



Is Systematic Biopsy Mandatory in Addition to Targeted Biopsy in Patients with a PI-RADS 5 Lesion Identified on Magnetic Resonance Imaging?

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Abstract

Objective: Most of the lesions classified as prostate imaging-reporting and data system (PI-RADS) 5 represent clinically significant prostate cancers; the utility of systematic biopsy (SB) in addition to magnetic resonance imaging-targeted biopsy (MRI-TB) is unclear. We evaluated clinically significant prostate cancer detection via SB, TB alone, and combined SB and TB in men with a PI-RADS 5 lesion. The aim of this study was to determine whether SB can be avoided in the case of PI-RADS 5.

Materials and Methods: Patients undergoing MRI-TB+SB with a PI-RADS 5 lesion were retrospectively reviewed in a prospectively collected database. Pathology obtained from the MRI-TB was then compared with that of the SB. All patients underwent multiparametric MRI followed by transrectal/transperineal TB of PI-RADS 5 lesion and 12-core SB. The prostate cancer and clinically significant prostate cancer (grade group ≥ 2) detection on SB, MRI-TB and MRI-TB+SB were determined for all men. A subgroup analysis of the combined group was also performed to identify performances of TB alone, SB alone, and combination of TB+SB for the prediction of final pathology at radical prostatectomy. Statistical significance was set at $p < 0.05$.

Results: We identified PI-RADS 5 lesions in 315 patients. 199/315 men, were found to have prostate cancer. Of these, 163 cases were clinically significant. The detection rate of prostate cancer for MRI-TB+SB, MRI-TB and SB was 63%, 59% and 49%, respectively, and the detection rate for clinically significant prostate cancer was 51%, 48% and 37%, respectively. SB detected an additional 6.5% of any grade prostate cancer and 6.7% clinically significant prostate cancer over TB. A total of 89 patients had prostate specific antigen density > 0.15 ng/mL. All patients with prostate-specific antigen density (PSAD) > 0.28 had cancer of any grade. The clinically significant prostate cancer detection rate improved with increased PSAD for SB. Among 102 patients, 8 had upgraded pathology from MRI-TB+SB. MRI-TB and SB pathology of the PI-RADS 5 lesion separately predicted final pathology with 81% and 69% concordance, respectively. The the downgrade was lowest in both methods, but the upgrade was higher in SB.

Conclusion: In the presence of a PI-RADS 5 lesion, SB offers minimal additional but not negligible clinical value. The safety of omitting SB awaits further research.

Keywords: Concordance, PI-RADS 5, prostate cancer, systematic biopsy, targeted biopsy

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Introduction

Prostate cancer (PCa) is the second most common malignancy among men worldwide (1). Prior research has shown that multiparametric magnetic resonance imaging (MRI) targeted biopsy (TB) identifies clinically significant PCas more accurately than conventional systematic biopsy (SB) in men with suspected localized PCa (2-5). MRI-TB has resulted in greater detection of clinically significant PCa with less detection of clinically insignificant cancer than SB alone (6,7). Nevertheless, systematic 12-core biopsy is often performed in addition to TB as the combination results in increased detection of clinically significant PCa (3,8). Additionally, such practice allows for tissue sampling of the gland beyond suspicious lesions, as 10-24% of clinically significant PCas are not visualized on MRI (9). Prostate imaging-reporting and data system (PI-RADS) 5 lesions represent clinically significant PCa [Gleason grade group (GG) 2 or greater] between 75% and 95% of the time (10). Given the high prevalence of such clinically significant cancer in these lesions, the utility of concurrent SB is uncertain. In a recent study evaluating the role of SB in patients on active surveillance, the added value from performing SB in patients with PI-RADS 5 lesions was minimal (11). In this context, we aimed to investigate the utility of SB in addition to TB in all patients with PI-RADS 5 lesions to determine whether some patients can be spared from additional and unnecessary biopsies.

Materials and Methods

We retrospectively reviewed completely anonymized data provided by nation-wide tertiary centers in the PCa Database of the Turkish Urooncology Association. MRI-targeted prostate biopsy in conjunction with 12 core systematic biopsies for PI-RADS 5 lesions at our database were included in the study. All patients gave consent for the study.

