

## Prostate cancer detection rate with MRI-targeted biopsy alone using outpatient transperineal prostate biopsy

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### ABSTRACT

**INTRODUCTION:** We aimed to compare the detection rate of prostate cancer (PCa) and clinically significant (cs) PCa by magnetic resonance imaging-guided targeted biopsy (MTBx) alone and MTBx plus systematic biopsy (SBx) using an outpatient transperineal (TP) approach under local anesthesia.

**METHODS:** A retrospective study of patients who underwent outpatient TP prostate biopsy under local anesthesia at our tertiary institution between 2019 and 2022 was performed. To compare the proportions of PCa and csPCa in both pathways, McNemar's tests were used. Multivariable logistic regression model was fitted to determine the predictors of csPCa.

**RESULTS:** Of 255 men included, 177 (69%) underwent MTBx alone. MTBx had similar detection rate for PCa (56%) and csPCa (47%) compared to the combination of MTBx and SBx (PCa 61%; csPCa 49%;  $p=0.1$  and  $p=0.3$ , respectively). MTBx had lower median number of biopsy cores compared to the combination of MTBx and SBx (6 vs. 11,  $p<0.001$ ). At multivariable logistic regression analysis, age (odds ratio [OR] 1.08, 95% confidence interval [CI] 1.04–1.13,  $p<0.001$ ), prior negative biopsy (OR 0.19, 95% CI 0.09–0.44,  $p<0.001$ ), prostate-specific antigen density cutoff  $\geq 0.15$  (OR 3.17, 95% CI 1.67–6.01,  $p<0.001$ ), and prostate imaging reporting and data system  $\geq 4$  (OR 12.2, 95% CI 4.21–35.6,  $p<0.001$ ) were independent predictors of csPCa.

**CONCLUSIONS:** MTBx showed similar diagnostic performance to the combination of MTBx and SBx in patients undergoing outpatient TP prostate biopsy. Future studies are needed to evaluate the role of MTBx in avoiding unnecessary biopsies.

### INTRODUCTION

The diagnostic pathway for prostate cancer (PCa) has evolved significantly over the past three decades.<sup>1</sup> Targeted biopsy of suspicious lesions identified on multiparametric magnetic resonance imaging (mpMRI) has been proposed as a tool to reduce overdiagnosis of clinically insignificant (ci) PCa. Furthermore, this approach has been shown to be non-inferior to systematic biopsy (SBx) in patients with elevated prostate-specific antigen (PSA).<sup>2,3</sup>

The recently published GÖTEBORG-2 prospective trial showed that performing mpMRI-guided targeted biopsy (MTBx) without SBx for screening and early detection of PCa in men with elevated PSA levels reduced the risk of overdiagnosis by half at the cost of delaying detection of intermediate-risk tumors in a small proportion of patients.<sup>3</sup> In the PRECISION and 4M trials, detection rate of ciPCa was significantly lower when adopting an MTBx without a SBx strategy;<sup>4,5</sup> however, whether SBx can be omitted is not universally agreed upon.<sup>6,7</sup>

In addition, the aforementioned large studies used a transrectal (TR) biopsy approach, which may have affected the detection rate of csPCa in both MTBx and SBx. The transperineal (TP) approach allows easier access to certain prostate zones, including the anterior zone and the apical and dorsolateral horns, which may be undersampled using the TR route.<sup>8</sup> Furthermore, the TP approach reduces the infection rate associated with the procedure. This has become increasingly

## KEY MESSAGES

- mpMRI-guided targeted biopsies reduce overdiagnosis and overtreatment.
- Transperineal targeted biopsies reduce infection rates.
- Transperineal prostate biopsy under local anesthesia is safe.

important due to the rising resistance rates and side effects of fluoroquinolones, which has led to both the European Commission and the U.S. Food and Drug Administration recommending limiting the use of these antibiotics for prostate biopsy (PBx).<sup>9-12</sup>

In the TP outpatient setting, the addition of SBx to MTBx may lead to unnecessary detection of cIPCa and higher rates of complications, such as bleeding and infection.<sup>13</sup> Therefore, the aim of our study was to compare the detection rate of PCa and csPCa by MTBx alone and MTBx plus SBx using an outpatient TP approach under local anesthesia and to evaluate the diagnostic yield of SBx in this population.

