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Is Prostate Biopsy Recommended in Turkish Men with a Prostate-Specific Antigen Level between 2.5 and 4 ng/mL?

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ABSTRACT

Background: Prostate cancer is the most common solid tumor. The incidence of prostate cancer shows regional and racial differences. The ideal PSA threshold for prostate biopsy is still being debated.
Objective: We aimed to investigate cancer detection rates in Turkish men who underwent transrectal ultrasound-guided prostate biopsy (TRUSPB) who had prostate-specific antigen (PSA) levels in the range of 2.5 to 4.0 ng/mL and compare them with the rates of cancer in patients with PSA levels in the range of 4.0 to 10.0 ng/mL.
Methods: All Turkish men who underwent TRUSPB in our clinic between January 2012 and May 2014 were included; that is, 101 patients (Group 1) with PSA level in the range of 2.5 to 4.0 ng/mL and 522 patients (Group 2) with PSA level in the range of 4.0 to 10.0 ng/mL. Mean PSA level, age, prostate volume, and cancer detection rates were evaluated.
Results: The mean age was 60.5 and 64 years in Group 1 and Group 2, respectively ($P = 0.06$). The mean PSA level was determined as 3.1 and 6.8 ng/mL in Group 1 and Group 2, respectively ($P = 0.03$). The cancer detection rate was 12.7% in Group 1 (n = 13) and 30.8% in Group 2 (n = 161), which revealed a statistically significant difference between the 2 groups ($P = 0.001$). In Group 1, 9 of 13 patients (69%) had Gleason score of 6, 3 (23%) had Gleason score of 7, and 1 (8%) had a Gleason score of 8.
Conclusions: The cancer detection rate is lower in Turkish men with PSA level in the range of 2.5 to 4.0 ng/mL when compared with men with PSA level in the range of 4.0 to 10.0 ng/mL. Furthermore, most patients in whom cancer was detected who have a PSA level in the range of 2.5 to 4.0 ng/mL are low risk. Therefore, the benefit of TRUSBP in Turkish men with PSA level between 2.5 and 4 ng/mL is low.

Introduction

Prostate cancer (PCa) is the most common solid tumor in Europe, with an incidence of 214 out of 100,000, and ranks second in cancer deaths.[1] In the United States in 2014, there were expected to be about 233,000 new PCa diagnoses and about 29,400 PCa deaths.[2] According to data from the Ministry of Health of the Republic of Turkey [3] and the results of a study,[4] incidence rate of PCa was 35 to 37.6 out of 100,000, and it was the second most common cancer in men.

The use of prostate-specific antigen (PSA) as a tumor marker was a substantial development in the diagnosis of PCa.[5] Currently, clinical stage T1c constitutes 40% to 50% of newly diagnosed prostate cancers and this shows the importance of PSA in the diagnosis of PCa.[6] To date, no specific lower PSA cutoff value has been indicated in the relevant guidelines for PCa diagnosis. The National Comprehensive Cancer Network[7] suggests biopsy for patients with PSA ≥ 2.6 ng/mL. An Italian panel group[8] suggests to perform a biopsy for patients with PSA ≥ 2.5 ng/mL if they report a family history of PCa. However, if patients have no family history of PCa, their recommended PSA threshold for prostate biopsy is > 4.0 ng/mL. The ideal PSA threshold for prostate biopsy is still being debated. However, there is a tendency to perform biopsy for lower PSA levels during the past few years.

Prostate cancer incidence shows regional and racial differences. Furthermore, lowering the PSA threshold may lead to

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overdiagnosis, increased rate of prostate biopsy, side effects due to biopsies and treatments, and costs. Thus, we think each country or region should set their lower PSA cutoff values while making the decision for biopsy. In this study, we aimed to determine the cancer detection rate in Turkish men with a PSA level in the range of 2.5 to 4.0 ng/mL and who underwent transrectal ultrasound-guided prostate biopsy (TRUSPB), and also to compare, with regard to cancer detection rate, the patients with PSA level in the range of 4.0 to 10.0 ng/mL.

Materials and Methods

We enrolled a total of 623 patients in the study, aged between 40 and 70 years with PSA level 2.5 to 10 ng/mL and whom TRUSPB was performed between January 2012 and May 2014 in our clinic. Patients were divided into 2 groups with respect to their PSA levels. One hundred one patients with PSA values in the range of 2.5 to 4.0 ng/mL constituted Group 1 and 522 patients with PSA values in the range of 4.0 to 10.0 ng/mL constituted Group 2. Patients who had abnormal findings from digital rectal examination, urinary tract infections, recent urethral catheterization, cystoscopy, history of transurethral resection, and previous TRUSBP history were excluded from the study. At least 2 PSA measurements were performed on all patients before biopsy.

