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Research Article

Risk factors associated with pain in fusion prostate biopsy

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ABSTRACT

Background: Multiparametric prostate magnetic resonance imaging (mpMRI)–guided fusion prostate biopsy is an emerging technique in the diagnosis of prostate cancer and provides extensive information on the prebiopsy anatomy of the prostate, anus, and rectum. We aimed to investigate the clinical and anatomical risk factors aggravating the pain experienced by patients undergoing mpMRI-guided fusion prostate biopsy.

Methods: The prospective study included 319 patients aged 45–75 years who had a prostate-specific antigen <10 ng/ml and a Prostate Imaging Reporting and Data System ≥3 lesion and underwent combined biopsy (targeted biopsy + 12-core standard prostate biopsy) under local anesthesia (intrarectal lidocaine gel + periprostatic nerve block). Immediately after the biopsy procedure, pain assessment was achieved using Visual Analog Scale (VAS). The relationship between the VAS and 13 clinical parameters was evaluated using ordinal logistic regression analysis.

Results: The 319 patients had a mean age of 62.39 ± 6.98 years and a median prostate-specific antigen level of 7.20 (range, 5.20–8.50) ng/ml. The VAS was found to be correlated with 4 of 13 parameters, including (i) a shorter prostate–anus surface distance (cutoff value, 55.5 mm), (ii) a narrower anorectal angle (cutoff value, 106.5°), (iii) a larger total prostate volume (cutoff, 61.6 mm^3), and (iv) having no history of prior biopsy (biopsy-naive patients).

Conclusion: Anatomical measurements that can be achieved by using mpMRI images (TPV, PASD and ARA) may be useful in the identification of patients at an increased risk of pain during biopsy and also in taking analgesic precautions in such patients.

1. Introduction

Prostate cancer (PCa) is the second leading cancer among men worldwide.[1] Although prostate-specific antigen (PSA) and suspicious digital rectal examination findings constitute an important place in the diagnosis of PCa, prostate biopsy is required for the definitive diagnosis of PCa.[2] However, the pain experienced by the patient during prostate biopsy poses significant challenges both for patients and the clinicians performing the biopsy procedure.[3]

Fusion prostate biopsy (FPB) is an emerging technique in the diagnosis of PCa. In this technique, patients are initially evaluated by multiparametric prostate magnetic resonance imaging (mpMRI) and then undergo targeted biopsy (TB) for the evaluation of suspicious lesions detected on mpMRI.[4] Some researchers advocated that TB alone could be sufficient for patients with suspected PCa while some others proposed that TB should be combined with standard prostate biopsy (SPB) [combined biopsy (CB)].[5,6] In CB, as expected, the number of cores sampled per target and the total biopsy time are increased.[7] On the other hand, the mpMRI images routinely obtained before biopsy provide extensive information on the prebiopsy anatomy of the prostate, anus, and rectum.[8,9]

In this study, we aimed to investigate the clinical and anatomical risk factors aggravating the pain experienced by patients undergoing CB.

2. Materials and methods

2.1. Patient selection and data collection

The prospective study included patients that were scheduled for prostate biopsy due to the presentation of elevated PSA and/or suspicious digital rectal examination findings in Erciyes University

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Department of Urology between April 2017 and March 2020. All the patients underwent an mpMRI examination before biopsy. Inclusion criteria were as follows: age 45–75 years, PSA<10 ng/ml, and a Prostate Imaging Reporting and Data System (PI-RADS) ≥3 lesion. Exclusion criteria were as follows: neurological diseases that could affect the sensation of pain such as paraplegia and hemiplegia, a history of analgesic use within the last two days before the procedure, requirement of general anesthesia (sedation) for the biopsy procedure, a history of rectal surgery, and diseases that could alter the pain threshold such as anal fissure and hemorrhoid disease.