All multiparametric MRI (mpMRI) for targeted biopsies was reviewed by designated institutional radiologists. In patients with a PI-RADS-lesion 5 [according to PI-RADS-v2 classification (10)], MRI-targeted ultrasound fusion biopsy using different software-based platforms, according to participant center's property (MIMS Symphony Dx® [MIM Software], bk3000® [BKMedical], UroNav® [InVivo Corp, Philips]), was conducted. MRI image fusion targeted biopsies were taken from each target, obtaining at least 2 core samples from each target lesion. In addition to targeted biopsies, the systematic biopsies were also performed using a 12-core approach.

Analysis was performed by reporting frequencies and percentages, in an effort to determine the number of cancers missed from omission of the SB. If patients had more than one PI-RADS 5 lesion, the lesions were analyzed together in such a way that analysis was performed per patient rather than per lesion.

The detection rates of PCa and clinically significant PCa (GG $\geq$ 2) on SB, TB, and SB+TB were determined for all men.

Statistical Analysis

Study data were collected and managed using research electronic data capture (REDCap) electronic data capture tools

hosted at Turkish Urooncology Association (12-14). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources (12,13).

The t-test, Mann-Whitney U test, and chi-square test were used to analyze the relationships among categorical and continuous variables between two biopsy methods and three biopsy schemes within the combined biopsy method. Statistical Package for the Social Sciences (SPSS) version 22.0 was used for all statistical analyses. P-values less than 0.05 were considered statistically significant.

Results

Data from 315 patients who underwent MRI-TB+SB and who had PI-RADS 5 lesions were evaluated. Patient demographics of the study cohort stratified by biopsy approach are depicted in Table 1. Median number of TB cores sampled per region of interest was 5.1. Mean age, prostate-specific antigen (PSA) and prostate volume were 65.7 years, 10.7 ng/mL, and 54 mL respectively.

Table 1. Descriptive characteristics and pathologic results of patients

		PI-RADS 5 (n=315)
Age		65.7 $\pm$ 7.5
BMI (n=267)		27.7 $\pm$ 5.4
PSA		10.7 $\pm$ 8.1
PSAD (n=89)		0.28 $\pm$ 0.28
DRE	Benign	254 (87.9%)
	Malign	35 (12.1%)
Prostate volume (n=89)		54.1 $\pm$ 28.7
PNI		41 (13.3%)
Transrectal		232
Transperineal		93
mpMRI number of lesion (ROI)		2.7 $\pm$ 2.2
Biopsy core per lesion		5.1 $\pm$ 4.7
PCa		
• Combine MRI-TB+SB		199 (63.2%)
• MR-TB		186 (59.7%)
• SB		157 (49.8%)
sPCa		
• Combine MRI-TB+SB		163 (51.7%)
• MR-TB		152 (48.3%)
• SB		119 (37.8%)
RP		(n=102)
• Upgrade		25 (24.5%)
• Concordance		59 (57.8%)
• Downgrade		18 (17.6%)

BMI: Body mass index, PNI: Perineural invasion, ROI: Region of interest, sPCA: Significant prostate cancer, PI-RADS: Prostate imaging-reporting and data system, SB: Systematic biopsy, TB: Targeted biopsy, MRI: Magnetic resonance imaging, PSA: Prostate-specific antigen, PSAD: Prostate-specific antigen density, DRE: Digital rectal exam

PCa was detected in 199 patients with combined MR targeted + SB (63%), in 186 patients with Targeted only, and in 157 patients with SB, respectively. SB alone missed 42 patients, and TB missed only 13 cases of any grade cancer. There was a significant difference in the missed cancer ratio between TB and SB (10.2% vs. 24.4%) in any grade of cancer, and significant cancer detection by SB alone was significantly lower than by TB alone. Most of the patients having cancer with PI-RADS 5 lesions biopsied were found to be significant cancer (81.9%). SB alone missed 44 patients and TB missed only 11 patients with significant PCa. SB added 11/163 (6.7%) of significant PCa detection.

We analyzed which clinical factors impact the risk of clinically significant PCa (csPCa) detection by MRI TB-SB. The multivariate regression model proved that the following clinical parameters were significantly increasing the probability of PCa detection: Age and abnormal DRE (Table 2). In our cohort, all patients with abnormal digital rectal exam (DRE), except one, were found to have PCa. The detection of PCa in the cohort with high PSA density (PSAD) was higher compared to other cohorts. However we are unable to test whether PSAD was a significant predictor of cancer detection in each biopsy technique due to small sample size of patients having PSAD values registered which were only 25% of the entire cohort.

One hundred-two patients who underwent radical prostatectomy were evaluated for concordance. TB showed significantly higher concordance over SB at RP (Table 3). Twenty-eight patients were found to have significant PCa on radical prostatectomy, which that went undetected or undergraded with SB biopsy. The number of downgrades was lowest in both methods, but the number of upgrades was highest in SB.

