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Value of Additional Systematic Cores During Magnetic Resonance Imaging–guided Targeted Biopsy in Prostate Cancer Screening for Young Men: Results from the PROBASE Trial

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Abstract

Background and objective: While magnetic resonance imaging (MRI)-guided targeted biopsy (TBx) is becoming an integral part of early detection of prostate cancer (PC), its role in screening of younger men remains unclear. We analyzed the additional value of systematic biopsy (SBx) in improving detection of clinically significant PC (csPC).
Methods: A total of 525 men aged 45–54 yr with confirmed prostate-specific antigen ≥3.0 ng/ml underwent multiparametric MRI followed by combined TBx and SBx between February 2014 and August 2023 within a multicenter prospective screening trial in Germany. Software-based MRI/ultrasound fusion TBx (2 cores per lesion) combined with SBx was performed via a transrectal or transperineal approach. The primary objective was to analyze differences in csPC detection rates between SBx and TBx in relation to MRI. Secondary objectives were detection rates by International Society of Urological Pathology grade group (GG) and the distribution of SBx and/or TBx findings.

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Magnetic resonance imaging
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Key findings and limitations: PC was detected in 209 men (39%), of which 148/209 cases were csPC (71%; GG ≥2). SBx missed 24/148 csPC cases (16%) and TBx missed 49/148 (33%). SBx detected 25 more low-risk PC cases than TBx (51 vs 26). For 64% of the cases in which SBx detected higher GG than TBx (n = 89, including GG 1), the positive cores were located within MRI-detected lesions. Five GG ≥3 PC cases were not identified on MRI. Limitations include the lack of centralized MRI review before biopsy, variability in biopsy technique, retrospective subgroup analysis, and short follow-up.
Conclusions and clinical implications: A relevant proportion of csPC cases were missed by two-core TBx, although they were correctly identified on MRI, suggesting limitations in targeting accuracy and/or the fusion technique. SBx cores or targeted perilesional sampling, particularly in young men with smaller prostate volume, might be a valuable complement to TBx to ensure reliable and early detection of (cs)PC in this age group.
Patient summary: We looked at the effectiveness of systematic biopsy (usually 12 cores taken from the prostate gland) and targeted biopsy (cores from a suspicious area seen on a scan) of the prostate among men aged 45–54 years as part of a prostate cancer screening trial. The results show that using only two targeted cores per lesion seen on an MRI (magnetic resonance imaging) scan may miss a significant number of clinically relevant prostate cancers. One reason could be that MRI-targeted biopsies are not always perfectly accurate. To improve diagnostic accuracy in younger men, it may be necessary to take additional systematic tissue samples, or at least more samples from around any suspicious area.

This trial is registered on ISRCTN as ISRCTN37591328.

1. Introduction

It has been shown that screening for prostate cancer (PC) using prostate-specific antigen (PSA) testing followed by systematic ultrasonography-guided biopsy for men with elevated PSA reduces PC-related mortality [1,2]. However, this approach is associated with a high rate of overdiagnosis of indolent PC, along with numerous unnecessary biopsies [3,4]. Multiparametric magnetic resonance imaging (mpMRI) has emerged as an essential tool in the PC diagnostic pathway [5–9]. Current guidelines recommend upfront MRI for primary diagnosis of PC, and various screening studies have incorporated MRI as a reflex test for cases with elevated PSA [10–14]. If MRI is suspicious (eg, Prostate Imaging-Reporting and Data System [PI-RADS] score 4–5), a subsequent prostate biopsy in a combined approach (systematic biopsy [SBx] and MRI-targeted biopsy [TBx]) has been the standard [15–18]. However, SBx leads to greater detection of clinically insignificant PC, which can be reduced via an approach using MRI-TBx alone [12]. Nevertheless, performing TBx alone is associated with a risk of missing csPC [11,12,19,20]. Previous studies have identified several factors contributing to missed csPC diagnoses on TBx [21]. High-quality imaging and accurate interpretation of mpMRI are critical for initial identification of suspicious lesions. However, MRI/ultrasound fusion–guided biopsy can still fail to detect csPC because of improper data transfer, inaccurate segmentation, or misregistration of the target area. In addition, there are notable learning curves throughout the diagnostic workflow that affect radiologists, urologists, and pathologists alike, which may impact the overall diagnostic accuracy [22]. Moreover, especially in young men, MRI reading is challenging and results depend on reader experience [23].

