

Özgür UĞURLU
Mesut ÇETİNKAYA
Cüneyt ÖZDEN,
Ç. Volkan ÖZTEKİN
A. Özgür AKDEMİR
Ali MEMİŞ
Mehmet YARIŞ

Department of Urology,
Ankara Numune Education and
Research Hospital,
Ankara - TURKEY

An abnormal digital rectal examination is an independent predictor of high radical prostatectomy Gleason's score (≥ 7) in patients with clinically localized prostate cancer

Aim: The aim of this study was to investigate the importance of digital rectal examination (DRE), serum total prostate specific antigen (PSA), percent free PSA (fPSA%), and PSA density (PSAD) in the prediction of high radical prostatectomy Gleason's scores (GSs) ≥ 7 in patients with clinically localized prostate cancer.

Materials and methods: Two hundred twenty-five patients who underwent radical prostatectomy for clinically localized prostate cancer were included in the study. The patients were grouped with respect to their radical prostatectomy GSs: group 1 including the patients with GSs < 6 ($n = 170$) and group 2 including the ones with GSs ≥ 7 ($n = 55$). The groups were compared with respect to potential predictors of a high GS, which were patient age, gland volume (V_p) obtained by transrectal ultrasound, DRE, PSA, fPSA%, and PSAD.

Results: The mean age, PSA, fPSA%, and PSAD values of groups 1 and 2 were 65.23 ± 7.7 and 65.05 ± 7.1 years, 11.20 ± 9.2 and 11.09 ± 6.8 ng/mL, 16.2 ± 8.6 and 15.5 ± 8.1 , and 0.25 ± 0.20 and 0.28 ± 0.18 ng/mL/cc, respectively. The groups were similar with respect to mean age, PSA, fPSA%, and PSAD ($P > 0.05$ for all). Mean prostate volume of patients in group 2 was significantly lower than that of patients in group 1 (43.1 ± 17.01 vs. 46.9 ± 17.6 mL, $P = 0.043$), and group 2 had more patients with abnormal DRE findings (72.7% vs. 51.2% , $P = 0.005$). DRE was the only independent factor for predicting high GS in multivariate logistic regression analysis. A DRE suspicious of prostate cancer increased the high GS risk by 2.82 times.

Conclusion: This study shows that an abnormal DRE is an independent predictor of high grade disease (GS ≥ 7) in patients with clinically localized prostate cancer.

Key words: Digital rectal examination, Gleason's score, prostate cancer, radical prostatectomy

Anormal parmakla rektal muayene klinik lokalize prostat kanserli hastalarda yüksek radikal prostatektomi Gleason skorunu (≥ 7) öngörmeye bağımsız bir parametredir

Amaç: Klinik lokalize prostat kanserli hastalarda yüksek Gleason skorlu (GS) (≥ 7) hastaların öngörülmesinde parmakla rektal muayene (PRM), total prostat spesifik antijen (PSA), serbest PSA yüzdesi (%f PSA) ve PSA dansitesinin (PSAD) önemini araştırmak.

Yöntem ve gereçler: Klinik lokalize prostat kanseri nedeniyle radikal prostatektomi yapılmış olan 225 hasta çalışmaya dahil edildi. Hastalar radikal prostatektomi GS'larına göre 2 gruba ayrıldı; grup 1 GS < 6 ($n = 170$), grup 2 GS ≥ 7 ($n = 55$) hastalardan oluştu. İki grup yüksek Gleason skorunun öngörülmesinde potansiyel değişkenler olan hasta yaşı, transrektal ultrason ile hesaplanan prostat volümü (V_p), PRM, PSA, % fPSA ve PSAD açılarından karşılaştırıldı.

Bulgular: Grup 1 ve 2'nin ortalama yaş, PSA, % fPSA ve PSAD'leri sırasıyla; $65,23 \pm 7,7$ ve $65,05 \pm 7,1$ yıl, $11,20 \pm 9,2$ ve $11,09 \pm 6,8$ ng/mL, $16,2 \pm 8,6$ ve $15,5 \pm 8,1$, ve $0,25 \pm 0,20$ ve $0,28 \pm 0,18$ ng/mL/cc idi. İki grup ortalama yaş, PSA, % fPSA ve PSAD açılarından benzerdi (tümü için $P > 0,05$). Grup 2'de yer alan hastaların ortalama prostat volümü grup 1 ile karşılaştırıldığında istatistiksel olarak anlamlı şekilde küçüktü ($43,1 \pm 17,01$ ve $46,9 \pm 17,6$ mL, $P = 0,043$). Grup 2'deki anormal

