Original Article

Magnetic resonance imaging–ultrasound fusion-targeted biopsy combined with systematic 12-core ultrasound-guided biopsy improves the detection of clinically significant prostate cancer: Are we ready to abandon the systematic approach?

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Abstract

Background: Multiparametric (mp) magnetic resonance imaging (MRI)–ultrasound fusion-targeted biopsy (TB) has improved the detection of clinically significant prostate cancer (csCaP) using the Prostate Imaging Reporting and Data System (PI-RADS) reporting system, leading some authors to conclude that TB can replace the 12-core systematic biopsy (SB). We compared the diagnostic performance of TB with SB at our institution.

Methods: Eighty-three men with elevated prostate-specific antigen levels (6.6 ng/mL, interquartile range [IQR] 4.5–9.2) and abnormal mp-MRI (127 lesions, PI-RADS ≥3, median size: 1.1 cm, IQR 0.8–1.6) underwent simultaneous TB and SB. Diagnosis of any CaP (Gleason score, [GS] ≥6) and csCaP (GS ≥7) was compared using the McNemar's exact test.

Results: SB showed higher, but not statistically significant, detection rates of any CaP and csCaP (51.8% and 34.9%) versus TB (44.6% and 28.9%) ($P = 0.286$ and $P = 0.359$, respectively). TB outperformed SB in the quantification of 56.6% CaP and detecting cancer in anterior sectors (7.2%). Compared to SB, TB missed twice the amount of any CaP and csCaP. SB alone detected 22.2% of all csCaPs and upgraded 20.6% of TB-detected CaP. SB identified cancer invisible on mp-MRI (13.7% of all CaP) or missed by TB due to a small size (<1 cm) and sampling error (7% of lesions).

Conclusion: A combination of SB with TB remained necessary for achieving the highest cancer detection rates. Limiting prostate biopsy to TB alone can miss csCaP due to the presence of synchronous high-grade cancer invisible on MRI or failure to hit the target. TB is the best approach for anterior lesions and tumor quantification.

Keywords: Cancer detection, fusion targeted biopsy, multiparametric magnetic resonance imaging, prostate biopsy, prostate cancer

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INTRODUCTION

The most widely utilized methods for screening of prostate cancer (CaP) are digital rectal examination and serum testing for prostate-specific antigen (PSA) levels. A biopsy procedure usually follows an abnormal screening test. The standard prostate biopsy (referred here to as systematic biopsy [SB]) retrieves 12 tissue cores in an extended dual sextant template.[1] While this approach has led to an improvement in the yield of cancer, the increased detection of CaP is not associated with a significant reduction in prostate cancer-specific or overall mortality.[2] Thus, the concept of "clinically significant" CaP (csCaP) has emerged to identify patients who may benefit significantly from aggressive treatment.[3] How csCaP should be defined is a matter of ongoing debate, but it is recognized that tumors with a Gleason score (GS) equal to or more than 7 have a higher risk of progression.[4] Multiparametric magnetic resonance imaging (mp-MRI) is now incorporated into diagnostic protocols because it provides a better characterization of prostate lesions using the Prostate Imaging Reporting and Data System (PI-RADS).[5] Therefore, a biopsy can be restricted to PI-RADS 3, 4, and 5 lesions, which have a higher likelihood of a diagnosis of csCaP.[6] Prostate lesion biopsy can be performed by the fusion-targeted biopsy (TB) method or by SB. The TB method involves merging of mp-MRI images with real-time ultrasound (US), allowing direct sampling of suspicious areas, instead of the random whole organ approach as applied in SB.[7] The success of TB depends on an accurate interpretation of MRI images and the generation of adequately merged images, which require considerable proficiency in reading mp-MRI prostate. This factor may limit the usefulness of TB techniques in centers that have recently adopted the procedure. In this single-center study, we compared the diagnostic performance of a recently implemented TB protocol and SB for the detection of csCaP.

METHODS

Case selection

Cases were collected using CoPath, the pathology database application at the Mount Sinai Medical Center, Department of Pathology and Laboratory Medicine. The search included all prostate biopsies obtained by simultaneous SB and TB procedures, which were submitted for pathologic evaluation during the 1st year of implementing TB at our institution. A retrospective review of the medical records was conducted. Patients with a prior prostate biopsy, negative MRI study, or lesions with PI-RADS <3 were excluded from the study. The Mount Sinai Medical Center Institutional Board Review approved the study.

