Does the Existence of Prostate Cancer Increase the Risk of Bleeding as a Complication of Transrectal Ultrasonography Guided Prostate Needle Biopsies?

Transrektal Ultrason Eşliğinde Yapılan Prostat İğne Biyopsileri, Prostat Kanseri Varlığında, Bir Komplikasyon Olarak Kanama Riskini Arttırır mı?

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ABSTRACT Objective: Prostate biopsy can be considered as a minimal invasive procedure and it is performed easily and frequently. However, prostate biopsy can also cause some morbid and mortal complications. With this article we aimed to evaluate wheather the prostate cancer cause an increase in bleeding ratio after prostate biopsy. **Material and Methods:** We evaluated 466 (including also re-biopsies) patients who underwent transrectal prostate biopsy between January 2008 and December 2010. We preferred 12 core samplings for all patients. Patients were divided into three groups. Group I: patients whose pathology was benign prostate hyperplasia; group II: patients whose pathology was adenocarcinoma with <7 Gleason score; group III: patients whose pathology was adenocarcinoma with ≥7 Gleason score. The existence of hematochezia, hematospermia and hematuria were evaluated in all patients. We analysed the relationship between pathology results and bleeding rates. **Results:** Median PSA values were 6.9; 8.4; 16.8 ng/ml for the group I, II and III, respectively. The difference of PSA level was statistically significant between all groups ($p<0.05$). Hematochezia rates were seen in 53 (16.8%), 34 (36.2%) and 40 (70.2%) patients; hematospermia rates were seen in 22 (7.9%), 19 (22.6%) and 20 (43.5%) patients; hematuria rates were seen in 78 (24.8%), 45 (47.9%) and 42 (73.7%) patients in groups respectively. We found that bleeding complications were seen more commonly in prostate cancer patients. It was also associated with high Gleason score. **Conclusion:** Prostate cancer patients, especially with higher Gleason scores have a greater risk for bleeding complications after biopsy according the patients with benign prostate hyperplasia.

Key Words: Prostatic neoplasms; hemorrhage

ÖZET Amaç: Minimal invaziv bir prosedür olan prostat biyopsisi, kolaylıkla uygulanabilmekte ve yaygın olarak yapılmaktadır. Ancak prostat biyopsisi bazı morbid ya da mortal komplikasyonlarla sonuçlanabilmektedir. Bu çalışma ile prostatdaki kanserli dokunun, prostat biyopsi sonrası kanamayı arttırıp arttırmadığını değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Ocak 2008- Aralık 2010 tarihleri arasında Transrektal prostat biyopsi yapılan 466 hasta (re-biyopsiler dahil) değerlendirilmiştir. Tüm hastalardan 12 kor biyopsi örneklemesi yapıldı. Hastalar grup I: prostat biyopsi patolojisi Benign Prostat Hiperplazi olanlar; grup II: Gleason skor <7 adenokarsinoma olanlar; grup III ise Gleason skor ≥7 adenokarsinoma olanlar olmak üzere 3 gruba ayrılmıştır. Hematokezya, hematospermi ve hematüri varlığı değerlendirilmiştir. Patoloji sonuçları ile kanama oranları arasındaki ilişki irdelenmiştir. **Bulgular:** Ortanca PSA değerleri Grup I, II ve III için sırasıyla 6.9; 8.4; 16,8 ng/ml olarak hesaplandı ve gruplar arasındaki bu farklılık istatistiksel olarak anlamlı bulundu ($p<0,05$). Grup I,II ve III için hematokezya oranları sırasıyla 53 (%16,8), 34 (%36,2) ve 40 (%70,2); hematospermi oranları 22 (%7,9), 19 (%22,6) ve 20 (%43,5); hematüri oranları ise 78 (%24,8), 45 (%47,9) ve 42 (%73,7) olarak bulunmuştur. Kanama komplikasyonlarının prostat kanserli hastalarda daha sık görüldüğü ve bu durumun özellikle yüksek Gleason skoru ile ilişkili olduğu görülmüştür. **Sonuç:** Prostat kanserli hastalar, özellikle yüksek Gleason skoruna sahip olanlar, benign prostat hiperplazili hastalara nazaran biyopsi sonrasında daha yüksek kanama riskine sahiptirler.

