by mpMRI-targeted biopsy, *n/N* (%)	608/1522 (39)
Added value of SBx, *n/N* (%)	145/944 (15)
Overdiagnosis by SBx, *n/N* (%)	146/656 (22)
Ratio of added value/overdiagnosis by SBx	0.68
No cancer, *n/N* (%)	377/1552 (24)
ISUP Grade 1, *n/N* (%)	422/1175 (36)
ISUP Grade 2, *n/N* (%)	335/1175 (28)
ISUP Grade 3, *n/N* (%)	114/1175 (10)
ISUP Grade 4, *n/N* (%)	232/1175 (20)
ISUP Grade 5, *n/N* (%)	72/1175 (6.1)

(B)

Characteristic	Added value		Overdiagnosis		PI-RADS 3 index lesion	PI-RADS 4 index lesion	PI-RADS 5 index lesion	Pre-biopsy		DRE positive	
	Yes	No	Yes	No				Yes	No	Yes	No
Number of patients, *n/N* (%)	145/944 (15)	799/944 (85)	146/656 (22)	510/656 (78)	199/1394 (14)	681/1394 (49)	514/1394 (37)	472/1332 (35)	860/1332 (65)	304/808 (38)	504/808 (62)
Age, years, median (IQR)	71 (65–76)	67 (60–72)	66 (60–72)	67 (60–72)	65 (58–71)	68 (62–73)	70 (65–76)	68 (62–74)	68 (62–74)	69 (63–75)	68 (62–73)
P	**<0.001**		0.9								
PSA, ng/mL, median (IQR)	8.2 (5.93–11.60)	7.4 (5.20–11.00)	6.20 (4.73–7.48)	6.12 (4.55–7.81)	7.47 (5.25–10.75)	7.38 (5.31–10.40)	9.98 (6.8–16)	9.5 (6.68–15)	7.47 (5.30–11.00)	8.38 (5.7–13)	7.84 (5.38–12.00)
P	0.1		0.9		**0.003**			**<0.001**		0.1	
PSA density, ng/mL/mL, median (IQR)	0.16 (0.11–0.25)	0.15 (0.10–0.21)	0.13 (0.09–0.17)	0.12 (0.08–0.17)	0.14 (0.10–0.20)	0.15 (0.10–0.23)	0.22 (0.14–0.37)	0.18 (0.12–0.28)	0.16 (0.10–0.26)	0.19 (0.12–0.32)	0.15 (0.10–0.24)
P	**0.03**		0.4		**<0.001**			0.1		**<0.001**	
Pre-biopsy, *n/N* (%)	46/145 (37)	282/690 (41)	47/118 (40)	140/440 (32)	71/187 (38)	211/536 (36)	140/442 (32)	472/472 (100)	0/860 (0)	62/299 (21)	188/499 (38)
P	0.4		0.1		0.2					**<0.001**	
DRE positive, *n/N* (%)	31/78 (40)	65/409 (16)	16/78 (21)	55/264 (21)	10/115 (8.7)	112/378 (30)	176/294 (60)	62/250 (25)	237/548 (43)	304/304 (100)	0/504 (0)
P	**<0.001**				**<0.001**			**<0.001**			
Index lesion PI-RADS 3, *n/N* (%)	12/133 (9.0)	167/705 (24)	30/129 (23)	98/446 (22)	(100)	(0)	(0)	71/422 (17)	116/789 (15)	10/298 (3.4)	105/489 (21)
Index lesion PI-RADS 4, *n/N* (%)	81/133 (61)	375/705 (53)	77/129 (60)	260/446 (58)	(0)	(100)	(0)	211/422 (50)	371/789 (47)	112/298 (38)	266/489 (54)
Index lesion PI-RADS 5, *n/N* (%)	40/133 (30)	163/705 (23)	22/129 (17)	88/446 (20)	(0)	(0)	(100)	140/422 (33)	302/789 (38)	176/298 (59)	118/489 (24)
P	**<0.001**		0.8					0.2		**<0.001**	
Detection rate of csPCa, *n/N* (%)	145/145 (100)		0/146 (0)		32/199 (16)	306/681 (45)	351/514 (68)	190/472 (40)	451/860 (60)	239/304 (79)	160/504 (32)
P					**<0.001**			**<0.001**		**<0.001**	
Detection rate of csPCa by mpMRI-targeted Biopsy, *n/N* (%)	0/145 (0)		0/146 (0)		20/199 (10)	225/681 (33)	311/514 (61)	144/472 (31)	328/472 (52)	208/304 (68)	113/504 (22)
P					**<0.001**			**<0.001**		**<0.001**	
Added value of SBx, *n/N* (%)	145/145 (100)		0/146 (0)		12/179 (6.7)	81/456 (18)	40/203 (20)	46/328 (14)	79/487 (16)	31/96 (32)	47/391 (12)
P					**<0.001**			0.4		**<0.001**	
Overdiagnosis by SBx, *n/N* (%)	0/145 (0)		146/146 (100)		30/128 (23)	77/337 (23)	22/110 (20)	47/187 (25)	71/371 (19)	16/71 (23)	62/271 (23)
P					0.8			0.1			
Ratio of added value/overdiagnosis by SBx					0.29	0.78	1	0.56		1.4	
ISUP Grade 1, *n/N* (%)	0/145 (0)	146/146 (100)									
ISUP Grade 2, *n/N* (%)	88/145 (61)	0/146 (0)									
ISUP Grade 3, *n/N* (%)	13/145 (9.0)	0/146 (0)									
ISUP Grade 4, *n/N* (%)	40/145 (28)	0/146 (0)									
ISUP Grade 5, *n/N* (%)	4/145 (2.8)	0/146 (0)									

