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An optimized prostate biopsy strategy in patients with a unilateral lesion on prostate magnetic resonance imaging avoids unnecessary biopsies

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Abstract

Purpose: The introduction of magnetic resonance imaging (MRI)-targeted biopsy (TBx) besides systematic prostate biopsies has resulted in a discussion on what the optimal prostate biopsy strategy is. The ideal template has high sensitivity for clinically significant prostate cancer (csPCa), while reducing the detection rate of clinically insignificant prostate cancer (iPCa). This study evaluates different biopsy strategies in patients with a unilateral prostate MRI lesion.

Methods: Retrospective subgroup analysis of a prospectively managed database consisting of patients undergoing prostate biopsy in two academic centres. Patients with a unilateral lesion (PI-RADS $\geqslant$ 3) on MRI were included for analysis. The primary objective was to evaluate the diagnostic performance for different biopsy approaches compared with bilateral systematic prostate biopsy (SBx) and TBx. Detection rates for csPCa (ISUP $\geqslant$ 2), adjusted csPCa (ISUP $\geqslant$ 3) and iPCa (ISUP = 1) were determined for SBx alone, TBx alone, contralateral SBx combined with TBx and ipsilateral SBx combined with TBx. A subgroup analysis was performed for biopsy-naive patients.

Results: A total of 228 patients were included from October 2015 to September 2021. Prostate cancer (PCa) detection rate of combined SBx and TBx was 63.5% for csPCa, 35.5% for adjusted csPCa, and 14% for iPCa. The best performing alternative biopsy strategy was TBx and ipsilateral SBx, which reached a sensitivity of 98.6% (95% CI: 95.1–99.6) for csPCa and 98.8% (95% CI: 96.3–99.9) for adjusted csPCa, missing only 1.4% of csPCa, while reducing iPCa detection by 15.6% compared with SBx and TBx. TBx or SBx alone missed a significant amount of csPCa, with sensitivities of 90.3% (95% CI: 84.4–94.2) and 86.8% (95% CI: 80.4–91.4) for csPCa. Subgroup analysis on biopsy-naive patients showed similar results as the overall group.

Conclusion: This study shows that performing TBx with ipsilateral SBx and omitting contralateral SBx is the optimal biopsy strategy in patients with a unilateral MRI lesion. With this strategy, a very limited amount of csPCa is missed and iPCa detection is reduced.

Keywords: magnetic resonance imaging, perilesional, prostate biopsy template, prostate cancer

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Introduction

Prostate magnetic resonance imaging (MRI) has proven to be a valuable diagnostic modality in patients with a clinical suspicion for prostate cancer (PCa). Randomized controlled trials have shown that the addition of prostate MRI and MRI targeted biopsy (TBx), to the standard systematic biopsy (SBx) template leads to an

increased detection of clinically significant prostate cancer (csPCa).[1] Consequently, the use of prostate MRI prior to prostate biopsy is currently endorsed by international guidelines.[2–4]

The implementation of pre-biopsy MRI followed by TBx has raised the question whether performing TBx alone is sufficient or SBx is still of additional value. The main arguments for omitting SBx are its high detection rate of clinically insignificant prostate cancer (iPCa) and increased costs and procedure time.[1] iPCa detection is associated with high costs and patient burden related to active surveillance (AS) and can lead to overtreatment and subsequent treatment-related morbidity.[5,6] In addition, studies randomizing patients for either TBx or SBx have shown that TBx detects significantly more PCa than SBx, thereby providing further rationale for a TBx-only strategy.[7,8] However, studies evaluating a combined TBx and SBx strategy showed significantly higher csPCa detection rates for this combined strategy, with SBx accounting for up to 5.2% additional csPCa detection compared with TBx alone.[1,9–11] Recently, alternative biopsy strategies have been proposed: extended TBx, saturation TBx and ipsilateral-only SBx.[12–14] These strategies are different approaches of the same principle: increasing the number of biopsies in the region of the target lesion to reduce the total number of biopsy cores taken while retaining diagnostic accuracy. Studies evaluating these strategies show that these techniques can significantly reduce the amount of iPCa detection, while increasing csPCa detection rates compared with TBx alone.[12–14] However, there are few studies available and further evidence is needed to validate these alternative strategies. The goal of this study is to investigate the optimal prostate biopsy strategy in patients with a unilateral lesion on MRI.

Patients and methods

This is an observational study with a retrospective analysis on a database, prospectively designed for outcome analyses in prostate biopsy patients in two large Dutch academic medical centres. Patients included in this database underwent prostate biopsy due to a clinical suspicion for PCa or in the context of AS for low-risk PCa in the period from October 2015 to September 2021. Clinical suspicion is generally determined using a risk calculator and is based on prostate-specific antigen (PSA) kinetics, digital rectal examination (DRE), prostate volume, patient history and prostate MRI results.[15] MRI lesions were classified by dedicated uroradiologists, with at least 5 years of experience in reading prostate MRIs, according to Prostate Imaging–Reporting and Data System classification version 2 (PI-RADS).[16] To assess PCa detection rates of ipsi- and contralateral prostate biopsy, patients with no pre-biopsy MRI, a negative pre-biopsy MRI (PI-RADS 1–2), or bilateral MRI lesions (PI-RADS $\geq$ 3) were excluded from the analysis. Patients with an insufficient number of SBx ($<$8), patients who did not undergo TBx, despite a targetable lesion, and patients with prior active treatment for PCa were also excluded.