Anahtar Kelimeler: Prostat tümörleri; kanama

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Prostate cancer is the most common malignancy and the second leading cause of cancer deaths in men.[1] A final diagnosis of prostate cancer is obtained via the histopathological examination of prostate tissues. Therefore a transrectal ultrasonography (TRUS) guided prostate biopsy is the standard method used for the diagnosis of prostate cancer. So this method which can be considered as a minimal invasive procedure is performed easily and frequently by urologists.

TRUS guided prostate biopsy can also cause some morbid and mortal complications that have been extensively described in previous studies.[2,3] Urosepsis that can cause death and severe rectal bleeding are some of major complications. Even though these are extremely rare occurrences (0% versus 0.1% respectively), they still require intervention.[3,4] According to the results of a European Cancer Detection Study, minor complications such as (mild hematuria, recurrent mild hematuria, severe hematuria, rectal bleeding, vasovagal episodes, fever, hematospermia, persistent dysuria and urinary tract infection) were reported at a rate of 92% at the first biopsy and 89% at the re-biopsy.[3] Minor complications such as hematuria, rectal bleeding, hematospermia are generally self-limiting and are seen in 20% to 70% of patients.[5]

It is generally expected that angiogenesis or neovascularization occurs at an increased rate in cancer tissues. Therefore, angiogenesis inhibitors are also on the agenda for the treatment of prostate cancer.[6,7] Recent studies have shown that it is possible to determine malignancy of prostate tissue by a transrectal doppler ultrasonography examination with high sensitivity.[8,9] However, no study exists to verify this hypothesis. In this study, we aimed to evaluate whether prostate cancer can cause an increase in the bleeding rate after prostate biopsies in clinical practice.

To the best of our knowledge, this is also the first research that explores the relationship between the bleeding rates in benign and malignant tissues of the prostate after a biopsy.

MATERIAL AND METHODS

Between January 2008 and December 2010, 512 TRUS-guided prostate needle biopsies were performed, with 20 of these being re-biopsies. Prostate biopsy indications were increased prostate specific antigen (PSA) (>2.5 ng/ml) and/or abnormal findings discovered on the digital rectal examination.

All patients were asked not to use anti-inflammatory drugs, antithrombolytic treatments or antiaggregant agents such as aspirin, for at least one week before the procedure. Oral ciprofloxacin was provided as antibiotic therapy at 500 mg twice a day. Patients were instructed to start taking the antibiotic the day before the procedure and continue for 1 week. In addition, they were given a rectal cleansing enema on the morning of the biopsy. Written informed consent providing information regarding possible complications was obtained from each patient before the procedure.

All patients were examined in the left lateral decubitus position. A digital rectal examination was performed just before the procedure, which also seemed to help the sphincter to relax.

Before the biopsy, 2 ml of lidocaine (2%) or prilocaine (2%) for each prostate lobe was injected into the periprostatic area, especially around the neurovascular bundle with a 20 gauge injection needle. A very effective analgesia was obtained using this procedure. Prostate volume was then calculated for each patient. Hypoechoic areas were detected but no additional biopsies were performed.

All biopsies were performed transrectally by using a rectal ultrasound probe and 18 gauge biopsy needle. Disposable needle guides were used with 362 patients, and re-usable needle guides were used with the others. Biopsy specimens were labeled separately and kept in 10% dilute formol.

Regarding the biopsy technique, our preference was to take 12 core samplings with six cores from each prostate lobes. Eight patients who had undergone saturation biopsies were excluded. Six patients who had used heparin or coumadin before, during, or after the biopsy were also excluded since these drugs would most likely have affected the results.

All of the patients were informed to come for control medical examination with their biopsy results within two weeks after the procedure. They were assessed 7 to 14 days after the procedure. The same physician who performed the biopsy also informed the patients regarding any complications, including those that needed emergency intervention. Those patients for whom prostate cancer was detected were referred to our uro-oncology clinic for an evaluation to determine their clinical stage of cancer.