## METHODS

## Patients and data collection

This retrospective, single-center study was conducted between May 2019 and July 2022 in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Patients were identified retrospectively from a prospectively maintained database that records all outpatient TP PBx performed under local anesthesia at the McGill University Health Centre. There were three indications to undergo mpMRI: 1) high clinical suspicion of PCa despite previous negative PBx; 2) followup PBx in active surveillance (AS) program; and 3) high clinical suspicion of PCa and no previous PBx but patient underwent direct mpMRI-ultrasound (US) fusion PBx.

Out of an initial cohort of 325 patients with suspicious PCa, those with missing data on Prostate Imaging Reporting and Data System (PI-RADS) score category ( $n=13$ ), metastatic PCa diagnosis ( $n=2$ ), or a history of prior PCa treatment ( $n=55$ ) were excluded. Clinical data were collected from patient medical records and included age, previous medical history, pre-PBx PSA level, mpMRI report, PBx procedure report, and pathology report.

## mpMRI and biopsy procedure

All prebiopsy mpMRI scans, consisting of multiplanar T2-weighted images, diffusion-weighted imaging, dynamic contrast-enhanced mpMRI, and T1-weighted images with fat suppression,<sup>14</sup> were performed either at our institutions or externally using a 1.5 T or 3 T scanner, and were reported according to the, PI-RADS v.2<sup>15</sup> (until 2019) and PI-RADS v.2.1<sup>16</sup> (since 2020) by dedicated radiologists. PSA value and prostate volume measured through mpMRI were recorded to obtain PSA density (PSAD).

Board-certified urologists or residents under supervision performed mpMRI fusion PBx via TP route under local anesthesia in an outpatient setting according to the center's clinical routine. A total of 10 ml of 1% lidocaine with 8.4% sodium bicarbonate mixed with 9:1 lidocaine was injected subcutaneously with a 22-gauge, 32 mm needle on the horizontal line of the anal canal at the upper margin, 20 mm from the midline, 5 ml on both sides of the midline of the perineum using a "fan technique" over an area of 3–4 cm. After insertion of the transrectal ultrasound (TRUS) probe, 2–4 ml of 1% lidocaine was injected under TRUS guidance in the trajectory along both neurovascular bundles, starting at the junction of the seminal vesicles and the prostate, using a 20-gauge, 80 mm spinal needle. The majority of lidocaine was injected in the periprostatic region. In addition, 3–6 ml of 1% lidocaine was injected bilaterally in the perineal and subcutaneous planes as the needle exited, depending on the size of the prostate.

Lesions with a PI-RADS score  $\geq 3$  on mpMRI were subjected to MTBx (with a minimum of four cores per lesion). MTBx were performed using mpMRI-US fusion software. SBx cores were also obtained at the discretion of the urologist, based on previous biopsy history. SBx cores, when included, did not cover the regions targeted by MTBx. The number of SBx cores was at the discretion of the urologist, based primarily on lesion location and prostate volume. All the specimens were assessed by institutional pathologists. All the pathologists were specialists in urogenital cancer and PBx results were reported separately for MTBx and SBx, and in accordance with the classification of the International Society of Urological Pathology (ISUP).<sup>17</sup> The number of positive cores, tumor percentages, length of cores, and ISUP grade group (GG) were provided.

## Study endpoints

The primary endpoint was to compare the detection rate of PCa and csPCa (ISUP GG  $\geq 2$ ) through MTBx and MTBx plus SBx approaches. Secondary endpoints

were the following: to assess the predictors of csPCa in the overall population; to assess upgrading and downgrading of ISUP GG on PBx specimens between MTBx and SBx in patients who underwent combined MTBx plus SBx; to assess how many SBx cores could have been avoided in patients who underwent combined MTBx plus SBx; and the proportion of missed csPCa.

