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Factors predicting transrectal ultrasound-guided systematic prostate biopsy failure

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ABSTRACT

Objectives: To determine the factors that predict the failure of systematic prostate biopsy by examining the clinical, laboratory, and radiological parameters of patients for whom prostate cancer was detected by magnetic resonance imaging (MRI)-targeted biopsy but not by systematic biopsy.

Methods: Patients were included in this study if they had undergone combined targeted and systematic biopsy and had cancer detected in the targeted biopsy. They were biopsy-naive patients and had lesions with a Prostate Imaging Reporting and Data System (PIRADS) score ≥ 3 in the peripheral zone on MRI. The clinical, biochemical, and radiological findings of the groups with and without cancer detected in the systematic biopsy were compared.

Results: A total of 100 patients had an index lesion in the peripheral zone and cancer detected by MRI-targeted biopsy. In 43 (43%) of the patients, no cancer was detected in the systematic biopsy, whereas it was detected in the other 57 (57%). Statistically significant differences were found between the two groups in terms of prostate volume and PSA density ($p < 0.001$ and $p < 0.001$, respectively). Moreover, the findings of univariate and multivariate logistic regression analyses indicated that prostate volume and lesion size are independent predictors of systematic biopsy failure.

Conclusions: The success of systematic biopsy may be lower in patients with high prostate volume and low peripheral zone index lesion size.

Keywords: Prostate biopsy, systematic, failure, targeted biopsy

Currently, the most widely used biopsy technique for diagnosing and grading prostate cancer is the 12-core systematic biopsy procedure performed under transrectal ultrasound (TRUS) guidance [1]. Almost all other cancers are diagnosed by performing a biopsy of the suspected area by radiological or physical examination. However, in systematic prostate biopsy, a total of 12 cores are randomly sampled, six from each lobe of the prostate. Although ultrasound reveals the borders of the prostate gland and adjacent organ structures well, it cannot adequately distinguish malignant from benign lesions [2]. Because approximately 40% of lesions are isoechoic, ultrasound alone is insufficient for targeting specific lesions [3].

With the publication of the Prostate Imaging Reporting and Data System (PIRADS) version 1 in 2012, a standard was set for multiparametric prostate magnetic resonance imaging (MRI) and reporting [4].

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Later, updates were made to the PIRADS system in ver. 2.0 in 2015 and ver. 2.1 in 2019. With the provision of this standardization, MRI-targeted biopsy applications have accelerated. In the 2021 European Association of Urology (EAU) guidelines, multiparametric prostate MRI is recommended for all patients who will undergo prostate biopsy; if PIRADS ≥ 3 lesions are detected through MRI in biopsy-naïve patients, a systematic biopsy together with a targeted biopsy are strongly recommended. In patients with previous negative biopsy, in the case of PIRADS ≥ 3 lesions detected on MRI, a targeted biopsy only from the index lesion is weakly recommended [5].

An MRI-targeted biopsy can be performed in cognitive, software-based MRI-ultrasound fusion as well as in-bore [6]. Many studies have compared all three methods with systematic biopsy.

The present study aimed to determine the factors that predict the failure of systematic biopsy by examining the clinical, laboratory, and radiological parameters of patients whose prostate cancer was detected by MRI-targeted biopsy but could not be detected by systematic biopsy.

METHODS

Our MRI-TRUS fusion-guided prostate biopsy database was reviewed retrospectively. Patients who had undergone combined targeted and systematic biopsy and had cancer detected in the targeted biopsy were included in the study. They were biopsy-naive patients and had PIRADS ≥ 3 lesions in the peripheral zone on MRI. Patients with missing data and additional malignancies were excluded. The clinical, biochemical, and radiological findings of the groups with and without cancer in the systematic biopsy were compared. In addition, logistic regression analysis was performed to determine the parameters that predict systematic biopsy failure. This study was approved by the Clinical Research Ethics Committee (date 02/21/2022, Decision No. 142).

