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Clinical-Prostate cancer

Systematic prostate biopsy still matters: A comprehensive analysis of MRI/TRUS-fusion targeted prostate biopsies across different indications

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Abstract

Objectives: To assess if a multiparametric magnetic resonance imaging (mpMRI)-targeted biopsy (TB) strategy is precise enough to replace systematic biopsies (SB) among men with different biopsy indications since an imaging-based pathway to guide indication and targeted prostate biopsy is currently under debate.

Materials and Methods: Retrospective analysis was performed of 594 patients with one or more lesions according to Prostate Imaging and Reporting Data System (PI-RADS) receiving a consecutive TB and SB for one of the 3 indications: primary cancer suspicion (51.7%), persistent cancer suspicion after prior negative biopsy (35.4%), or control of a confirmed cancer (12.9%). Detection rates for overall cancer (CaP) and clinically significant cancer (csCaP, Gleason Score ≥3+4) were compared between TB and SB and to a combined approach for all patients and within the subgroups. Characteristics of cancers missed by one biopsy strategy were analyzed.

Results: TB detected less CaP (302 vs. 366, $P < 0.001$) and csCaP (204 vs. 210 patients, $P = 0.409$) compared to SB except for men with prior negative biopsies (65 vs. 64 csCaP, $P = 0.363$). Cancer detection by TB or SB was independent of cancer localization and imaging characteristics. Combined TB and SB outperformed the single approaches for CaP and csCaP detection in each subgroup.

Conclusions: A single mpMRI and TB approach leads to a substantial number of missed CaP and csCaP across biopsies with different indications. Ongoing improvements of imaging, reading standardization, and biopsy techniques are required before replacing SB. © 2019 Elsevier Inc. All rights reserved.

Keywords: Biopsy; Cancer; Localization; Magnetic resonance imaging; Prostatic neoplasms; Ultrasound

1. Introduction

Improved prostate biopsy techniques have revolutionized prostate cancer diagnosis within the past decade. Introduction of mpMRI enabled visualization of cancer-suspicious prostatic lesions [1,2]. Utilizing the image information to target lesions improved cancer detection. A wealth of trials indicates that, compared to standard systematic biopsy (SB), targeted biopsy (TB) may increase detection of clinically significant prostate cancer (csCaP), while low-risk cancers are found less frequently by imaging and biopsy [3−6]. Whereas international guidelines recommend mpMRI and TB after a previous negative 10 to 12 core SB,

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recent studies evaluate an initial mpMRI as a triage test before a first biopsy [7,8]. This mpMRI-based pathway aims to avoid unnecessary biopsies, thereby reducing overdiagnosis of insignificant low-risk cancers and associated comorbidities and costs for patients and healthcare systems. Another group of patients that might profit from an mpMRI-based biopsy paradigm is those undergoing active surveillance. In these patients, mpMRI could help to identify suitable candidates and reduce systematic follow-up biopsies [9].

However, contradictory findings of trials comparing TB and SB approaches reveal skepticism in the current capacity of imaging and biopsy to detect or rule out significant cancers reliably. These series report a risk to miss up to 16% of csCaP by omitting SB [10].

Thus, the aim of this study was to assess whether SB still has a role for detection of csCaP in patients with different biopsy indications or if we are ready to change to an mpMRI-based paradigm. We provide realistic clinical data from a urological university center where prostate cancer diagnosis by mpMRI and TB are performed by clinicians with a range of experience levels, and address potential pitfalls of a TB strategy.

2. Material and methods

2.1. Study design

This retrospective study was approved by the institutional ethical review board. Data collection and reporting followed the Standards of Reporting on MRI-Targeted Biopsy Studies (START) criteria [11]. Recruitment occurred from 2014 through March 2018.

2.2. Study population

All patients signed written informed consent for mpMRI and intervention. Men were eligible for analyses if they received an mpMRI and a conclusive TB and SB. Indications for mpMRI and fusion biopsy were an initial cancer suspicion (abnormal digital rectal examination or prostate-specific antigen [PSA] value ≥4 ng/ml or a PSA velocity <4 ng/ml and patients asking for a primary MRI), a persistent suspicion after one or more negative prior biopsies, or a control biopsy when cancer was already confirmed in patients undergoing active surveillance. For this analysis, all patients with at least one suspicious mpMRI-lesion were included.

2.3. Acquisition and reporting of multiparametric MRI

Patients underwent an mpMRI either at the in-house radiological department ($n = 352$) or external departments ($n = 242$). Magnetic field-strength was 3.0T for mpMRI (Magnetom Skyra and Trio, Siemens Healthineers, Erlangen, Germany) at the in-house department and either 1.5T or 3T at external departments, without use of an endorectal coil in most cases. T2-weighted sequences, diffusion-weighted imaging (DWI; b-values of 50, 400, 800 s/mm^2, additional b-value of 2000 s/mm^2 for Magnetom Skyra), and dynamic contrast-enhanced perfusion sequences were acquired according to the recommendations of the European Society of Urogenital Radiology [2]. Images were read by the respective uroradiologists of the departments that performed the mpMRI. In-house radiological readings were performed or supervised by experienced uroradiologists (with >4 years experience reading prostate mpMRIs). If external mpMRI reports indicated uncertainty, images were reviewed by the in-house radiologists. MpMRI results were reported in a prose report, accompanied by an illustration in some cases. PI-RADS was used to classify intraprostatic lesions suspicious for cancer. The version used (PI-RADS v1 or v2) was dependent on the current standard of reporting when the mpMRI was generated. In multifocal lesions, the one with the highest PI-RADS score was defined as the index lesion.