Prophylactic ciprofloxacin was administered on all patients before biopsy. An ultrasound-guided biopsy was performed transrectally under periprostatic nerve block by using an 18-G needle and biopsy was performed in 12 quadrants in all patients. Prostate volume of the patients was also calculated during the process. The mean PSA level, age, prostate volume, and PCa detection rate were compared between the 2 groups.

Statistical analyses were performed with SPSS version 22.0 for Windows (IBM-SPSS Inc, Armonk, New York). Numerical variables were summarized with mean (SD) and categorical variables with frequency and percentage. The significance of differences among groups was assessed by Student t test and logistic regression analysis, and analysis of categorical variables was examined by χ^2 test and logistic regression analysis. A P value < 0.05 was considered statistically significant.

Results

Group 1 had 101 patients and Group 2 had 522 patients. The mean age was 60.5 years (range, 50–68 years) in Group 1, whereas 64 years (range, 50–70 years) in Group 2 ($P = 0.06$). The mean PSA level was found to be 3.1 and 6.8 ng/mL in Group 1 and Group 2, respectively ($P = 0.03$). The mean prostate volume was 42.9 mL in Group1 and 44.5 mL in Group 2 ($P = 0.18$), which showed no statistically significant difference (Table I).

Prostate cancer was detected in 12.7% of patients (n = 13) in Group 1, and in 30.8% of patients (n = 161) in Group 2. There was a statistically significant difference between the 2 groups (odds ratio, 2.5; 95% CI, 1.407–4.482; $P = 0.001$) (Table I). PSA levels ≥ 4 ng/mL are associated with 2.5-fold increased risk of PCa. Of Group 1 patients diagnosed with PCa, it was found that 9 of 13 patients (69%) had Gleason score of 6 (3 + 3), 3 (23%) had Gleason score of 7 (3 + 4), and 1 (8%) had Gleason score of 8 (4 + 4). In other words, low-risk PCa was identified in 69% of patients and intermediate and high-risk PCa was identified in 31% of patients. The treatment protocols of the patients are summarized in Table II.

Table I
Distribution of patient data according to groups.*

Characteristic	Group 1	Group 2	P value
Age, y	60.5 (48-72)	64 (48-82)	0.06
prostate-specific antigen, ng/dL	3.1 (0.5)	6.8 (1.5)	0.03†
Prostate volume, mL	42.9 (13.1)	44.5 (21.1)	0.18
Cancer ratio, %	12.7	30.8	0.001†

* Values for age are presented as median (range), whereas values for prostate-specific antigen and prostate volume are presented as mean (SD).
† Statistically significant.

Table II
Analysis of treatment in prostate cancer patients in whom prostate-specific antigen level is between 2.5 and 4 ng/mL.

Patient No.	Age, y	Gleason score	Treatment
1	62	3 + 3	Active surveillance
2	64	3 + 3	Active surveillance
3	63	3 + 3	Active surveillance
4	66	3 + 3	Active surveillance
5	63	3 + 3	Active surveillance
6	67	3 + 3	Radical prostatectomy
7	65	3 + 3	Radical prostatectomy
8	66	3 + 3	Radical prostatectomy
9	56	3 + 3	Radical prostatectomy
10	65	3 + 4	Radical prostatectomy
11	64	3 + 4	Radiotherapy
12	64	3 + 4	Radiotherapy + hormone therapy
13	68	4 + 4	Radiotherapy + hormone therapy

Discussion

PSA is a glycoprotein produced in the epithelial cells of the prostate and secreted into prostatic fluid.[9] The use of PSA as a tumor marker has been a significant improvement in the diagnosis of PCa.[5] Today, 40% to 50% of newly diagnosed PCas are clinical stage T1c and this shows the importance of PSA level in the diagnosis of PCa.[6]

PCa is a slowly progressing tumor. Although some studies have reported that PSA screening decreased mortality rates due to prostate cancer, no definite evidence is yet available showing that screening could reduce PCa-related deaths.[10] However, reducing the cutoff of PSA below 4 ng/mL has led to increases in detection rates of clinically insignificant cancers.[11] A publication by Johansson et al [12] on PCa patients with no treatment outcomes between 1989 and 2004 and the publications by Albertsen et al[13,14] that include long-term results of a risk analysis of patients diagnosed with localized PCa between 1971 and 1984, have increased our knowledge about disease progression. PCa patients with Gleason score of 6 or lower have 70% to 96% progression-free survival rate, whereas cancer-related deaths are expected at a rate of 42% to 87% within 10 years of diagnosis in patients with a Gleason score $\geq$ 7.[15] Chisholm et al [16] claimed that they could not predict whether or not detecting early-stage tumors would increase cancer-specific survival without performing a randomized controlled screening study, regardless of whether a radical intervention was performed. Gilbert et al[17] evaluated the results of 36,316 TRUSBP procedures. They found that PCa detection rate was 27.4% in patients with PSA level of 2.5 to 4.0 ng/mL, and 30% in patients with PSA level of 4.0 to 10.0 ng/mL. They concluded that there was no statistical difference between the 2 groups in terms of PCa detection rate. In the Prostate Cancer Prevention Trial study,[18] TRUSBP was performed to 2950 patients with PSA levels ≤ 4 ng/mL and with normal findings from digital rectal exam. As a result, PCa was detected in 15.2% of men with PSA ≤ 4 ng/mL. Rate of PCa diagnosis increased to 26.9% in the group with PSA levels between 3.1 to 4.0 ng/mL.