Our group recently reported results from the PROBASE trial comparing TBx and SBx for detection of csPC [20]. In an accompanying editorial, Stabile and Nordström [24] raised concerns regarding the relatively low detection rate with TBx. Here we provide a more detailed analysis to clarify the differences observed in comparison to previously published data for screening populations, and assess potential reasons for missing csPC on TBx for younger men with suspicion of PC.

2. Patients and methods

2.1. PROBASE trial design

This analysis was conducted for a cohort from the PROBASE trial [25]. Between February 2014 and December 2019, 46 495 eligible participants aged 45 yr were recruited from the general population and randomized to two screening groups in a 1:1 ratio: PSA testing at age 45 yr (immediate screening arm) versus delayed first PSA testing at age 50 yr (deferred screening arm). Participants with confirmed elevated PSA ≥3.0 ng/ml were recommended MRI-TBx independent of further risk classification. PROBASE was designed before the 2019 European Association of Urology guidelines recommended mpMRI for primary diagnosis of PC, so biopsy was recommended to all participants in PROBASE with confirmed PSA ≥3 ng/ml. Prostate biopsies involved TBx with MRI/transrectal ultrasound (TRUS) fusion guidance (transrectal or transperineal) and SBx. mpMRI scans were read by local radiologists at each of the four study locations, with images rated according to PI-RADS v2.1 and suspicious areas defined for TBx. In cases with a PI-RADS score of 1 or 2, TBx was performed in the area defined in the local MRI report that best characterized the appearance of the prostate best (eg, prostatitis or benign prostatic hyperplasia). Histopathological analysis of the cores was conducted locally and was reviewed centrally by an experienced genitourinary pathologist with 20 yr of experience.

2.2. *Study cohort*

From the overall cohort of 46 495 participants, 722 men (1.6%) had undergone biopsy up to August 2023. For the present analysis, data for primary biopsies between February 2014 and August 2023 were extracted from the electronic central study database, programmed in Onkostar. Repeat biopsies from the same participant were excluded. All cases with external MRI and/or external biopsy performed outside the PROBASE study centers were also excluded, primarily because of lack of traceability of the targeted cores and of external biopsy and MRI reports (n = 67; Fig. 1). Thus, only subjects with primary mpMRI and combined TBx and SBx at one of the four study sites were included. We systematically evaluated clinical, MRI (including PSA density [PSAD] and PI-RADS category), and biopsy data according to local reading.

2.3. *MRI performance*

MRI parameters were chosen according to international recommendations [5]. All scans were conducted on 3-T MRI scanners. Examinations included T2-weighted turbo spin-echo sequences in three planes, diffusion-weighted imaging (b values of 0/50, 500, and 1000 with a calculated high b-value $\geq$1400 s/mm^2), and dynamic contrast enhancement. Intravenous administration of a gadolinium-based contrast agent at a dosage of 0.1 mmol/kg body weight was performed by default with a temporal resolution of 5–9 s. Interpretation of mpMRI was conducted locally by board-certified radiologists who had access to clinical details. There was no centralized review before biopsy. The likelihood of csPC was evaluated using PI-RADS v2.1.

2.4. *Biopsy performance*

SBx and TBx were performed using software-guided MRI/TRUS fusion biopsy at all sites. For TBx, a maximum of four MRI lesions (according PI-RADS) were defined. For SBx, a scheme according to the size of the prostate was used, consisting in most cases of 12 independent systematic cores. TBx was performed transrectally or transperineally with a median of two cores per target. Biopsies were conducted using dedicated biopsy software (eg, Koelis, La Tranche, France; BiopSee, MedCom, Darmstadt, Germany; UroNAV, Invivo, Gainesville, FL, USA). All biopsy procedures were performed by trained urologists at the study centers who were qualified for fusion biopsies as described in a quality control standard operating procedure. PC of ISUP Grade Group (ISUP GG) $\geq$2 was considered to be csPC.

2.5. *Data analysis*

PC detection rates were analyzed separately for TBx and SBx. Fusion failure was defined as a case with positive SBx cores originating from the suspicious area on MRI but TBx being negative. Cases in which SBx found csPC and TBx was negative were analyzed separately. If MRI revealed a suspicious lesion (PI-RADS 3–5) in the same area in which SBx revealed a positive core, this was defined as an in-field positive result. If the area (according to the PI-RADS location scheme) was next to the positive core (in all spatial directions), this was defined as a penumbra positive result.