**Statistical analysis**

Descriptive statistics were used to characterize our cohort based on the PBx approach. Comparisons between the two groups were performed with  $\chi^2$  and Fisher's exact tests for categorical data and Student's t-test or Wilcoxon rank sum test for continuous data. The median and interquartile range (IQR) were used to report results for continuous variables, and the frequency with percentage for categorical variables. Continuous variables were described as medians with IQR. Categorical variables were described with integers and percentages. To compare the proportions of csPCa and ciPCa in both pathways, McNemar's tests were used. Multivariable logistic regression models (MLRMs) were fitted to determine the predictors of csPCa. The diagnostic accuracy of MLRM was reported as area under the receiver operator characteristic (ROC) curve. The number of SBx avoided was determined by subtracting the number of negative tests from the total number of SBx cores in patients receiving MTBx plus SBx.<sup>18</sup> Statistical significance was set at  $p < 0.05$ . Statistical analysis was done with STATA® 16.1 (StataCorp, College Station, TX, U.S.).

**RESULTS**

**Baseline characteristics**

The baseline characteristics of the patients stratified according to the biopsy approach are summarized in Table 1. Of 255 men included, 177 (69%) underwent MTBx alone. Overall, 148/255 (58%) were diagnosed as PCa and 121/255 (48%) as csPCa. Patients who underwent MTBx alone had higher proportion of prior negative biopsy (29% vs. 12%,  $p = 0.003$ ) and higher median MTBx cores (6 vs. 4,  $p < 0.001$ ). Patients who underwent combined MTBx plus SBx had a higher proportion of family history (0% vs. 3%,  $p = 0.032$ ) and higher median total cores (6 vs. 11,  $p < 0.001$ ).

**PCa and csPCa detection rate**

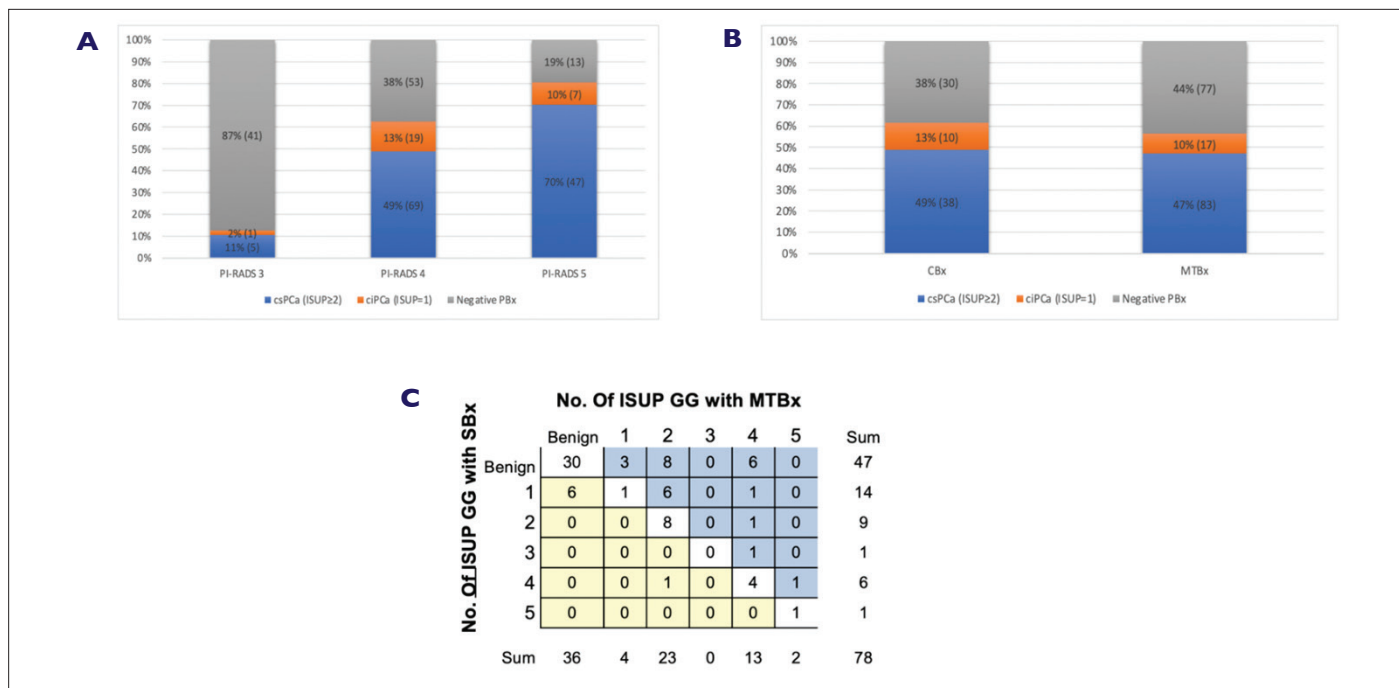
The distribution of PCa and csPCa stratified according to PI-RADS score of index lesion are shown in Figure 1A. csPCa was diagnosed in 11% (5/47) of