Age, body mass index, serum PSA level, prebiopsy PI-RADS score, prior biopsy history, prostate–anus surface distance (PASD) as measured on mpMRI, anorectal angle (ARA), total prostate volume (TPV) and transitional zone volume measured during biopsy, number of biopsy regions, number of biopsy cores, biopsy duration (i.e. the time between the insertion and removal of the probe), Visual Analog Scale (VAS) scores, and histopathologic examination findings were recorded for each patient. Clinically significant PCa was considered in patients with a biopsy Gleason score ≥3 + 4 or a maximum cancer core length ≥5 mm.[9]

2.2. Multiparametric magnetic resonance imaging and PI-RADS scores

Before biopsy, an mpMRI scan without an endorectal coil was performed in each patient using a 1.5 T MRI device (Siemens-Magnetom, Malvern, USA). The suspicious lesions detected on contrast-enhanced T2-, T1- and diffusion-weighted images were classified using PI-RADS, version 2.[10] In patients with more than one lesion, the lesion with the higher PI-RADS score was accepted as the index PI-RADS score.

2.3. TheVAS score

The VAS is a pain assessment scale consisting of a 100-mm line, on which the extreme left of the line (0 points) indicates no pain and the extreme right (100 points) indicates severe and unbearable pain.[11] In the present study, the VAS was administered to each patient both visually and verbally after the biopsy, and the patients were asked to indicate their pain severity on the 100-mm line.

2.4. PASD and ARA

The PASD and ARA measurements were performed using contrast-enhanced T2-weighted mpMRI sequences. The PASD was calculated as the arithmetic mean of three measurements: distance from the anus (a) to the prostate apex, (b) to the prostate base, and (c) to the median lobe of the prostate. The ARA was measured as the angle between the rectal and anal canal axis (Fig. 1). All the measurements were performed electronically on mpMRI sequences.

2.5. Biopsy procedures and local anesthesia

The biopsy procedure was performed using an ultrasound (US) fusion device based on rigid registration (LOGIQ-E9, General Electric (GE) Healthcare, Wauwatosa, WI, USA) with an endorectal probe [IC5-9-D (3-10 MHz) 145° field of view, footprint: 21.2 × 17.2 mm, with a thicker head]. Rectal lidocaine gel (2%) was applied as intrarectal local anesthetic before the introduction of the rectal US probe. After a 10-min waiting period, the US probe was inserted in the rectum. Periprostatic nerve block (PNB) was administered with the injection of 5 ml solution (1:1 dilution) involving 2% prilocaine into the neurovascular bundle between the prostate base and seminal vesicles in the sagittal plane using a 30-cm 18 G needle. Subsequently, prostate volume was measured for the calculation of transitional zone volume and TPV. In the CB procedure, the patients initially underwent 12-core SPB and then the mpMRI images were transferred to the US fusion device. After the segmentation of US and mpMRI, the suspicious lesions were marked on the US and then TB was performed by sampling 2–4 cores per suspicion lesion.

2.6. Statistical analysis

Data were evaluated using SPSS 22.0 for Windows (IBM Corp. Released 2013, Armonk, USA). Data with normal distribution were expressed as mean ± standard deviation, and data with nonnormal distribution were expressed as median (1^{st}-3^{rd} quartile). Categorical variables were expressed as percentages (%). Continuous variables with normal distribution were compared using independent samples *t* test with the Levene test, and the continuous variables with nonnormal distribution were compared using the Mann–Whitney *U* test. Correlations between ordinal-dependent variables and independent variables were analyzed using ordinal logistic regression analysis. The cutoff values of categorical dependent variables were determined using Receiver operating characteristic (ROC) analyzes were performed to determine the cutoff values of categorical dependent variables. The optimal cutoff values for TPV, PASD, and ARA were determined mathematically based on the maximum Youden's Index (defined as