Received: July 02, 2008
Accepted: April 21, 2009

Correspondence

Özgür UĞURLU
Kuzgun sokak 67/15,
Aşağı Ayrancı,
Ankara - TURKEY

ugurluo@hotmail.com

PRM'li hasta yüzdesi grup 1'den istatistiksel olarak anlamlı olarak daha azdı (% 72,7 ve % 51,2, $P = 0,005$). Çoklu logistik regresyon analizine göre yüksek GS'ünü öngörmeye sadece anormal PRM bağımsız bir faktördü. PRM'de kanser şüphesi olması yüksek GS riskini 2,82 kat arttırmaktadır.

Sonuç: Klinik lokalize prostat kanserli hastalarda anormal PRM yüksek GS'ünü ($GS \geq 7$) öngörmeye bağımsız bir göstergedir.

Anahtar sözcükler: Parmakla rektal muayene, Gleason skor, prostat kanseri, radikal prostatektomi

Introduction

There has been a decrease in the number of prostate cancers (PCa) diagnosed by digital rectal examination (DRE) in the last 2 decades after prostate specific antigen (PSA) was introduced as a tool for prostate cancer diagnosis (1). Hence, some authors questioned the place of DRE in PCa diagnosis and some reported that it was not useful in staging and treatment planning, particularly in patients with early stage disease (1,2). On the other hand, there are some studies in the literature concluding that high grade PCa (Gleason's score [GS] ≥ 7) is more frequently observed in needle biopsies of patients with abnormal DRE findings (3,4).

Percent free PSA (fPSA%) is a derivative used in order to increase the sensitivity of total PSA when serum total PSA is within the normal limits, and to increase the specificity of PSA when it is between 4 and 10 ng/mL (5,6). There are numerous studies with conflicting results regarding the use of fPSA% in prediction of high grade PCa (7-10).

High GS (≥ 7) in radical prostatectomy specimen is a clinically important finding in patients with localized prostate cancer, as it is a proven indicator of aggressive behavior (11). Preoperative prediction of patients with high radical prostatectomy GSs (≥ 7) may influence treatment selection. The aim of this study was to compare the DRE findings, total PSA, fPSA%, and PSAD of patients with high (≥ 7) and low (< 7) radical prostatectomy GSs and investigate the power of these parameters in predicting patients with high GSs.

Materials and methods

Two hundred twenty-five patients who underwent radical prostatectomy for clinically localized PCa between March 1997 and June 2007 were included in

the study. The patients with a clinical stage higher than cT2 or who had received neoadjuvant hormonal therapy or radiation therapy were excluded.

Patients' data were retrospectively analyzed and patients were grouped with respect to their GSs in the radical prostatectomy specimens. Patients with a GS < 6 were included in the first ($n = 170$) and those with a GS ≥ 7 were included in the second group ($n = 55$). The groups were compared with respect to the potential predictors of a high GS, which were patient age, Vp, DRE, PSA, fPSA%, and PSAD.

DRE was performed by at least 2 experienced urologists. A DRE was accepted to be abnormal when a palpable nodule, glandular asymmetry, or induration was noted. Abbott AXSYM 3C19 and 3C20 kits were used for total and free PSA measurements, respectively. Blood samples reached the laboratory in a maximum of 3 h and were analyzed within 12 h. Percent free PSA was calculated using the formula: $fPSA/totalPSA \times 100$ and PSAD was calculated by dividing total serum PSA by Vp, indicating a PSA value for each gram of prostate tissue in ng/mL. A Hitachi EUB-400 ultrasound device and a 6.5 MHz biplanar transrectal probe were used for imaging and Vp determination. Ellipsoidal formula was used for Vp calculation (transverse diameter \times antero-posterior diameter \times cefalo-caudal diameter $\times 0.52$). The clinical and pathological prostate cancer staging was performed using the 1992 TNM staging system from the American Joint Committee on Cancer (12). Gleason's system was used for tumor grading (13).