2.4. MRI/ultrasound-fusion biopsy

Fusion biopsy was conducted using the software-based robot-assisted Artemis platform (Eigen, CA) with elastic fusion of mpMRI and real-time ultrasound images, except for 12 biopsies where images were fused by visual registration. The procedure was performed by urologists ($n = 27$) under the patients' preference of general or local anesthesia. Distribution of cases among urologists is presented in **Supplementary Material 1.** The majority ($n = 499$ biopsies) was performed by 10 urologists. All patients received antibiotic prophylaxis or targeted antibiotic therapy in case of significant bacteriuria. TB cores were obtained, followed by a 12-core SB by the same urologist. For SB, the Artemis template of preselected biopsy sites was used with the target visible in the 3D model. The median number of TB cores per lesion was 2 (interquartile range (IQR) 2−3). Detailed biopsy technique was previously described [12].

2.5. Data analysis

Demographic, clinical, imaging, and histopathological data were assessed by descriptive analysis. CsCaP was defined as Gleason Score ≥3+4. Cancer detection rates (CDRs) of mpMRI and TB were analyzed on per-patient and per-lesion levels, using the 12-core systematic biopsy as the reference standard. Cancer detection rates were compared between biopsy techniques by McNemar (for qualitative parameters) and Wilcoxon tests (for quantitative parameters) and between the subgroups of biopsy indications using Chi-square test. Correlation of Gleason Scores and PI-RADS with biopsy results was analyzed by Cochrane-Armitage test and Spearman‘s correlation coefficient. We elaborated csCaP foci missed by TB but detected by SB and vice versa and mapped their localization to a prostate scheme. A target was listed for all prostate sectors in which it was reported by mpMRI, meaning that it could appear in more than one sector. Clinicopathological and imaging parameters of patients with a negative TB or SB but cancer detected by the other technique were compared by Chi-square test, Fisher's exact test, or t test. A test was considered to be statistically significant at $P = <0.05$. SAS 9.3 software was used for statistical analysis.

3. Results

Demographic, imaging, and biopsy results are presented in Table 1. Overall, 656 patients received an MRI/transrectal ultrasound (TRUS)-fusion biopsy. Patients who either had no index lesion classified by PI-RADS or received an mpMRI before control-biopsy after focal therapy ($n = 62$) were excluded. Of the 594 patients eligible for analyses, 307 (51.7%) were biopsy-naïve, 210 (35.4%) had at least one negative previous biopsy, and 77 (12.9%) had a previous cancer-positive biopsy (Fig. 1). Median patient age was 67 years (IQR 61−73), median PSA level at intervention was 7.6 ng/ml (5.6−11.9), and median prostate volume was 48 ml (35−70). 764 lesions were detected by mpMRI and classified according to PI-RADS. The median number of lesions per patient was 1 (1−4), the median diameter of the index lesion was 12 mm (9−16.5).

The overall CDR was 67% (398/594 patients). SB found significantly more CaP than TB (61.6% vs. 50.8%,

Table 1
Patient characteristics, magnetic resonance imaging results, biopsy data and prostatectomies of all 594 patients with an MRI/TRUS-fusion biopsy and by subgroups

