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Original Article

Does extent of prostate-specific antigen fluctuation can predict Gleason score upgrading in low-risk prostate cancer patients?

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ABSTRACT

Objective: To evaluate the effect of prostate-specific antigen (PSA) fluctuation on Gleason score (GS) upgrading, disease upstaging, oncological outcomes in low-risk prostate cancer (PCa) patients who underwent robot-assisted laparoscopic radical prostatectomy (RARP) and met the inclusion criteria for active surveillance (AS).

Material and methods: Data of 354 low-risk PCa patients who underwent RARP were retrospectively evaluated. Patients were divided into two groups: PSA fluctuation rate<9.5%/month (Group 1, n=192) and >9.5%/month (Group 2, n=162). Mainly compared parameters were GS upgrading, disease upstaging, biochemical recurrence (BCR) and surgical margin positivity (SMP) rates.

Results: GS upgrading, disease upstaging and SMP were detected in 128 (36.2%), 56 (15.8%) and 42 (11.9%) patients, respectively. After a median follow-up of 46 months, BCR was observed in 40 (11.3%) patients. GS upgrading (41.1% vs. 30.2%, p=0.033), disease upstaging (19.8% vs. 11.1%, p=0.028), SMP (15.1% vs. 8%, p=0.035) and BCR development (15.6% vs. 6.2%, p=0.005) rates were statistically significantly higher in Group 1 than Group 2. In multivariate analysis, digital rectal examination positivity, the presence of two positive cores and low PSA fluctuation rate were found to be significant predictors of GS upgrading.

Conclusion: Low PSA fluctuation rate is associated with higher GS upgrading.

Keywords: Biochemical recurrence; fluctuation; Gleason score upgrading; prostate cancer; prostate-specific antigen.

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Introduction

Prostate cancer (PCa) is the second most common cancer type and it is the fifth leading cause of death from cancer in men.[1] In these patients, treatment is planned according to the risk stratification based on prostate-specific antigen (PSA) values, Gleason scores (GS) and clinical stage in PCa patients and low-risk PCa is defined as PSA <10 ng/mL, GS ≤6 and clinical stage ≤T2a based on D'Amico criteria.[2] In low-risk PCa patients, PCa will probably not affect the disease-specific survival and it may be managed expectantly with active surveillance (AS).[3] However, GS upgrading is detected in 28% to 43% of low-risk PCa patients when they will undergo surgery.[4,5] This condition is clinically important, because, Gleason pattern 4 or 5 results in an increased risk of progression, biochemical recurrence, and disease-specific mortality.[6]

The roles of high PSA value, low free/total PSA, high PSA density on GS upgrading are well established.[7-10] However, a perfect nomogram to predict GS upgrading has not been defined and the predictive accuracy of current nomograms is not perfect (80.4%).[11] Therefore, we need to find some predictive factors to increase accuracy of nomograms. Recently, it has been shown that several kinds of biochemi-

cal PSA derivatives such as PCA3 or ProPSA may be used to predict the presence of high-grade PCa.[12-14] However, these tests are quite costly and cannot be applied especially in developing countries.

Majority of our PCa patients wait for surgery for a while, because, our clinic is one of the most popular referral center for robot-assisted laparoscopic radical prostatectomy (RARP) surgery in our country. We observed fluctuating PSA values in many patients during the time interval from PCa diagnosis (at the time of prostate biopsy) to surgery. Twenty years ago, the variations in daily PSA levels in non-cancer patients were reported by Nixon and coworkers.[15] More recently, Kim et al.[16] found that the patients with prostate cancer had a narrow (mean PSA fluctuation rate, 9.6%/month) range of fluctuation in serial PSA measurements while non-cancer patients had a wide (mean PSA fluctuation rate, 19%/month) range of fluctuation.

To date, many articles have been published evaluating the relationship between GS upgrading with PSA derivatives such as PSA density and velocity. However, to the best of our knowledge no publication exists about the effect of PSA fluctuation rate on GS upgrading. Our primary aim was to assess the effect of PSA fluctuation rate on GS upgrading rate in low risk PCa patients who underwent RARP and who met the inclusion criteria for AS. Secondary aims were to evaluate the effect of PSA fluctuation rate on other oncological outcomes such as disease upstaging, biochemical recurrence (BCR), and surgical margin positivity (SMP).

