CLINICAL PRACTICE ARTICLE

Impact of Prostate Specific Antigen Level on Oncological Outcomes after Open Radical Prostatectomy

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ABSTRACT

Objective: To compare the impact of prostate specific antigen (PSA) on oncological outcomes in the patients with 4-10 and 10.01-20 ng/ml PSA level.

Study Design: Retrospective comparative study.

Place and Duration of Study: Hitit University, Çorum Erol Olçok Training and Research Hospital, Çorum, Turkey, between February 2010 and January 2018.

Methodology: Patients who underwent open radical prostatectomy in our department were reviewed retrospectively. The patients were divided into two groups according to the PSA level at diagnosis between 4 and 20 ng/ml. The patients with PSA level of 4-10 ng/ml was in group 1 and 10.01-20 ng/ml was in group 2. Preoperative data including age, biopsy Gleason score (GS), PSA level, postoperative pathological reports, T stage, GS, positive surgical margin, upgrading and downgrading, were compared between groups.

Results: There were 109 (71.24%) and 44 patients (28.75%) in group 1 and group 2, respectively. The median age and PSA level of the patients was 67 and 64.5 years; 6.12 and 12.45 ng/ml in both groups, respectively. There was no significant difference for age, GS, number of positive biopsy cores except the PSA level ($p<0.001$). The difference did not reach statistical significance for stage, upgrading, downgrading, positive surgical margin, and prostatectomy GS between groups.

Conclusion: Serum high PSA level at the time of the diagnosis was unrelated to final pathology. The proportion of local advanced disease and positive surgical margin was higher in patients with low PSA values than high levels without statistically significance.

Key Words: *Prostate specific antigen, Prostatectomy, Stage, Grade.*

INTRODUCTION

Prostate cancer (PCa) is the second most common malignancy and one of the leading causes of death among male population in the world.[1] Prostate specific antigen (PSA) is the most widely used biomarker for PCa screening and biopsy indications. Treatment options of PCa include surgery, active surveillance, and radiotherapy.[2] Radical prostatectomy (RP) is the gold standard treatment which can be performed by open, laparoscopic, and robotic approaches.

Although PSA is a specific marker for the prostate tissue, it is not cancer specific as it can be elevated in benign conditions as well.[3] Enlargement of prostate volume, inflammation of prostate tissue, tumor of the prostate can increase the level of PSA.[1] Approximately, 70% of males with an increased serum PSA levels (>4 ng/ml) do not have PCa and thus go unnecessary biopsies.[4] The cancer is detected in only 25% of the patients in the intermediate level of PSA (4-10 ng/ml) that called grey zone.[5] Unfortunately, 30% of these patients with PCa have locally advanced or metastatic disease. The detection rate of PCa in the PSA of 10-20 ng/ml is about 50-66%.[6]

The level of PSA has been shown to be associated with races.[5] African males living in USA have higher levels of PSA than white people. Additionally, the incidence of PCa among East Asian population is 10.5 per 100000 men and mortality is 3.1 deaths per 100000 which are significantly lower than Western men.[7] The investigators found the overall age-adjusted incidence rate of PCa was 35/100000 in Turkey between 2008 and 2009.[8] The incidence of PCa in Turkey is higher than Asian males and lower than Western population.

The aim of this study was to compare the final pathological results of the patients with PSA level of 4-10 and 10.01-20 ng/ml who underwent open radical prostatectomy.

METHODOLOGY

The patients diagnosed with PCa and underwent open radical retropubic prostatectomy at Hitit University, Çorum Erol Olçok Training and Research Hospital, Çorum, Turkey, between February 2010 and January 2018 were listed retrospectively. The inclusion criteria for the study was PSA level at diagnosis between 4 and 20

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ng/ml performed before 12-core prostate biopsy. The patients who were treated by laparoscopic and perineal prostatectomy (because of homogeneity), insufficient data, less than 12 core biopsy, history of radiotherapy and androgen deprivation therapy were excluded from the study.