	All patients		Biopsy-naive		Prior negative biopsy		Prior positive biopsy	
No. of patients (%)	594		307	(51.7)	210	(35.4)	77	(13)
Patient characteristics								
Median age (IQR), y	66.9	(61−73.1)	66.1	(60.3−71.8)	68.4	(62.2−74.9)	66.5	(59.6−72.5)
Median PSA (IQR), ng/ml	7.6	(5.6−11.9)	6.2	(4.9−8.9)	9.4	(6.7−15.1)	7.2	(5.2−9.9)
Median prostate volume (IQR), cm^3	48	(35−70)	46.5	(35−67)	55	(40−75)	39	(30−55.3)
No. of patients with abnormal digital rectal examination (%)	128	(21.5)	84	(27.4)	32	(15.2)	12	(15.4)
Magnetic resonance imaging								
Total no. of lesions	764		393		265		106	
Median no. of lesions per patient (range)	1	(1−4)	1	(1−4)	1	(1−4)	1	(1−3)
No. of patients with unifocal lesion (%)	457	(76.9)	235	(76.6)	54	(70.1)	169	(79.7)
No. of patients with multifocal lesions (%)	137	(23.1)	72	(23.4)	23	(29.9)	43	(20.3)
No. of index lesions (%)								
PI-RADS 5	159	(26.8)	87	(28.3)	51	(24.3)	21	(27.3)
PI-RADS 4	250	(42.1)	140	(45.6)	83	(39.5)	27	(35.1)
PI-RADS 3	164	(27.6)	73	(23.8)	66	(31.4)	25	(32.5)
PI-RADS <3	21	(3.5)	7	(2.3)	10	(4.7)	4	(5.2)
No. of total lesions (%)								
PI-RADS 5	176	(23)	98	(24.9)	56	(21.1)	22	(20.8)
PI-RADS 4	316	(41.3)	172	(43.7)	107	(40.4)	37	(34.9)
PI-RADS 3	230	(30.1)	104	(26.4)	86	(32.5)	40	(37.7)
PI-RADS <3	37	(4.8)	15	(3.8)	16	(6)	6	(5.7)
No PI-RADS	5	(0.7)	1	(0.9)	1	(0.9)	0	(0)
Median max. diameter of the index lesion (IQR), mm	12	(9−16.5)	11	(8.5−16)	13	(10−18)	10	(9−15)
Biopsy								
Median no. of SB cores per patient (IQR)	12	(12−12)	12	(12−12)	12	(12−12)	12	(12−12)
No. of SB cores positive for CaP/total SB cores (%)	1131/7116	(15.9)	687/3672	(18.7)	297/2520	(11.8)	147/924	(15.9)
No. of SB cores positive for csCaP/total SB cores (%)	787/7116	(11.1)	482/3672	(13.1)	215/2520	(8.5)	90/924	(9.7)
Median no. of TB cores per target (IQR)	2	(2−3)	2	(2−3)	2	(2−3)	2	(2−3)
No. of TB cores positive for CaP/total TB cores (%)	684/2033	(33.6)	398/1047	(38)	208/711	(29.3)	78/275	(28.4)
No. of TB cores positive for csCaP/total TB cores (%)	486/2033	(23.9)	292/1047	(27.9)	153/711	(21.5)	41/275	(14.9)
Median SB cancer core infiltration (IQR), mm	5.2	(2.4−8.1)	5.6	(2.8−8.9)	3.9	(1.9−6)	5	(2−8.6)
Median TB cancer core infiltration (IQR), mm	6	(2.5−9.6)	6	(2.4−9.6)	5.1	(2.9−7)	7.5	(3.1−9.8)
No. of Gleason Scores (%)								
3+3	192	(32.2)	106	(34.5)	51	(24.3)	35	(45.5)
3+4	142	(23.9)	84	(27.4)	39	(18.6)	19	(24.7)
3+5	2	(0.3)	2	(0.7)	0	(0)	0	(0)
4+3	82	(13.8)	41	(13.4)	29	(13.8)	12	(15.6)
4+4	49	(8.2)	27	(8.8)	18	(8.6)	4	(5.2)
4+5	9	(1.5)	5	(1.6)	4	(1.9)	0	(0.0)
5+4	5	(0.8)	2	(0.7)	3	(1.4)	0	(0.0)
5+5	4	(0.7)	1	(0.3)	3	(1.4)	0	(0)
Prostatectomy								
Total no. of interventions (%)	136	(22.8)	79	(25.6)	37	(17.5)	20	(26)
No. of upgrading to TB (%)	35	(25.7)	16	(20.3)	13	(35.1)	6	(30)
No. of upgrading to SB (%)	44	(32.4)	24	(30.4)	14	(37.8)	6	(30)

CaP = prostate cancer; csCaP = clinically significant prostate cancer; PSA = prostate-specific antigen; SB = systematic biopsy; TB = targeted biopsy.

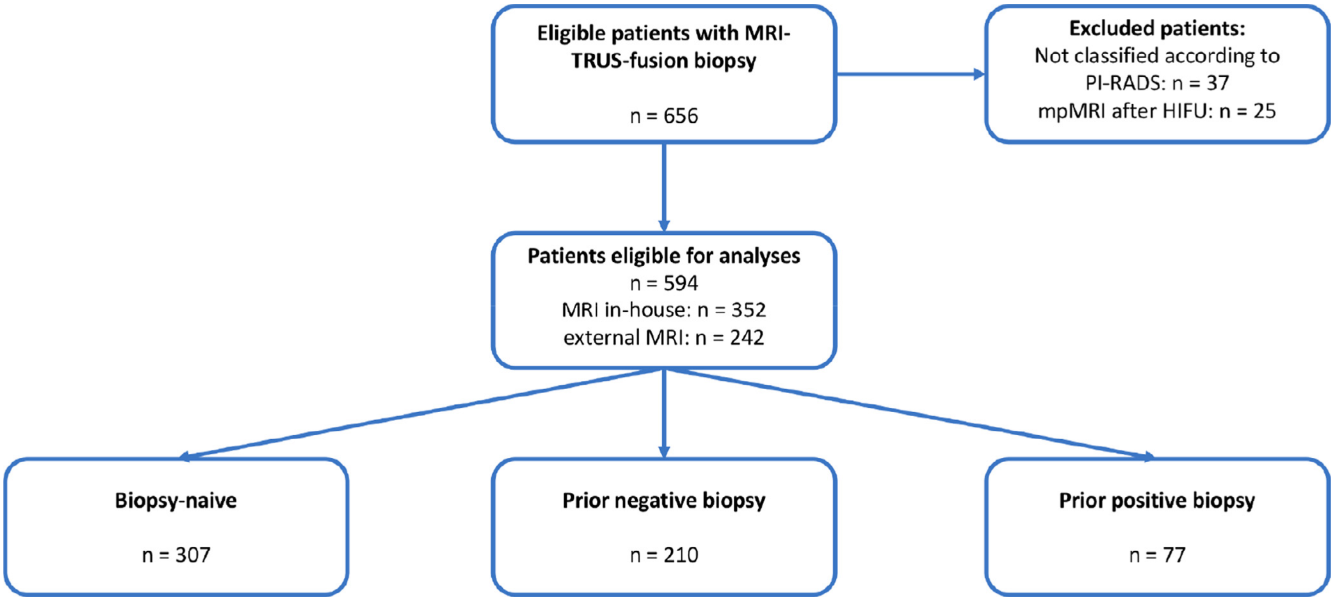

Fig. 1. Study flow chart.

