Original Article

DOI: 10.4274/uob.galenos.2018.1149

Bull Urooncol 2019;18:46-50

Risk Factors Affecting Complications Due to Prostate Biopsy

Sinan Avcı MD, Sedat Öner MD, Efe Önen MD, Volkan Çağlayan MD, Metin Kılıç MD, Murat Şambel MD

Health Sciences University, Bursa Higher Specialization Training and Research Hospital, Clinic of Urology, Bursa, Turkey

Abstract

Objective: Currently, transrectal ultrasound (TRUS) guided prostate biopsy is the standard method used for prostate cancer detection. In the last decade, hospitalization due to complications has increased, especially due to infectious causes. Therefore, it is important to determine the risk factors affecting the complications of prostate biopsy.

Materials and Methods: One hundred and sixty-four patients who underwent TRUS-guided prostate biopsy due to prostate cancer suspicion were included in our study. Patients' ages, total and free prostate specific antigen (PSA) levels, prostate volumes, digital rectal examination findings, level of education, pathology results and pain related to the procedure were recorded. A 10-cm long visual analogue scale (VAS) was used to assess the pain of the patients. Complications related to the procedure were questioned firstly on the same day and secondly during the visit of the patient for pathology. As a result of these evaluations, complications divided into three groups as none, minor (no intervention) and major (medically or surgically treated).

Results: In our study, minor complications included rectal bleeding in 42 patients and hematuria lasting longer than 48 hours in 11 patients. Major complications were fever of >38 °C in two patients and epididymitis in one patient. There was no statistically significant effect of age, total and free PSA, prostate volume, level of education, digital rectal examination findings and pathology results on complications. There was no statistically significant relationship between VAS pain score and rectal bleeding, hematuria, epididymitis. On the other hand, a statistically significant relationship was found between VAS pain score and fever.

Conclusion: In the limited number of studies on the determination of risk factors for complications associated with prostate biopsy, the level of education, digital rectal examination findings, and pain due to the procedure were evaluated. In the light of our results, we believe that patients with high pain scores may be at risk for complications, especially for fever.

Keywords: Prostate biopsy, complications, risk factors

Introduction

Prostate cancer is the second most common cancer among men worldwide (1). Currently, transrectal ultrasound (TRUS) guided prostate biopsy is the standard method used for prostate cancer detection. In recent years, there has been an increase in the number of prostate biopsies and consequent complications due to prostate biopsy in younger patients, widespread use of prostate specific antigen (PSA) worldwide, and prolonged human life. Infection rates increase with recurrent biopsies due to active follow-up (2). In the last decade, hospitalization due to complications has increased, especially due to infectious causes (3). Therefore, it is important to determine the risk factors affecting the complications of prostate biopsy. In our study, the effects of age, total and free PSA, prostate volume, level of education, pain related to the procedure, digital rectal examination findings and pathology results on complications were evaluated.

Materials and Methods

Our study was prospectively designed and 164 patients who applied to our clinic between January 2012 and May 2012 and underwent prostate needle biopsy with TRUS for suspected prostate cancer were included in our study.

Our study was approved by the ethics committee of our hospital (no: 2012/9/3) and all patients included in the study were informed about TRUS guided prostate biopsy and complications. Written informed consent was obtained from the patients.

In our study, having abnormal rectal examination and/or serum PSA levels above 2.5 ng/mL formed our indication for prostate

Address for Correspondence: Sinan Avcı MD, Health Sciences University, Bursa Higher Specialization Training and Research Hospital, Clinic of Urology, Bursa, Turkey
Phone: +90 224 295 50 00 **E-mail:** sinavci@yahoo.com **ORCID:** orcid.org/0000-0002-3354-5352
Received: 11.10.2013 **Accepted:** 11.10.2013

biopsy. Exclusion criteria were as follows: a) patients with painful conditions of the prostate, rectum or anus, such as acute prostatitis, prostadinia, hemorrhoid, anal fissure or stricture; b) patients having neurological disorders, such as lower limb paraplegia, with decreased or diminished pain sensation; c) patients with bleeding diathesis; d) patients using analgesics, anxiolytic or narcotic drugs; and e) previous TRUS-guided prostate biopsy. Anticoagulant, antiaggregant and thrombolytic drugs were discontinued at least one week prior to prostate biopsy.