Imaging assessment

Biopsy-naïve patients with an elevated PSA level and clinical suspicion for CaP were screened before prostate biopsy with a diagnostic mp-MRI study.[7] These prostate images underwent a centralized radiologic evaluation to identify lesions according to the PI-RADS version 2.0 reporting system, a 5-point scale in which the presence of CaP was considered to be: 1 – highly unlikely, 2 – unlikely, 3 – equivocal, 4 – likely, or 5 – highly likely. The location of each lesion was reported using a map of 39 sectors (12 in the base, 12 in the midportion, 12 in the apex of the prostate, 2 seminal vesicles, and 1 urethral sphincter).[6]

Biopsy protocol

All patients with lesions PI-RADS equal to or more than 3 underwent TB first, followed by SB of the imaging-detected lesions. In the SB method, one US-guided tissue core was taken transrectally from each of the 12 sectors in an extended sextant template including the lateral and medial aspects of the posterior peripheral zone (PZ) at the level of the base, mid, and apical prostate (blinded to the target lesion). Of note, the central zone (CZ), transitional zone (TZ), anterior fibromuscular stroma (AS), and anterior aspects of the PZ are not routinely sampled in the standard 12-core SB procedure. In the TB, prebiopsy mp-MRI images were segmented, registered, and fused in real-time with transrectal US images.[7] All the targeted lesions were sampled, obtaining at least four core biopsies per target.

Pathologic assessment

Pathologists examined the tissue cores for the diagnosis, quantification, and grading of CaP using the GS system.[8] Pathologic features collected for this study included the presence or absence of CaP, high-grade prostatic intraepithelial neoplasia (HG-PIN), acute and chronic inflammation, highest GS in any of the 12 SB sectors, GS recorded in the SB sample that matched the targeted lesion location, GS in the TB sample, and percentage of tissue involvement (%TI) by CaP.

Statistical analysis

The difference in the detection rate of CaP using TB versus SB was evaluated using the McNemar's exact test for matched pairs. Contingency tables were designed to compare the overall method performance as well as for agreement at the matched pair lesion location. For the latter, the pathologic results at the exact or immediately contiguous sectors in the SB extended sextant template were matched to the TB results. The ability of both biopsy procedures to diagnose any form of CaP (GS ≥6) and csCaP (GS ≥7) was also evaluated. The number of

CaPs that were upgraded from GS = 6 versus GS ≥7 was tabulated. The correlation analysis of GS was performed using a mixed effect intraclass correlation coefficient, while Spearman or Pearson tests were used for other categorical or continuous variables, respectively. Receiver operating characteristic (ROC)-area under the curve (AUC) values were determined for each biopsy method and were compared using a nonparametric Wilcoxon method, as previously described.[9] All the above analyses used an alpha value of 0.05 to denote statistical significance and were conducted using STATA 13.0 (StataCorp, College Station, TX, USA) and IBM SPSS Statistics 22.0 (IBM, Chicago, IL, USA). The graphs were designed in Prism 5 6.0 (GraphPad Software Inc., La Jolla, CA, USA).