Pre-biopsy prostate MRI image acquisition was performed according to the most recent PI-RADS guidelines, using either a 1.5 Tesla AVANTO® MRI scanner (Siemens, Healthcare, Erlangen, Germany) or a 3 Tesla INGENIA® MRI scanner (Philips Medical Systems, Best, the Netherlands). MRI sequences included at least T1-weighted, T2-weighted, diffusion-weighted imaging (DWI) and calculation of apparent diffusion coefficient (ADC) maps.

Prostate biopsy procedures were performed by dedicated operators ($>$150 procedures per year), using the transrectal approach until July 2020 and the transperineal approach from August 2020 onwards. Transrectal prostate biopsy was performed using a Philips iU-22 ultrasound system (Philips Healthcare, Bothell) with an end-firing probe, after antibiotic prophylaxis, consisting of a 12- or 16-core SBx (depending on biopsy status) and (generally) a 2- to 3-core TBx per suspicious MRI lesion (PI-RADS $\geq$ 3). Transrectal TBx is enabled by elastic and rigid MRI/US-fusion software of ProFuse® (Eigen, Grass Valley, USA) in combination with the Artemis fusion system. Transperineal prostate biopsy was performed using the BK5000 ultrasound system with a biplane probe (BK Medical Europe, Herlev, Denmark). The probe was mounted on a stabilizer and stepper, and biopsy was performed using a brachytherapy template grid.

Transperineal biopsy was performed without antibiotic prophylaxis and consisted of a 14-core SBx and (generally) a 2- to 3-core TBx per suspicious MRI lesion. Transperineal TBx is performed by integrated elastic MRI/US-fusion software of MIM® (MIM Software Inc., Cleveland, USA). Figures 1 and 2 give a schematic overview of the standard SBx templates

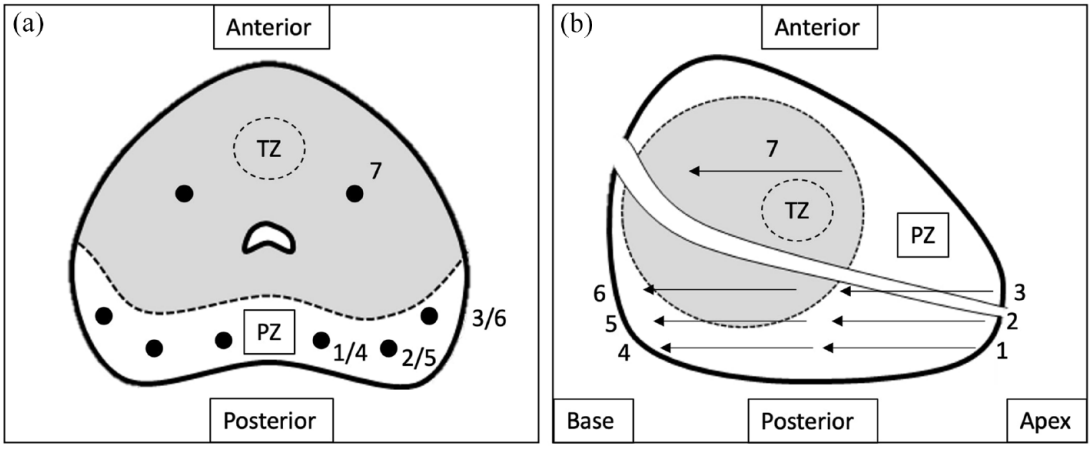

Figure 1. Schematic representation of the standard transperineal SBx template. (a). Transversal view of the prostate. (b) Sagittal view of the prostate. Biopsy cores are taken from (1) Posteromedial PZ, apex; (2) Posterolateral PZ, apex; (3) Lateral anterior horn PZ, apex; (4) Posteromedial PZ, base; (5) Posterolateral PZ, base; (6) Lateral anterior horn PZ, base and (7) Anterior TZ.
PZ, Peripheral Zone; TZ, Transition Zone.