The data were analyzed using SPSS 11.5. While continuous variables were expressed as mean \pm standard deviation, qualitative data were presented as number of patients and percentages. Mean ages were compared by Student's t test. Mean ranks were evaluated by Mann-Whitney U test. For categorical

comparisons Pearson’s chi-square test was applied. Multiple Logistic Regression Analysis “Enter Method” was performed to determine the best predictors of a GS equal to or higher than 7. Odds ratio and 95% CI for each independent variable were calculated. A P value less than 0.05 was considered statistically significant.

Results

The mean age, PSA, fPSA%, PSAD, and Vp of the 225 patients were 65.19 ± 7.6 years, 11.17 ± 8.6 ng/mL, 16 ± 8%, 0.26 ± 0.19 ng/mL/cc, and 46.04 ± 17.4 mL,

respectively. The clinical stage of 98 patients was cT1c and of 127 patients was cT2. The distribution of the patients with respect to pathological stage (pT) is shown in Table 1.

Table 2 shows the clinical parameters of patients with GS < 6 (group 1) and GS ≥ 7 (group 2). The mean age, PSA, fPSA%, and PSAD of groups 1 and 2 were 65.23 ± 7.7 and 65.05 ± 7.1 years, 11.20 ± 9.2 and 11.09 ± 6.8 ng/mL, 16.2 ± 8.6 and 15.5 ± 8.1, and 0.25 ± 0.20 and 0.28 ± 0.18 ng/mL/cc, respectively. There were no significant differences between the mean age (P = 0.882), PSA (P = 0.677), fPSA% (P = 0.592), and

Table 1. Patient distribution with respect to pathological T (tumor) stage.

Pathological stage	Group 1 Gleason’s score ≤ 6		Group 2 Gleason’s score 7-10		Total	
	n	%	n	%	n	%
T2a	74	43.5	9	16.4	83	36.9
T2b	50	29.4	20	36.4	70	31.1
T2c	28	16.5	10	18.2	38	16.9
T3	18	10.6	16	29	34	15.1
Total, n (%)	170	100	55	100	225	100

Table 2. Clinical parameters of the patients in the 2 groups.

	Group 1 Gleason’s score ≤ 6 (n = 170)	Group 2 Gleason’s score 7-10 (n = 55)	P value
Age (years) (Mean ± SD)	65.23 ± 7.7	65.05 ± 7.1	0.882
Prostate volume (mL) (Mean ± SD)	46.9 ± 17.5	43.1 ± 17.1	0.043*
Total PSA** (ng/mL) (Mean ± SD)	11.2 ± 9.2	11.09 ± 6.8	0.677
Percent free PSA (Mean ± SD)	16.2 ± 8.6	15.5 ± 8.1	0.592
PSA density (ng/mL/cc) (Mean ± SD)	0.25 ± 0.20	0.28 ± 0.18	0.194
Abnormal DRE*** n (%)	87 (51.2)	40 (72.7)	0.005*

* Statistically significant ** Prostate specific antigen *** Digital rectal examination

PSAD ($P = 0.194$) values of the 2 groups. Group 2 had significantly lower Vp (43.1 ± 17.01 vs. 46.9 ± 17.6 mL, $P = 0.043$) and a higher percentage of patients with abnormal DRE (72.7% vs. 51.2%, $P = 0.005$) when compared to group 1. Multiple logistic regression analysis showed abnormal DRE to be the only independent predictor of a high radical prostatectomy GS. Analysis also revealed that presence of cancer suspicion on DRE increases the risk of high GS 2.82 times (OR, 2.82, 95% CI 0.6-3.4, $P = 0.003$). No significant relations were observed between high GS and fPSA% (OR, 1.48, 95% CI 0.6-3.4, $P = 0.355$), PSAD (OR, 0.9, 95% CI 0.18-4.8, $P = 0.935$), and Vp (OR 0.9, 95% CI 0.9-1.0, $P = 0.123$).