Continuous values are presented as median (IQR); categorical values are given as number (%). Documentation of clinical data is inconsistent throughout the presented cohort and recorded as follows: Age in 1552/1552 patients (100%), PSA level in 1552/1552 patients (100%), history of prior prostate biopsy in 1332/1552 patients (86%), result of DRE in 808/1552 (52%) patients, PI-RADS classification of the index lesion in 1394/1552 (90%) patients, and histopathological evaluation in 1552/1552 (100%) patients.
Bold values statistically significant at $P < 0.05$.

Table 2 Multivariable logistic regression analysis on clinicopathological parameters associated with (A) an added value of SBx and (B) overdiagnosis by SBx.

Variable	Multivariable	
	P	OR (95% CI)
(A)		
Age [continuous] (years)	**<0.001**	**1.05 (1.03–1.08)**
PSA level [continuous] (ng/mL)	0.2	1.01 (0.99–1.03)
Pre-biopsy (yes vs no)	0.2	0.77 (0.50–1.18)
PI-RADS 3 [Reference]	–	–
PI-RADS 4	**0.001**	**3.19 (1.66–6.78)**
PI-RADS 5	**0.006**	**2.89 (1.39–6.46)**
(B)		
Age [continuous] (years)	0.9	1.00 (0.97–1.03)
PSA level [continuous] (ng/mL)	0.7	1.02 (0.93–1.13)
Pre-biopsy (yes vs no)	0.2	1.32 (0.84–2.08)
PI-RADS 3 [Reference]	–	–
PI-RADS 4	0.6	0.86 (0.52–1.45)
PI-RADS 5	0.5	0.78 (0.39–1.54)

Bold values statistically significant at P < 0.05.

2103 patients undergoing both mpMRI-US fusion-guided biopsy and SBx, the authors reported a detection rate of csPCa (ISUP Grade ≥2) of 44%. In contrast to our study, the study by Ahdoot et al. [3] involved a central review of mpMRI by two expert genitourinary radiologists with more than a decade of experience in mpMRI review. The difference in detection rate might be inherent to the different study populations. The median (IQR) age in our study was 68 (62–74) years and the median (IQR) PSA level was 8.05 (5.7–12.04) ng/mL compared to the mean (SD) age of 63.3 (7.6) years and median (IQR) PSA level was 6.7 (4.6–10.2) ng/mL in the study population by Ahdoot et al. [3]. Comparison of preoperative likelihood of csPCa by mpMRI of the study population by Ahdoot et al. [3] and our study is not applicable as many mpMRIs in the study by Ahdoot et al. [3] are not classified according to PI-RADS. The detection rate of csPCa of 39% by mpMRI-targeted biopsy in our study is also comparable to large multicentre studies. The multicentre, randomised controlled PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION) trial reported a detection rate of csPCa of 38% by mpMRI-targeted biopsy. Comparing clinical characteristics, the age of our study cohort was older (median [IQR] 68 [62–74] years) than in the PRECISION trial (mean [SD] 64.4 [7.5] years). Also, the PSA level in our study cohort was higher (median [IQR] 8.05 [5.7–12.04] ng/mL) than that in the PRECISION trial (median [IQR] 6.75 [5.16–9.35] ng/mL). The distribution of preoperative likelihood of csPCa by mpMRI in the PRECISION trial showed a larger ratio of patients with PI-RADS 3 index lesions compared to our study (29% vs 14%) and a lower ratio of patients with PI-RADS 4 and PI-RADS 5 index lesions, respectively (40% vs 49% for PI-RADS 4, 31% vs 37% for PI-RADS 5).