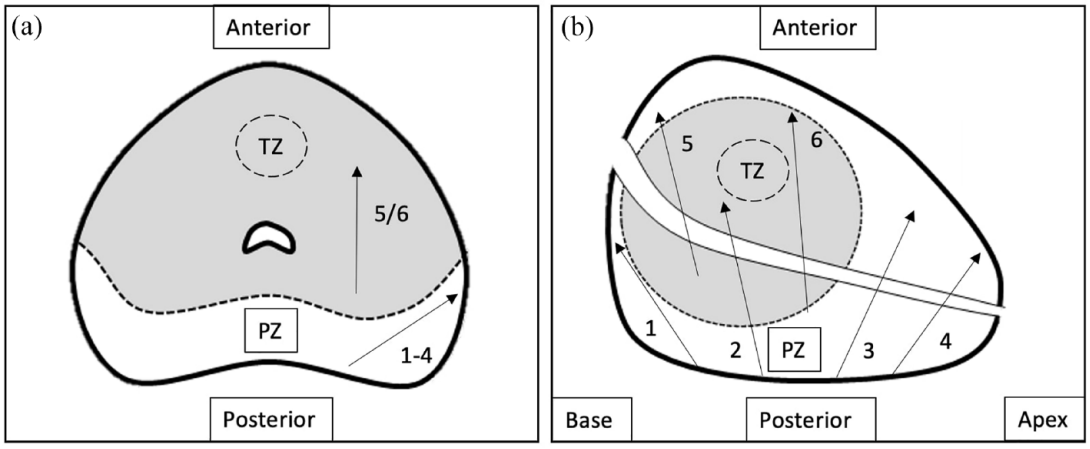

Figure 2. Schematic representation of the standard 12- to 16-core transrectal SBx template. Number of biopsy cores depended on biopsy status (12 cores for biopsy-naive and prior-positive patients and 16 cores for prior-negative patients). (a) Transversal view of the prostate. (b) Sagittal view of the prostate. Biopsy cores are taken from (1) Posteromedial to lateral PZ, base; (2) Posteromedial to lateral PZ, mid-base; (3) Posteromedial to lateral PZ, mid-apex; (4) Posteromedial to lateral PZ, apex; (5) Anteromedial TZ, mid-base; (6) Anteromedial TZ, mid-apex; (7/8) Additional cores in case of prior negative biopsy status, posteromedial to lateral PZ, mid-prostate.
PZ, Peripheral Zone; TZ, Transition Zone.

for the transperineal and transrectal approaches. Core biopsy needle specimens were examined by a dedicated uropathologist (>10 years of experience) and graded according to the International Society of Urological Pathology (ISUP) grade group consensus for the grading of PCa.[17]

The primary objective is to evaluate the diagnostic accuracy of different, predefined biopsy strategies in patients with a unilateral lesion on prostate MRI. This is done by comparing the csPCa, adjusted csPCa and iPCa detection rates of (1) SBx only, (2) TBx only, (3) contralateral SBx (contra-SBx) and TBx and (4) ipsilateral SBx (ipsi-SBx) and TBx, with SBx and TBx (reference standard), in patients with a unilateral lesion on pre-biopsy prostate MRI. iPCa is defined as ISUP 1, csPCa is defined as ISUP $\geqslant 2$ and adjusted csPCa as ISUP $\geqslant 3$.

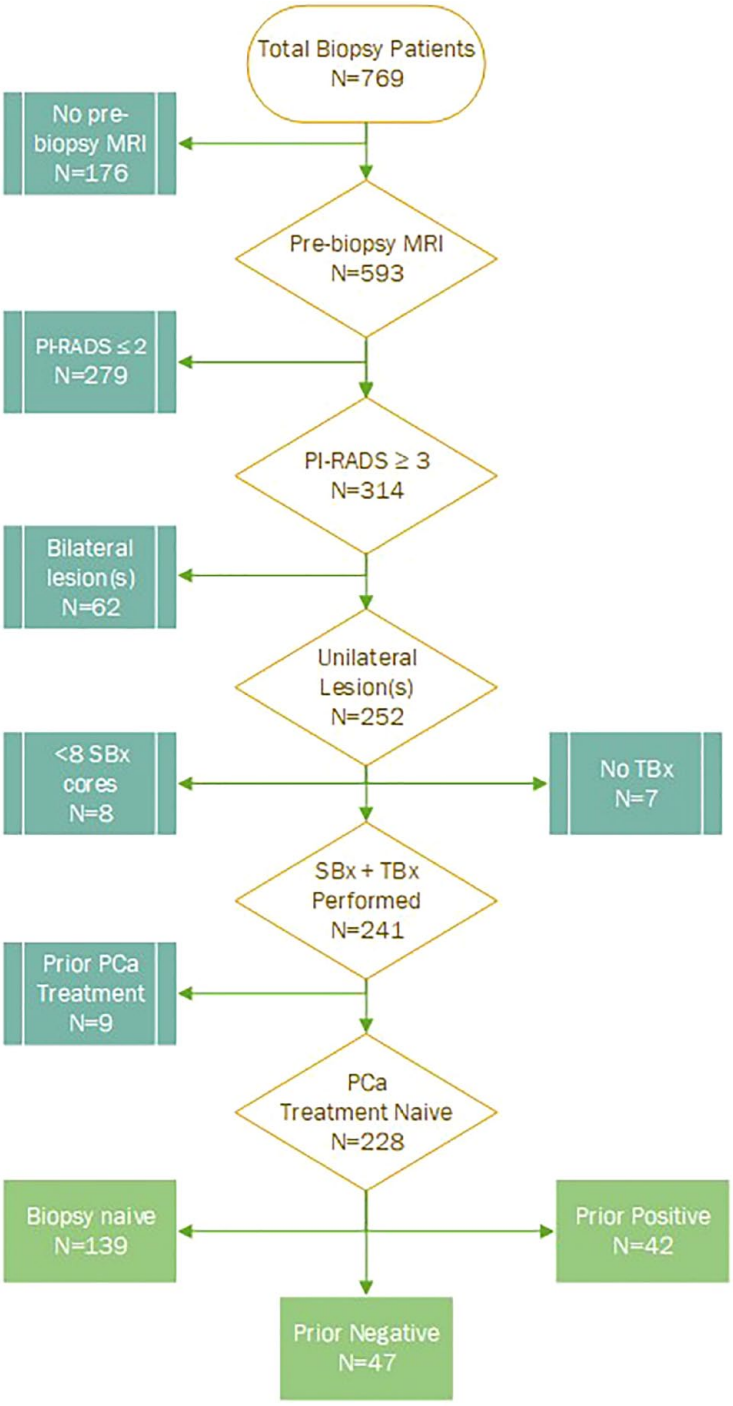

Figure 3. Inclusion flowchart.