2.6. *Statistical analysis*

Basic tabulations were used to analyze patient characteristics, MRI, and biopsy data. Median values with the interquartile range (IQR) are reported for PSA, PSAD, PI-RADS, and prostate volume, and median values with the range are reported for age at biopsy. To evaluate the magnitude of differences in detection rates between the biopsy approaches for low-risk PC and csPC, we calculated rate differences and the 95% confidence interval (CI) for paired-sample comparisons and performed McNemar tests, as described by Tango [26]. Statistical analyses were performed using SPSS v27 (IBM Corp, Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

3. Results

3.1. *Baseline characteristics*

The overall study cohort consisted of 525 participants with confirmed screening PSA $\geq$3.0 ng/ml, complete MRI data, and primary TBx and SBx (Fig. 1). Baseline clinical characteristics are described in Table 1. PSAD was significantly higher and prostate volume lower in the group with a positive biopsy ($p < 0.001$). MRI revealed one suspicious area/lesion in 216 cases, two areas in 198 cases, three areas in 96 cases, and four areas in 15 cases.

3.2. *PC detection*

Histopathology revealed a diagnosis of PC in 209 cases (39% of the study cohort). The distribution of SBx and TBx concordance by grade group is shown in Table 2; Supplementary Table 1 provides a cross-tabulation. Most of the PC cases were csPC with GG $\geq$2 (148/209, 71%). The risk of missing csPC on TBx did not significantly differ by biopsy route (transrectal vs. transperineal). Regarding biopsy performance, SBx revealed csPC in 94% of cases (139/148), and TBx in 74% of cases (109/148). Comparison revealed that 39 csPC cases (GG $\geq$2) were found only on SBx (39/148, 26%), while nine csPC cases were only diagnosed via TBx (9/148, 6%). One-fifth of all PC cases (42/209, 20%) were classified as high risk (GG 3–5). Of these, seven cases were detected exclusively via TBx (7/42, 16.7%; 4 GG 3, 2 GG 4, and 1 GG 5) and 22 cases were upgraded and classified as high risk on SBx cores (22/42, 52%; 17 GG 3, 4 GG 4, and 1 GG 5).

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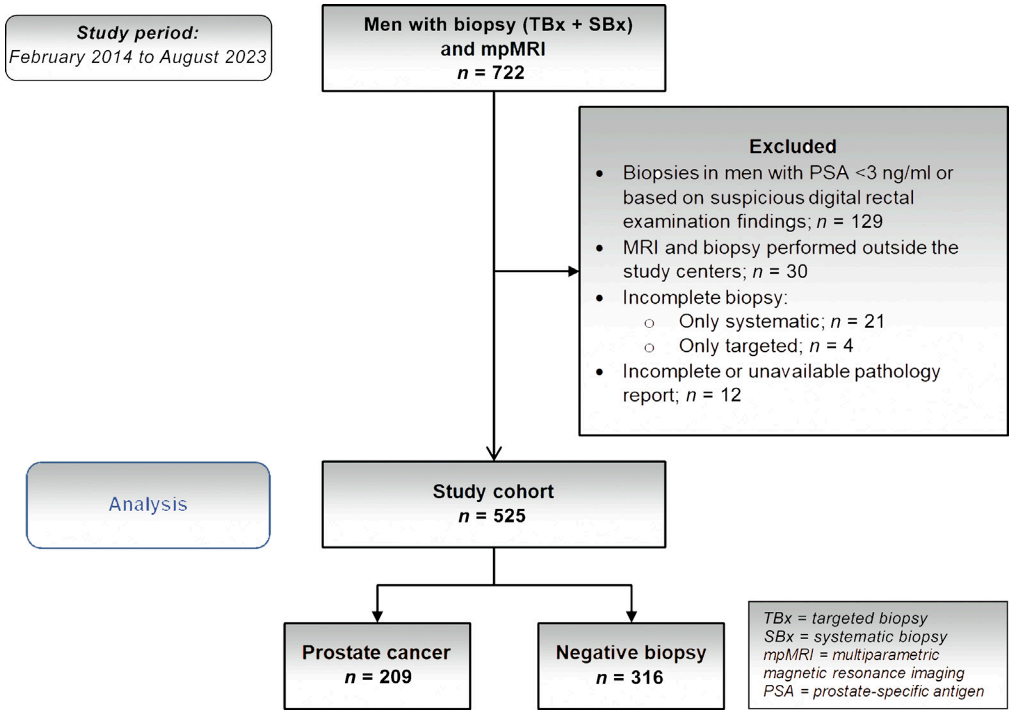

Fig. 1 – Flowchart of the study cohort.