The patients' ages, total and free PSA levels, prostate volumes, digital rectal examination findings, levels of education, pathology results and pain related to the process were recorded and the effects of these data on the complications were evaluated statistically for each complication type separately and for all the complications.

Digital rectal examination findings of the patients were evaluated as benign or suspicious. The patients with the findings of stiffness, nodule, irregularity, loss of sulcus etc. in digital rectal examination were evaluated in the suspicious group. Patients were divided into two groups in terms level of education as below eight years of compulsory education (primary education or lower) and above eight years of compulsory education (higher than primary education). Pathology results of the patients were recorded as benign or malignant.

A 10-cm long visual analogue scale (VAS) was used to evaluate the pain of the patients. On this scale, the starting point zero (0) describes no pain and the end point ten (10) describes the most severe pain experienced. Following the explanation of the VAS by the physician, the patients were asked to give a point on the scale for the pain they felt. In order to prevent incorrect pain scoring, the biopsy shot sound was listened before the procedure and the patients were told not to take this sound into consideration. All the informing about VAS and biopsy applications were performed by the same physician. The data obtained by measuring the distance of the marks on the scale to the zero starting point were measured in millimeters as pain scores. Pain score measurements were made immediately after the biopsy procedure was completed and the rectal probe was removed.

The patients were positioned in the left lateral decubitus position and the hips and knees were flexed. The "LOGIQ 100 PRO Series" ultrasound device equipped with a 6.5 MHz rectal probe with a maximum diameter of 23 mm was used for TRUS imaging. Once the probe was placed rectally, the prostate was visualized in the sagittal and transverse plane and the prostate volume was automatically calculated with the ellipsoid formula on the ultrasound instrument. The anesthetic agent for periprostatic nerve blockade was injected with a 30 cm 18 gauge (G) spinal needle in the sagittal plane in 5 cc doses separately into the region of both neurovascular bundles between the prostate base and the seminal vesicle after checking to prevent intravascular injection. After periprostatic nerve blockade, an 18 gauge 30 mm automatic biopsy gun was used to obtain specimens from 12 cores from the posterolateral region of the peripheral zone in accordance with the European Association of Urology (EAU) guideline. Since all patients in our study were biopsied for the first time, no transitional zone (TZ) sampling was performed. In all patients, 12 core biopsy specimens were taken at the same anatomical order.

All patients took ciprofloxacin (500 mg) orally twice a day for one day before and four days after biopsy. A fleet enema was performed rectally to each patient in the morning before biopsy.

After the procedure, all patients were kept for at least one hour and complications were recorded. Patients with no problem were discharged. The second evaluation of the patients for complications was made during their visit for pathology results. As a result of these evaluations, complications were divided into three as no complication, minor (no intervention) and major (medically or surgically treated) complications. Patients were advised to admit the hospital in cases of high fever (≥38°C), dysuria, hematuria or rectal bleeding.

Statistical Analysis

Independent sample t-test was used for the quantitative data having normal distribution. Kruskal-Wallis test was used for quantitative data that did not have normal distribution. Pairwise comparisons were made with Mann-Whitney U test. Qualitative data with independent variables were evaluated with chi-square test and Fischer's exact test. $P<0.05$ was considered statistically significant.

Results

The mean age of the patients was 66.1 years. The median value for total PSA was 8.8, the median value for free PSA was 1.5, the median value for prostate volume was 64 and the median value for VAS pain score was 10. While the number of patients with lower education level was 133, the number of patients with higher education level was 31. The number of patients with benign digital rectal examination findings was 89 and the number of patients with suspicion was 75. The numbers of patients with benign and malignant pathology were 130 and 34, respectively. The standard deviation, minimum, maximum and percentage ratios for this data are shown collectively in Table 1.