The primary objective is additionally evaluated in a smaller cohort including only biopsy-naive patients.

Statistical analysis

Statistical analysis was performed in IBM SPSS Statistics (version 26).

The following (overlapping) subgroups were defined to perform statistical analysis:

- TBx and SBx (the reference standard): TBx cores plus all SBx cores (usually consisting of 14–17 total cores)
- MRI-TBx only: biopsy cores targeted specifically at the MRI lesion (PI-RADS ≥ 3), usually consisting of 2–3 cores per MRI lesion.
- SBx bilateral: biopsy cores taken from predefined locations according to the local standardized template, usually consisting of 12–14 cores equally divided over the left and right prostate lobe.
- TBx and contra-SBx only: TBx cores plus the SBx cores taken from the contralateral side, relative to the MRI lesion.
- TBx and ipsi-SBx: TBx cores plus the SBx cores taken from the ipsilateral side, relative to the MRI lesion.

Detection rates for csPCa, adjusted csPCa and iPCa were determined for each biopsy subgroup. Patient served as their own control as they appear in each of the subgroups. Sensitivities were calculated through cross-tabulation using the TBx and SBx subgroup as the reference standard. 95% Confidence intervals (95% CI) were calculated using the Wilson method. Significance of differences in cancer detection rates (CDR) between subgroups was determined by comparison of the 95% CIs. No overlap in 95% CI was considered as a significant difference. In case of overlapping 95% CIs, the McNemar's test was used to determine statistical significance.

Results

A total of 769 patients underwent prostate biopsy between October 2015 and September 2021 at both locations of the Amsterdam University Medical Centers. After excluding patients with no pre-biopsy MRI, negative MRI or bilateral MRI lesions, 252 patients were identified with one or more unilateral MRI lesions. Another 24 patients were excluded due to insufficient number of SBx, no TBx or active prior PCa treatment, resulting in a total of 228 patients included for this analysis (Figure 3). Out of the 228 included patients, 139 patients (61%) were biopsy-naive, 47 patients (20.6%) had a prior-negative biopsy and 42 patients (18.4%) were on AS. Table 1 provides an overview of patient characteristics at biopsy.

Table 1. Patient characteristics.

No. of patients		228
Age at biopsy (years) Mean (SD)		65.6 (±7.76)
PSA (ng/ml) Median (IQR)		7.6 (5.88)
PSAD (ng/ml/cc) Median (IQR)		0.15 (0.15)
Prostate volume (cc) Median (IQR)		46 (27)
Biopsy setting, n (%)	Biopsy-naïve	139 (61)
	Prior negative	47 (20.6)
	Prior positive	42 (18.4)
DRE results, n (%)	T0	129 (56.6)
	T2	85 (37.3)
	T3	8 (3.5)
	NA	6 (2.6)

DRE, digital rectal exam; IQR, interquartile range; NA, not available; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; SD, standard deviation.

Radiological tumour staging, based on prostate MRI, showed T2 in 182 patients (79.8%), T3a in 38 patients (16.7%) and T3b in 8 patients (3.5%). The majority of patients had a single lesion on MRI (95.6%), 9 patients (3.9%) had two lesions and 1 patient (0.4%) had three lesions. These lesions had a PI-RADS classification score of 3 in 64 patients (26.8%), 4 in 101 patients (42.3%) and 5 in 74 patients (31%). The lesions had a median (IQR) size of 12.5 (9) mm. Tables 2 and 3 include information for prostate MRI results and biopsy characteristics.

Cancer detection rates

The reference standard, consisting of combined SBx and TBx, had an overall CDR of 77.6% ($n=177$), csPCa was detected in 63.5% ($n=145$) and adjusted csPCa in 35.5% ($n=81$) (Table 4 and Figure 4). Either SBx or TBx alone missed a substantial amount of csPCa, when compared with TBx and SBx, with sensitivities of 86.8% (95% CI: 80.4–91.4) and 90.3% (95% CI: 84.4–94.2), respectively. For adjusted csPCa, the detection rates for either SBx or TBx alone further declined, with a sensitivity of 80.2% (95% CI: 70.3–87.5) for SBx and 76.5% (95% CI: 66.2–84.4) for TBx (Table 5). TBx and SBx, both showed added value when combined with each other, SBx detected 14 cases (9.6%) of csPCa that were missed by TBx, and TBx detected 19 cases (13.1%) of csPCa that were missed by SBx. Finally, ipsi-SBx without TBx had a detection rate for csPCa of 52.6% (120 out of 228) and contra-SBx alone found csPCa in 18.0% of patients (41 out 228).

The best performing alternative biopsy strategy was TBx and ipsi-SBx, reaching sensitivities for csPCa and adjusted csPCa of 98.6% (95% CI: 95.1–99.6) and 98.8% (95% CI: 96.3–99.9), respectively (Table 5). TBx and ipsi-SBx only missed two cases of csPCa (1.4%) and did not show a significant difference in csPCa detection ($p=0.500$) compared with the reference standard. One case of upgrading from ISUP 2 to ISUP 3 was detected due to contra-SBx results. There was a clear additional value of ipsi-SBx to TBx, with the combination resulting in a significantly higher detection of csPCa with 12 additional cases of csPCa (8.2%) and 18 additional cases of adjusted csPCa (22.2%) compared with TBx alone.