Furthermore, PCa was detected in 6.6% and 10.1%, among men with PSA $\leq$0.5 ng/mL and between 0.6 and 1.0 ng/mL, respectively. It can be eventually claimed that there is no lower cutoff of PSA for detecting PCa, but as PSA increased, PCa detection rate— particularly high-grade PCa rate—showed an increase.[18]

A significant increase was observed in detection rates of low-grade and clinically insignificant PCa with an increase in PCa screening studies. Hence, active surveillance is becoming widespread in recent years for monitoring low-risk PCa. Data analysis of the Randomized European Study [19] for PCa screening showed that 30% of patients with PCa underwent active surveillance after a median follow-up of 40 months. In a Johns Hopkins study,[20] disease progression was reported in the control biopsy in 31% of patients after a median follow-up of 23 months. As a result, curative treatment must be given within 3 years to approximately 25% to 30% of patients undergoing an active surveillance protocol. Active surveillance studies in the literature generally reveal a success rate in PCa-specific survival of 97% to 100% despite relatively shorter active follow-up periods. Another study demonstrated that PCa-related mortality rate at an average 10-year follow-up was low (3.4%) in the low-risk group and radical prostatectomy had no advantage over watchful waiting.[21] This study shows that the survival rate in the low-risk group was not different in the active treatment arm when compared with a watchful waiting approach.

In a study examining the psychological state of patients diagnosed with PCa, those who were given curative therapy and those who were followed-up with an active surveillance program were analyzed. Overall, anxiety was determined in 16% of patients and depression in 6%. Anxiety and depression were significantly correlated with younger age and longer period after the diagnosis, but not correlated with active surveillance.[22,23]

Additionally, TRUSBP can lead to complications such as hematuria, hematospermia, rectal bleeding, prostatitis, epididymitis, sepsis, and urinary retention.[24–26] Therefore, each TRUSBP constitutes a risk in terms of complications. Some blood-based and urinary biomarkers such as the Prostate-Health Index, prostate cancer antigen 3, TMPRESS2 (transmembrane protease, serine 2)-ERG, ExoDx™ Prostate (IntelliScore), SelectMDx (MDxHealth), and circulating tumor cells have been suggested to decrease unnecessary prostate biopsies and overcome biopsy complications.[27,28]

In our study, PCa detection rate was found to be 12.7% in Group 1 and 69% were at low risk. In addition, only 1 patient with PCa was younger than age 60 years, whereas others were older than age 60 years. Our lower detection rates of cancer compared with other studies in the literature may be due to race-related factors and also to the small number of patients. Sample size is the most important limitation of our study. Also, it is a retrospective study with an inherent potential for bias.

Adverse psychological effects of PCa diagnosis, satisfactory results of active surveillance, complications of TRUSBP, and slow progression rate of PCa should be kept in mind while screening for PCa. Therefore, benefit and loss ratios related to cancer detection should be considered when deciding to order TRUSBP.

Conclusions

PCa is a slowly progressing tumor. Detecting the tumors that will remain clinically silent throughout a patient's life and that will not adversely affect quality of life is not the primary goal because the main objective of screening is to reduce cancer-related deaths. The cancer detection rate is lower in Turkish men with PSA in the range of 2.5 to 4.0 ng/mL when compared with men with PSA in the range of 4.0 to 10.0 ng/mL. Furthermore, most patients in whom cancer was detected who had a PSA in the range of 2.5 to 4.0 ng/mL are low risk. The benefit of TRUSBP in Turkish men with PSA level between 2.5 and 4 ng/mL is low.

Acknowledgments

All authors contributed equally.