In our study, minor complications included rectal bleeding in 42 patients and hematuria lasting longer than 48 hours in 11 patients. Major complications were high fever in two patients and epididymitis in one patient. All of the patients had stopped rectal bleeding at the first hour. Rectal hemorrhage and hematuria were evaluated as Clavien grade 1 complications, and high fever and orchitis as Clavien grade 2 complications. Hematospermia, vasovagal episode, urinary retention and bacterial sepsis, which are other complications due to prostate biopsy, were not seen in our study. The numerical and percentage distribution of the complications is shown in Table 2.

There was no statistically significant relationship between age, total-free PSA, prostate volume, level of education, digital rectal examination findings and pathology, with rectal bleeding, hematuria, fever and epididymitis. When all the complications were evaluated together, no statistically significant results were found for these parameters. There was no statistically significant relationship between VAS pain score and rectal bleeding, hematuria, epididymitis and all complications; however, a

statistically significant relationship was found for high fever. P values for these results are shown in Table 3. The relationship between VAS pain score and high fever was evaluated by ROC analysis. Accordingly, a cut-off value of >46.5 for VAS pain score was found to be a value for possible complications (AUC=0.935).

Discussion

In their study evaluating the complications related to prostate biopsy, Rietbergen et al. (4) reported that rectal bleeding with increasing age tended to increase slightly but this was not significant. In our study, no significant relationship was found between age and both rectal bleeding and other complications. This situation is similar to many studies in the literature (3, 5,6,7,8,9). Again, in three studies that age was not a risk factor for complications, a negative correlation was found between age and hematospermia (4,10,11). This finding was explained by the decrease in the sexual activity of the patients with increasing age. In our study, hematospermia was not seen, however, hematospermia was found to be 37.4% according to the guidelines of the EAU. We think that this difference in our study is due to the fact that the number of patients having sexual intercourse may be low in this period which can be considered as early after the biopsy since the patients' inquiries about the complications were made in the visits they came to show the pathology results after about two weeks.

There was no significant relationship between prostate volume and any complications seen in our study. There are studies reporting similar results in the literature (5,7,8,9,12). However, Loeb et al. (13) found a significant relationship between prostate volume and fever. In this study, the patients between 1993 and 2011 were examined and trimethoprim-sulfamethoxazole was used for prophylaxis until 2008 and ciprofloxacin was used after this date. Ciprofloxacin was continued for five days only in high-risk patients. In the same study, it was reported that trimethoprim-sulfamethoxazole resistance was around 80% in patients who were hospitalized and from whom urine/blood cultures were obtained. In our study, ciprofloxacin was administered to all patients for a total of five days. We think that the difference between the two studies is related to different protocols applied in prophylaxis. Shigemura et al. (14) found a significant relationship between prostate volume and infectious complications. In this study, TZ sampling was performed in 51 patients (42.5%) and bowel cleansing was

Table 1. Mean, standard deviation, median, minimum, maximum, numerical and percentage data calculated for variables

Age, mean (± SD)		66.1 (±8.66)
Total PSA, median (minimum-maximum)		8.8 (1-314)
Free PSA, median (minimum-maximum)		1.5 (0-66)
Prostate volume, median (minimum-maximum)		64 (13-256)
VAS pain score, median (minimum-maximum)		10 (2-97)
Level of education	Primary education or lower, n (%)	133 (81.1%)
	Higher than primary education, n (%)	31 (18.9%)
	Total, n (%)	164 (100%)
Digital rectal examination	Benign, n (%)	89 (54.3%)
	Suspicious, n (%)	75 (45.7%)
	Total, n (%)	164 (100%)
Pathology report	Benign, n (%)	130 (79.3%)
	Malignant, n (%)	34 (20.7%)
	Total, n (%)	164 (100%)