**Table 1. Baseline characteristics stratified by the biopsy approach**

	MTBx only n=177	CBx (MTBx plus SBx) n=78	p
Age, years, median (IQR)	66 (61–70)	63 (57–72)	0.3
Suspicious DRE, yes, n (%)	3 (2)	0 (0.0)	0.3
Family history, yes, n (%)	0 (0.0)	2 (3)	<b>0.032</b>
Active surveillance, yes, n (%)	39 (22)	11 (14)	0.1
Prior negative biopsies, yes, n (%)	51 (29)	9 (12)	<b>0.003</b>
Total PSA, ng/ml, median (IQR)	8 (5–11)	8 (5–12)	0.8
Prostate volume at mpMRI, cm <sup>3</sup> , median (IQR)	48 (34–71)	43 (33–56)	0.068
Lesion volume at mpMRI, cm <sup>3</sup>	12 (8–16)	12 (9–16)	0.8
PSAD cutoff			
<0.15	84 (48)	35 (45)	0.7
≥0.15	93 (53)	43 (55)	
PI-RADS score, n (%)			
3	30 (17)	17 (22)	0.6
4	98 (55)	43 (55)	
5	49 (28)	18 (23)	
csPCa, yes, n (%)	83 (47)	38 (49)	0.8
PCa, yes, n (%)	100 (57)	48 (62)	0.4
Total cores, median (IQR)	6 (5–8)	11 (8–14)	<b>&lt;0.001</b>
MTBx, median (IQR)	6 (5–8)	4 (4–5)	<b>&lt;0.001</b>
Target lesion location, n (%)			
Transitional zone	71 (40)	22 (28)	0.1
Peripheral zone	98 (55)	54 (69)	
Both	8 (5)	2 (3)	

The ANOVA test was used to compare categorical variables, while the Mann-Whitney U test was used to compare continuous variables. All values are reported as median and interquartile range. Significant p-values are in bold. ANOVA: analysis of variance; CBx: combined biopsy; csPCa: clinically significant prostate cancer; DRE: digital rectal examination; IQR: interquartile range; mpMRI: multiparametric magnetic resonance imaging; MTBx: magnetic resonance imaging-guided targeted biopsy; PCa: prostate cancer; PI-RADS: Prostate Imaging Reporting and Data System; PSA: prostate-specific antigen; PSAD: PSA density; SBx: systematic biopsy.

PI-RADS 3, 49% (69/141) of PI-RADS 4, and 70% (47/67) of PI-RADS 5 patients. The distribution of detection rate for PCa and csPCa between combined MTBx plus SBx and MTBx alone are illustrated in Figure



**Figure 1.** Prostate cancer detection rates according to Prostate Imaging Reporting and Data System (PI-RADS) score and biopsy pathway. (A) The results of ciPCa and csPCa detection rate % (n) stratified according to PI-RADS score. (B) The results of ciPCa and csPCa detection rate % (n) stratified according to biopsy strategy (combined MTBx plus SBx vs MTBx alone). (C) The cross-tabulation of ISUP GG detected by SBx and MTBx in patients who received combined MTBx plus SBx. The areas shaded in yellow indicate the men who were upgraded to higher ISUP GG by SBx against MTBx, and the areas shaded in blue indicate the men who were upgraded to higher ISUP GG by MTBx against SBx. CBx: combined magnetic resonance imaging-targeted biopsy plus systematic biopsy; ciPCa: clinically insignificant prostate cancer; csPCa: clinically significant prostate cancer; GG: grade group; ISUP: International Society of Urological Pathology; MTBx: magnetic resonance imaging-targeted biopsy; PBx: prostate biopsy; PCa: prostate cancer; SBx: systematic biopsy.