Clinically insignificant prostate cancer detection

The overall iPCa detection rate was 14% ($n=32$). iPCa detection rate was 8.3% ($n=19$), 10.1% ($n=23$), 11.0% ($n=24$) and 11.8% ($n=27$), for TBx, SBx, TBx and contra-SBx, and TBx and

Table 2. MRI characteristics.

		n	%
MRI T-stage	T2	182	79.8
	T3a	38	16.7
	T3b	8	3.5
	T4	0	0
No. of MRI lesions	1	218	95.6
	2	9	4
	3	1	0.4
PI-RADS V2 score	3	64	26.8
	4	101	42.3
	5	74	31
Laterality	Left	123	53.9
	Right	105	46.1
Lesion size (mm), median (IQR)		12.5 (9)	
MRI tesla	1.5 T	99	43.4
	3 T	121	53
	NA	8	3.5

IQR, interquartile range; MRI, magnetic resonance imaging; NA, not available; PI-RADS, prostate imaging reporting and data system.

Table 3. Biopsy procedure.

		n	%
No. of SBx cores per patient, median (IQR)	12 (2)		
No. of SBx cores per patient	8–10	8	3.5
	11 or 12	112	49.1
	13 or 14	57	25
	15–17	51	22.4
No. of TBx cores per lesion, median (IQR)	3 (1)		
No. of TBx cores per lesion	1	14	6
	2	73	30.5
	3	134	56
	4	16	6.7
	5	2	0.8

IQR, interquartile range; SBx, systematic biopsy; TBx, targeted biopsy.

ipsi-SBx, respectively (Table 4). Not performing contra-SBx in the TBx and ipsi-SBx group resulted in a decrease in iPCa detection of 15.6% (5 out of 32 cases). This reduction was not statistically significant ($p = 0.22$).

Biopsy-naive patients

The analysis in biopsy-naive patients ($n = 139$) showed comparable results with the overall cohort. CDR increased further, with detection rates for any PCa, csPCa and adjusted PCa of 82%, 70.5% and 41%, respectively (Figure 5). TBx and ipsi-SBx nearly matched the performance of the reference standard ($p = 1.0$), reaching sensitivities of 99% (95% CI: 94.4–99.8) for csPCa and 98.2% (95% CI: 90.7–99.7) for adjusted csPCa. Other biopsy strategies performed significantly worse, especially for adjusted csPCa detection, with the second-best performing strategy (TBx and contra-SBx) reaching a sensitivity of 80.7% (95% CI: 68.7–88.9) (Table 6). TBx and SBx detected one additional case for both definitions of csPCa, when compared with TBx and ipsi-SBx. Hence, overall TBx and ipsi-SBx missed 0.7% (1 out of 139 cases) of csPCa in the biopsy-naive group. In addition, TBx and ipsi-SBx resulted in a reduction of iPCa detection of 25% (4 out of 16 cases). Yet, this reduction did not reach statistical significance ($p = 0.13$).

Discussion

In the current diagnostic pathway for PCa, where pre-biopsy MRI and subsequent TBx or SBx are becoming standard of care, the question raises what the optimal biopsy strategy is. In case of a positive MRI, multiple studies have shown TBx alone, although decreasing iPCa detection misses a significant amount of csPCa when not combined with SBx.[1,9,10] The major downside of a standard SBx template is the high amount of iPCa detection.[1] By focusing the SBx template around the MRI lesion, targeting inaccuracies can be compensated for, thereby maximizing csPCa detection while minimizing the detection of iPCa.

This study demonstrates that in patients with a unilateral MRI lesion, TBx and ipsi-SBx can be used as an alternative prostate biopsy strategy. This strategy reached a sensitivity of 98.6% for csPCa detection, when compared with bilateral SBx together with TBx, missing only two cases of csPCa in 226 men (0.8%), while detecting 15.6%

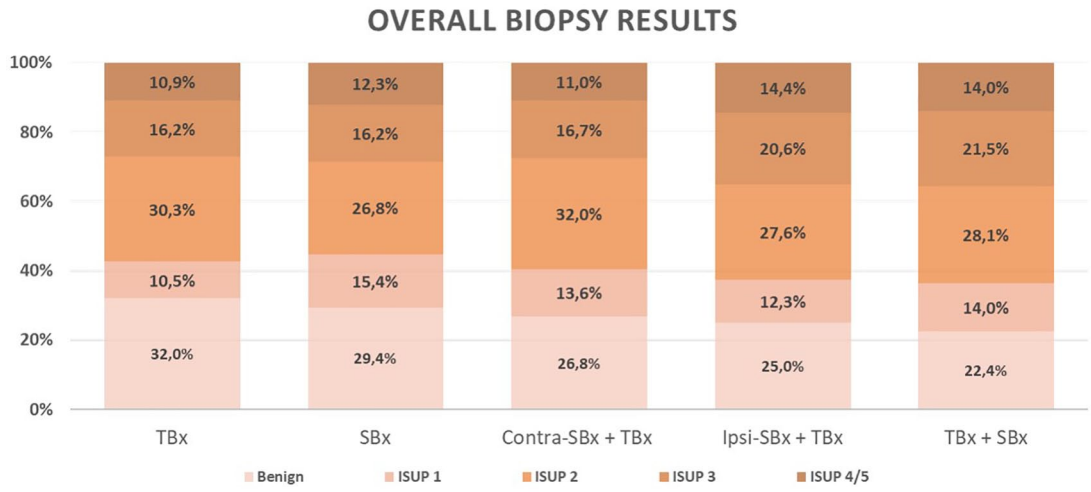

Figure 4. Overall biopsy outcomes ($N = 228$) categorized by ISUP grade group for each biopsy strategy.
Contra-SBx, contralateral systematic biopsy; csPCa, clinically significant prostate cancer; iPCa, insignificant prostate cancer; ipsi-SBx, ipsilateral systematic biopsy; ISUP, International Society of Urological Pathology; SBx, systematic biopsy; TBx, targeted biopsy.