Material and methods

Ethical approval for this study was obtained from Ethics Committee of Ankara Yıldırım Beyazıt University School of Medicine (decision protocol No:289 dated 12.21.2016). Written informed consent was obtained from all patients and the study was conducted according to World Medical Association Declaration of Helsinki. We retrospectively evaluated the data of 1046 patients who underwent RARP at our institution between February 2009 and May 2016. We explained to all low-risk prostate cancer patients the follow-up schedule, success rate, rate of local recurrence and metastasis risk of active surveillance, probability of tumor progression and Gleason score upgrading. On the other hand, we explained to these patients the risk of complication and success rate, rate of local recurrence and risk of metastasis after radical prostatectomy surgery. Patients decided on their own treatment modalities. Totally, 354 (33.8%) low-risk PCa patients who had at least two PSA measurements were included in the study. We defined low-risk PCa patients based on following criteria: PSA <10 ng/mL, GS ≤6, clinical stage ≤T2a and ≤2 positive cores, and ≤50% cancer involvement in each positive core. Patients who had urinary tract infection, cystoscopic or uretroscopic evaluation, neoadjuvant androgen deprivation therapy and 5-alpha reductase inhibitor treatment during the last 6 months were excluded from the study. The indications for prostate biopsy include suspicious findings at digital rectal examination (DRE) and a serum PSA level above >2.5 ng/mL. All prostate biopsy procedures were performed under transrectal ultrasound guidance and at least 10 cores were taken targeting the peripheral zone of the prostate. During TRUS, prostate size was also recorded. In all patients, clinical staging was performed according to Tumor-Node-Metastasis 2010 criteria together with findings of DRE and abdominopelvic computed tomography or pelvic magnetic resonance imaging. All RARP procedures were performed by two experienced surgeons (AFA, AEC) who used the surgical technique previously described in the literature.[17]

In all patients, data regarding age, body mass index (BMI), PSA levels, prostate size measured during TRUS, GS at biopsy, tumor involvement per core, number of positive cores at biopsy, GS estimated for RARP specimen, clinical and pathological disease stage, time from diagnosis to surgery, SMP, presence of extraprostatic extension (EPE), seminal vesicle invasion (SVI), perineural invasion (PNI), capsule invasion, and BCR were collected.

Definition of PSA fluctuation and PSA density: We recorded two PSA levels: before biopsy (total PSA1) and at the day before RARP (total PSA2). We calculated the PSA fluctuation rate according to (total PSA2-total PSA1)/total PSA1 per month formula which was described by Kim et al.[16] PSA density was calculated by dividing total PSA1 by prostate size estimated during TRUS.

Definition of GS upgrading, disease upstaging and BCR: Gleason score upgrading was defined as increase in Gleason score greater than 6 points or International Society of Urological Pathology (ISUP) grade I. Disease upstaging was defined as the presence of pathological T3 or T4 disease. BCR was defined based on two consecutive PSA measurements of ≥0.2 ng/mL after RARP.

Statistical analysis

Statistical Package for the Social Sciences 15.0 (SPSS Inc.; Chicago, IL, USA) was used for all statistical analysis. Receiver operating characteristic (ROC) analysis was used for determination of cut-off value for PSA fluctuation. Comparisons between groups were performed with *chi*-square and t-tests. Correlations between PSA fluctuation rate and other variables were assessed with Spearman's Rho test. Univariate and multivariate logistic regression analyses were conducted to identify variables predictive of GS upgrading. P value <0.05 was accepted as the level of statistical significance.

Results

The mean values for age, BMI, total PSA1, free PSA1, free/total PSA1 and total PSA2 of our patients were 60.8±7.1 years, 26.6±2.4, 5.87±1.9 ng/mL, 0.93±0.6 ng/mL, 0.16±0.09 and 6.2±2.3 ng/mL, respectively. The mean time from biopsy to RARP was 2.2±1.1 months. The mean prostate volume and PSA density were 51±18 ml and 0.11±0.06 ng/mL, respectively. Two hundred and eighty-nine (81.6%) patients had clinical T1C stage tumor and 65 (18.4%) of them T2A stage tumor. GS upgrading and disease upstaging were detected in 128 (36.2%) and 56 (15.8%) patients, respectively. Presence of EPE, SMP, PNI, capsule invasion and SVI were observed in 45 (12.7%), 42 (11.9%), 156 (44.1%), 38 (10.7%) and 11 (3.1%) patients, respectively. After a median follow-up of 46 months (range: 9-93), BCR was observed in 40 (11.3%) patients. General patient demographics and tumor characteristics were detailed in Table 1.