PSA: Prostate specific antigen, VAS: Visual analogue scale, SD: Standard deviation
n: Number of the patients

Table 2. Numerical and percentage distribution of complications

Minor complications Clavien grade 1						**Major complications Clavien grade 2**					
Rectal bleeding, n (%)			**Hematuria, n (%)**			**Fever, n (%)**			**Epididymitis, n (%)**		
Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total
42 (25.6%)	122 (74.4%)	164 (100%)	11 (6.7%)	153 (93.3%)	164 (100%)	2 (1.2%)	162 (98.8%)	164 (100%)	1 (0.6%)	163 (99.4%)	164 (100%)

n: Number of the patients

Table 3. P values calculated for the effects of variables on complications

	p				
	Rectal bleeding	**Hematuria**	**Fever**	**Epididymitis**	**All complications**
Age	0.350	0.731	0.892	0.321	0.602
Total PSA	0.286	0.229	0.858	0.874	0.518
Free PSA	0.434	0.173	0.946	0.899	0.557
Prostate volume	0.605	0.308	0.495	0.899	0.752
Level of education	0.654	0.209	1	1	0.414
Digital rectal examination findings	0.630	0.643	0.498	1	0.540
Pathology report	0.177	1	1	1	0.606
VAS pain score	0.356	0.783	**0.037**	0.332	0.190

PSA: Prostate specific antigen, VAS: Visual analogue scale

not performed with rectal enema. In our study, since we included patients who underwent biopsy for the first time, TZ was not sampled in accordance with the guidelines of the EAU, and all patients underwent bowel cleansing with rectal enema on the morning of biopsy. In our study, infectious complications such as acute prostatitis and sepsis have not been observed and there are studies in the literature indicating that there is no relationship between prostate volume and these complications (15,16,17). Although we did not observe complications such as urinary retention and syncope in our study, there are studies in the literature that correlate prostatic volume with these complications (6,10,11,18). Some studies have shown a significant relationship between prostate volume and hematuria (10,11,19). In these studies, Raaijmakers et al. (10) performed prostate biopsy without any anesthesia. We think that application of this procedure without anesthesia, in which patients feel a great amount of pain, affects the hematuria rates. Because Obek et al. (20) reported that periprostatic nerve blockage reduces rectal bleeding. They explained this situation in a similar way to Rodríguez and Terris et al. (12), who stated that the pain felt by the patients was proportional to the rectal bleeding. In another study, Zaytoun et al. (11) sampled a mean of 15.2 cores and prostate biopsy was performed even though the patients continued to receive anticoagulant and antiplatelet drugs. In this study, we believe that the mean number of cores and the use of drugs that may cause bleeding diathesis affected the relationship between prostate volume and hematuria. Chiang et al. (6) and Namekawa et al. (18) reported no significant relationship between hematuria and prostate volume, similar to our study. In the literature, the rate of rectal bleeding seen after prostate biopsy ranges between 1.3-13% and the rate of hematuria ranges between 10-84% (21). In our study, these rates were 25.6% and 6.7%, respectively.

In our study, PSA levels did not significantly affect complications. As far as we know, other studies in the literature also report similar results (5,15,18). Simşir et al. (15) reported no significant relationship between sepsis and PSA levels, and Namekawa et al. (18) reported no significant relationship between both urinary retention and hematuria and PSA levels.

Almost all studies have shown that there is no significant relationship between pathology results and complications (7,8,9,16,22,23,24,25). To the best of our knowledge, only Rietbergen et al. (4) reported that hematuria and hematospermia rates were significantly lower in patients diagnosed with prostate cancer. They interpreted this result as the increasing threshold for reporting these complications in patients receiving bad news. Supporting this situation, Rodríguez and Terris et al. (12) they stated that the pathology result for the complications was not a risk factor in their evaluation before the pathology result was reported. The results of our study are in parallel with the vast majority of the literature.