IB. Using combined MTBx plus SBx as reference standard, MTBx had similar detection rate for PCa (56% [100/177]) and csPCa (47% [83/177]) compared to combined MTBx plus SBx (PCa 61% [48/78]; csPCa 49% [38/78]; p 0.1 and 0.3, respectively). Considering the effects of two different biopsy approaches on the reduction of biopsy cores in the overall population, MTBx had lower median number of biopsy cores compared to combined MTBx plus SBx (6 [IQR 5–8] vs. 11 [IQR 8–14], p<0.001, respectively). If the optimized strategy is used, men with suspicious lesions on mpMRI undergoing MTBx alone can achieve an excellent PCa (68% [100/148]) and csPCa detection rate (69% [83/121]) at lower costs (median biopsy core of six) compared to combined MTBx plus SBx.

### Predictors of csPCa

At MLRM, age (odds ratio [OR] 1.07, 95% confidence interval [CI] 1.03–1.12, p<0.001); prior negative biopsy (OR 0.21, 95% CI 0.09–0.50, p<0.001); PSAD cutoff ≥0.15 ng/ml (OR 3.02, 95% CI 1.57–5.80, p=0.001); PI-RADS ≥4 (OR 10.8, 95% CI 3.54–33.1, p<0.001); and MTBx alone (OR 6.02, 95% CI 2.34–10.2, p=0.001) were identified as independent predictors of csPCa, as

shown in Table 2. The accuracy of a model including age, family history, suspicious digital rectal examination, prior negative biopsy, AS, PSAD cutoff, number of lesions, total cores, received SBx cores, received MTBx alone, received MTBx plus SBx, lesion location, and PI-RADS score was 0.84 (95% CI 0.74–0.92) (Figure 2).

### Subgroups analyses of patients who underwent combined MTBx plus SBx

MTBx resulted in higher overall detection rate for PCa (54% [42/78] vs. 40% [31/78], p<0.010) and csPCa (49% [38/78] vs. 22% [17/78], p-value<0.001) than did by SBx in patients who underwent combined MTBx plus SBx (Table 3). Overall, MTBx detected 88% (42/48) PCa and 100% (38/38) csPCa, while SBx missed 35% (17/48) PCa and 55% (21/38) csPCa in patients who underwent combined MTBx plus SBx (Table 3).

In paired comparison matrix, MTBx redetected 17/78 (22%) additional PCa lesions and 7/78 (9%) additional csPCa lesions against SBx in patients underwent combined MTBx plus SBx (Figure 1C). On the contrary, SBx redetected only 6/78 (8%) new PCa lesions and no new csPCa lesions against MTBx. A total of 328 (328/560) SBx cores could have been avoided in 78

**Table 2. Multivariate logistic regression model for the prediction of clinically significant prostate cancer**

Predictor	Multivariate regression		
	OR	(95% CI)	p
Age	1.07	(1.03–1.12)	<b>&lt;0.001</b>
Family history	0.89	(0.03–26.7)	0.9
Suspicious DRE	0.58	(0.03–10.4)	0.8
Prior negative biopsies	0.21	(0.09–0.50)	<b>&lt;0.001</b>
Active surveillance	2.20	(0.98–4.97)	0.095
PSAD cutoff			
<0.15	Ref.		
≥0.15	3.02	(1.57–5.80)	<b>0.001</b>
Number of lesions	0.97	(0.62–1.53)	0.8
Total cores	0.95	(0.82–1.09)	0.5
Target lesion location			
Transitional zone	Ref.		
Peripheral zone	1.30	(0.75–2.15)	0.2
Both	1.21	(0.96–2.56)	0.1
PI-RADS score			
3	Ref.		
≥4	10.8	(3.54–33.1)	<b>&lt;0.001</b>
Received SBx cores	1.54	(0.54–4.33)	0.6
Received MTBx alone	6.02	(2.34–10.2)	<b>0.001</b>
Received MTBx plus SBx	1.60	(0.67–3.86)	0.3

Significant p-values are in bold. For the multivariate analysis, we considered only significant parameters in the univariate analysis. CI: confidence interval; DRE: digital rectal examination; MTBx: magnetic resonance imaging-guided targeted biopsy; OR: odds ratio; PCa: prostate cancer; PI-RADS: Prostate Imaging Reporting and Data System; PSAD: prostate-specific antigen density; SBx: systematic biopsy.

men who underwent combined MTBx plus SBx, with no missing csPCa.