Table 1. Comparison of the variables of the groups with and without cancer in systematic biopsy

	SB Benign (n = 43)	SB Malign (n = 57)	Total (n = 100)	*p* value
Age (year), median (Q1, Q3)	65 (60-69.5)	64 (57-69)	64 (59-69.2)	0.643
tPSA (ng/ml), median (Q1, Q3)	6.2 (5.3-8.6)	7.8 (5.5-11.5)	6.9 (5.4-10.3)	0.057
Prostate Volume (ml), median (Q1, Q3)	58 (39.5-80)	38 (28-50)	43 (32.7-65.2)	**< 0.001**
PSAD (ng/ml/ml), median (Q1, Q3)	0.124 (0.082-0.194)	0.206 (0.138-0.323)	0.170 (0.111-0.280)	**< 0.001**
PIRADS score, n (%)				0.285
3	5 (11.6)	6 (10.5)	11 (11)	
4	25 (58.1)	25 (43.9)	50 (50)	
5	13 (30.2)	26 (45.6)	39 (39)	
Index lesion diameter (mm), median (Q1, Q3)	13 (10-17.7)	14 (11-19.7)	13.5 (10-18.2)	0.223
Number of index lesion, n (%)				0.480
Single	33 (76.7%)	47 (82.5%)	80 (80)	
Multiple	10 (23.3%)	10 (17.5%)	20 (20)	
Type of anesthesia, n (%)				0.116
Local	36 (83.7)	40 (70.2)	76 (76)	
General	7 (16.3)	17 (29.8)	24 (24)	
Core length (mm), median (Q1, Q3)	10.6 (9.2-12.6)	11 (9.1-12.1)	10.8 (9.1-12.3)	0.831

SB = Systematic Biopsy, tPSA = Total Prostate-Specific Antigen, PSAD = PSA Density, PIRADS = Prostate Imaging Reporting and Data System

Statistical Analysis

The normal distribution of continuous variables was evaluated using analytical methods (i.e., Kologorov-Smirnov and Shapiro-Wilk tests). In the descriptive findings, categorical variables were presented as numbers (percentages), and continuous variables were presented with medians (interquartile range) for normal nonscattering data. The cut-off value for prostate volume was determined with a receiver operating characteristic (ROC) curve analysis and Youden's index and then reported using the area under the curve (AUC) with a 95% confidence interval (CI). For the categorical variables, statistical differences among the groups were determined using chi-square tests. For the continuous variables, statistical differences among the groups were determined using Mann–Whitney U tests. Next, univariate and multivariate logistic regression analyses were performed to determine the prognostic factors that predict systematic biopsy failure. Statistical significance was accepted as $p < 0.05$. All statistical analyses were performed with R version 4.0.4 through R Studio version 1.4.1106.

RESULTS

There were a total of 100 patients with an index lesion in the peripheral zone and cancer detected by MRI-targeted biopsy. In 43 (43%) of these patients, no cancer was detected in the systematic biopsy (Group 1), whereas cancer was detected in 57 (57%) of them (Group 2). When the clinical, biochemical, and radiological findings of the two groups were compared, no statistically significant differences were found in terms of age, total prostate-specific antigen (PSA), PIRADS score, lesion size, number of lesions, anesthesia type, and mean core length. However, statistically significant differences were found between the two groups in terms of prostate volume and PSA density (PSAD; $p < 0$ .001 and $p < 0.001$, respectively; Table 1). The findings of the univariate and multivariate logistic re-

Table 2. Univariate and multivariate logistic regression analysis to identify parameters predicting systematic biopsy failure