The mean PSA fluctuation rate was 22% per month (range: 0.2% to 130%) in our population. To date, there is no data about acceptable PSA fluctuation rate. Our primary endpoint was to evaluate the effect of PSA fluctuation rate on GS upgrading. Therefore, we performed ROC analysis to predict the probability of higher GS upgrading. We detected a cut-off value of 9.5 % per month (sensitivity 91.6%, specificity 85.9%) for PSA fluctuation rate (Figure 1). When, we divided all patients into two groups according to this cut-off value, monthly PSA fluctuation rates were <9.5% in Group 1 (n=192) and >9.5% in Group 2 (n=162).

When we compared both groups statistically significant differences were observed in terms of mean free/total PSA1 (p=0.044)

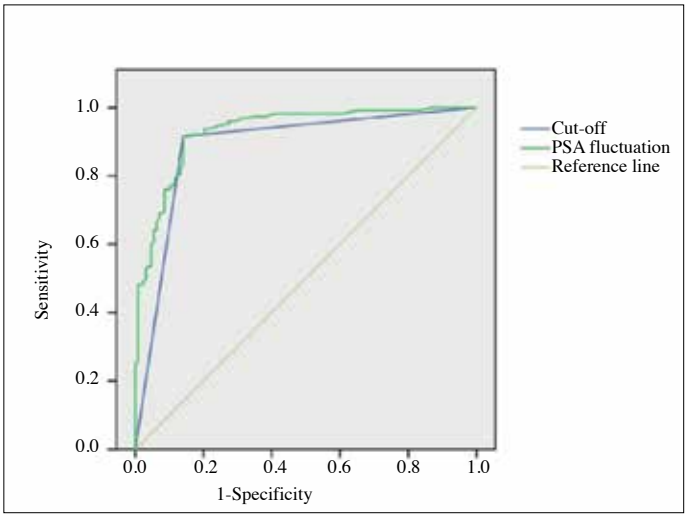

Figure 1. Receiver operating characteristic curve for prostate-specific antigen fluctuation to predict Gleason score upgrading. The area under the curve (AUC) value is 9.5% per month (sensitivity 91.6%, specificity 85.9%)

and mean time from biopsy to RARP (p=0.001). There were no statistical significant differences in other preoperative variables and patient demographics. GS upgrading rate was statistically significantly higher in Group 1 than Group 2 (41.1% vs. 32.2%, p=0.033). We also observed significantly higher disease upstaging (19.8% vs. 11.1%, p=0.026) and BCR (15.6% vs. 6.2%, p=0.005) rates in Group 1 relative to Group 2. Other oncological variables were statistically similar. All comparisons were detailed in Table 1.

Variables of age, total PSA1, free/total PSA1, BMI, mean time from diagnosis to surgery, tumor involvement per core, prostate volume, PSA density, DRE positivity, number of positive cores, PSA fluctuation rate variables were subjected to logistic regression analyses to determine factors associated with GS upgrading. High total PSA1, DRE positivity, presence of two positive cores and low PSA fluctuation rate were found to be associated with increased risk of GS upgrading in univariate analysis. Outcomes of univariate analysis are summarized in Table 2. Multivariate analysis was performed to determine the independent predictors of GS upgrading. DRE positivity (OR: 6, 95% CI: 4.667-9.848, p<0.001), presence of two positive cores (OR: 5.2, 95% CI: 3.037-8.843, p<0.001) and low PSA fluctuation rate (OR:3, 95% CI: 1.974-4.854, p=0.001) were found to be significant predictors of GS upgrading.

Discussion

Active surveillance (AS) is considered as an management option based on comparable long-term survival outcomes to those obtained with definitive treatment modalities in low-risk localized PCa patients. In a recent large study, 10-year disease-specific survival, and metastasis development rates in AS patients were reported as 98.1% and 2.8%, respectively.[18] However, one of the major concerns in AS patients is the risk of GS upgrading. Indeed, recent studies have showed that the GS upgrading rate ranged between 28% and 43% in low-risk PCa patients.[4,5] GS upgrading is important, because, it is related with high BCR, progression to systematic disease, and low cancer specific survival rate.[6] Therefore, the ability to identify the patients with GS upgrading earlier and more accurately results in improved oncologic outcomes.