Table 4. CDR per biopsy strategy in the overall cohort ($N = 228$).

Biopsy strategy	Any cancer (ISUP ⩾ 1)	csPCa (ISUP ⩾ 2)	Adjusted csPCa (ISUP ⩾ 3)	iPCa (ISUP = 1)
	n (%)	*n* (%)	*n* (%)	*n* (%)
SBx and TBx	177 (77.6)	145 (63.5)	81 (35.5)	32 (14.0)
TBx and ipsi-SBx	171 (75.0)	143 (62.7)	80 (35.1)	28 (12.3)
TBx and contra-SBx	167 (73.2)	136 (59.6)	63 (27.6)	31 (13.6)
TBx	155 (68.0)	131 (57.5)	62 (27.2)	24 (10.5)
SBx	161 (70.6)	126 (55.3)	65 (28.5)	35 (15.4)

Contra-SBx, contralateral systematic biopsy; csPCa, clinically significant prostate cancer; iPCa, insignificant prostate cancer; ipsi-SBx, ipsilateral systematic biopsy; ISUP, International Society of Urological Pathology; SBx, systematic biopsy; TBx, targeted biopsy.

less iPCa. In addition, it would have led to a reduction of 6–7 biopsy cores per patient, thereby reducing patient burden, procedure time and pathology costs. Further decreasing the number of biopsy cores by completely omitting SBx and performing only TBx continues to be inferior, with TBx alone missing 14 cases of csPCa (9.7%). It is important to note that in 3 out of these 14 missed cases, only a singly TBx core was taken; therefore, the MRI lesions can be considered as inadequately sampled. However, adjusted for these patients, TBx alone still missed 7.6% of csPCa cases. Ipsi-SBx showed to have a significant additional value to TBx, increasing ISUP ⩾ 2 PCa detection by 8.2% and ISUP ⩾ 3 PCa detection by 22.2%.

The current study strengthens the results of previous findings.[11–13] Three studies evaluating PCa detection rates of ipsi- and contralateral prostate biopsy have been published, and all show results in favour of the TBx and ipsi-SBx approach. In a cohort consisting of 211 patients with unilateral MRI lesions, Bryk *et al.*[12] found that TBx and ipsi-SBx had a sensitivity for ISUP ⩾ 2 PCa detection of 96%, while avoiding detection of 18.6% iPCa. Freifeld *et al.*[13] also reported good results for the TBx and ipsi-SBx approach in their cohort

Table 5. Sensitivity for different biopsy approaches compared with reference standard.

Biopsy approach	Any cancer (ISUP ⩾ 1)			csPCa (ISUP ⩾ 2)			Adjusted csPCa (ISUP ⩾ 3)			iPCa (ISUP = 1)		
	n	Sensitivity	95% CI	*n*	Sensitivity	95% CI	*n*	Sensitivity	95% CI	*n*	Sensitivity	95% CI
TBx and SBx (reference)	177	100		145	100		81	100		32	100	
TBx and ipsi-SBx	171	96.6	92.8–98.4	143	98.6	95.1–99.6	80	98.8	96.3–99.9	27	84.4	68.2–93.1
TBx and contra-SBx	167	94.4	89.9–96.9	136	93.8	88.6–96.7	63	77.8	67.6–85.5	25	78.1	61.2–89.0
TBx alone	155	87.6	81.9–91.6	131	90.3	84.4–94.2	62	76.5	66.2–84.4	19	59.4	42.3–74.5
SBx alone	161	91	85.8–94.4	126	86.8	80.4–91.4	65	80.2	70.3–87.5	23	71.9	54.6–84.4

CI, confidence intervals; contra-SBx, contralateral systematic biopsy; csPCa, clinically significant prostate cancer; iPCa, insignificant prostate cancer; ipsi-SBx, ipsilateral systematic biopsy; ISUP, International Society of Urological Pathology; SBx, systematic biopsy; TBx, targeted biopsy.