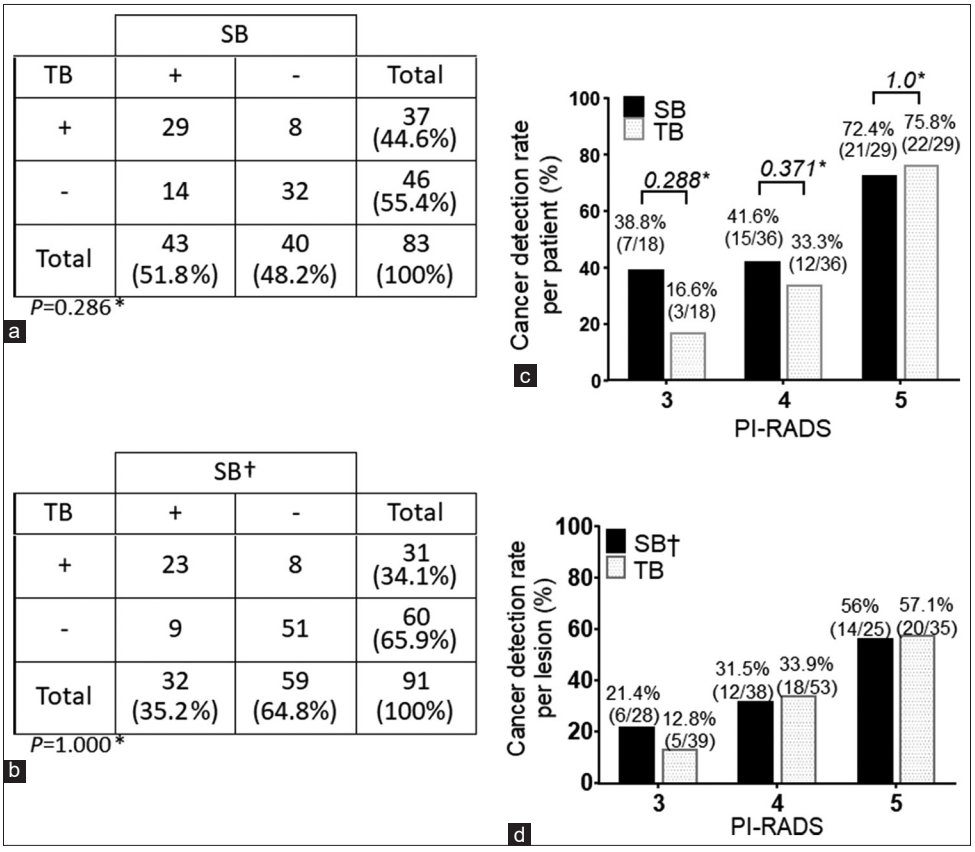
RESULTS

Patient cohort

The median age of the 83 study participants was 66 years (range 50–87) with a median PSA level of 6.6 ng/mL (interquartile range [IQR] 4.5–9.2). Overall, 127 lesions were identified: 83 patients (65.4%) had at least 1 lesion, 35 patients (27.6%) had 2 or more lesions, and 9 patients (7.1%) had 3 lesions. Based on the lesion with the highest PI-RADS, 39 patients (30.7%) were PI-RADS 3, 53 patients (41.7%) were PI-RADS 4, and 35 patients (27.6%) were PI-RADS 5. The median PI-RADS was 4 (IQR 3–5), and the median lesion size was 1.1 cm (IQR: 0.8–1.6). According to the TB location map, 91 lesions (71%) were located within the posterior PZ, and 36 lesions (29%) were within the anterior PZ, AS, CZ, and TZ.

Overall performance for the detection of prostate cancer

The overall cancer detection rate was slightly higher in SB (51.8%, 43/83 patients) versus TB (44.6%, 37/83). The difference in the detection rate was 7.2% (95% confidence interval [CI]: −4.9–19.4) and not statistically significant ($P = 0.286$, McNemar's test) [Figure 1a and b]. The analysis restricted to lesions located in the posterior PZ revealed high agreement in the detection rate by TB (34.1%, 31/91 lesions) with SB (35.2%, 32/91) ($P = 1.000$, McNemar's test). Overall, the detection of CaP was slightly higher in the posterior PZ (43.95%, 40/91 lesions) in comparison with anterior sectors (36.11%, 13/36 lesions). For the 36 lesions located anteriorly and sampled only with TB, 7 lesions (19.4%) were CaP and correlated with a second cancer in the posterior PZ, 6 lesions (16.6%)



	SB		
TB	+	-	Total
+	29	8	37 (44.6%)
-	14	32	46 (55.4%)
Total	43 (51.8%)	40 (48.2%)	83 (100%)

P=0.286*

a

	SB†		
TB	+	-	Total
+	23	8	31 (34.1%)
-	9	51	60 (65.9%)
Total	32 (35.2%)	59 (64.8%)	91 (100%)

P=1.000*

b

Figure 1: The diagnosis of prostate cancer as a pair comparison of systematic biopsy versus targeted biopsy in all patients (a), per lesion (b), and detection rates per patient (c) and per lesion (d) according to the Prostate Imaging Reporting and Data System categories. *McNemar's Test. †lesions within the posterior peripheral zone only

were CaP and correlated with no cancer in the posterior PZ, 8 lesions (22.2%) were negative for malignancy, but the cancer was detected in the posterior PZ, and 15 lesions (41.6%) were negative for malignancy and correlated with no cancer in the posterior PZ.