The effects of age, tumor involvement per core, the number of positive cores on GS upgrading are well understood.[7-10] Moreover, the association between biochemical PSA derivatives/kinetics (such as lower free/total PSA, higher PSA density, PCA3 or ProPSA) and GS upgrading has been reported in many articles.[12-14] Despite the presence of these factors, a perfect nomogram to predict GS upgrading has not been defined yet. Moreover, PCA3 and ProPSA tests are quite costly and cannot be applied especially in developing countries. Therefore, we need

Table 1. Patient characteristics and comparison of two groups

Parameters	All patients (n=354)	Group 1 (n=192)	Group 2 (n=162)	p
Age (years), Mean±SD	60.8±7.1	60.6±7	61.1±7.3	0.52
BMI (kg/m^2), Mean±SD	26.6±2.4	26.4±2.5	26.7±2.3	0.26
Total PSA1 (ng/mL), Mean±SD	5.87±1.9	6.1±1.8	5.71±2	0.07
Free PSA1 (ng/mL), Mean±SD	0.93±0.6	0.89±0.46	0.93±0.67	0.5
Free/Total PSA1, Mean±SD	0.16±0.09	0.15±0.07	0.18±0.19	0.044*
Total PSA2 (ng/mL), Mean±SD	6.2±2.3	6±1.7	6.5±2.9	0.053
Prostate volume (mL), Mean±SD	56±21 (18-202)	54±20	59±22	0.6
PSA density (PSA1/prostate volume) Mean±SD	0.10±0.06	0.11±0.01	0.09±0.07	0.8
Time from biopsy to RARP (month), Mean±SD	2.2±1.1	2.4±1.2	1.8±0.8	0.001*
Suspicious finding at DRE, n	122 (34.5%)	65 (33.9%)	57 (35.2%)	0.79
Clinical T stage distribution, n				
T1C	289 (81.6%)	154 (80.2%)	135 (83.3%)	
T2A	65 (18.4%)	38 (19.8%)	27 (16.7%)	0.34
Tumor involvement per core (%), Mean±SD	28.7±13.3 (10-50)	28.4±12	29.1±14	0.6
Number of positive cores, n				
One core positivity	221 (62.4%)	114 (59.4%)	107 (66%)	
Two core positivity	133 (37.6%)	78 (40.6%)	55 (34%)	0.19
Presence of GS upgrading, n	128 (36.2%)	79 (41.1%)	49 (30.2%)	0.033*
Distribution of ISUP grades among radical prostatectomy specimens, n				
ISUP grade I	226 (63.8%)	113 (58.8%)	113 (69.8%)	
ISUP grade II	62 (17.6%)	38 (19.8%)	24 (14.8 %)	
ISUP grade III	46 (13%)	27 (14.1%)	19 (11.8%)	
ISUP grade IV	12 (3.4%)	8 (4.2%)	4 (2.4%)	
ISUP grade V	8 (2.2%)	6 (3.1%)	2 (1.2%)	0.2
Presence of disease upstaging, n	56 (15.8%)	38 (19.8%)	18 (11.1%)	0.026*
SMP, n	42 (11.9%)	29 (15.1%)	13 (8%)	0.035*
Presence of EPE, n	45 (12.7%)	23 (12%)	22 (13.6%)	0.65
Presence of PNI, n	156 (44.1%)	83 (43.2%)	73 (45.1%)	0.73
Presence of SVI, n	11 (3.1%)	5 (2.6%)	6 (3.7%)	0.55
Presence of capsule invasion, n	38 (10.7%)	18 (9.4%)	20 (12.3%)	0.36
BCR development, n	40 (11.3%)	30 (15.6%)	10 (6.2%)	0.005*

*Statistically significant

BCR: biochemical recurrence; BMI: body mass index; DRE: digital rectal examination; EPE: extraprostatic extension; ISUP: International Society of Urological Pathology; LVI: lenfosvascular invasion; PNI: perineural invasion; PSA: prostate-specific antigen; SMP: surgical margin positivity; SVI: seminal vesicle invasion

different and inexpensive tests for PSA derivatives or kinetics to predict GS upgrading.

In 2007, Celhay et al.[19] compared the risk of having a positive repeat prostate biopsy between groups with steadily rising and fluctuating PSA values in patients who had their first negative biopsy results. They defined PSA fluctuation as a PSA series with at least one PSA value lower/higher than the one immediately preceding it. The incidence of PCa was lower in PSA fluctuation group than steadily rising PSA group (21% and 32%, respectively p=0.14). Conversely, in another study, it was highlighted that the risk of detection prostate cancer at recurrent prostate biopsies was higher in men with a fluctuating PSA level and PSA velocity ≥1.0 ng/mL/year than in those with a fluctuat-

Table 2. Univariate analysis for Gleason score upgrading

	Univariate analysis		
Variables	**OR**	**95% CI**	**p**
Age	1.1	0.527-1.836	0.26
Total PSA1	1.7	1.056-5.242	0.01
Free/total PSA1	1.1	0.384-2.043	0.51
BMI	1.3	0.794-3.214	0.57
Mean time from diagnosis to surgery	1.02	0.326-1.482	0.57
Tumor involvement per core	1.4	0.854-1.149	0.65
Prostate volume	1.6	0.631-1.741	0.91
PSA density	1.4	0.421-2.532	0.2
Suspicious findings at DRE (Positive vs. negative)	5.7	3.664-6.558	<0.001
Number of positive cores (Two vs. one)	4	2.832-6.052	<0.001
Low PSA fluctuation rate(<9.5% per month vs. >9.5% per month)	3.3	2.362-4.014	<0.001