Table 1 – Clinical characteristics of men who underwent systematic and targeted biopsy in the PROBASE trial up to August 31, 2023

Parameter	Overall cohort	Biopsy-positive	Biopsy-negative
Participants, *n* (%)	525	209 (40)	316 (60)
Median age, yr (range)	50 (44–54)	50 (44–54)	50 (45–54)
Median PSA, ng/ml (IQR)	3.98 (3.45–5.09)	3.98 (3.50–5.45)	3.96 (3.42–4.99)
Median prostate volume, ml (IQR)	36 (28–46)	31 (24–40)	39 (31–49)
Median PSAD, ng/ml^2 (IQR)	0.12 (0.09–0.16)	0.14 (0.10–0.18)	0.11 (0.08–0.14)

IQR = interquartile range; PSA = prostate-specific antigen; PSAD = PSA density.

3.3. *Analysis of discrepancies*

In 41 PC cases, TBx resulted in upgrading, of which 19 cases were negative and ten were GG 1 on SBx. In 94 PC cases, SBx resulted in upgrading, of which 74 were negative and 35 were GG 1 on TBx. In 38 of 49 cases upgraded to csPC on SBx, more than one area/lesion was identified on MRI (78%). Of five cases with PI-RADS 2 on MRI, three were csPC. In 32 of 89 cases with a PI-RADS score ≥3 (36%; 15 GG ≥2, 17 GG 1), positive biopsy cores were not located in the MRI target area (out-of-field; Table 3). We observed fusion/biopsy mismatches in 57/89 cases (64%) for which SBx revealed higher GG PC (including GG 1 cases) and the positive SBx core was from the same area identified on pre-biopsy MRI (in-field or penumbra). The median maximal lesion diameter on MRI for these cases was 10 mm (IQR 8–13 mm). Details for cases missed on SBx are listed in Table 4. A relevant proportion were located anteriorly (*n* = 9) and the median maximum lesion diameter on MRI for these cases was 12 mm (IQR 9–13 mm). Details and pos-

Table 2 – Distribution of SBx and TBx concordance by grade group

Concordance status	Overall	GG 1	GG 2	GG 3	GG 4	GG 5
Patients, *n* (%)	209	61 (29)	106 (51)	26 (12)	11 (5.3)	5 (2.4)
GG same on TBx and SBx, *n* (%)	74 (35)	16	48	5	3	2
GG higher on SBx (*n* = 94)						
TBx negative, *n*	74	35	28	9	1	1
TBx result GG 1, *n*	10	NA	9	1	–	–
TBx result GG 2, *n*	10	NA	NA	7	3	–
GG higher on TBx (*n* = 41)						
SBx negative, *n*	19	10	6	1	1	1
SBx result GG 1, *n*	15	NA	15	–	–	–
SBx result GG 2, *n*	4	NA	NA	3	1	–
SBs result GG 3, *n*	3	NA	NA	NA	2	1

GG = International Society of Urological Pathology group grade; TBx = targeted biopsy; SBx = systematic biopsy; NA = not applicable.

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Table 3 – Correlation between positive SBx cores and MRI targets among 89 patients with PI-RADS ≥3 for whom SBx was superior to TBx (detected higher grade group)[a]

Location in relation to target, *n*	Positive SBx cores in relation to MRI targets (*n*)					
	GG 1	GG 2	GG 3	GG 4	GG 5	Overall
In field	9	18	8	0	0	35
Penumbra	7	7	8	0	0	22
Out of field	17	10	1	3	1	32
Total	33	35	17	3	1	89

SBx = systematic biopsy; TBx = targeted biopsy; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; GG = International Society of Urological Pathology grade group
[a] Five cases with PI-RADS 2 findings were excluded (2 with GG 1, 2 with GG 2, 1 with GG 4).