Detection of prostate canceraccording to the Prostate Imaging Reporting and Data System

The percentage of CaP per patient and per lesion increases proportionately with increased PI-RADS in both TB and SB [Figure 1c and d]. The cancer detection rate per patient according to the highest PI-RADS showed no statistical difference between TB and SB methods (P = 0.250, Wilcoxon signed-rank test). In addition, the proportion of discordant cases was homogeneous in each PI-RADS category [P > 0.05, McNemar's tests, actual P values shown on n-zigzag line in Figure 1c and d]. ROC-AUC values were calculated to determine variations in the diagnostic performance of PI-RADS categories, assuming the outcome of both biopsy methods to be independent events. The difference between AUC_{SB} (0.649, 95% CI: 0.531–0.768) and AUC_{TB} (0.753, 95% CI: 0.646–0.859) was not significant ($AUC_{SB} - AUC_{TB} = -0.123$, $P = 0.133$).

Detection of clinically significant prostate cancer

For CaP with a GS ≥ 7, the detection rate of the SB method was 34.9% (29/83 patients), whereas the rate of TB was 28.9% (24/83). The difference in the detection rate of csCaP was 6.0% (95% CI: −5.4–17.4) and not statistically significant (P = 0.359, McNemar's test). Overall, both methods agreed in only 56.8% (29 of 51) of the patients with any grade of CaP and in 47.2% (17 of 36) of csCaP. SB detected CaP that was missed by TB in 27.4% of the cases (14 patients); 22.2% (8 patients) of the total cases had csCaP. If only TB had been used, patients with the following GS would have been wrongly diagnosed as free of cancer: Gleason 9 (1 patient), 8 (3 patients), and 7 (4 patients). TB detected CaP that was missed by SB in 15.7% of the cases (8 patients); 11.1% (4 patients) of the total had csCaP. If only SB had been used, patients with the following GS would have been diagnosed as free of cancer: Gleason 9 (1 patient), 8 (0 patients), and 7 (3 patients) [Table 1]. When both the methods agreed in the detection of cancer, the number of cancers that were upgraded to csCaP was 17.2% (5 of 29 patients) by TB and 20.6% (6 of 29 patients) by SB.

Features of discordant cases

Of the 8 patients who were diagnosed with CaP by TB but negative on SB (SB−/TB+), 7 patients had lesions ≥1 cm and 6 patients presented with lesions located in anterior sectors. SB missed only 2 CaP lesions located within the posterior PZ. On the other hand, CaP was detected by SB, but not by TB (SB+/TB−), in 14 patients which included a total of 18 lesions, 4 of which were located in anterior sectors and 14 in the posterior PZ. Of the 4 lesions located in anterior sectors, 3 lesions were PI-RADS 3, of which 1 corresponded acute inflammation and 2 normal histology in TB tissue cores, while 1 lesion was PI-RADS 4, showing acute inflammation. Of the 14 lesions located in the posterior PZ, 9 lesions were mapped to the same sector positive for cancer in SB samples, while 4 lesions were located elsewhere. The imaging assessment of these 14 lesions was PI-RADS 3 in 6 lesions, of which 2 lesions were diagnosed with acute inflammation in TB tissue cores, PI-RADS 4 in 3 lesions, of which 2 lesions were diagnosed with acute inflammation in TB tissue cores, and PI-RADS 5 in 5 lesions, of which 3 lesions were diagnosed with HG-PIN in TB tissue cores. The lesion size ranged from 0.5 to 2.9 cm; five patients had subcentimeter lesions and nine patients presented with lesions ≥1 cm.