Discussion

The main goal of our study was to investigate whether omitting SB in PI-RADS 5 lesions could impact the csPCa detection rate. Our results confirmed that in PI-RADS 5, TB has a significantly higher csPCa detection rate compared to SB, with 48% vs. 37%, respectively. We also confirmed that omitting SB may contribute to a slight reduction in the csPCa detection rate by 6.7%. Our

results are consistent with data from recent studies. Ahdoot et al. (3) found that TB-only biopsy misses 5.8% of csPCa. In a Cochrane meta-analysis, the added value of SB in csPCa detection in a biopsy-naïve setting was 4.3% (14). The results from our study and recent studies in the literature indicate that concomitant SB has a marginal impact on csPCa detection in PI-RADS 5 patients.

There are several arguments that advise against SB omission. We should consider the limited sensitivity of mpMRI in detecting all csPCa foci, as approximately 30% of csPCa are invisible on mpMRI (15). Moreover, PCa is characterized by multifocal growth, which is present in about 20% of the cases (16). In the study by Checcucci et al. (17), PCa was detected via concomitant SB, contralaterally to index lesions in 36% of csPCa cases detected via TB. It has also been proven (18) that a higher PI-RADS score increases the likelihood of csPCa presence outside the index lesion. In PI-RADS 5 patients, csPCa presence outside the index lesion can be seen in up to 60% of cases (19).

In addition to the PI-RADS score, other potential predictors of csPCa detection via SB are under investigation, such as PSA, PSAD, biopsy setting, DRE status, lesion location, and prostate volume. However, no risk-adapted strategy or nomogram has clearly been proposed to avoid concomitant SB yet. In our work, we also confirmed that PSAD is another significant predictor that increases the detection rate of csPCa in PI-RADS 5 patients. We determined that a PSAD level of 0.28 ng/mL² is important for detecting PCa. The results of our analysis are consistent with the available literature, which indicates that PSAD and PI-RADS scores are complementary in the detection of PCa. Recent publications based on a comparison of histopathology reports from a biopsy and radical prostatectomy indicate that high PSAD values are also associated with higher tumor volume and a higher probability of underestimating the Gleason score (20).

In our cohort, 102 patients who underwent radical prostatectomy were evaluated for concordance. MRI-TB was superior in predicting the result of final histopathological analysis for PI-RADS 5 compared to systematic biopsies. TB showed significantly higher concordance than SB at RP. Twenty-eight patients were found to have significant PCa on radical prostatectomy whom went undetected or undergraded with SB only. Downgrade was lowest in both methods but upgrade was

Table 2. Multivariable logistic regression analyses predicting factors effecting biopsy results

	PI-RADS 5 MRI- TB+SB		
	Benign (n=129)	PCa (n=186)	p
Age	63.9±7.1	66.9±7.6	<0.001
BMI	27.1±4.2	27.9±5.7	1
DRE positive	1 (0.07%)	34 (18.3%)	<0.001
PSA	9.4±6.8	11.6±8.8	0.03
PV	54.1±1	54.1±28.7	0.570
mpMRI number of lesion	1.6±1.2	1.7±1.6	0.760
Number of cores per lesion	5.4±4.9	4.9±4.5	0.351

DRE: Digital rectal exam, BMI: Body mass index, PV: Prostate volume PCa: Prostate cancer, PI-RADS: Prostate imaging-reporting and data system, SB: Systematic biopsy, TB: Targeted biopsy, MRI: Magnetic resonance imaging

Table 3. Concordance at radical prostatectomy

	RP insPCa (n=10)	RP sPCa (n=92)
Combine MRI-TB+SB		
• insPCa	6 (60%)	8 (8.7%)
• sPCa	4 (40%)	84 (91.3%)
MRI-TB		
• benign	3 (30%)	7 (7.6%)
• insPCa	5 (50%)	10 (10.9%)
• sPCa	2 (20%)	75 (81.5%)
SB		
• benign	0 (0%)	14 (15.2%)
• insPCa	6 (60%)	14 (15.2%)
• sPCa	4 (40%)	64 (69.6%)