Table 4 – PC cases missed on SBx

Case	PSA (ng/ml)	PSAD (ng/ml^2)	PV (ml)	GG on TBx	Local PI-RADS	D_{max} (mm)	PC location on MRI	Comment
GG 1 on TBx								
1	3.1	0.11	27	1	4	14	Anterior	Low ADC, possibly HG
2	3.95	0.04	99	1	3	4	Anterior	Diffuse changes, no FL
3	3.1	0.07	45	1	4	15	Anterior, apical	Low ADC, possibly HG
4	3.64	0.21	17	1	2	12	Anterior	
5	9.24	0.23	40	1	2	8	Apical	Nonsuspicious lesion
6	3.23	0.05	62	1	3	11	Middle posterior	Diffuse changes, no FL
7	3.85	0.07	58	1	3	9	Middle posterior	SL
8	5.61	0.17	34	1	3	12	Base lateral	Diffuse changes, no FL
9	3.28	0.09	36	1	3	11	Apical	Diffuse changes, no FL
10	3.11	0.07	42	1	4	12	Anterior	
GG ≥2 on TBx								
11	4.59	0.11	43	2	2	12	Anterior	Diffuse changes, no FL
12	3.01	0.09	32	2	4	6	Apical	Very lateral, SL, INF 90%
13	4.1	0.08	50	2	4	5	Apical	Lateral, SL, INF 80%
14	4.83	0.14	35	2	5	16	Anterior	
15	3.14	0.11	28	2	4	14	Middle posterior	Low ADC, possibly HG
16	4.63	0.15	31	2	3	12	Anterior	Low ADC, possibly HG
17	4.87	0.13	37	3	4	8	Base lateral	SL
18	3.75	0.09	40	4	3	12	Anterior	
19	9.3	–	NA [a]	5	5	15	Base lateral	

PSA = prostate-specific antigen; PSAD = PSA density; PV = prostate volume; GG = International Society of Urological Pathology grade group; D_{max} = maximum lesion diameter; PC = prostate cancer; MRI = magnetic resonance imaging; ADC = apparent diffusion coefficient; SBx = systematic biopsy; TBx = targeted biopsy; FL = focal lesion; SL = small lesion; HG = high grade; INF = infiltration.
[a] Not available on MRI; 23 ml on ultrasound.

sible reasons why csPC was missed by TBx for out-of-field lesions are shown in Table 5. Of note, image quality was limited in 9/15 cases (60%). Median PSA (4.7 ng/ml) and PSAD (0.17 ng/ml^2) for these cases were higher than for the biopsy-negative group.

4. Discussion

For men aged ≥55 yr, it has been shown that PC detection using an MRI pathway with or without additional biomarkers (kallikreins, Stockholm3 test) and TBx alone reduces unnecessary biopsies and overdiagnosis of insignificant PC while maintaining csPC detection [16,17,27]. However, for men aged 45–55 yr, data on the MRI pathway are still sparse [10,28]. Our group has published results for comparison of TBx versus SBx for csPC detection in the PROBASE trial [20]. An accompanying editorial by Stabile and Nordström [24] raised concerns about the reasons for the low detection rate with TBx. Here we present more detailed findings to explain the difference in detection in comparison to previous studies in screening populations. Our findings indicate that the combination of TBx and SBx provides the most accurate PC classification in terms of grade group. Moreover, 33% of csPC cases were detected by additional SBx. However, to a large extent, these csPC cases had been identified as a visible lesion on mpMRI by the radiologists. This indicates that despite the great challenges with MRI in this age group, its value is very high, not only for avoiding biopsies but also for correctly identifying lesions. Care must be taken to identify and eliminate possible sources of error in MRI/ultrasound fusion–guided TBx [21].

Our analysis of cases in which TBx was negative despite suspicious MRI with PI-RADS scores ≥3 revealed two possible reasons for mismatch: imprecise fusion biopsy and suboptimal (local) MRI/reporting. First, in two-thirds of the cases MRI identified the PC lesion and the positive SBx core originated from the same area identified on MRI or penumbra. Reasons for such biopsy discrepancies could include, for example, incorrect data overlay, suboptimal image quality, and/or small lesion size (median 10 mm). A possible solution to this source of error could be sampling of more targeted cores from the penumbra of the MRI-visible lesion

Table 5 – Cases missed on TBx with out-of-field lesion and clinically significant prostate cancer