Studies evaluating the added value of SBx to mpMRI-US fusion-guided biopsy report a wide range of 1.3% to 11% [14]. In our study, 145/944 (15%) patients were diagnosed with csPCa by SBx, while mpMRI-US fusion-guided biopsy showed ciPCa or no malignancy. At first glance, our findings exceed the reported range in current literature. However, determining the appropriate denominator for calculating the added value and overdiagnosis by SBx varies strongly. Previous studies reported an added value referring to all patients undergoing biopsy, resulting in a proportion of patients with csPCa that would have been missed if a target-only approach had been utilised [4]. This way, Rouviere et al. [4] reported an added value of 5.2%. However, the PAIRED CAP trial (ClinicalTrials.gov, identifier: NCT02425228) by Elkhoury et al. [15] reported an added value ranging from 11.5% to 33.3% when using all patients with csPCa as the denominator. A Cochrane meta-analysis from 2019 comprising 20 studies and 3998 patients evaluated an added value of 4.6% [16]. There, the authors defined the added value of SBx as the proportion of patients missed by an mpMRI-targeted biopsy but detected by SBx [16]. In our study, the csPCa of 145/1552 (9.3%) patients undergoing biopsy would not have been detected in the case of an mpMRI-target-only approach. However, we report an added value of 15% to express the proportion of patients who got upgraded by SBx and would otherwise be diagnosed wrong negatively.

Interestingly, in our study cohort, we could not identify a subgroup of patients with a significantly lower added value of SBx. This has been described for patients with prior negative biopsy compared to biopsy-naïve patients. In our study, added value of SBx for biopsy-naïve patients was 16% compared to 14% for patients with prior negative biopsy ($P = 0.4$). The Cochrane meta-analysis reported an added value of 4.9% for biopsy-naïve patients and 2.7% for all patients undergoing biopsy with prior negative biopsy [16]. The EAU guideline recommends omitting SBx in patients with prior negative biopsy by a strength rating of 'weak'. This recommendation cannot be supported after evaluation of our study cohort. Similarly, national guidelines do not recommend omitting SBx in any clinical situation [12]. However, the added value of SBx should be evaluated against the risk of overdiagnosis. Studies showed that combination of SBx and mpMRI-guided biopsy leads to a higher detection rate of ciPCa compared to mpMRI-guided biopsy alone [3,16]. In our study, 146 of the 656 patients with negative mpMRI-targeted biopsy and a PSA level of <10 ng/mL (22%) were over diagnosed by SBx. Even though, we cannot endorse the omission of SBx, patients should be informed about the elevated risk of overdiagnosis by SBx.

Studies defined nomograms to predict the detection rate of csPCa by SBx. In a prospective study by Alqahtani et al. [6] evaluating 198 patients undergoing mpMRI-targeted biopsy