	Simple Logistic Regression			Multivariate Logistic Regression		
	95% CI	OR	*p* value	95% CI	OR	*p* value
Age	0.949-1.043	0.995	0.839			
tPSA	0.994-1.165	1.062	0.257			
Prostate Volume	0.58-0.852	0.713	**< 0.001**	0.946-0.991	0.969	**0.007**
PSAD	1.024-1.114	1.064	**< 0.004**	0.985-1.068	1.022	0.266
Core length	0.914-1.229	1.055	0.481			
Index lesion diameter	0.995-1.13	1.055	0.091	1.012-1.190	1.089	**0.039**
Number of index lesion						
Single	Reference		0.481			
Multiple	0.26-1.894	0.702				
PIRADS Score						
3	Reference					
4	0.215-3.115	0.833	0.785			
5	0.412-6.587	1.667	0.462			
Type of anesthesia						
Local	Reference					
General	0.839-6.21	2.186	0.121	0.658-6.357	1.978	0.233

CI = Confidence Interval, OR = Odds Ratio, tPSA = Total Prostate-Specific Antigen, PSAD = PSA Density, PIRADS = Prostate Imaging Reporting and Data System

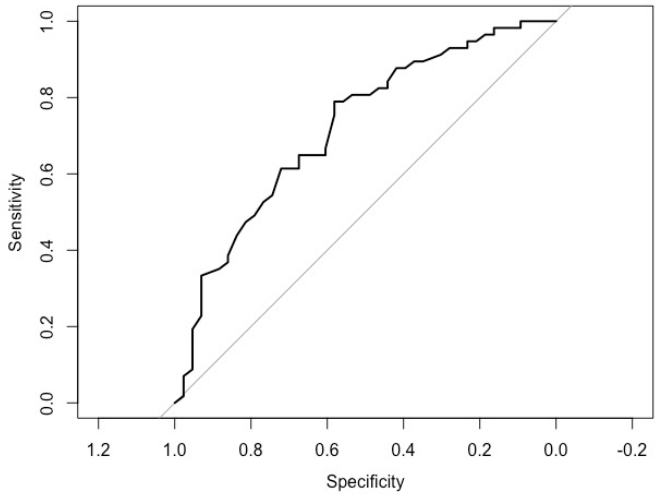

Fig. 1. ROC curve when the cut-off value of the prostate volume was determined as 53 cc.

gression analyses indicated that prostate volume and lesion size are independent predictors of systematic biopsy failure (Table 2). This study determined that a cut-off value of 53 cc on the ROC curve drawn for prostate volume exhibited 78% sensitivity and 58% specificity (Fig. 1).

DISCUSSION

The results of this study revealed that systematic biopsy is more unsuccessful when the patients has small index lesion and large prostate.

The success of targeted and systematic prostate biopsy has been investigated in many studies. A meta-analysis of 29 studies demonstrated that MRI-targeted biopsy has superior diagnostic value to systematic biopsy in terms of detecting clinically important prostate cancer and high-grade cancer in biopsy-naive patients. The same study also demonstrated that not performing a systematic biopsy in this group reduced the rate of clinically insignificant cancer detection without changing the rate of clinically significant and high-grade cancer [7].

Prostate volume is a critical factor that affects the cancer detection rate in systematic biopsy. In a series of 750 patients, Ung *et al*. [8] found the cancer detection rate to be 40% in patients with a prostate volume less than 34 cc, while it was 24% in those whose prostate volume was greater than 64 cc. Similarly, in a series of 1021 patients with sextant biopsy, these rates were 38% and 23%, respectively, when the prostate volume limit was set as 50 cc [9]. Furthermore, in our study, increased prostate volume was determined to be an independent predictive factor for systematic biopsy failure. The cut-off value of 53 cc on the ROC curve exhibited 78% sensitivity and 58% specificity.