Regarding ISUP GG upgrading at biopsy specimens, MTBx was responsible for upgrading of events in 27/78 (35%) patients against SBx (blue-shaded area in Figure 1C), while SBx was responsible for upgrading of events in 7/78 (9%) patients against MTBx (yellow-shaded area in Figure 1C). Fourteen out of 38 cases (37%) were upgraded from benign at SBx to csPCa at MTBx and 7/38 (18%) were upgraded from ciPCa at SBx cores to csPCa at MTBx. Conversely, 6/48 (13%) benign cases were upgraded to ciPCa by SBx.

## DISCUSSION

This large series of mpMRI-positive patients analyzed the impact of MTBx in the detection rate of csPCa in men undergoing outpatient TP PBx under local anesthesia. According to our results, performing prebiopsy mpMRI and MTBx seems a valuable strategy to avoid SBx without compromising csPCa detection rate in this subset of patients. These results confirm the usefulness of MTBx through a TP approach to rule out csPCa.<sup>13</sup>

In our study cohort, MTBx had a similar detection rate for PCa (56% vs. 61%, p 0.1) and csPCa (47% vs. 49%, p 0.3) compared to the combination of MTBx plus SBx. We reported that performing MTBx plus SBx not only did not improve the detection rate of csPCa, but also increased the number of biopsy cores, which could lead to increased post-biopsy complications.<sup>12</sup> Our findings are consistent with several studies showing that MTBx improves csPCa detection rate.<sup>19-21</sup>

Schoots et al performed a meta-analysis of 16 studies, including men with suspicious mpMRI findings who underwent both MTBx and SBx. Consistent with our results, the use of MTBx resulted in 20% more csPCa being identified compared to SBx (p < 0.001).<sup>22</sup> Using a TR approach, MTBx alone has already been shown to be superior to SBx in the PRECISION trial.<sup>5</sup> In accordance with our results, MTBx alone detected more csPCa than SBx (38% vs. 26%) and fewer ciPCa (9% vs. 22%) with fewer cores (median 4 vs. 12).

In our cohort of patients undergoing PBx through a TP approach under local anesthesia, men with suspicious lesions on mpMRI who underwent MTBx alone achieved excellent PCa and csPCa detection rates (56% and 47%, respectively) at a lower cost (median biopsy core, 6 vs. 11, p < 0.001) compared to the combination of MTBx and SBx; however, the majority of the studies seem to show that combining SBx with MTBx increases the detection of both PCa and csPCa.<sup>22-25</sup>

In our subgroup analysis, 37% of cases were upgraded from benign on SBx to csPCa on MTBx and 18% were upgraded from ciPCa on SBx cores to csPCa on MTBx. Conversely, 13% of benign cases were upgraded to ciPCa by SBx, highlighting the benefit of avoiding SBx, thereby reducing overdiagnosis and potential overtreatment of ciPCa.<sup>26</sup> Overdiagnosis and overtreatment of PCa are major concerns, thus biopsy techniques that reduce them need to be considered when deciding on the optimal approach.<sup>27,28</sup>

Recently, Hugosson et al reported that performing MTBx alone reduced the risk of detecting ISUP GG 1 by half in patients with elevated PSA.<sup>3</sup> Therefore, avoiding SBx could improve cost-effectiveness and patient

satisfaction, reducing discomfort, adverse events, and complications.<sup>13</sup> Patient engagement in such a decision is critical; we believe that the decision to perform an MTBx alone must be fully shared with the patient, taking into account the risk of misdiagnosing csPCa while significantly reducing the risk of over diagnosing ciPCa.

Finally, our detection rate of PCa by PI-RADS score is consistent with a recent meta-analysis reporting that the performance of mpMRI to detect csPCa is 16% (7–27%) for PI-RADS 3, 59% (39–78%) for PI-RADS 4, and 85% (73–94%) for PI-RADS 5.<sup>29</sup> These results demonstrated the feasibility of a TP approach under local anesthesia in an outpatient setting.<sup>30</sup>