Table 1: Correlation of matched pair highest Gleason score per patient using two different sampling methods, fusion-targeted biopsy, and systematic biopsy

Diagnosis	GS – SB					Total (%)
	No cancer	6	7	8	9	
GS-TB						
No Cancer	32	6	4	3	1	46 (55.4)
6	4	5	3	1	0	13 (15.6)
7	3	3	6	1	1	14 (16.8)
8	0	0	1	6	0	7 (8.4)
9	1	0	1	0	1	3 (3.6)
Total (%)	40 (48.1)	14 (16.8)	15 (18)	11 (13.2)	3 (3.6)	83 (100)

GS: Gleason Score, TB: Targeted biopsy, SB: Systematic biopsy

Impact on tumor grading and quantification

There was a moderate agreement between SB and TB regarding the determination of GS in matched pair locations, but the agreement was lower for TI quantification [Table 2]. When comparing the change of GS in SB versus TB, the percentage case distribution was symmetrical (no skewness) using the highest GS per patient. However, the degree of skewness and kurtosis of the curve for GS change at matched pair locations differed from the curve obtained with the highest GS per patient (skewness: 1.019, matched pair vs. 2.038, highest GS; kurtosis: 0.689, matched pair vs. 4.319, highest GS) [Figure 2]. This means that the GS tends to be lower in SB samples at matched pair locations but not if using the highest GS recorded at other locations. The correlation analysis of GS with lesion size revealed no statistical significance (r = 0.14, P = 0.66 for GS at matched pair locations; r = −0.32, P = 0.32 for highest GS per patient); however, the highest GS per patient in SB tended to be lower than the GS in TB when the lesion size increases. The influence of lesion size was significant for TI quantification; the amount of TI is less in SB (vs. TB) when

Table 2: Correlation of radiologic and pathologic variables for comparison of targeted biopsy versus systematic biopsy

Variable	Parameter	PSA level	PI-RADS	Lesion Size	TB	GS - TB	Percentage TI - TB	SB†	GS - SB†	Percentage TI - SB†
PSA level (ng/mL)	*r*	X	0.10	0.39*	0.17	0.48*	0.20	0.07	0.31	-0.97
	P		0.24	<0.001	0.05	0.001	0.19	0.45	0.08	0.59
	N		127	127	127	44	44	91	32	32
PI-RADS	*r*	0.10	X	0.18*	0.35*	0.16	0.55*	0.27*	0.37*	0.34
	P	0.24		0.04	<0.001	0.30	<0.001	0.009	0.03	0.05
	N	127		127	127	44	44	91	32	32
Lesion size (cm)	*r*	0.39*	0.18*	X	0.16	0.21	0.51*	0.03	0.18	0.14
	P	<0.001	0.04		0.05	0.15	<0.001	0.71	0.30	0.43
	N	127	127		127	44	44	91	32	32
TB (cancer detection)	*r*	0.17	0.35*	0.16	X	X	X	0.58*	0.04	0.21
	P	0.05	<0.001	0.05				<0.001	0.82	0.24
	N	127	127	127				91	32	32
GS – TB	*r*	0.48*	0.16	0.21	X	X	0.29	0.23	0.63**	−0.41
	P	0.001	0.30	0.15			0.05	0.20	0.001**	0.85
	N	44	44	44			44	31	23	23
Percentage TI – TB	*r*	0.20	0.55*	0.51*	X	0.29	X	0.25	0.39	0.48*
	P	0.19	<0.001	<0.001		0.05		0.17	0.06	0.01
	N	44	44	44		44		31	23	23
SB (cancer detection)†	*r*	0.07	0.27*	0.03	0.58*	0.23	0.25	X	X	X
	P	0.45	0.009	0.71	<0.001	0.20	0.17			
	N	91	91	91	91	31	31			
GS – SB†	*r*	0.31	0.37*	0.18	0.04	0.63**	0.39	X	X	0.27
	P	0.08	0.03	0.30	0.82	0.001**	0.06			0.12
	N	32	32	32	32	23	23			32
Percentage TI – SB†	*r*	-0.97	0.34	0.14	0.21	-0.41	0.48*	X	0.27	X
	P	0.59	0.05	0.43	0.24	0.85	0.01		0.12	
	N	32	32	32	32	23	23		32	

*The correlation is significant, †Matched pairs of lesions located within the SB sampling range, **Mixed effect intra-class correlation coefficient.
X: Cannot be calculated or nonapplicable, GS: Gleason score, TB: Targeted biopsy, SB: Systematic biopsy, PSA: Prostate-specific antigen, PI-RADS: Prostate Imaging Reporting and Data System, TI: Tissue involvement

the lesion size increases ($r = -0.51$, $P = 0.027$). Overall, the %TI in SB was less in 56.62% of the cases and greater in 21.74%. The amount of tissue involved by cancer did not influence changes in grading ($r = 0.008$, $P = 0.97$).