In a standard systematic biopsy, a total of 12 cores are sampled, of which six are sampled randomly from both lobes of the prostate. Due to the fact that the number of cores taken is independent of prostate size and as prostate cancer can be multifocal, the probability of taking tissue from the tumor area in a large prostate decreases, and thus, sampling may be insufficient. Therefore, cancer diagnoses can be missed in patients with prostate cancer in addition to benign prostatic hyperplasia, and repeated systematic and saturation biopsies may be required. This result is associated with increased cost, complications, and morbidity [10-12]. On the other hand, one cannot consider prostate volume to be a factor that predicts the detection of cancer under all conditions. In a retrospective study investigating the effect of PSA level on cancer detection, 2079 patients who had undergone 10-core systematic biopsy were evaluated, and prostate volume was found to be a significant parameter only with a PSA level below 10 ng/mL [13].

Another critical parameter in the detection of prostate cancer is PSAD. In a study by Washino *et al*. [14] on 288 patients, PSAD was demonstrated to be an independent predictive factor for clinically signifi-

cant prostate cancer. In addition, a meta-analysis that included 11 studies demonstrated that PSAD is a marker that can be used to predict prostate cancer [15]. In our study, the median PSAD of patients with cancer detected in the systematic biopsy was 0.206, while this value was 0.124 in patients without cancer. A statistically significant difference was found between the two groups ($p < 0.001$), which is consistent with the literature. However, because no significant p value was found in the multivariate logistic regression analysis, we concluded that PSAD cannot be an independent predictive factor for prostate cancer in systematic biopsy. In a study of 5291 patients, Nordström *et al*. [16] demonstrated that by not performing a biopsy in patients with a PSAD < 0.07, 19.7% of them would be saved from unnecessary biopsy; however, 6.9% of clinically important prostate cancer cases would be missed. We believe that the systematic biopsy decision should not be abandoned based only on the PSAD value, since 6.9% is an important rate.

According to the MRI findings in our study, although no statistically significant difference existed in index lesion sizes between the two groups, the multivariate logistic regression analyses revealed that a small lesion size was an independent predictive factor for systematic biopsy failure. Similarly, Park *et al*. [17] performed combined targeted and systematic biopsies on 313 patients. In those with an index lesion smaller and larger than 10 mm, the clinically significant cancer detection rates were 32.5% and 69.5%, respectively, which were also statistically significant ($p < 0.001$). In another study, in which 219 patients underwent combined targeted and systematic biopsy, these rates were 8.6% and 33.1%, respectively, with a 10 mm index lesion size cut-off value; moreover, a statistically significant difference existed between the two groups ($p < 0.001$) [18].

The results of this study revealed that systematic biopsy is more unsuccessful when the patients has small index lesion and large prostate. We believe that 16-core or 20-core systematic biopsy may be preferred instead of 12-core for better sampling for these patients.

In the randomized prospective PRECISION study, it was demonstrated that compared with systematic biopsy, a clinically significant cancer rate was detected when only MRI targeted biopsy was performed (which was statistically significantly higher); however, a lower rate of clinically insignificant cancer was detected [19]. In the present study, we aimed to determine the situations in which systematic biopsy is ineffective, and therefore, clinical significance or non-significance was not distinguished. Therefore, the detection of ISUP grade 1 cancer in the targeted biopsy while the systematic biopsy was negative was accepted as systematic biopsy failure.

Limitations

This study had some limitations. First, it was retrospective; second, the interventions were performed by different clinicians; and third, targeted and systematic biopsies were performed by the same clinician.

CONCLUSION

Systematic biopsy success may be lower in patients with a high prostate volume and low peripheral zone index lesion size. We believe that MRI-targeted biopsy should be performed together with systematic biopsy in these patients. However, we believe that 16-core or 20-core systematic biopsy may be preferred instead of 12-core for better sampling. In future research, if prospective studies with larger patient cohorts are designed, then stronger conclusions can be derived.

Authors' Contribution

Study Conception: TSS, İŞ; Study Design: SÇ, MK; Supervision: TSS, İŞ; Funding: N/A; Materials: N/A; Data Collection and/or Processing: EB, AO; Statistical Analysis and/or Data Interpretation: ECB, MK; Literature Review: EB, AO; Manuscript Preparation: SÇ, MK and Critical Review: SÇ,ECB.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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