The patients were divided into three groups according to their pathology results. Group I was composed of patients with benign prostatic hyperplasia (BPH). Group II featured those with adenocarcinoma and a Gleason score of <7 while group III was comprised of patients with adenocarcinoma and a Gleason score of ≥7. All patients were evaluated for the presence of hematochezia, hematospermia, and hematuria. There were also patients with prostatitis in all groups. The relationship between the malignant tissue of the prostate and bleeding resulting from complications due to transrectal prostate biopsies was investigated in this study.

The outcomes were analyzed with using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 15.0 for Windows program. The Kruskal-Wallis H test, corrected by the Bonferroni method, was used to determine the results of the normality test.

The differences between the groups were analyzed, and a value of $p<0.05$ was considered to be statistically significant.

The relationships between variables were also analyzed with the x2 test, and a value of $p<0.05$ denoted a relationship between variables.

RESULTS

There were 315 patients in group I, 94 in group II, and 57 in group III. The groups were compared with regard to age, prostate volume, mean and median PSA levels, and biopsy pathology results.

Two of the patients were lost to follow-up after the procedure. Three patients were excluded from the study because dementia precluded them from providing reliable information. Twenty-seven patients were not sure about the existence of bleeding after the biopsy, so they were also excluded, In addition, six patients using coumadin or heparin, and eight patients who had previously undergone saturation biopsies were not included in the study.

The mean ages were 65.70 years (42-85) for group I, 70.35 years (52-85) for group II, and 70.32 years (50-82) for group III. The mean age level was lower than the other groups in group I ($p<0,05$). The mean prostate volumes were 45.24 cc (14-154) for group I, 41.13 cc (15-90) for group II, and 39.73 cc (16-78) for group III, and the difference was not statistically significant between the groups ($p>0.05$). Group I had mean total PSA values of 10.93 ng/nl (0.39-150) and median PSA values of 6.9 ng/ml. The mean total PSA values for group II were 31.89 ng/ml (4.45-300), and the median PSA values were 8.4 ng/ml. Finally, group III had mean total PSA values of 35.43 ng/ml (5.56-150) and median PSA values of 16.8 ng/ml. The differences in the PSA levels were statistically significant between all groups ($p<0.05$) (Table 1).

There were 53 cases of hematochezia (16.8%) in group I, 34 (36.2%) in group II, and 40 (70.2%) in group III. Twenty-two cases of hematospermia (7.9%) were reported in group I, 19 (22.6%) in group II, and 20 (43.5%) in group III. Additionally, 78 patients had hematuria (24.8%) in group I, with 45 recorded cases (47.9%) in group II and 42 (73.7%) in group III (Figure 1). Due to an inability to ejaculate, 38 patients in group I, 10 in group II,

TABLE 1: Patient characteristics.

Characteristics	Group I (n:315)	Group II (n: 94)	Group III (n: 57)	Chi-square test
Age (yr)				
Mean	65.70	70.35	70.32	
Range	42-85	52-85	50-82	p<0,05
Prostate volume (cc3)				
Mean	45.24	41.13	39.73	
Range	14-154	15-90	16-78	p>0.05
Serum PSA level (ng/ml)				
Mean	10.93	31.89	35.43	
Median	6.9	8.4	16.8	p<0,05
Range	0.39-150	4.45-300	5.56-150	

and 11 in group III could not be evaluated for hematospermia.

Statistically significant differences were found concerning the rates of hematuria, hematochezia and hematospermia ($p<0.05$ between group I and II, I and III, II and III). While all bleeding complications were significantly higher in group III, they were lower in group I (Figure 1).

The self-limited bleeding lasted from one to 14 days. None of the groups reported prolonged bleeding nor did they require intervention.

DISCUSSION

Bleeding is the most frequent complication seen in prostate biopsies. In a study published by Berger et al, the hematospermia rate was 36.3%, followed by hematuria at 14.5% and rectal bleeding without intervention at 2.3%.[10] As previously stated, the results of a European cancer detection study yielded at 92% rate of minor complications at the first biopsy and an 89% rate at the re-biopsy. Mild hematuria occurred at a rate of 62% in the first biopsy but at the slightly lower rate of 57% in the re-biopsy. The rectal bleeding rates were similar with a 2.1% rate at the first biopsy versus a 2.4% rate at the re-biopsy. The rates for severe hematuria were nearly identical with rates of 0.7% and 0.5% at the first biopsy and re-biopsy, respectively. A bigger difference occurred in the vasovagal episodes with the first biopsy having a rate of 2.8% and the re-biopsy reporting a rate of 1.4%. The percentage of patients suffering from fever was slightly higher at the first biopsy with a rate of 2.9% versus