$P < 0.001$). Total csCDR was 42.9% (255/594 patients). SB detected csCaP in 35.4% whereas TB detected csCaP in 34.3% ($P = 0.409$) on a per-patient level (TB-P). Additionally, more insignificant CaP were found by SB (26.1% vs. 16.7%, $P = 0.217$). On a per-lesion level, TB detection rates were 45.6% (CDR) and 29.8% (csCDR).

Combination of TB and SB was significantly superior in CDR compared to SB and TB alone (both $P < 0.001$) and superior in csCDR ($P = 0.055$ and $P = 0.031$).

Comparison of subgroups with different biopsy indications revealed that CDR differed significantly, with the highest CDR in prior positive and the lowest CDR in prior negative men (76.6% and 56.7%, $P < 0.001$). No significant differences were detected regarding csCDR. SB performed better for CDR in all subgroups ($P < 0.05$). Among prior negative patients, TB-P found one more case of csCDR than SB ($P = 0.363$). A combined TB and SB improved CDR and csCDR in all subgroups (Fig. 2, Table 2).

Detection of csCaP according to PI-RADS score of the index lesion is illustrated in Fig. 3. In men with a PI-RADS 4 index lesion csCDR by SB was higher than by TB. However, combined SB and TB outperformed

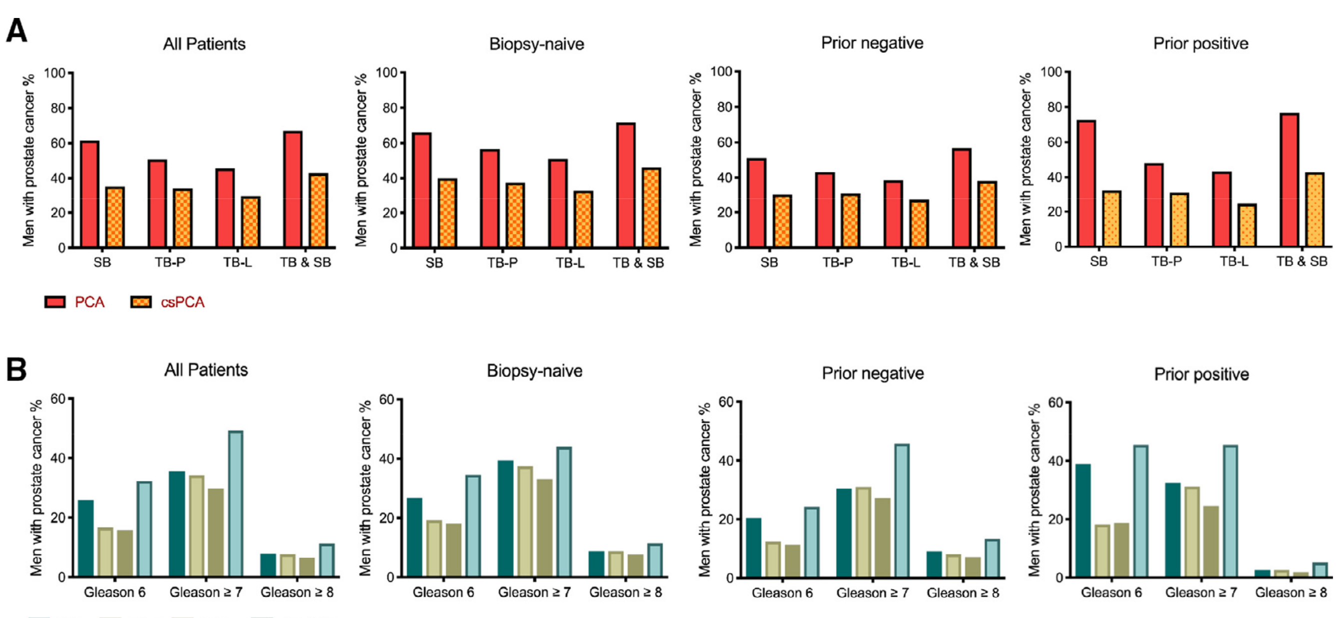

Fig. 2. Cancer detection rates of all patients and among subgroups. (A) CDR and csCDR are displayed for each biopsy technique (red bars: CDR; orange bars: csCDR). (B) Gleason Scores detected by the respective biopsy technique.CDR = cancer detection rates; SB = systematic biopsy; TB-P = targeted biopsy on a per-patient level; TB-L = targeted biopsy on a per-lesion level; SB & TB = combined biopsy results. (Color version of figure is available online.)