RP: Radical prostatectomy, insPCa: Insignificant prostate cancer, sPCa: Significant prostate cancer, SB: Systematic biopsy, TB: Targeted biopsy, MRI: Magnetic resonance imaging

higher in SB. Upgrading may be due to inadequate sampling by SB, where small foci of Gleason 4-5 are undetected at biopsy but documented at radical prostatectomy (21). MRI targeted biopsies are more prone to downgrading and systematic biopsies are more frequently upgraded. Downgrading may occur for several reasons, including over-sampling of the very small (less than 5%) foci of Gleason pattern 4 or 5 cancer (22). There is a risk of oversampling with an increased number of targets registered by a radiologist and an increased number of biopsy cores taken at the discretion of the biopsy performer. If SB is omitted, our results showed that 7 patients with clinically significant PCa at radical prostatectomy would be missed initially. Several recent studies indicate that SB may reduce the likelihood of Gleason score underestimation (22). Moreover, taking cores from areas surrounding a suspicious lesion can reduce sampling error and may provide a better estimation of the Gleason score (23). Similarly, several technical issues of TB are also under investigation. For example, the number of targeted cores taken per lesion may impact csPCa detection and Gleason score estimation (24). In particular, obtaining three to four cores (current standard) from high-volume lesions, such as PI-RADS 5, may not be sufficient to adequately estimate the Gleason score (25). Moreover, mpMRI alone has a limited ability to predict local stage and extra-prostatic extension (26). As a result, a TB-only approach may impact clinical decisions, such as qualification for local treatment or planning the extension of surgical intervention. For example, the presence of a PCa outside the index lesion can preclude focal treatment. The local stage of PCa also provides implications regarding neurovascular bundle sparing during radical prostatectomy. It is also worth noting that the percentage of PCa involvement in the systemic cores is an important prognostic factor, indicating the risk of biochemical progression or pelvic lymph node involvement (27). Therefore, the omission of SB may have a negative impact on adequate PCa local staging and prognostic risk group determination.

Study Limitations

The major limitations of our study are its retrospective nature and analysis. Our study was multi-center and retrospective. The study population was heterogeneous, as it included both transperineal and transrectal biopsies. The analysis did not include epidemiological factors such as body mass index or comorbidities. The mpMRI images were obtained from external radiological centers, and they were described by radiologists with different levels of experience; therefore, there may have been certain discrepancies in the assessment of the PI-RADS scores. Another limitation is that TB data were obtained from 5 different centers performed by 7 different urologists using different MRI and MRI-US fusion devices. Failure of mpMRI fusion biopsy due to incorrect mpMRI image registration and mismatch of image planes, inaccurate sampling, and intralesion Gleason score heterogeneity, may have impacted our results. Another important limitation is that there was no centralized pathological examination; instead, multicentric pathological examinations were conducted by uropathologists at their respective centers. However, our data reflect the real-life nationwide picture. The comparisons of biopsy methods were performed per patient rather than per lesion. The mean number of cores were 5 in our study which may reflect overdiagnosis in TB group.

Conclusion

The results of our study indicate that in PI-RADS 5 lesions, the probability of detecting csPCa in SB is significantly lower than in TB. Omitting SB is also associated with risk of missing csPCa in 6.7% of cases. In patients with PI-RADS 5 lesions, SB in addition to TB adds minimal but not negligible clinical value. Sparing these patients from SB may be considered to reduce patient morbidity. However, the omission of SB may impact local staging by failing to detect multifocal csPCa and thus may affect therapeutic decisions. Further prospective studies are needed to set strict recommendations.

Ethics

Ethics Committee Approval: Ethics committee approval is not required for the study however several ethics committee approval have been registered earlier for our Turkish Urooncology Cancer Database.

Informed Consent: All patients gave consent for the study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: G.A., S.S., L.T., S.B., C.Y.B., E.S., İ.A., Concept: G.A., S.Ç., Design: G.A., S.Ç., Data Collection or Processing: S. Çet., S.S., S.Ç., L.T., S.E., S.B., İ.A., C.Y.B., S.Y., Analysis or Interpretation: B.Ş., L.T., G.A., S.Ç., S.S., Literature Search: S.Çet., Writing: G.A.

Conflict of Interest: Güven Aslan, Sinan Sözen, Levent Türkeri, Sümer Baltacı, and Saadettin Eskiçorapçı are members of the Editorial Board of the journal. However, they were not involved in the editorial evaluation, peer-review process, or decision-making regarding this manuscript. Bahadır Şahin joined the journal as an editor in June 2025, after the manuscript had been accepted (Received: November 18, 2024; Accepted: February 7, 2025), and therefore had no involvement in the editorial or peer-review process of this manuscript. The other authors declared no conflict of interest.

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