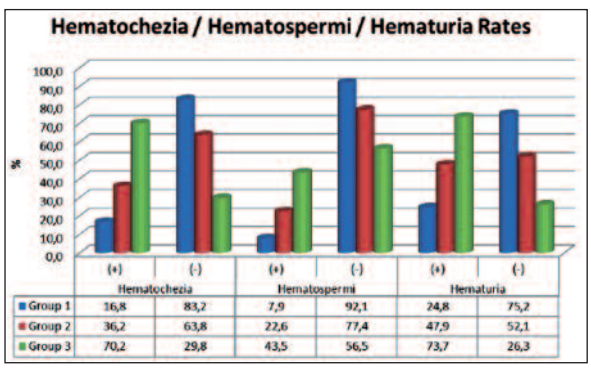

FIGURE 1: Hematochezia, hematospermia and hemauria rates.
(See for colored form http://uroloji.turkiyeklinikleri.com/)

2.3% at the re-biopsy. However, a 9.8% rate was seen for hematospermia at the first biopsy, with a minimally higher rate of 10.2% for patients at the re-biopsy. The recurrent mild hematuria rate was 15.9% for the first biopsy and 16.6% for the re-biopsy. Persistent dysuria was slightly higher in patients at the first biopsy with a rate of 7.2% versus 6.8% at the re-biopsy. Finally, the urinary tract infection was 10.9% at the first biopsy and 11.3% at the re-biopsy.[3] In our study, the rates for hematochezia, hematospermia, and hematuria were 27.3%, 15%, and 35.4% respectively for all patients. In 2006, de Jesus et al. reported a cohort of 177 men who underwent TRUS-guided prostate biopsies and noted an overall major complication rate of 2.9% and a hospitalization rate of 2.3%. The sepsis, gross hematuria, and urinary retention rates were relatively low at 1.7%, 0.6% and 0.6%, respectively.[11] In our study, we chose to focus on the incidence of bleeding complications after TRUS-guided prostate biopsies.

Angiogenesis is vital for the continued tumor growth of solid tumors. It is also needed to gain access to the vasculature with metastasis occurring soon afterwards. Thus, angiogenesis has a necessary biological correlation with malignancy. Solid tumors cannot enlarge beyond 1 to 2 mm in diameter unless they are vascularized. The vessels of tumors are leaky, dilated, and have a haphazard pattern of connection.[12] Mucci et al. investigated the microvessel densities and morphological measurements of angiogenesis as it related to tumor characteristics and lethal prostate cancer among 572 men treated via a prostatectomy. They found that vascular size and irregularity can potentially lead to prostate cancer. Poorly differentiated tumors are characterized by greater microvessel density, smaller vessels, and irregularity of the vessel lumen.[13] Also, their data on vessel morphology and architecture further supports the connection between angiogenesis and prostate cancer progression. It also reinforces the hypothesis that disease progression is marked by a rapid formation of neovasculature in tumors that are smaller and poorly formed.

In a study of 120 patients, it was discovered that sextant biopsies in conjunction with color doppler

imaging are more sensitive than sextant biopsies alone.[14] In an other study, while the increased flow signal on color or power doppler sonography was considered to be a sign of prostate cancer, these modalities had a sensitivity of 82.6%, a specificity of 76.5%, and a positive predictive value of 82.6%. The author of that particular study concluded that color and power doppler ultrasonography are useful in the identification of diffuse prostatic lesions.[15]

In another study, Nelson et al. showed that 40% of patients with prostate cancer had no abnormalities on ultrasonography but hypervascular areas carry twice as much of a risk of malignancy as normal tissue. Hypervascularity on color doppler ultrasonography is especially associated with lesions that have a high Gleason score of between 8 and 10.[16]

As we have noted, studies exist which have evaluated the increased vascularization of prostate cancer, but we could find no other studies which investigated the clinical findings concerning adenocarcinoma and bleeding. In our study, we demonstrated that prostate tissue with adenocarcinoma is more prone to bleeding. We believe this is related to increased angiogenesis and leaky vessels. We also showed that the bleeding rate significantly increases with higher Gleason scores (≥7), and the risk of bleeding is also associated with the same scores.