DISCUSSION

Our results corroborate prior studies showing that the introduction of imaging techniques for the identification and direct sampling of prostate lesions increases the overall detection of CaP.[7,10-15] The cancer detection rate was slightly higher in SB in comparison to TB (51.8% vs. 44.6%) with a higher agreement in detecting any grade of CaP than csCaP (56.8% vs. 47.2%); however, these differences were not statistically significant. In addition, ROC-AUC values demonstrated that the predictive value of PI-RADS stratification categories remains the same in both the procedures. Therefore, TB was as effective as SB, but their combination leads to the identification of more nonsignificant CaP and csCaP. Both the procedures missed cancer that was independently detected by the other. Although this study is limited by the lack of correlation with radical prostatectomy and follow-up of patients with negative prostate biopsy, the numbers are comparable to what has been previously reported, i.e., there are no significant differences in overall detection rates.[10-12]

For detecting csCaP, TB was not superior to SB in our study, but it has been in others.[10,11,14,15] In agreement with our findings, other studies reported no remarkable difference in detection rates of csCaP between TB only and SB only and concurred with the superiority of a combined approach.[12,16-19] Moreover, taking into consideration the discordant cases, SB alone was responsible for detecting 22.2% of all csCaPs, a percentage that ranges from 7% to 18% in other studies.[16-18] SB upgraded 20.6% of the cases to csCaP, which could be secondary to the presence of synchronous CaP of a higher grade. Indeed, the GS tended to be lower in SB samples at matched pair locations but not if using the highest GS recorded at other locations. SB can demonstrate the presence of bilateral csCaP in cases of unilateral lesions diagnosed by TB.[17,18] In addition to multifocality, intra-lesion grade heterogeneity is a source of variations in GS across samples.[20] Filson *et al.* showed an incidence of 16% of csCaP employing SB only in men with no suspicious MRI target.[19]

TB cannot immediately replace SB as a single biopsy method. In absolute numbers, TB missed twice the amount of any grade and csCaP. Suboptimal performance of TB in some patients can be attributed to undetectable lesions due to reader oversight, invisible cancer, and biopsy technique errors such as MRI-US image misalignment.[21,22] Based