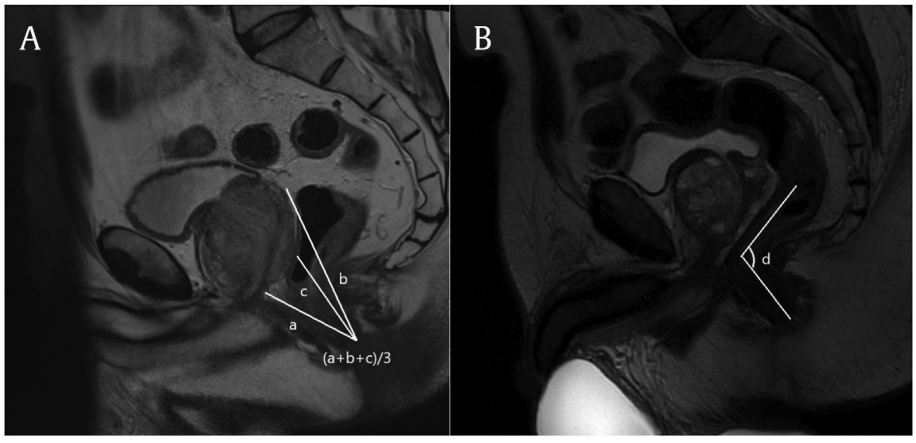

Fig. 1. Measurements performed using T2-weighted sagittal multiparametric magnetic resonance imaging (MRI) sequences. Prostate–anus surface distance (PASD) [distance from the anus to the prostate apex (a), to the prostate base (b), and to the median lobe of the prostate c)]. (B) anorectal angle (d = angle between the rectal and anal canal axis).

"sensitivity + specificity - 1"). A p value of <0.05 was considered significant.

2.7. Ethical issues

The study was approved by the Ethics Committee of Erciyes University (Approval No.: 2014/508). A written consent was obtained from each patient (T.D.).

2.8. Financial support

This study was funded by Erciyes University Scientific Research Projects Coordination Unit (Project No.: TSG-2016-5200).

3. Results

3.1. Patient characteristics

The 319 patients had a mean age of 62.39 ± 6.98 years, a mean body mass index of 27.63 ± 6.03 kg/m^2, and a median PSA level of 7.20 (range, 5.20–8.50) ng/ml. The median biopsy duration was 22.00 (range, 20.00–25.00) min, and the mean clinically significant PCa detection rates for TB, SPB, and CB were 28.2%, 32.0%, and 44.5%, respectively. Table 1 presents the demographic, clinical, and biopsy characteristics of the patients.

3.2. Relationship between the VAS score and clinical parameters

The analysis of the relationship between the VAS and 13 clinical parameters indicated that the VAS established a significant relationship with only 4 parameters including biopsy history, TPV, PASD, and ARA. Moreover, VAS scores were lower in patients with a prior negative biopsy than in biopsy-naïve patients. It was also revealed that the patients experienced less pain as PASD and ARA increased while the patients experienced more severe pain as their TPV increased (Table 2).

Table 1
Demographic, clinical, and biopsy characteristics of the patients.

Parameters	Value
Age (year)	62.39 ± 6.98
BMI (kg/m^2)	27.63 ± 6.03
PSA (ng/ml)	7.20 (5.20-8.50)
Negative biopsy history (n, %)	30/319 (9.4%)
Transitional zone volume (mm^3)	30.78 (17.71-50.61)
Total prostate volume (mm^3)	52.87 (37.97-73.07)
Number of biopsy regions (n)	14.00 (13.00-14.00)
Number of cores (n)	17.00 (16.00-19.00)
VAS score	30.00 (10.00-50.00)
Duration of procedure (minute)	22.00 (20.00-25.00)
Prostate–anus surface distance (mm)	59.22 ± 8.02
Anorectal angle (degree)	111.87 ± 15.59
PI-RADS scores	
• 3	160 (50.2%)
• 4	102 (32.0%)
• 5	57 (17.9%)
csCDR (%)	
• Target biopsy (TB)	90 (28.2%)
• Standard biopsy (SB)	102 (32.0%)
• Combined biopsy (TB + SB)	142 (44.5%)
ISUP scores	
• 1	92 (28.8%)
• 2	29 (9.1%)
• 3	13 (4.1%)
• 4	17 (5.3%)
• 5	5 (1.6%)

PSA, prostate-specific antigen; BMI, body mass index; VAS, Visual Analog Scale; csCDR, clinically significant prostate cancer detection rate; ISUP, International Society of Urological Pathology; PI-RADS, Prostate Imaging Reporting and Data System.