### Limitations

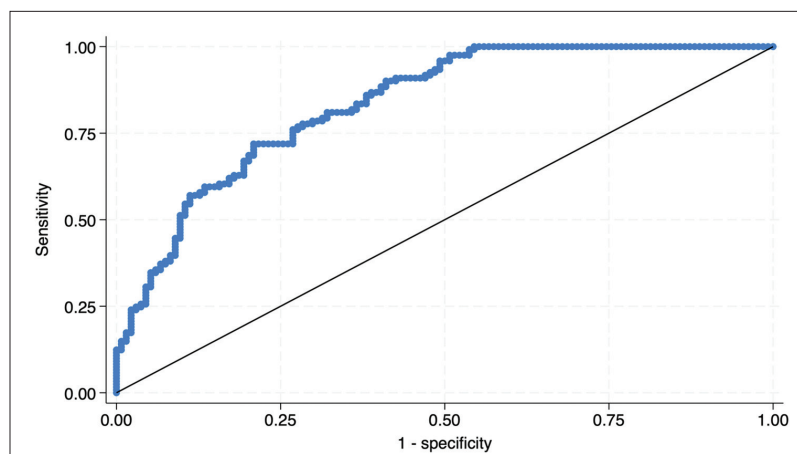
There are several limitations of our study that need to be mentioned.

It is a single-center, retrospective study with a relatively small number of patients included. Therefore, the results may not be generalizable. Moreover, the study cohort is heterogeneous, as patients in different biopsy settings were included. SBx cores were obtained at the discretion of the urologist, based on previous biopsy history. The number of SBx cores was also at the discretion of the urologist, based primarily on lesion location and prostate volume. While this reflects common urologic practice, it may affect the generalizability of the results.

Furthermore, although the two cohorts have similar baseline characteristics, no attempt was made to balance the two study groups in the present study; however, selection bias remains a limitation of observational studies, regardless of the statistical methods used. Although we performed a subgroup analysis of patients undergoing combined MTBx plus SBx to examine the csPCa detection rate in both groups, a large study design considering only these subgroups of patients could have better analyzed the clinical benefit of adding SBx in patients undergoing TP-PBx; however, the data were collected prospectively, and this represents one of the largest series comparing csPCa detection rate of MTBx vs. MTBx plus SBx through a TP approach in an outpatient setting.

In addition, all biopsies were performed by urologists with extensive experience in performing MTBx at a tertiary center, raising concerns about generalizability to non-tertiary centers.

Further, including only patients with suspicious findings at mpMRI makes it impossible to assess the diagnostic accuracy of mpMRI, possibly leading to misleading results. mpMRI results did not routinely undergo



**Figure 2.** Diagnostic accuracy of the multivariate logistic regression model represented as area under ROC. Area under the ROC curve: 0.84 (95% CI 0.74–0.92). AUC: area under curve; CI: confidence interval; ROC: receiving operator characteristics curve.

**Table 3. PCa and csPCa detection rates in patients who underwent combined MTBx plus SBx**

	MTBx	SBx	p
<b>Patients who underwent combined MTBx plus SBx (n=78)</b>			
PCa	42/78 (54%)	31/78 (40%)	<b>0.01</b>
csPCa	38/78 (49%)	17/78 (22%)	<b>&lt;0.001</b>
<b>Subgroup of patients with PCa (n=48) and csPCa (n=38)</b>			
PCa	42/48 (88%)	31/48 (65%)	<b>&lt;0.001</b>
csPCa	38/38 (100%)	17/38 (45%)	<b>&lt;0.001</b>

Significant p-values are in bold. csPCa clinically significant prostate cancer; MTBx: magnetic resonance imaging-guided targeted biopsy; PCa: prostate cancer; SBx: systematic biopsy.

internal re-evaluation by the institutions' radiologists and were performed with both 1.5 T and 3.0 T scanners. While this reflects common urologic practice, it may lower the diagnostic performance of mpMRI in the study population.

Finally, the number of SBx and MTBx cores collected per patient was not standardized, which could potentially yield an underestimate of csPCa in patients with fewer biopsy cores; however, in the current study, an ideal reference standard, such as TP template mapping biopsies, was used for all patients, resulting in an improved overall csPCa detection rate.

### CONCLUSIONS

Outpatient MTBx without SBx appears to be an ideal diagnostic tool able to rule out csPCa in patients with suspicious mpMRI findings. In our study population,

this approach seems to have reduced overdiagnosis, overtreatment, and undertreatment of PCa, possibly improving oncologic outcomes, quality of life, and cost-effectiveness. Future research should further evaluate this promising strategy in terms of decision-making and cost-effectiveness.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer reviewed.

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