Discussion

There has been a significant increase in the diagnosis of non-palpable prostate cancers since PSA was widely used as a diagnostic tool; and in this PSA era, some authors started to question the use of DRE in diagnosis and staging of PCa (1,2). Philip et al. (2), in their study of 408 patients with PSA levels between 2.5 and 10 ng/mL, stated that DRE did not correlate well with biopsy results and provided no additional information regarding the choice of treatment. On the other hand, Borden et al. (4) reported DRE to be an independent predictor of a positive prostate needle biopsy as well as presence of a high grade cancer. Various retrospective analyses of radical prostatectomy specimens revealed that clinically palpable tumors (cT2) had higher GSs in the final pathological examination when compared to PSA diagnosed (cT1) tumors (14-16). Similarly, it was demonstrated in Prostate Cancer Prevention Trial that an abnormal DRE predicts a high GS in prostate biopsies (3). Likewise, in our study, in which we evaluated the patients with clinically localized prostate cancer who underwent radical prostatectomy, we found not only that an abnormal DRE increased the probability of a high GS in the radical prostatectomy specimens, but it is also an independent predictor for high GS in the final pathological examination.

The reason why palpable tumors tend to have higher grades is yet to be understood. Greene et al. (17) concluded that peripherally localized tumors which are most likely to be palpable in DRE have

relatively higher grades. Similarly, Ghavamian et al. (14) compared the radical prostatectomy specimens of patients with clinically palpable and non-palpable tumors and stated that palpable tumors had had higher tumor volumes and higher Gleason's grades.

The efficacy of fPSA% in predicting GS is debatable as various studies report conflicting results (7-10). Although it has been reported in some studies that there were no significant correlations between fPSA% and GS (18), Grossklaus et al. (19) reported a negative correlation between fPSA% and GS in their prospective analysis of 124 PCa patients after radical prostatectomy. Okegawa et al. (20) found significantly lower pre-treatment free to total PSA levels in patients with recurrent tumors, when compared to patients who had no recurrences, and that high grade tumors demonstrated different biological behavior and aggression. In our study, however, fPSA% had no significance in predicting a high GS.

A high GS (≥ 7) is an indicator of clinical importance and aggressive behavior of a prostate cancer, which underscores the importance of prediction of a high GS with DRE in clinical practice (11). Klotz (21) reported that patients with a GS ≥ 7 who are younger than 70 years and who have a life expectancy of 10 years are not ideal candidates for active surveillance, due to high mortality rates related to prostate cancer. It could logically be speculated that patients with abnormal DREs should not be directed to active surveillance as they have an almost 3 times higher risk for high GSs in the final pathology when compared to patients with non-palpable tumors. On the other hand, PCa screening with DRE or PSA is not always recommended for patients with a life expectancy less than 10 years. However, our study suggests a role for DRE in patients with a short life expectancy as DRE can predict aggressive disease and possibly prevent disease-specific mortality by early and active treatment. Our study suggests a possible role for DRE also in patients with a shorter life expectancy. Because DRE can predict a more aggressive disease, minimizing the prostate cancer specific mortality may be possible by aggressive treatment in this group of patients. However, this possibility must be further evaluated and confirmed by future prospective studies.

The GSs in needle biopsies of the prostate do not correlate well with GSs in radical prostatectomy specimens (22). Undergrading rates between 23% and 50% for prostate biopsies are reported in the literature (22,23). As a general approach, more conservative treatment options are recommended for well-differentiated low volume tumors diagnosed on needle biopsies. However, this approach may be misleading, as a small and well-differentiated tumor on a biopsy may actually have a larger volume and poorer differentiation. At this point, DRE gains importance as it can predict the high radical prostatectomy GSs (≥ 7). For instance, aggressive

treatment may be preferred in a patient with a low biopsy GS but an abnormal DRE.

Conclusions

This study shows that an abnormal DRE is an independent predictor of high GS disease in patients with clinically localized PCa. DRE may be important when deciding how to treat clinically localized PCa. The findings of this study should be further evaluated and supported in prospective studies including larger series.