Conflicts of Interest

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics. *CA Cancer J Clin.* 2008;58(2):71–96.
2. Siegel R, Ma J, Zou Z, Jemal AC. *A Cancer J Clin.* 2014;64(1):9–29.
3. Türkiye Cumhuriyeti Sağlık Bakanlığı: Sağlık İstatistikleri Yıllığı 2010. http://sbu.saglik.gov.tr/Ekutuphane/kitaplar/ saglikistatistikleriyilligi2010.pdf.
4. Zorlu F, Divrik RT, Eser S, Yorukoglu K. Prostate cancer incidence in Turkey: An epidemiological study. *Asian Pac J Cancer Prev.* 2014;15(21):9125–30.
5. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med.* 1987;317(15):909–16.
6. Klotz L. Active surveillance for prostate cancer: trials and tribulations. *World J Urol.* 2008;26(5):437–42.
7. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines(r)): Prostate Cancer Early Detection. Version 1.2012. 2012 [May 1, 2012]; Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
8. Bertaccini A, Fandella A, Prayer-Galetti T, Scattoni V, Galosi AB, Ficarra V, et al. Systematic development of clinical practice guidelines for prostate biopsies: a 3-year Italian project. *Anticancer Res.* 2007;27(1B):659–66.
9. Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men: Establishment of age-specific reference ranges. *JAMA.* 1993;270(7):860–4.
10. Rahal AK, Badgett RG, Hoffman RM. Screening Coverage Needed to Reduce Mortality from Prostate Cancer: A Living Systematic Review. *PLoS One.* 2016;11(4):e0153417.
11. Murphy Am, McKiernan JM, Olsson CA. Contraversies in prostate cancer screening. *J Urol.* 2004;172:1822–4.
12. Johansson JE, Adami HO, Andersson SO, Bergström R, Krusemo UB, Kraaz W. Natural history of localised prostatic cancer. A population-based study in 223 untreated patients. *Lancet.* 1989;1(8642):799–803.
13. Bill-Axelson A, Holmberg L, Ruutu M, Häggman M, Andersson SO, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med.* 2005;352(19):1977–84.
14. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. Long-term survival among men with conservatively treated localized prostate cancer. *JAMA.* 1995;274(8):626–31.
15. Albertsen PC. When is active surveillance the appropriate treatment for prostate cancer? *Acta Oncol.* 2011;50:120–6.
16. Chisholm GD. Prostate cancer screening: accepting the consequences of PSA testing. *Br J Urol.* 1993;71(4):375–7.
17. Gilbert SM, Cavallo CB, Kahane H, Lowe FC. Evidence suggesting PSA cutpoint of 2,5 ng/ mL for prompting prostate biopsy: review of 36,316 biopsies. *Urology.* 2005;65(3):549–53.
18. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate specific antigen level $<$ 4.0 ng per milliliter. *N Engl J Med.* 2004;350(22):2239–46.
19. Roemeling S, Roobol MI, de Vries SH, Wolters T, Gosselaar C, van Leenders GJ, et al. Active surveillance for prostate cancers detected in 3 subsequent rounds of a screening trial: characteristics, PSA doubling times, and outcome. *Eur Urol.* 2007;51(5):1244–50.
20. Tosoian JJ, Mamawala M, Epstein JI, Landis P, Wolf S, Trock BJ, et al. Intermediate and Longer-Term Outcomes From a Prospective Active-Surveillance Program for Favorable-Risk Prostate Cancer. *J Clin Oncol.* 2015;33(30):3379–85.
21. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. *N Engl J Med.* 2011;364:1708–17.
22. Tosoian JJ, Carter HB, Lepor A, Loeb S. Active surveillance for prostate cancer: current evidence and contemporary state of practice. *Nat Rev Urol.* 2016;13(4):205–15.
23. Bellardita L, Valdagni R, van den Bergh R, Randsdorp H, Repetto C, Venderbos LD, et al. How does active surveillance for prostate cancer affect quality of life? A systematic review. *Eur Urol.* 2015;67(4):637–45.

24. Ekin RG, Zorlu F, Akarken I, Yildirim Z, Tarhan H, Koc G, et al. Anterior apical cores in the initial prostate biopsy does not increase detection of significant prostate cancer. *Urol J.* 2015;12(2):2084–9.
25. Borghesi M, Ahmed H, Nam R, Schaeffer E, Schiavina R, Taneja S, et al. Complications After Systematic, Random, and Image-guided Prostate Biopsy. *Eur Urol.* 2017;71(3):353–65.
26. Roberts MJ, Bennett HY, Harris PN, Holmes M, Grummet J, Naber K, et al. Prostate Biopsy-related Infection: A Systematic Review of Risk Factors, Prevention Strategies, and Management Approaches. *Urology.* 2016. http://dx.doi.org/10.1016/j.urology.2016.12.011 [Epub ahead of print].
27. Hendriks RJ, van Oort IM, Schalken JA. Blood-based and urinary prostate cancer biomarkers: a review and comparison of novel biomarkers for detection and treatment decisions. *Prostate Cancer Prostatic Dis.* 2017;20(1):12–9.
28. Gorin MA, Verdone JE, van der Toom E, Bivalacqua TJ, Allaf ME, Pienta KJ. Circulating tumour cells as biomarkers of prostate, bladder, and kidney cancer. *Nat Rev Urol.* 2017;14(2):90–7.