BMI: body mass index; DRE: digital rectal examination; GS: Gleason score; OR: odds ratio; CI: confidence interval; PSA: prostate-specific antigen

ing PSA level <1.0 ng/mL/year.[20] In Park et al.'s[20] study, PSA fluctuation rate was defined as PSA velocity of ≥1.0 ng/mL/year. The definition of PSA fluctuation in Park et al.'s [20] study may lead to confusion. Because, PSA fluctuation and PSA velocity kinetics may be confused with each other. PSA velocity represents the rate of change of PSA over time that optimally requires three consecutive measurements of PSA over a 2-year period, as described by Carter et al.[21] However, PSA fluctuation is simply a mathematical estimate of the absolute monthly changes in PSA (ng/mL/month) between two measurements, as described by Kim et al.[16]

In a current study, PSA fluctuation rates were compared between cancer and non-cancer patients by Kim et al.[16] PSA fluctuation was defined as a change rate of PSA (second PSA-first PSA/ first PSA) per month and PSA fluctuation rate was significantly greater in non-cancer group than prostate cancer group (19.9% vs 9.6%/month, respectively p<0.001).[16] They emphasized that the patients with prostate cancer had a narrow range of fluctuation while non-cancer patients had a wide range of fluctuation. Furthermore, they defined a cut-off value for PSA fluctuation to detect PCa (8.48%/ month) with 61.6% sensitivity and 59.6% specificity, p=0.004). Unfortunately, in Kim et al.[16] study, the mechanism of PSA fluctuation could not be explained.

Different from previous studies, we evaluated the effect of changes in PSA fluctuation rates on oncologic outcomes. We defined a cut-off value for PSA fluctuation (9.5%/month) with 91.6% sensitivity and 85.9% specificity) to predict GS upgrading. We found higher GS upgrading, disease upstaging and BCR rates in the group with PSA fluctuation rate of <9.5% (per month). As is known, PSA is not a disease-specific biomarker and it may increase in various benign conditions and PCa as well. The positive correlation between higher PSA and larger prostate volume or between high PSA and prostatitis (acute or chronic prostatitis) are reported in many studies.[22-24] On the other hand, the correlation between PSA value and aggressiveness of inflammation in subclinical prostatitis been also reported in some studies.[25,26] Concomitant chronic prostatitis and microscopic prostatic inflammation may be even detected in 95% and 57% of the PCa patients, respectively.[27] Indeed, we found positive correlation between PSA fluctuation rate and larger prostate volume. Furthermore, in histopathological examination, we found concomitant prostatitis in our 112 (31.6%) patients. The detection rate of focal prostatitis was higher in the group with PSA fluctuation of >9.5% than the group with PSA fluctuation of <9.5% (58% vs. 4.5%). Keeping these findings in mind, we think that significant fluctuations can be detected in PCa patients who have large prostates or concomitant prostatitis. Steady change in PSA fluctuation rate is more likely to be related with pure PCa patients.

Although a considerable number of patients were included in our study, the most important limitation of our study is its retrospective nature. We did not include information on the presence of lymph node invasion in the analyses, because we did not perform routine lymphadenectomy during radical prostatectomy in all low-risk PCa patients. Data of tertiary Gleason pattern was not included due to low sample size (n=5). Although all radical prostatectomy specimens were evaluated by experienced uropathologists, central pathological review of the specimens was not performed. Moreover, all radical prostatectomy specimens were evaluated in our pathology department, while prostate biopsy specimens were evaluated in different pathology departments and by different pathologists. This condition may lead to detection of high Gleason score upgrading rates. Finally, our results reflected results of a single tertiary center that is experienced in robotic surgery and our results should be supported by multicenter and prospective studies.

In conclusion, our results have demonstrated that GS upgrading, disease upstaging and BCR rate were higher in patients with low PSA fluctuation rates. Moreover, we observed that the low PSA fluctuation rate is a predictor of GS upgrading. We think that the PSA fluctuation rate might be included in nomograms to predict GS upgrading as a cost-effective and easily accessible tool.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Yıldırım Beyazıt University School of Medicine (Decision protocol No:289, Decision date: 21.12.2016).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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