Patients were divided into two groups based on their VAS scores: Group I (VAS <50) and Group II (VAS ≥50). In Group I and II, mean TPV was 44.83 (range, 32.56-55.18) mm^3 and 85.99 (range, 67.37-111.00) mm^3, respectively ($p < 0.001$). In addition, both PASD and ARA were significantly higher in Group I than in Group II (Table 3).

3.3. Cutoff values of PASD, ARA, and TPV

The cutoff values of TPV, PASD, and ARA at a VAS score of 50 were 61.6 mm^3 (AUC = 0.895), 55.5 mm (AUC = 0.874), and 106.5° (AUC = 0.747), respectively. The sensitivity and specificity values of these cutoff values are presented in Table 4.

4. Discussion

The results of our study indicated that some clinical and anatomical parameters (biopsy history, TPV, PASD, and ARA) are associated with the pain experienced during prostate biopsy. Accordingly, these findings implicate that (i) biopsy-naïve patients, (ii) patients with a larger prostate, (iii) patients with a shorter PASD, and (iv) patients with a narrow ARA are likely to experience a relatively more severe pain during biopsy. Given the growing use of mpMRI before prostate biopsies, these four parameters can be easily calculated before biopsy, and as a result, the administration of biopsies with more efficient analgesic techniques in patients with risk factors of PCa can be considered.

In our study, a linear relationship was found between prostate volume and the pain experienced during biopsy. The patients were divided into two groups as patients with a VAS score of <50 and ≥ 50, and it was revealed that patients with higher VAS scores had a larger prostate volume. In the literature, there are several studies investigating the relationship between prostate volume and the pain experienced during prostate biopsy.[12-14] Gómez-Gómez et al. evaluated a large cohort of 1,188 patients and reported that patients with a prostate volume of >40 ml experienced greater pain compared with patients with a prostate volume of ≤40 ml.[12] Another prospective study evaluated the severity of pain experienced by 71 patients undergoing prostate biopsy and revealed that patients with a larger prostate volume experienced greater pain.[13] Similarly, in a 2016 study, Luan et al.[14] evaluated 568 patients and also revealed that patients with a larger prostate volume indicated greater pain intensity. In none of these studies, however, no cutoff value was determined for prostate volume. In our study, a cutoff value of 61.6 mm^3 was determined for prostate volume (sensitivity and specificity 83%), which indicates that patients with a prostate volume of >61.6 mm^3 are at a higher risk of experiencing pain during prostate biopsy.

A leading cause of the pain experienced by patients undergoing transrectal prostate biopsy is the stress experienced by the patients during the passage of the US probe through the anus, which is mostly associated with the presence of a larger number of nerve cells in the anus compared with the rectum.[15-17] Similarly, our findings indicated that patients with a longer PASD (i.e. patients in whom the prostate was localized further to the anus) experienced less pain compared with patients with a shorter PASD. Although there is no sufficient data regarding this issue in the literature, these findings suggest that the pain level decreases as we move away from the anus region where nerve fibers are predominant. In addition, this finding could also be associated with the shape of rectal probes used for mpMRI. The rectal probe used in our study, as in many other rectal probes, had a thicker head than its body. Accordingly, in cases with a shorter PASD, the thicker part of the probe is localized at a site that is closer to the anus, thus causing greater dilatation in the anus as well as increased stress in the

Table 2
Effects of clinical parameters on Visual Analog Scale (VAS) scores (ordinal logistic regression analysis).