To the best of our knowledge, the relationship between digital rectal examination (DRE) and complications was only examined by Namekawa et al. (18). In this study, there was no relationship between hematuria and DRE, and there was a significant relationship between urinary retention and DRE findings. In our study, urinary retention was not observed and there was no significant relationship between DRE and any complication including hematuria.

As a result of our study, no significant relationship was found between levels of education and complications. As far as we know, this assessment has not been done in any previous study.

There are studies in the literature showing the relationship between pain and complications (25,26,27). In the study of Celebi et al. (27), it was stated that the mean pain scores were higher in the patients with complications. Similar to this study, Djavan et al. (25) stated that patients with rectal bleeding were more likely to have pain than the patients with other complications. However, in one of these studies, no anesthesia was reported, while in the other, only rectal lidocaine gel was applied. We think that there is a relationship between rectal bleeding and pain due to these anesthesia methods, which may be considered as insufficient with the current guidelines. Because, similar to our study, Hossack and Woo et al. (28), which performed periprostatic nerve blockage, did not find any relationship between bleeding and pain scores. There was no relationship between pain and infection in this study; however, there was a significant relationship between pain scores and fever in our study. The cut-off value for pain score was 46.5. Accordingly, the likelihood of fever is significantly increased in patients with pain scores above this value. However, the fact that this value was determined as a result of the evaluation of two patients with fever suggests that new studies are needed. In EAU guidelines, epididymitis was reported as 0.8% and fever as 0.7%. In our study, these rates were 1.2% and 0.6%, respectively, and they were consistent with the guideline.

Study Limitations

The limitations of our study were as follows: a) the cut-off value for high fever regarding pain score was calculated only in two patients, b) lack of assessment of comorbidities that may affect the complications of patients, c) lack of multivariant analysis because there was a relationship between pain scores and complications only, and d) low number of cases.

Conclusion

As prostate biopsies are frequently applied in urology practice, it is important to determine the risk factors for prostate biopsy-related complications. In this study, we believe that the evaluation of the level of education, digital rectal examination findings and pain related to the treatment in this study contribute to the literature, as these were previously evaluated in a limited number of studies. Again in the light of our evaluations, we believe that patients with high pain scores may form a risky group in terms of complications, especially fever. However, in order to increase the scientific value of these results, we think that new studies with larger patient population are needed.

Ethics

Ethics Committee Approval: This study was approved by the ethics committee of University of Health Sciences, Bursa Higher Specialization Training and Research Hospital (no: 2012/9/3) and all patients included in the study were informed about

TRUS guided prostate biopsy and complications.

Informed Consent: Written informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., V.Ç., M.Ş., Concept: S.A., S.Ö., V.Ç., Design: S.A., S.Ö., M.K., Data Collection or Processing: S.A., V.Ç., E.Ö., Analysis or Interpretation: S.A., E.Ö., S.Ö., Literature Search: S.A., M.Ş., M.K., Writing: S.A., S.Ö.