We acknowledge several limitations within this study. The most important one is that the study is retrospective in nature. In patients with prostatitis, angiogenesis might be increased, therefore increased bleeding might occur in these patients. An other limitation of this study is the presence of patients with prostatitis in all groups. Therefore, our findings must be confirmed by further prospective randomized studies. Despite these shortcomings, this is an important study since there is no previous data in the literature about this topic.

CONCLUSION

In this study hematochezia, hematospermia, and hematuria were more frequent in patients with prostate cancer than in patients without cancer. The present results demonstrate that a connection exists between prostate needle biopsies and high complication rates associated with bleeding in malignant tissues, especially tissues with high Gleason scores. Thus, we suggest that more detailed information should be given to patients with prostate cancer, and they should be followed up closely after the procedure. This especially applies to those patients suspected of having advanced stages of prostate cancer as identified by clinical and laboratory findings.

REFERENCES

1. Doyle-Lindrud S. Prostate cancer: a chronic illness. Clin J Oncol Nurs 2007;11(6):857-61.
2. Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002;60(5):826-30.
3. Djavan B, Waldert M, Zlotta A, Dobronski P, Seitz C, Remzi M, 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(3):856-60.
4. Carlson WH, Bell DG, Lawen JG, Rendon RA. Multidrug resistant E.coli urosepsis in physicians following transrectal ultrasound guided prostate biopsies--three cases including one death. Can J Urol 2010;17(2):5135-7.
5. Giannarini G, Mogorovich A, Valent F, Morelli G, De Maria M, Manassero F, et al. Continuing or discontinuing low-dose aspirin before transrectal prostate biopsy: results of a prospective randomized trial. Urology 2007;70(3):501-5.
6. Kluetz PG, Figg WD, Dahut WL. Angiogenesis inhibitors in the treatment of prostate cancer. Expert Opin Pharmacother 2010;11(2):233-47.
7. Aragon-Ching JB, Dahut WL. The role of angiogenesis inhibitors in prostate cancer. Cancer J 2008;14(1):20-5.
8. Nelson ED, Slotoroff CB, Gomella LG, Halpern EJ. Targeted biopsy of the prostate: the impact of color Doppler imaging and elastography on prostate cancer detection and Gleason score. Urology 2007; 70(6):1136-40.
9. Günay LM, Özen H. [The effect of advances in the image techniques used for prostate biopsy for the results of prostate biopsy]. Üroonkoloji Bülteni 2010; 9(4):38-41.
10. Berger AP, Gozzi C, Steiner H, Frauscher F, Varkarakis J, Rogatsch 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(4):1478-80; discussion 1480-1.
11. de Jesus CM, Corrêa LA, Padovani CR. Complications and risk factors in transrectal ultrasound-guided prostate biopsies. Sao Paulo Med J 2006;124(4): 198-202.
12. Kumar V, Abbas AK, Fausto N, Aster JC. Angiogenesis. Robbins and Cotran Pathologic Basis of Disease. 8th ed. Milano: Elsevier; 2010. p.297-8.
13. Mucci LA, Powolny A, Giovannucci E, Liao Z, Kenfield SA, Shen R, et al. Prospective study of prostate tumor angiogenesis and cancer-specific mortality in the health professionals follow-up study. J Clin Oncol 2009;27(33):5627-33.
14. Kravchick S, Cytron S, Peled R, London D, Sibi Y, Ben-Dor D. Optimal combinations for detection of prostate cancer: systematic sextant and laterally directed biopsies versus systematic sextant and color Doppler-targeted biopsies. Urology 2004;63(2):301-5.
15. Cho JY, Kim SH, Lee SE. Diffuse prostatic lesions: role of color Doppler and power Doppler ultrasonography. J Ultrasound Med 1998;17(5):283-7.
16. Nelson ED, Slotoroff CB, Gomella LG, Halpern EJ. Targeted biopsy of the prostate: the impact of color Doppler imaging and elastography on prostate cancer detection and Gleason score. Urology 2007;70(6):1136-40.