References

1. Roberts RO, Bergstralh EJ, Lieber MM, Jacobsen SJ. Digital rectal examination and prostate-specific antigen abnormalities at the time of prostate biopsy and biopsy outcomes, 1980 to 1997. *Urology* 2000; 56: 817-22.
2. Philip J, Dutta Roy S, Ballal M, Foster CS, Javle P. Is a digital rectal examination necessary in the diagnosis and clinical staging of early prostate cancers? *BJU Int* 2005; 95: 969-71.
3. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS et al. Assessing prostate cancer risk: results from the prostate cancer prevention trial. *J Natl Cancer Inst* 2006; 98: 529-34.
4. Borden LS Jr, Wright JL, Kimt J, Latchamsetty K, Porter CR. An abnormal digital rectal examination is an independent predictor of Gleason ≥ 7 prostate cancer in men undergoing initial prostate biopsy: a prospective study of 790 men. *BJU Int* 2006; 99: 559-63.
5. Partin AW, Catalona WJ, Southwick PC. Analysis of percent free prostate-specific antigen (PSA) for prostate cancer detection: influence of total PSA, prostate volume and age. *Urology* 1996; 48: 55-61.
6. Akdaş A, Cevik I, Turkeri L, Dalaman G, Emerk K. The role of free prostate-specific antigen in the diagnosis of prostate cancer. *Br J Urol* 1997; 79: 920-23.
7. Arcangeli CG, Humphrey PA, Smith DS, Harmon TJ, Shepherd DL, Keetch DW et al. Percentage of free serum PSA as a predictor of pathologic features of prostatic carcinoma in a screening population. *Urology* 1998; 51: 558-64.
8. Pannek J, Rittenhouse HG, Chan DW, Epstein JI, Walsh PC, Partin AW. The use of percent free PSA for staging clinically localized prostate cancer. *J Urol* 1998; 159: 1238-42.
9. Elabbady AA, Khedr MM. Free/total PSA ratio can help in the prediction of high gleason score prostate cancer in men with total serum prostate specific antigen (PSA) of 3-10 ng/ml. *Int Urol Nephrol* 2006; 38: 553-57.
10. Pepe P, Panella P, Pietropaolo F, Pennisi M, Allegro R, Aragona F. Is free/total PSA predictive of pathological stage and gleason score in patients with prostate cancer and serum PSA ≤ 10 ng/ml? *Urol Int* 2006; 76: 232-35.
11. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994; 271: 368-74.
12. Beahrs OH, Henson DE, Hutter RVP eds, American Joint Committee on Cancer Manual for Staging Cancer. Philadelphia, PA: JB Lippincott, 1992.
13. Gleason DF. Histologic grading and staging of prostatic carcinoma. In Tannenbaum M ed. *Urologic Pathology*. Philadelphia, PA: Lea and Febiger. 171-187, 1977.
14. Ghavamian R, Blute ML, Bergstralh EJ, Slezak J, Zincke H. Comparison of clinically nonpalpable prostate-specific antigen-detected (cT1c) versus palpable (cT2) prostate cancers in patients undergoing radical retropubic prostatectomy. *Urology* 1999; 54: 105-10.
15. Ramos CG, Carvalhal GF, Smith DS, Mager DE, Catalona WJ. Clinical and pathological characteristics, and recurrence rates of stage T1c versus T2a or T2b prostate cancer. *J Urol* 1999; 161: 1525-29.
16. Armatys SA, Koch MO, Bihle R, Gardner TA, Cheng L. Is it necessary to separate clinical stage T1c from T2 prostate adenocarcinoma? *BJU Int* 2005; 96: 777-80.
17. Greene DR, Fitzpatrick JM, Scardino PT. Anatomy of the prostate and distribution of early prostate cancer. *Semin Surg Oncol* 1995; 11: 9-22.
18. Egawa S, Suyama K, Soh S, Kuwao S, Uchida T, Koshiba K. Inadequacy of free prostate-specific antigen parameters in the prediction of pathologic extent of prostate cancer in Japanese men. *Urology* 1998; 52: 230-36.

19. Grossklau DJ, Coffey CS, Shappel SB. Percent free PSA is reflective of prostate cancer pathology in surgical specimen. *J Urol* 2001; 165: 282 abst no. 1159.
20. Okegawa T, Kato M, Nutahara K, Higashihara E. Prognostic value of three molecular forms of prostate-specific antigen ratios in patients with prostate adenocarcinoma. *Urology* 2001; 57: 936-42.
21. Klotz L. Active surveillance for prostate cancer: for whom? *J Clin Oncol* 2005; 23: 8165-9.
22. Djavan B, Kadesky K, Klopukh B, Marberger M, Roehrborn CG. Gleason scores from prostate biopsies obtained with 18-gauge biopsy needles poorly predict Gleason scores of radical prostatectomy specimens. *Eur Urol* 1998; 33: 261-70.
23. Emillozzi P, Maymone S, Paterno A, Scarpone P, Amini M, Proietti G, et al. Increased accuracy of biopsy Gleason Score obtained by extended needle biopsy. *J Urol* 2004; 172: 2224-6.