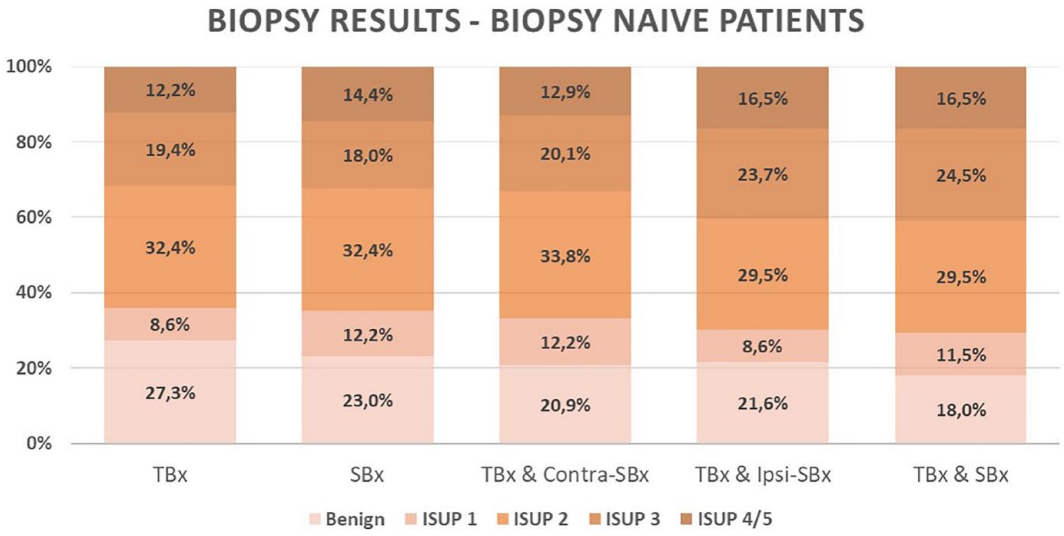

Figure 5. Biopsy outcomes for the biopsy-naïve subgroup (*N* = 139) categorized by ISUP grade group for each biopsy strategy.
Contra-SBx, contralateral systematic biopsy; csPCa, clinically significant prostate cancer; iPCa, insignificant prostate cancer; ipsi-SBx, ipsilateral systematic biopsy; ISUP, International Society of Urological Pathology; SBx, systematic biopsy; TBx, targeted biopsy.

of 116 men, with a sensitivity of 96.4% for ISUP ⩾ 2 PCa compared with standard 12-core SBx and TBx and a decrease in iPCa detection. Finally, Hansen *et al.*, evaluated four different adjusted biopsy templates based on the Ginsburg scheme in 490 men and demonstrated a sensitivity of 91% for both TBx and ipsi-SBx, and saturation TBx only, compared with an extensive 2-core TBx and 18- to 24-core SBx template.[14,18]

The additional value of the current trial lies in its' sample size and the subgroup analyses performed. In the study by Bryk *et al.*, the overall csPCa detection rate is relatively low (23.2%) providing a small cohort of 49 csPCa patients. This is likely due to patient selection because MRI images were not evaluated according to PI-RADS and patients with an MRI result of 'clinically significant disease unlikely to be present' were not

Table 6. Sensitivity for cancer detection for different biopsy approaches compared with reference standard – biopsy-naïve patients only.

Biopsy approach	Any cancer (ISUP ⩾ 1)			csPCa (ISUP ⩾ 2)			Adjusted csPCa (ISUP ⩾ 3)			iPCa (ISUP = 1)		
	n	Sensitivity	95% CI	*n*	Sensitivity	95% CI	*n*	Sensitivity	95% CI	*n*	Sensitivity	95% CI
TBx and SBx (reference)	114	100		98	100		57	100		16	100	
TBx and ipsi-SBx	109	95.6	90.1–98.1	97	99	94.4–99.8	56	98.2	90.7–99.7	12	75	50.5–89.8
TBx and contra-SBx	110	96.5	91.3–98.6	93	94.9	88.6–97.8	46	80.7	68.7–88.9	13	81.3	57.0–93.4
TBx alone	101	88.6	81.5–93.2	89	90.8	83.5–95.1	44	77.2	64.8–86.2	9	56.3	33.2–76.9
SBx alone	107	93.6	87.9–97.0	90	91.8	84.7–95.8	45	78.9	66.7–87.5	13	81.3	57.0–93.4

CI, confidence intervals; contra-SBx, contralateral systematic biopsy; csPCa, clinically significant prostate cancer; iPCa, insignificant prostate cancer; ipsi-SBx, ipsilateral systematic biopsy; ISUP, International Society of Urological Pathology; SBx, systematic biopsy; TBx, targeted biopsy.

excluded.[12] Freifeld *et al.*[13] reported higher csPCa detection rates (47%), but evaluated a smaller cohort, resulting in 55 patients with csPCa. Comparatively, the current cohort reports an overall sample size of 228 and a csPCa population of 145.

Hansen *et al.*[14] investigated a larger cohort, but did not perform a separate analysis for ISUP ⩾ 3 PCa detection rates (only for ISUP ⩾ 2 PCa). However, the distinction between the different definitions for csPCa is highly relevant for treatment decisions. Due to the excellent cancer-specific survival in selected patients diagnosed with (favourable) ISUP 2 PCa, these patients can safely be followed according to an AS protocol.[19,20] Consequently, ISUP 2 PCa is no longer being considered clinically relevant in every case. Interestingly, when using the adjusted csPCa definition, the current study shows a much higher discrepancy in CDR for different biopsy strategies. The sensitivity of TBx for adjusted csPCa detection drops to 76.5% compared with TBx and SBx. The addition of ipsi-SBx detects 18 extra ISUP ⩾ 3 (29%) patients and increases sensitivity to 98.8%. A possible explanation for this discrepancy is undersampling of the lesion when only performing TBx, with biopsy cores sampling the less aggressive sections of the lesion and missing the higher graded sections. There are different reasons for undersampling, such as inaccuracies during MRI-ultrasound fusion or by deflection of the biopsy needle. The data from the current study prove that extending the TBx template using, for example, ipsi-SBx can compensate for the undersampling of MRI lesions.