and SBx, the authors retrospectively defined a nomogram with a discriminative ability by a C-index of 78%. In line with our results, patients with a high clinical likelihood of PCa showed the highest added value according to the calculated nomogram [6]. In a retrospective evaluation of 398 patients undergoing mpMRI-targeted biopsy and SBx, Sathianathen et al. [17] defined a nomogram with a discriminative ability by a C-index of 70%. The assessment of this nomogram was based on an even higher added value of SBx of 11.6% compared to our study [17]. The authors did not support subgroup analysis but showed a decrease of adjusted OR on multivariable analysis for diagnosing csPCa by SBx in patients with previous negative biopsy compared to biopsy-naïve patients (adjusted OR 0.19, 95% CI 0.05–0.52) [17]. With an approximately fourfold larger study population of mixed mpMRI expertise, our results did not show a difference of added value in patients with previous biopsy compared to biopsy-naïve patients. In fact, as our study showed substantial added value of SBx in any evaluated subgroup, we do not endorse a nomogram to omit it. Similarly, Dell'Oglio et al. [5] recently published a manuscript titled 'There Is No Way to Avoid Systematic Prostate Biopsies in Addition to Multiparametric Magnetic Resonance Imaging Targeted Biopsies'. In a retrospective analysis of 780 patients at two tertiary centres, the authors failed to establish a risk calculator to identify patients, where SBx might be omitted [5]. The authors observed that even in men with a low likelihood of csPCa, no clinical model could be developed to safely identify patients who could avoid SBx [5]. These results are in line with our study.

As an observational study, our results do not provide causal information on added value and overdiagnosis by SBx. Besides the plethora of radiology offices with heterogenous mpMRI expertise, the reported index lesion could have been missed by the mpMRI-targeted biopsy. Overall, 57/145 (39%) patients showed a csPCa-positive SBx located in proximity (penumbra) to the reported index lesion. However, this retrospective evaluation of the penumbra was conducted according to the radiology report and not by digital review of the mpMRI-targeted biopsy and SBx. By digital comparison of 3552 biopsy cores from 927 men undergoing mpMRI-targeted biopsy and SBx, Brisbane et al. [18] showed that 26% of csPCa-positive cores were located outside the index lesion, but within a 1 cm penumbra. Therefore, the authors suggest implementing a systematic sampling of the 1 cm penumbra of the index lesion rather than complete SBx [18]. Also, increasing the number of biopsy cores could potentially improve detection rate of csPCa by mpMRI-targeted biopsy. In a retrospective study by Lu et al. [19] the authors showed that the detection rate of csPCa could be improved by nearly 25% by using a standardised five-core target biopsy approach compared to a limited two-core target biopsy approach. However, after evaluation of 451 patients undergoing mpMRI-targeted biopsy Beetz et al. [20] showed that the most relevant histopathology was diagnosed by the first three mpMRI-targeted biopsy cores. Addition of a fourth or fifth MRI-guided biopsy did not improve detection rate significantly. This is in line with our study protocol, where a mean of three cores per index lesion was taken.

The present study is not without of limitations. First, it is a single-centre retrospective design. Nevertheless, we report, to our knowledge, one of the largest single-centre cohort studies with multiple surgeons and a heterogeneity of mpMRI expertise aiming to represent routine practice. Furthermore, we cannot report long-term follow-up data of our study cohort. If a positive mpMRI-targeted biopsy and a negative SBx result are present, studies indicate that the impact on cancer-specific mortality is minimal [21]. The impact of our study results on therapy and long-term follow-up remains unknown. Another limitation is the fact that, in most patients, SBx was not altered according to the index lesion. Therefore, overlap between SBx and mpMRI-targeted biopsy is likely to occur, especially in large index lesions. Another limitation is the incompleteness of certain clinical characteristics e.g., DRE status. Finally, we could not determine the role of our multi-radiology approach compared to a central radiology assessment as our study protocol lacks secondary central review.

Conclusion

In summary, the results of this study indicate a substantial added value of SBx to the detection rate of csPCa in combination with mpMRI-guided biopsy. We provide comprehensive data from a large contemporary cohort with a focus of representation of routine practice. In subgroup analysis, we could not identify a significant decrease of added value by SBx. However, we recommend that patients should be informed about the elevated risk of overdiagnosis of ciPCa by SBx. Based on our findings, we do not endorse omitting SBx in this setting.

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Disclosure of Interests

None declared.