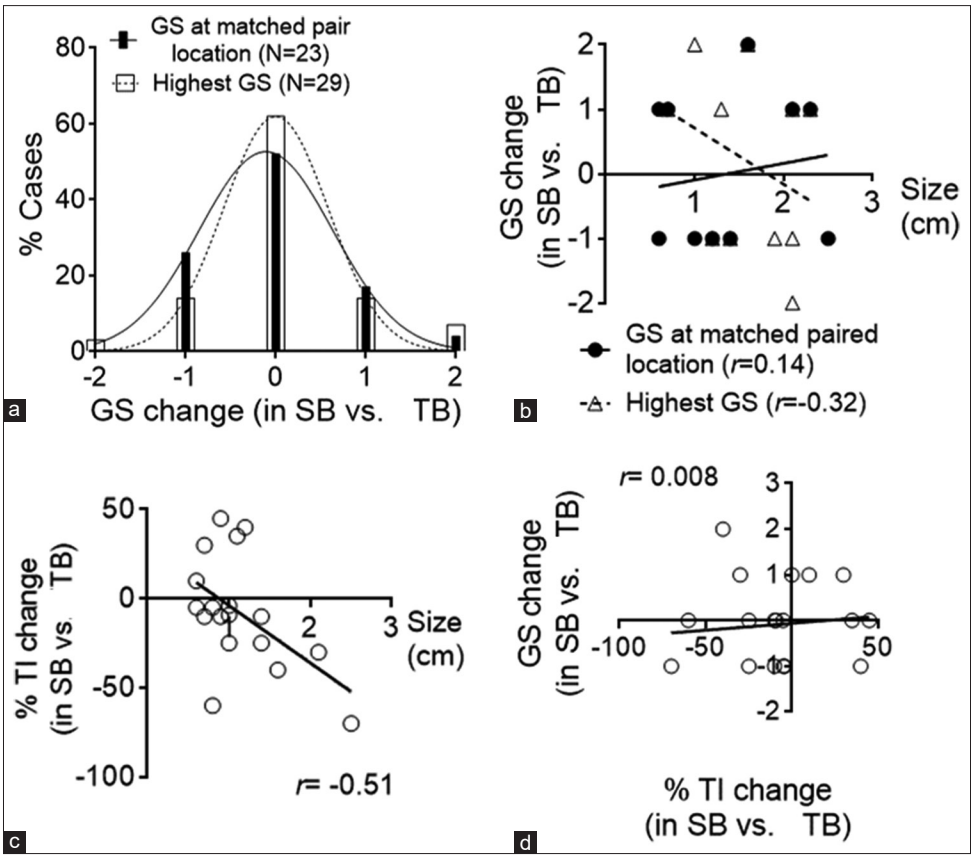


Figure 2: Case distribution according to the Gleason score change (a), correlation of lesion size with Gleason score change (b) and percentage of tissue involvement change (c), and Gleason score change versus percentage of tissue involvement change (d). Continuous and discontinuous lines in A: nonlinear regression analysis (Gaussian fit model: y = Amplitude × exp [−0.5×[[*x* − mean]/standard deviation]^2])

on cases in which the CaP was detected in SB sectors away from the suspected lesion location, we infer that 13.7% (7 of 51 patients with any grade CaP) of the cases went undetected by mp-MRI. Likewise, based on cases in which the CaP was detected in SB sectors that matched the suspected lesion location, the TB method failed to hit the target for at least 7% of the lesions (9 of 127). Moreover, the interpretation of TB findings in isolation can potentially be misleading and carries the risk of underdiagnosing CaP. For instance, a diagnosis of acute inflammation on TB may erroneously be interpreted as the explanation for elevated PSA levels, particularly for lesions classified as PI-RADS <4. In this study, if only TB had been used, the presence of acute inflammation in TB-derived tissue cores would have jeopardized the clinical recognition of 4.7% of the lesions (6 of 127), leading to the diagnosis of a benign condition when, in fact, they were CaP.

TB was demonstrated to be valuable for detecting cancer located in anterior anatomic sectors of the prostate gland as well as for tumor quantification. Of interest, higher PSA levels were associated with larger lesions and higher GS in tissue cores obtained by TB but not by SB [Table 2]. In addition, the higher the PI-RADS and lesion size, the greater the amount of tissue involved by cancer in TB but not in SB tissue cores. An accurate estimation of tumor volume is needed to consider a patient as a candidate for active surveillance. Our data suggest that TB outperforms SB in terms of providing sampling adequacy for the quantification of disease. Although a higher involvement of tissue cores by cancer did not translate into GS changes, modern definitions of csCaP incorporate tumor burden as a variable of high-risk progression for low-GS CaP.[4]

The accuracy of tumor volume evaluation can be affected by the lesion size. For lesions >1.1 cm, TI was always higher in TB samples. For a few subcentimeter cancers, TI in SB samples from matched pair locations was the highest. Venderink *et al.* found that the cancer detection rate of TB increases after incrementally raising the minimal lesion size threshold and obtaining a plateau of detection rates at 1.6 cm for csCaP and 2.4 cm for any CaP.[23] In our study, the proportion of discordant cases was similar for lesions ≥1cm, while for subcentimeter lesions, SB rarely missed cancers compared to TB. Indeed, Coker *et al.* demonstrated that cases with lower MRI lesion volumes, lesion density, and PI-RADS scores are predictors of cancer likely to be missed by TB but are detected by SB.[24] Thus,

technical TB errors that lead to a failure to hit the targeted lesion may compromise the evaluation of small CaP.

CONCLUSION

In summary, our data affirm that a combination of SB and TB remains necessary to achieve the highest yield in detecting CaP. Limiting prostate biopsy to only TB protocol can miss csCaP, which may be due to the presence of synchronous higher grade cancer invisible on MRI, failure to sample small lesions, and technical errors. TB is the best approach for tumor quantification, which is a critical factor in the decision of active surveillance, and for evaluating CaP located in anterior sectors of the prostate gland, which would otherwise remain undiagnosed by an SB-only approach. Additional studies are needed to overcome the causes of TB failure before it can supplant SB.

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Conflicts of interest
There are no conflicts of interest.

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