Parameter	B	Std. error	*P*	Odds ratio	95% CI
Age (year)	−0.24	0.0152	0.119	0.977	[0.948-1.006]
BMI (kg/m^2)	−0.20	0.0251	0.434	0.981	[0.933-1.030]
PSA (ng/ml)	−0.059	0.0545	0.275	0.942	[0.847-1.049]
Biopsy history	1.000	0.4013	**0.013**	2.719	[1.238-5.972]
Transitional zone volume (mm^3)	0.10	0.0107	0.363	1.010	[0.989-1.031]
Total prostate volume (mm^3)	0.050	0.0088	**<0.001**	1.051	[1.033-1.069]
Number of biopsy regions (n)	−0.383	0.2029	0.059	0.682	[0.458-1.015]
Number of cores (n)	−0.074	0.0817	0.366	0.929	[0.791-1.090]
Duration of procedure (minute)	−0.016	0.0225	0.480	0.984	[0.942-1.029]
Prostate–anus surface distance (mm)	−0.160	0.0191	**<0.001**	0.852	[0.821-0.885]
Anorectal angle (degree)	−0.037	0.0077	**<0.001**	0.964	[0.950-0.979]
PI-RADS score	0.045	0.2929	0.878	1.046	[0.589-1.857]
CsCDR (%)	−0.207	0.2208	0.349	0.813	[0.527-1.253]

BMI, body mass index; PSA, prostate-specific antigen; csCDR, clinically significant prostate cancer detection rate; PI-RADS, Prostate Imaging Reporting and Data System; CI, confidence interval.
Statistically significant p values are written in bold.

Table 3
Comparison of total prostate volume, prostate-anus surface distance, and anorectal angle according to VAS scores.

Measurement	VAS score<50 (n = 220)	VAS score≥ 50 (n = 99)	*P*
Total prostate volume (mm3)	44.83 (32.56-55.18)	85.99 (67.37-111.00)	<0.001
Prostate–anus surface distance (mm)	62.16 ± 7.29	52.70 ± 5.35	<0.001
Anorectal angle (degree)	115.92 ± 14.64	102.86 ± 13.80	<0.001

VAS, Visual Analog Scale.

patient. This phenomenon could also explain the relationship between PASD and pain in patients undergoing prostate biopsy. In addition, some previous studies also noted that the use of thick probes leads to increased pain intensity in such patients.[18] In our study, the cutoff value of PASD was determined to be 55 mm.

ARA is measured as the angle between the rectal and anal canal axis.[19] The normal range of ARA is 90-180°. This angle has been shown to form a narrowing curve in the anorectal region, thereby functioning as a natural sphincter.[20] To our knowledge (according to PubMed, Embase, and Cochrane Central Trials Registry), there has been no study in the literature investigating the relationship between this angle and the pain experienced by patients undergoing prostate biopsy. In our study, it was revealed that patients with an ARA of close to 90° are likely to experience a greater pain during biopsy. Meaningfully, the increased pain intensity in such patients could be associated with the use of flat and rigid rectal probes in prostate biopsy, mainly because a greater force is needed to be applied in patients with an ARA of close to 90°. This means that the normal physiological state of the intestines is altered. In our study, the cutoff value of ARA was determined as 106°, which implicates that patients with an ARA of <106° are likely to experience a greater pain intensity.

The effect of prior prostate biopsy on pain remains controversial.[13,21,22] A 2015 study reported that patients with a history of biopsy indicated greater pain intensity during the second biopsy procedure.[13] On the contrary, Djavan et al. [21] indicated that there was no difference between the first and second biopsies with regard to pain intensity. Similarly, Bastide et al. [22] found no significant relationship between the history of biopsy and pain intensity. In our study, unlike in other studies, patients with a prior biopsy experienced less pain compared with biopsy-naïve patients, which could be attributed to two notions: (I) patients with a prior biopsy are well aware of this pain and thus feel ready to experience it again (learned pain behavior) and (II) only a small portion of the patients included in our study (9.6%) had a history of biopsy, which could have resulted in statistical inadequacy.