Conflict of Interest: No conflict of Interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-386.
2. Ehdaie B, Vertosick E, Spaliviero M, et al. The impact of repeat biopsies on infectious complications in men with prostate cancer on active surveillance. J Urol 2014;191:660-664.
3. Nam RK, Saskin R, Lee Y, et al. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. J Urol 2010;183:963-968.
4. Rietbergen J B, Kruger A E B, Kranse R, F H Schröder. Complications of transrectal ultrasound-guided systematic sextant biopsies of the prostate: evaluation of complication rates and risk factors within a population-based screening program. Urology 1997;49:875-880.
5. Lee SH, Chen SM, Ho CR, et al. Risk factors associated with transrectal ultrasound guided prostate needle biopsy in patients with prostate cancer. Chang Gung Med J 2009;32:623-627.
6. Chiang IN, Chang SJ, Pu YS, et al. Major complications and associated risk factors of transrectal ultrasound guided prostate needle biopsy: a retrospective study of 1875 cases in taiwan. J Formos Med Assoc 2007;106:929-934.
7. de Jesus CM, Corrêa LA, Padovani CR. Complications and risk factors in transrectal ultrasound-guided prostate biopsies. Sao Paulo Med J 2006;124:198-202.
8. Pinkhasov GI, Lin YK, Palmerola R, et al. Complications following prostate needle biopsy requiring hospital admission or emergency department visits–experience from 1000 consecutive cases. BJU Int 2012;110:369-374.
9. Kam SC, Choi SM, Yoon S, et al. Complications of Transrectal Ultrasound-Guided Prostate Biopsy: Impact of Prebiopsy Enema. Korean J Urol 2014;55:732-736.
10. Raaijmakers R, Kirkels W J, Roobol M J, Wildhagen M F, Schrder F H. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002;60:826-830.
11. Zaytoun OM, Anil T, Moussa AS, et al. Morbidity of prostate biopsy after simplified versus complex preparation protocols: assessment of risk factors. Urology 2011;77:910-914.
12. Rodríguez LV, Terris MK. Risks and complications of transrectal ultrasound guided prostate needle biopsy: a prospective study and review of the literature. J Urol 1998;160: 2115-2120.
13. Loeb S, van den Heuvel S, Zhu X, et al. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. Eur Urol 2012;61:1110-1114.
14. Shigemura K, Arakawa S, Nakano Y, et al. Larger prostate causes higher frequency of infectious complications in prostate biopsy. Urol Int 2006;76:321-326.
15. Simsir A, Kismali E, Mammadov R, et al. Is it possible to predict sepsis, the most serious complication in prostate biopsy?. Urol Int 2010;84:395-399.
16. Bruyère F, Malavaud S, Bertrand P, et al. Prosbiotate: a multicenter, prospective analysis of infectious complications after prostate biopsy. J Urol 2015;193:145-150.
17. Kim SJ, Kim SI, Ahn HS, et al. Risk Factors for Acute Prostatitis after Transrectal Biopsy of the Prostate. Korean J Urol 2010;51:426-430.
18. Namekawa T, Fukasawa S, Komaru A, et al. Prospective evaluation of the safety of transrectal ultrasound-guided transperineal prostate biopsy based on adverse events. Int J Clin Oncol 2015;20:1185-1191.
19. Borghesi M, Ahmed H, Nam R, et al. Complications After Systematic, Random, and Image-guided Prostate Biopsy. Eur Urol 2017;71:353-365.
20. Obek C, Onal B, Ozkan B, et al. Is periprostatic local anesthesia for transrectal ultrasound guided prostate biopsy associated with increased infectious or hemorrhagic complications? A prospective randomized trial. J Urol 2002;168:558-561.
21. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. Eur Urol 2013;64:876-892.
22. Norberg M, Holmberg L, Häggman M, Magnusson A. Determinants of complications after multiple transrectal core biopsies of the prostate. Eur Radiol 1996;6:457-461.
23. Aus G, Ahlgren G, Bergdahl S, Hugosson J. Infection after transrectal core biopsies of the prostate. Br J Urol 1996;77:851-855.
24. Berger AP, Gozzi C, Steiner H, et al. Complication rate of transrectal ultrasound guided prostate biopsy: a comparison among 3 protocols with 6, 10 and 15 cores. J Urol 2004;171:1478-1481.
25. Djavan BOB, Waldert M, Zlotta A, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. J Urol 2001;166:856-860.
26. Roberts RO, Bergstralh EJ, Besse JA, et al. Trends and risk factors for prostate biopsy complications in the pre-PSA and PSA eras, 1980 to 1997. Urology 2002;59:79-84.
27. Celebi I, Irer B, Kefi A, et al. Relationship between complications due to prostate biopsy and the scores of pain and discomfort. Urol Int 2004;72:303-307.
28. Hossack T, Woo H H. Acceptance of repeat transrectal ultrasonography guided prostate biopsies with local anaesthesia. BJU Int 2011;107:38-42.