Table 2
Comparison of cancer detection rates for CaP (CDR) and csCaP (csCDR) for all patients and among subgroups with different biopsy indications

	CDR			csCDR		
All patients, n (%)	TB & SB 398 (67)			TB & SB 255 (42.9)		
	TB	SB	TB vs. SB	TB	SB	TB vs. SB
	302 (50.8)	366 (61.6)	P <0.001	204 (34.3)	210 (35.4)	P = 0.409
	TB & SB vs. TB	TB & SB vs. SB		TB & SB vs. TB	TB & SB vs. SB	
	P < 0.001	P < 0.001		P = 0.031	P = 0.055	
Biopsy-naive, n (%)	TB & SB 220 (71.7)			TB & SB 142 (46.3)		
	TB	SB	TB vs. SB	TB	SB	TB vs. SB
	174 (56.7)	203 (66.1)	P <0.001	115 (37.5)	121 (40)	P = 0.784
	TB & SB vs. TB	TB & SB vs. SB		TB & SB vs. TB	TB & SB vs. SB	
	P <0.001	P <0.001		P = 0.146	P = 0.211	
Prior negative biopsy, n (%)	TB & SB 119 (56.7)			TB & SB 80 (38.1)		
	TB	SB	TB vs. SB	TB	SB	TB vs. SB
	91 (43.3)	107 (51.0)	P = 0.011	65 (31.0)	64 (30.5)	P = 0.363
	TB & SB vs. TB	TB & SB vs. SB		TB & SB vs. TB	TB & SB vs. SB	
	P <0.001	P <0.001		P = 0.273	P = 0.289	
Prior positive biopsy, n (%)	TB & SB 59 (76.6)			TB & SB 33 (42.9)		
	TB	SB	TB vs. SB	TB	SB	TB vs. SB
	37 (48.1)	56 (72.7)	P <0.001	24 (31.2)	25 (32.5)	P = 0.965
	TB & SB vs. TB	TB & SB vs. SB		TB & SB vs. TB	TB & SB vs. SB	
	P <0.001	P = 0.083		P = 1.000	P = 1.000	

CaP = prostate cancer; csCaP = clinically significant prostate cancer; SB = systematic biopsy; TB = targeted biopsy; TB & SB = combined targeted and systematic biopsy.

the single techniques independent of the lesion's classification.

The efficiency to detect csCaP was significantly higher by TB compared to SB (486/2033 vs. 787/7116 cores positive, P <0.001).

In the analysis of 136 patients with a consecutive prostatectomy, the overall Gleason score upgrading rate was higher for those cancers detected by SB (32.4 vs. 24.3%, P = 0.055), except for the prior positive biopsy group (31.6% for SB and TB). Upgrading to a higher Grade Group (2−5) was found for SB more frequently (Table 3).

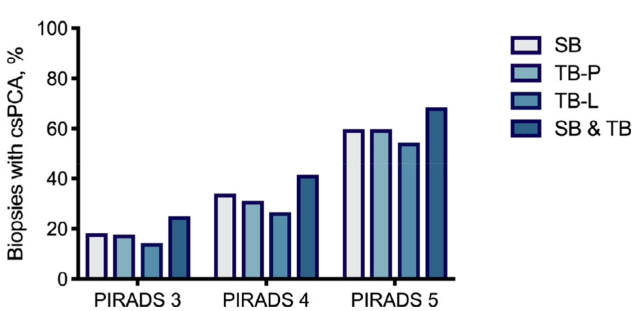

Fig. 3. Detection rates of csCaP in relationship to PI-RADS scores. SB = systematic biopsy; TB-P = targeted biopsy on a per-patient level; TB-L = targeted biopsy on a per-lesion level; SB & TB = combined biopsy results.

Distribution of cancers missed by either SB or TB alone and detected by the other approach is displayed in Fig. 4 and Table 4. Whereas the combined strategy found CaP in 270 of 398 cancer-positive patients, SB was positive in 96 men with a negative TB compared to 32 men with a positive TB but a negative SB (P <0.001). TB was negative in 32/255 patients with csCaP (12.5%) and SB was negative in 15/255 patients with csCaP (5.9%, P = 0.013) (Fig. 4**A**). When TB was negative and SB found csCaP, positive cores were located in the same prostate sector as the lesion in 56.3% and in the sector adjacent to the lesion in 84.4%. In 9.4% SB revealed csCaP in a distant sector (Table 5).

There were no significant differences between clinicopathologic and lesion characteristics on mpMRI between patients with csCaP missed by TB and detected by SB alone or missed by SB and detected by TB alone (Table 6). Comparison of localizations where cancers remained undetected by a single biopsy approach revealed a homogeneous distribution over prostate sextants for TB, but the majority of cancers missed by SB were located in the medial mid gland (33.3%) (Fig. 4**B**).

4. Discussion

The major finding of this study was that SB was comparable to TB in the detection of csCaP. Although patient

Table 3
Histopathological results, number and type of upgrading among 136 patients who received a radical prostatectomy after MRI/TRUS-fusion biopsy