In clinical practice, a patient's prostate biopsy history is highly important for risk classification. Therefore, the subgroup analysis on biopsy-naive patients in the current trial provides relevant information. Similar to the overall cohort, TBx and ipsi-SBx was the best performing biopsy strategy, missing only one case of csPCa in 139 biopsy-naive men, when compared with TBx and SBx.

Regarding iPCa, there was a decrease in detection in both the overall cohort and the biopsy-naive subgroup when only performing TBx and ipsi-SBx, reducing iPCa detection in both cohorts with 15.6% and 25%, respectively. However, these differences did not reach statistical significance. This is possibly due to the low total number of iPCa patients in the current cohort, with 32 overall cases of iPCa, and a larger cohort might be necessary to definitively prove this alternative biopsy strategy will lead to less iPCa detection. However, it can reasonably be assumed that obtaining less biopsy cores will lead to less iPCa detection, and prior studies have shown results to substantiate this assumption.[12–14]

To further consider the clinical impact of omitting contra-SBx, the two cases of missed csPCa and the single case of upgrading were analysed in further detail. Both cases of missed csPCa showed a Gleason Score of 3 + 4 = 7 (ISUP 2) without

cribriform growth in a single contralateral biopsy core. One of these patients opted for AS in another clinic, and no further data are available. The other patient had a higher risk profile, based on a PSA of 24 ng/ml. Prostate specific membrane antigen (PSMA)-PET showed bilateral intensity in the prostate, without any distant or local metastasis, and the patient was treated with external beam radiotherapy. Interestingly, only a single TBx core was taken from this patient, who had a PI-RADS 4 lesion in the anterior prostate. Considering that the standard SBx template does not extensively sample the anterior region of the prostate, this missed case of csPCa could very well be due to undersampling. Moreover, TBx and ipsi-SBx showed ISUP 1 in this patient, which would have resulted in AS and possible deferred treatment after upgrading at 1-year re-biopsy, ensuring a low risk of disease progression. Finally, a single case of upgrading from ISUP 2 to ISUP 3 due to contra-SBx was found in this cohort. This patient, aged 68 years, had a PI-RADS 5 lesion of 22 mm on MRI, prostate volume of 42 ml and a PSA of 4.0 ng/ml. TBx and ipsi-SBx contained Gleason Score 3 + 4 = 7 adenocarcinoma without cribriform growth in a total of 4 cores (tumour volume > 50%). Contralateral biopsy showed a single core containing Gleason Score 4 + 3 = 7 adenocarcinoma, including cribriform growth. The patient opted for brachytherapy and has a stable, low PSA level at 14 months after treatment. Due to the clinical factors and number of cores containing csPCa in the TBx and ipsi-SBx, it is likely that the upgrading in this case did not lead to a change in treatment. However, currently it is increasingly common to apply AS for patients with ISUP 2 PCa, which could have resulted in disease progression for this particular patient.[19]

Before completely omitting contra-SBx, it is important to consider that contra-SBx found csPCa in 18.0% (41 out of 228) of the current cohort. The presence of csPCa in the contralateral lobe might be relevant for patients eligible for brachytherapy or focal therapy.

This study has several limitations. First, although the database was prospectively managed, the analysis was retrospective making it prone to bias. Second, in the current study, outcomes of a 12- to 14-core SBx and TBx were used as a reference standard. Consequently, the true prevalence of PCa is only approximated, when ideally the reference standard consists of direct comparison with radical prostatectomy specimen or template mapping biopsy. However, the study is a representation of standard clinical practice and, therefore, allows accurate comparison among the investigated strategies. In addition, the high overall detection rates for PCa and csPCa in this study imply adequate sampling, especially considering other baseline characteristics were similar to corresponding studies.[12–14] Finally, the results of this study are based on data collected at two high expertise centres, with dedicated uroradiologists, biopsy operators and pathologists. Consequently, caution is warranted when extrapolating the results of this study to general clinical practice. The overall CDR of 77.6% and csPCa detection rate of 63.5% in this study are relatively high.[1,9,11–13] CDR at biopsy is dependent on multiple factors, which can differ between sites. Diagnostic accuracy of the prostate MRI varies widely, with positive predictive values (PPV) for csPCa ranging from 19% to 68% for PI-RADS ⩾ 3 in a study comparing 26 sites.[20] MRI is also subject to considerable interobserver variability, with kappa values (0.31–0.60) reaching only fair to moderate agreement for experienced radiologists.[21–23] Biopsy operator experience is a significant predictor for the detection of PCa at biopsy, reaching odds ratios of 2.40.[24] Finally, the targeting technique used during TBx can impact the accuracy. Although no clear advantage for either cognitive TBx or software-assisted fusion TBx, both can lead to inaccuracies due to registration errors.[25] It is advisable to take these factors into careful consideration before opting for a specific biopsy strategy. To ensure the best quality of care for an individual patient, biopsy strategies should be based on locally available expertise and site-specific biopsy outcome evaluation.

Conclusion

TBx and ipsi-SBx is a safe and cost-effective alternative to the standard SBx and TBx template, missing only 1.4% of csPCa cases, while reducing iPCa detection, number of biopsy cores, cost and procedure time.

Declarations

Ethics approval and consent to participate

A waiver of ethical approval and informed consent was provided by the Medical Research Ethics Committee Academic Medical Centre Amsterdam (MREC AMC, ID: W21_534 # 21.590).

Consent for publication
Not applicable.

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Jorg R. Oddens: Conceptualization; Supervision; Writing – review & editing.

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