Comparison of FPB and SPB with regard to pain intensity has been conducted in several previous studies.[7,23] In those studies, however, no evaluation was performed on the direct relationship between the number of cores/biopsy time and pain. Moreover, in those studies, similar pain scores were reported for FPB and SPB although FPB requires a higher number of target cores and longer time when compared with SPB. Arsov et al. [24] reported that patients undergoing in-bore biopsy indicated greater pain intensity than patients undergoing FPB as this procedure requires longer time when compared with FPB. In that study, however, in-bore biopsy and FPB were administered with different anesthetic techniques. In a recent study evaluating patients undergoing transperineal biopsy, Marra et al. [25] reported the mean procedural time for mpMRI fusion biopsy as 19 min and also noted that the patients undergoing SPB and FPB reported similar pain intensities, although the SPB group had a mean procedural time of 11 min. In a similar way, our patients had a median procedural time of 22 min, and no significant correlation was found on regression analysis between biopsy time/number of target cores and the pain experienced by the patients.

Temiz et al. [26] proposed a relationship between the pain experienced by patients and the histopathology of biopsy specimens. The authors attributed this to the biopsy technician's inability to adequately manipulate the probe and effectively to the biopsy regions of the prostate where cancer is more likely to occur,

Table 4
ROC (receiver operating characteristic) analysis results and cutoff values at a VAS score of 50.

Measurement	AUC	Cutoff value	Sensitivity (%)	Specificity (%)
Total prostate volume	0.895	61.6	83	83
Prostate–anus surface distance	0.874	55.5	83	78
Anorectal angle	0.747	106.5	75	67

AUC, area under curve; VAS, Visual Analog Scale.

such as the apical and far lateral regions, when patients are in pain during the procedure. In a more recent study, however, Bolat et al. [27] advocated that there is no significant relationship between histopathology results and pain intensity. Based on the findings of our study, we consider that the histopathology results and preoperative PI-RADS scores have no relationship with the pain experienced during prostate biopsy.

In our study, all patients received the same dose of painkillers to ensure standardization. In addition, we used the PNB + intrarectal local anesthetic technique for local anesthesia as suggested in previous studies.[15,16,26] Therefore, data about the analgesic need of patients with high and low pain risk could not be obtained. In the literature, Ateş et al. [28] reported that 4 ml of 2% lidocaine is more effective in PNB than 2 ml of 2% lidocaine. In contrast, in another study, there was no difference between 10 ml of 1% lidocaine administered by periprostatic injection and 20 ml of 1% lidocaine.[29] Another important point is the type of anesthesia. According to previous studies, spinal anesthesia has been reported to be more effective than other types of anesthesia.[30] Logically, in patients with risk factors for pain, it may be considered to use a more effective method of anesthesia (such as spinal anesthesia) or to give a higher dose of painkillers. However, it should be noted that whether the dose of painkillers affects the level of pain is controversial, and more data are needed on the subject.

Our study was limited in several ways. First and foremost, the study had a small patient population. Second, no manometric measurement was performed, and thus, no evaluation was performed for the relationship between the pain experienced during biopsy and the pressure in the anal sphincter. Third, the ARA measurements were performed based on dynamic mpMRI images obtained at rest. Moreover, these measurements were not achieved by using effective techniques such as defecography, and thus the evaluation of rectal motility could not be achieved. Fourth, in our study, a standard dose of lidocaine was used for PNB. Therefore, it has not been established whether dose adjustment is effective in patients at high risk of pain. Finally, pain assessment with the VAS could not be performed at each stage of the prostate biopsy procedure (probe introduction, needle piercing, probe maniplations).

In conclusion, given the growing use of mpMRI before prostate biopsies, particularly FPB, some anatomical measurements that can be achieved by using mpMRI images (TPV, PASD, and ARA) may be useful in the identification of patients at an increased risk of pain during biopsy and also in taking analgesic precautions in such patients. Moreover, it should also be kept in mind that a history of prior biopsy could be a beneficial factor in reducing the pain experienced by patients. Further larger-scale prospective studies conducting manometric measurements are needed to obtain more objective findings.

Conflicts of interest

All authors declare that there are no conflicts of interest in connection with this article.

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