	All patients		Biopsy-naïve		Prior negative biopsy		Prior positive biopsy	
Total no. of interventions (%)	136	(22.8)	81	(26.3)	36	(17.0)	19	(24.7)
Gleason Score of prostatectomy specimen (no., %)								
3 + 3	22	(16.2)	15	(18.5)	5	(13.9)	2	(10.5)
3 + 4	64	(47.1)	37	(45.7)	15	(41.7)	12	(63.2)
3 + 5	2	(1.5)	0	(0)	1	(2.8)	1	(5.3)
4 + 3	37	(27.2)	22	(16.2)	11	(30.6)	4	(21.1)
4 + 4	5	(3.7)	3	(3.7)	2	(2.5)	0	(0)
4 + 5	5	(3.7)	3	(3.7)	2	(2.5)	0	(0)
5 + 4	1	(0.7)	1	(1.2)	0	(0)	0	(0)
Total no. of upgrading to TB (%)	33	(24.3)	15	(18.5)	11	(30.6)	6	(31.6)
Total no. of upgrading to SB (%)	44	(32.4)	24*	(29.6)	13	(44.4)	6	(31.6)
No. of upgrading from low to intermediate risk (GG 1 to GG 2/3)								
TB	19	(14)	8	(9.9)	6	(16.7)	4	(21.1)
SB	26	(19.1)	15	(18.5)	7	(19.4)	4	(21.1)
No. of upgrading from low to high risk (GG 1 to GG 4/5)								
TB	1	(0.7)	0	(0)	0	(0)	1	(5.3)
SB	1	(0.7)	0	(0)	0	(0)	1	(5.3)
No. of upgrading within intermediate risk group (GG 2 to GG 3)								
TB	10	(7.4)	5	(6.2)	4	(11.1)	1	(5.3)
SB	11	(8.1)	7	(8.6)	3	(8.3)	1	(5.3)
No. of upgrading from intermediate to high risk (GG 2/3 to GG 4/5)								
TB	3	(2.2)	2	(2.5)	1	(2.8)	0	(0)
SB	6	(4.4)	1	(1.2)	3	(8.3)	0	(0)
Gleason Score of prostatectomy specimen in patients with a negative TB and positive SB								
Total no. of patients	27		15		8		4	
3 + 3	10	(37)	5	(33.3)	3	(37.5)	2	(50)
3 + 4	11	(40.7)	6	(40)	4	(50)	1	(25)
3 + 5	1	(3.7)	0	(0)	1	(12.5)	0	(0)
4 + 3	4	(14.8)	3	(20)	0	(0)	1	(25)
4 + 4	1	(3.7)	1	(6.7)	0	(0)	0	(0)
Gleason Score of prostatectomy specimen in patients with a negative SB and positive TB								
Total no. of patients	13		4		7		2	
3 + 3	2	(15.4)	1	(25)	1	(14.3)	0	(0)
3 + 4	4	(30.8)	0	(0)	3	(42.9)	1	(50)
3 + 5	0	(0)	0	(0)	0	(0)	0	(0)
4 + 3	7	(53.9)	3	(75)	3	(42.9)	1	(50)
4 + 4	0	(0)	0	(0)	0	(0)	0	(0)

* One patient was upgraded within the high-risk group (Gleason Score 4 + 4 to 4 + 5).GG = Grade Group; SB = systematic biopsy; TB = targeted biopsy.

demographics did not differ from published large series, making this cohort representative for men under consideration for an MRI fusion biopsy, these results are contradictory to a majority of published data, where csCDR is reported to be up to 40% higher for TB compared to SB [4,5,13,14].

The only prospective randomized multicenter PRECISION trial, comparing an mpMRI-guided TB pathway with a systematic 10- to 12-core biopsy in 500 biopsy-naïve patients, recently found a higher csCDR of 12% for TB. Further, the authors concluded that mpMRI helped to identify patients with a csCaP before biopsy and could avoid 28% unnecessary biopsies [7].

However, many previous studies assessed biopsy approaches in smaller patient cohorts. In contrast, the largest prospective single-arm trials of Siddiqui et al. and Filson et al., with more than 1000 patients, found a higher detection rate for csCaP in favor of TB of only 3.7% and 3.8%, which was significant but similar to our results [4,5]. Both studies included patients with and without prior biopsies, also as in our study. Filson et al. used the same biopsy platform Artemis but importantly, as the authors state, only well-versed experts conducted mpMRI and fusion biopsy, which might have affected total detection rates. Two other recent prospective multicenter trials, analyzing MRI-guided biopsy and systematic biopsy in biopsy-naïve patients in centers of excellence for both MRI and biopsy, found an identical csCaP detection rate of both biopsy approaches [15,16].

It has to be taken into consideration that the frequently demanded fusion biopsies should be practicable for all urologists in routine clinical and outpatient settings and not only utilized by a few experts, indicating that our results of a urological center with many different urologists and