References

1 **Mottet N, van den Bergh RCN, Briers E et al.** EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2021; 79: 243–62

2 **Kasivisvanathan V, Rannikko AS, Borghi M et al.** MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018; 378: 1767–77

3 **Ahdoot M, Wilbur AR, Reese SE et al.** MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. *N Engl J Med* 2020; 382: 917–28

4 **Rouviere O, Puech P, Renard-Penna R et al.** Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2019; 20: 100–9

5 **Dell'Oglio P, Stabile A, Soligo M et al.** There is No way to avoid systematic prostate biopsies in addition to multiparametric magnetic resonance imaging targeted biopsies. *Eur Urol Oncol* 2020; 3: 112–8

6 **Alqahtani S, Zhang X, Wei C et al.** Predicting the performance of concurrent systematic random biopsies during image fusion targeted sampling of multi-parametric MRI detected prostate cancer. A prospective study (PRESET study). *Cancers* 2021; 14: 1

7 **Johnson DC, Raman SS, Mirak SA et al.** Detection of individual prostate cancer foci via multiparametric magnetic resonance imaging. *Eur Urol* 2019; 75: 712–20

8 **Muller S, Lilleaasen G, Sand TE et al.** Poor reproducibility of PIRADS score in two multiparametric MRIs before biopsy in men with elevated PSA. *World J Urol* 2018; 36: 687–91

9 **Greer MD, Brown AM, Shih JH et al.** Accuracy and agreement of PIRADSv2 for prostate cancer mpMRI: a multireader study. *J Magn Reson Imaging* 2017; 45: 579–85

10 **Moldovan PC, Van den Broeck T, Sylvester R et al.** What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. *Eur Urol* 2017; 72: 250–66

11 **von Elm E, Altman DG, Egger M et al.** The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453–7

12 Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Prostatakarzinom, Langversion 6.2, 2021, AWMF Registernummer: 043/022OL. http://www.leitlinienprogramm-onkologie.de/leitlinien/prostatakarzinom/ (abgerufen am: 13.11.2022). 2021

13 **Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J.** Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol* 2006; 175: 1605–12

14 **Connor MJ, Miah S, Jayadevan R et al.** Value of systematic sampling in an mp-MRI targeted prostate biopsy strategy. *Transl Androl Urol* 2020; 9: 1501–9

15 **Elkhoury FF, Felker ER, Kwan L et al.** Comparison of targeted vs systematic prostate biopsy in men who are biopsy naive: the Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) study. *JAMA Surg* 2019; 154: 811–8

16 **Drost FH, Osses DF, Nieboer D et al.** Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database Syst Rev* 2019; 4(4): CD012663

17 **Sathianathen NJ, Warlick CA, Weight CJ et al.** A clinical prediction tool to determine the need for concurrent systematic sampling at the time of magnetic resonance imaging-guided biopsy. *BJU Int* 2019; 123: 612–7

18 **Brisbane WG, Priester AM, Ballon J et al.** Targeted prostate biopsy: umbra, penumbra, and value of perilesional sampling. *Eur Urol* 2022; 82: 303–10

19 **Lu AJ, Syed JS, Ghabili K et al.** Role of core number and location in targeted magnetic resonance imaging-ultrasound fusion prostate biopsy. *Eur Urol* 2019; 76: 14–7

20 **Beetz NL, Drager F, Hamm CA et al.** MRI-targeted biopsy cores from prostate index lesions: assessment and prediction of the number needed. *Prostate Cancer Prostatic Dis* 2022; 26(3): 543–51

21 **Vickers AJ.** Effects of magnetic resonance imaging targeting on overdiagnosis and overtreatment of prostate cancer. *Eur Urol* 2021; 80: 567–72

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Abbreviations: EAU, European Association of Urology; IQR, interquartile range; ISUP, International Society of Urological Pathology; mpMRI, multiparametric MRI; OR, odds ratio; (ci)(cs)PCa, (clinically insignificant) (clinically significant) prostate cancer; PI-RADS, Prostate Imaging-Reporting and Data System; PRECISION, PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (trial); SBx, systematic randomised US-guided biopsy; US, ultrasonography.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Comparison of patients with clinically significant prostate cancer with and without added value of concurrent systematic randomised ultrasound-guided biopsy. Continuous values are presented as median and interquartile range (IQR); categorical values are given as number (%). ciPCa, clinically insignificant prostate cancer; csPCa, Clinically significant prostate cancer; PI-RADS, Prostate Imaging-Reporting and Data System ; PSA, Prostate specific antigen; PSAd, PSA denstity; P-Vol, prostate volume; SBx, systematic randomised ultrasound-guided biopsy.