Case	PSA (ng/ml)	PSAD (ng/ml/ml)	PV (ml)	GG on SBx	Local PI-RADS	PI-QUAL score	Comments
1	4.32	0.20	22	GG 2	2	3	Diffuse changes, no FL, limited image quality; 1/12 SBx cores positive, GG 2, 20% pattern 4, 2 mm infiltration
2	7.69	0.33	23	GG 2	2	3	Lesion missed by local radiology, limited image quality; 4/12 SBx cores positive, GG 2, positive in PZ medial/lateral mid/apex right and left
3	3.38	0.07	47.0	GG 2	3	4	Diffuse changes, no clear FL, local MRI ROI in PZ left; 2/12 SBx cores positive, GG 2 on right side, 20% pattern 4, 3 mm infiltration
4	6.63	0.29	22.8	GG 2	3	3	Artifacts on DWI, lesion visible on right side, limited image quality, MRI ROI in mid left TZ; 3/6 SBx cores positive, GG 2 on right side, 5% pattern 4, 5 mm infiltration
5	5.96	0.33	18	GG 2	3	4	Diffuse changes, no clear FL, MRI ROI in TZ mid right and PZpl apex right; 1/12 SBx cores positive, GG 2 in PZ lateral apex left, 5% pattern 4, infiltration 4 mm
6	3.73	0.12	30	GG 2	4	3	Diffuse changes, no clear FL, limited image quality, local MRI ROI in PZpl apex left; 1/12 SBx cores positive, GG 2 in PZ medial base right, 40% pattern 4, 1.5 mm infiltration
7	3.89	0.10	37.1	GG 2	4	3	Diffuse changes, limited image quality, local MRI ROI in PZpm mid left; 2/12 SBx cores positive, GG 2 in PZ medial/lateral apex right, 5% pattern 4, infiltration 5mm
8	4.42	0.17	25.6	GG 2	4	4	Anterior lesion, MRI ROI in TZ anterior basal right; 3/12 SBx cores positive, GG 2 anterior left and right, 40% pattern 4, infiltration max. 10 mm
9	13.7	0.65	21	GG 2	4	4	Diffuse changes, no clear FL, local MRI ROI in TZ mid right; 4/12 SBx cores positive, GG 2 left side, max. 10% pattern 4, max. 6 mm infiltration
10	5.13	0.17	30	GG 2	4	3	Diffuse changes, limited image quality, local MRI ROI PZpl mid left; 2/12 SBx cores positive, GG 2 in PZ lateral mid/apex right, 10% pattern 4, 6 mm infiltration
11	7.24	0.40	18	GG 3	3	3	Diffuse changes, no clear FL, limited image quality, local MRI ROI in TZ base left; 2/12 SBx cores positive, GG 3 in PZ medial/lateral apex right
12	4.46	0.11	41	GG 4	2	5	Local MRI PI-RADS 2, no lesion visible, very small lesion; 1/12 SBx cores positive, GG 4 in PZ lateral base left, 0.2 mm infiltration
13	4.54	0.13	34	GG 4	3	3	Diffuse changes, limited image quality, local MRI ROI TZ mid left, TBx GG 2; 2/12 SBx cores positive, GG 4 in PZ medial apex right and PZ lateral apex left
14	8.2	0.27	30.5	GG 4	5	3	Limited image quality, local MRI ROI PZ right, TBx GG 2; 6/6 SBx cores positive, GG 4 in PZ mid left, 20% pattern 4 and 5% pattern 5
15	4.8	0.15	33	GG 5	3	5	Small subcapsular lesion; local MRI ROI in PZpl apex right; 1/12 SBx cores positive, GG 5 in PZ left lateral apex, 5 mm infiltration

PSA = prostate-specific antigen; PSAD = PSA density; PV = prostate volume; PI-RADS = Prostate Imaging-Reporting and Data System; PI-QUAL = Prostate Imaging-Quality v1; GG = International Society of Urological Pathology grade group; DWI = diffusion-weighted imaging; SBx = systematic biopsy; TBx = targeted biopsy; FL = focal lesion; MRI = magnetic resonance imaging; ROI = region of interest; TZ = transition zone; PZ = peripheral zone; PZpl = posterolateral PZ; PZpm = posteromedial PZ.

and improvements in quality control or certification of biopsy centers, with quality analysis for individual biopsies similar to the PI-QUAL score for MRI [29–32]. Taking only two targeted cores per lesion faces the risk of missing small lesions or sampling only less aggressive parts of a tumor area. This may have led to overestimation of the added value of SBx. Sampling of more TBx cores might have increased the detection of csPC, especially in bigger lesions. Second, in out-of-field PC cases, the MRI report did identify the biopsy-detected PC lesion. Besides potentially MRI-invisible lesions, reasons include limited image quality (eg, due to rectal air, motion artifacts), small tumor diameter, and/or the experience of the local radiologist interpreting MRI in younger patients. The challenge of interpreting MRI in this age group has already been described, so quality assurance via central/reference reading might be required in these cases [23]. Moreover, artificial intelligence (AI) tools have the potential to improve image reading [33–35]. The impact of MRI reference reading with or without the use of AI tools and their significance in a screening setting will be further investigated in PROBASE.