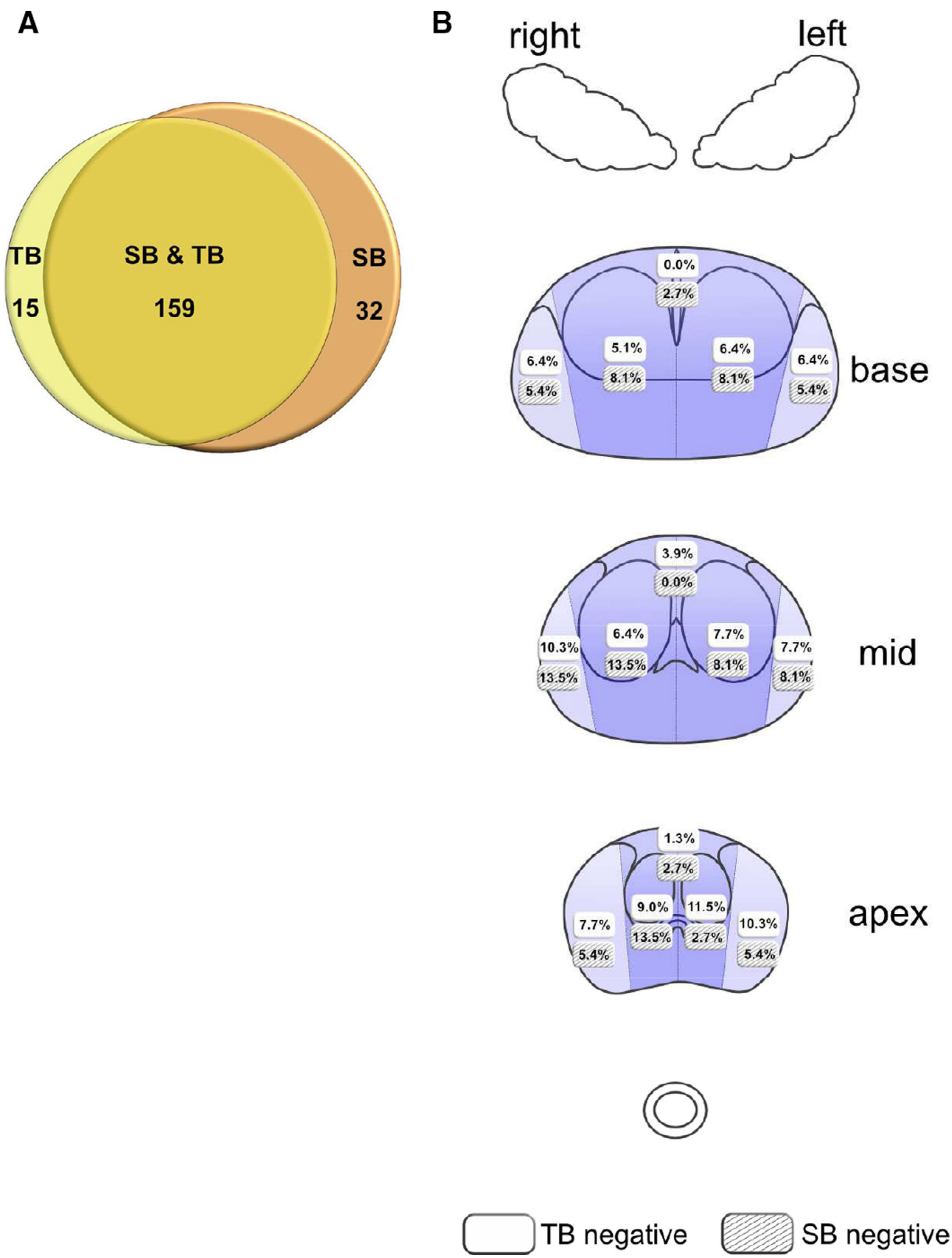

Fig. 4. (A) Number of patients in whom csCaP was detected by TB only and no cancer was detected by SB (light yellow), vice versa (orange), and where TB and SB revealed csCaP (yellow). (B) Schematic distribution of intraprostatic localizations where csCaP were missed by either TB or SB alone and detected by the other biopsy approach in the same prostate sector. Data represents the amount of all cancers missed by the respective biopsy technique. SB = systematic biopsy; TB = targeted biopsy. (Color version of figure is available online.)

radiologists involved in the procedures, could be more representative for a range of other departments.

We analyzed characteristics of patients with either a negative TB or SB and localizations of missed cancers. TB missed significantly more patients with CaP than SB and more patients with csCaP. Frequently, in TB negative patients SB revealed csCaP within or adjacent to the prostate sector that includes the MRI lesion which potentially

Table 4
Comparison of histopathological results from standard systematic biopsies and targeted MRI/ultrasound-fusion biopsies

	Systematic biopsies		
	No cancer	Insignificant cancer (Gleason 3 + 3)	Clinically significant cancer (Gleason ≥ 3 + 4)
Targeted biopsies			
No cancer	196	64	32
Insignificant cancer (Gleason 3 + 3)	17	62	20
Clinically significant cancer (Gleason ≥ 3 + 4)	15	29	159

Table 5
Lesion-based analysis of 32 patients with a negative TB and csCaP detected by SB

	csCaP in SB				
	Same sector	Sector adjacent to lesion	Sector on same lobe but one sector in between without cancer	Sector on contralateral lobe	Same sector and other sector
TB negative	18 (56.3)	27 (84.4)	3 (9.4)	15 (46.9)	15 (48.9)

Localization of positive SB cores was analyzed in relation to the MRI lesion based on the sextant sector map of the prostate.
SB = systematic biopsy; TB = targeted biopsy.

Table 6
Clinical, imaging and histopathological parameters of patients with either a negative TB or SB and csCaP detected only by the other biopsy approach

	Negative TB ($n = 32$)		Negative SB ($n = 15$)		P-value
No. of lesions (%)					
1	30		11		
2	2		4		
Median (IQR)	1	(1–2)	1	(1–2)	0.072
Median PSA (IQR), ng/ml	12	(7.8–16.3)	8.4	(5.6–11.1)	0.621
No. of patients with abnormal digital rectal examination (%)	6	(18.8)	3	(20)	0.959
Median prostate volume (IQR), cm^3	42.5	(35.8–75.5)	49	(40–63.3)	0.830
PSA-density (IQR), $ng/ml/cm^3$	0.22	(0.16–0.27)	0.14	(0.11–0.23)	0.687
No. of index lesions (%)					
PI-RADS 5	12	(37.5)	7	(26.7)	
PI-RADS 4	12	(37.5)	4	(26.7)	
PI-RADS 3	8	(25)	4	(46.6)	
Median lesion diameter (IQR), mm	10	(9–14.5)	13	(11.5–16)	0.606
No. of Gleason Scores (%)					
3 + 4	21	(65.6)	9	(60)	
4 + 3	7	(21.9)	5	(33.3)	
4 + 4	4	(12.5)	0	(0)	
5 + 4	0	(0)	1	(6.7)	
Localization*, n (%)					
Basal medial	10	(14.1)	6	(25)	0.558
Basal lateral	9	(12.7)	3	(12.5)	0.546
Mid medial	11	(15.5)	8	(33.3)	0.219
Mid lateral	11	(15.5)	5	(20.8)	0.944
Apex medial	15	(21.1)	5	(20.8)	0.378
Apex lateral	12	(16.9)	2	(8.3)	0.077
Anterior	3	(4.2)	1	(4.2)	0.752
Biopsy status, n (%)					
Naive	14	(43.8)	6	(40)	0.808
Prior negative	12	(37.5)	7	(46.7)	0.552
Prior positive	6	(18.8)	2	(13.3)	0.639

* Localization of the parts of a lesion within each prostate sector in which it was located according to the MRI report.PSA = prostate-specific antigen; SB = systematic biopsy; TB = targeted biopsy.

indicates registration errors, sampling errors or both. However, we found no significant differences regarding imaging and cancer characteristics between the groups that could explain these detection rates. Significant cancers were missed independent of their sector localization in the prostate, although TB missed more apical cancers and SB missed more cancers in the midgland. These results do not confirm the previous analysis of Schouten et al., who found that TB missed more dorsolateral sectors and SB missed more anteriorly located sectors [17]. Thus, here we demonstrate limitations of both techniques in all parts of the gland.

Several reasons explain restrictions of TB in this cohort and in general. First, mpMRI sensitivity and specificity are still limited. Median NPV of a recent meta-analysis is 88% for csCaP and 82% for CaP [18]. Second, mpMRI reading is dependent on experience and needs further standardization. A learning curve for radiologists has been clearly demonstrated [19]. Third, mpMRI reporting has to be optimized: in a previous study, where mpMRI results were offered as written reports without an illustration and urologists defined the target in mpMRI based on this information, we showed that target definition differed between radiologist and urologist and impaired TB detection rates significantly [20]. Fourth, targeting accuracy is limited by sampling errors and varies depending on the fusion technique, which was shown ex vivo and in vivo [21,22]. The way of image registration (rigid vs. elastic) has an effect on fusion accuracy since elastic fusion compensates for deformation of the prostate during TRUS whereas rigid registration does not. Imprecise segmentation of the prostate in mpMRI and ultrasound images and the lack of a motion compensation mode further reduce fusion quality. The needle navigation by itself can be affected by deflection, especially depending on the distance of tissue that has to be passed. The median number of 2 cores per target in our series might have caused an undersampling by TB. A recent study by Kenigsberg et al. showed that 11.1% of csCaP were detected by the third and fourth targeted core for the first time [23]. Experience improves detection rates by TB [24,25]. Fifth, with Artemis a systematic array of preselected biopsy sites is automatically adapted for each constructed 3D prostate model as a guide for SB [12]. On the one hand, this might lead to improved coverage of the gland compared to regular TRUS-guided free-hand biopsies. On the other hand, since the same urologist performed TB followed by SB, visible targets could lead to placement of a systematic core close to or within the target. Therefore, the detection rate by SB could be “false high” in a cohort like this.

This study has some further limitations. Due to the retrospective study design, a variety of radiologists and urologists generated the results. One could suggest that this reduces comparability to other studies. However, we are convinced that publication of realistic data of representative urological centers is of the highest importance to give a foundation for decisions on biopsy regimens. This study did not account for the effect of biopsy experience on TB detection rates, but in a previous study software-based robotic-assisted fusion biopsies were shown to require a short learning curve [25]. Besides, a major limitation is that SB in the same patient and by the same clinician was the reference standard in our cohort. Whole-mount pathology and template mapping biopsies represent the optimal reference for evaluation of single targets. Using the 12-core biopsy potentially reduces the true number of missed cancer foci by both TB and SB and could have favored results of a biopsy approach in this series. Nevertheless, our large and homogeneous study population enables a comprehensive comparison of the quality of the different biopsy approaches.

5. Conclusions

We observed that SB was comparable to TB in csCaP detection, and omitting SB would have led to a significantly higher number of missed csCaP than omitting TB. Missing of cancer foci by either TB or SB was independent of PI-RADS score, localization, and tumor volume. Best cancer detection rates were achieved by a combined systematic and targeted approach. These findings strengthen the need for SB until mpMRI and lesion targeting are sufficiently precise to guide biopsy and allow discontinuation of SB. Optimization of imaging modalities and further standardization of interpretation and biopsy techniques could improve the future role of a single TB.

Conflict of interest

All authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.07.004.

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