Prostate volume is significantly lower in younger men (age 45–54 yr) than in older men; median prostate volume for PROBASE participants was 36 ml (IQR 28–46). This could also be a plausible reason for the good performance of SBx in younger men with a median of 12 cores and MRI-guided software assistance for placement, if applicable. This also stands in line with our finding that prostate glands harboring PC were significantly smaller than glands with benign biopsy results. Closer inspection of the cases that were missed by SBx reveals two possible factors that might primarily explain this: (1) unfavorable locations and/or (2) small size (median 12 mm). We especially observed discrepancies for anterior, apical, and lateral lesions, which are more often difficult to reach via transrectal access. In our cohort, a considerable proportion of examinations had PI-RADS 3 findings. Owing to the often diffuse signal changes in T2-weighted sequences and diffusion with widespread perfusion enhancement, PC detection in MRI is more challenging in younger men [23,36].

Although MRI offers clear advantages in PC detection, its implementation for systematic screening across Europe remains at an early stage. The Gothenburg study showed that avoiding SBx reduced the GG 1 detection rate by 50%, with only slight underdiagnosis of csPC [12]. Application of this proposed standard to our cohort would have resulted in a higher rate of missed csPC cases. In our population, 71% of cases detected with reference pathology review were csPC, while 29% were GG 1, so the proportion of low-risk PC cases was significantly lower than in the Gothenburg study. Both TBx and SBx detected one additional csPC case for one GG 1 PC case. For older men, GG 1 PC and some GG 2 cases are considered indolent and subject to overtreatment. Nevertheless, little is known about the long-term risk of low-grade PC in a 45-yr-old patient. Data reported by Hamdy et al [37] indicate that for cases managed with simple monitoring, metastasis may occur in the long-term disease course. However, a possible reason for progressive GG 1 PC could also be a sampling error during the initial biopsy, as up to 50% of the PC might harbor csPC [38]. Given this uncertainty, overdiagnosis in young patients should be interpreted with caution until more data on long-term outcomes are available. Furthermore, we observed cases with upgrading to csPC on TBx, so data published data by Gaffney et al [39], who cast doubt on the definition of risk groups according to the highest biopsy GG, should be taken into consideration. However, high-quality MRI offers advantages in detection, provides the possibility of fusion biopsy, and can reduce the number of negative biopsies. MRI avoids overdiagnosis, particularly when the cutoff for biopsy is PI-RADS 4 on expert reading [23]. In addition, software-assisted biopsy significantly improves SBx quality of the SB [40].

In addition to the sample size, which cannot be extrapolated to the general population because of the study design (only men aged 45–55 yr), our study has several limitations. First, experience in MRI reading and image quality differed widely at the time of initiation, as mpMRI was newly implemented at some study sites at the start of the enrolment period. Therefore, different learning curves per site and different MRI scanner generations might have had an influence on the PC detection rate. Second, local MRI reports were used for biopsy and targeting. Expert reading by reference radiologists might possibly improve the performance of TBx in this setting. However, as of now, local reading probably better describes a real-world setting for a population-based screening program. Third, the biopsy approach differed by study site (transperineal or transrectal) which might possibly have had an influence on PC detection. In addition, biopsy experience was not assessed. However, the literature indicates that both approaches are widely established and lead to comparable detection rates. Fourth, several studies and some guidelines recommend TBx with more/multiple cores per lesion (eg, perilesional sampling). In our study we took two cores per reported MRI area, so that sampling of more targeted cores might increase the detection of csPC by TB and decrease the value of SB.

5. Conclusions

The majority of PC cases missed by two-core TBx had visible lesions on MRI, which highlights the importance of proven experience in all disciplines and methods involved, especially image quality, accurate MRI interpretation, and technical precision in fusion-guided biopsy. SBx cores or targeted perilesional sampling, particularly in young men with smaller prostate volume, might be a valuable complement to TBx to ensure reliable and early detection of (cs)PC in this age group.

Author contributions: Lars Schimmöller had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

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