The studied variables include patient age, PSA level at diagnosis, biopsy result and pathological report of the surgical specimen. Patients who had PSA level between 4 and 10 ng/ml was in Group 1; and the other patients who had PSA level between 10.01 and 20 ng/ml were in Group 2. Gleason score upgrading was defined as any increase in GS between biopsy and radical prostatectomy specimens.

Statistical analyses were made using Chi-square for frequency and Mann-Whitney test for median values. The data were expressed as median (interquartile range (IQR) and frequency (%). The statistical analyses were performed using MedCalc Statistical Software Demo Version 16.2.0 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

RESULTS

There were 153 patients in this study. Of them, 109 (71.24%) were in group 1 and 44 patients (28.75%) were in group 2. In group 1, the median age and PSA level of the patients was 67 years and 6.12 ng/ml, respectively. According to the GS at prostate biopsy, 81 patients were 6 (3+3), 22 patients were 7 (3+4 and 4+3), 5 patients were 8 (4+4), and one patient was 9 (5+4). Gleason score concordance was detected in 73 patients (66.97%), with higher and lower-grades reported in 32 (29.35%) and 4 patients (3.67%), respectively. At final pathology, 89 patients (81.65%) had localised PCa and 20 patients (18.34%) had locally advanced disease.

In group 2, the median age and PSA level of the patients was 64.5 years and 12.45 ng/ml, respectively. Number of the patients with GS 6 (3+3), 7 (3+4 and 4+3) and 8 (4+4) was 29 (65.90%), 13 (29.54%) and 2 patients (4.54%), respectively. Of these 44 patients, 26 patients (59.09%) matched the pathological findings, 14 patients (31.81%) had higher-graded and four patients (9.09%) had lower-graded at final pathology. The result of analyses on radical prostatectomy specimens: 37 patients (84.09%) and seven patients (15.90%) were diagnosed as organ-confined and locally advanced PCa.

Table I: Demographic data of the patients.

	Group 1	Group 2	p-value
No. of the patients, n (% of total cases)	109 (71.24)	44 (28.75)	
Median (IQR) age, years	67 (60-70)	64.5 (59-69)	0.130
Median (IQR) PSA, ng/ml	6.12 (5.06-7.5)	12.45 (11-16.75)	<0.001*
Median (IQR) Positive biopsy cores	2 (1-3)	2 (1-4)	0.632
Median (IQR) Biopsy GS	6 (6-7)	6 (6-7)	0.350
Gleason 6 n (% of group)	81 (74.31)	29 (65.90)	
Gleason 7 n (% of group)	22 (20.18)	13 (29.54)	
Gleason 8 n (% of group)	5 (4.58)	2 (4.54)	
Gleason 9 n (% of group)	1 (0.91)		

*GS = Gleason score, IQR = interquartile range. Mann-Whitney test was used for comparison of the groups (*statistically significant).*

Table II: Pathological results of the patients after radical prostatectomy (Mann-Whitney and Chi-square tests were used for median and frequency).

	Group 1	Group 2	p-value
Median (IQR) GS in prostatectomy specimens	6 (6-7)	7 (6-7)	0.627
Gleason 6 n (% of group)	59 (54.12)	21 (47.72)	
Gleason 7 n (% of group)	40 (36.70)	20 (45.45)	
Gleason 8 n (% of group)	3 (2.75)	2 (4.54)	
Gleason 9 n (% of group)	7 (6.42)	1 (2.27)	
GS concordance n (%)	73 (66.97)	26 (59.09)	0.357
Upgrading n (%)	32 (29.35)	14 (31.81)	0.764
Downgrading n (%)	4 (3.66)	4 (9.09)	0.174
T-stage			
Organ confined disease n (%)	89 (81.65)	37(84.09)	0.720
Local advanced disease n (%)	20 (18.34)	7 (15.90)	
Positive surgical margin n (%)	9 (8.25)	3 (6.81)	0.765

Table I shows the comparison of the groups for pre-operative data. There was significant difference for PSA levels between groups (p<0.001). At final pathology, there was no statistical difference for localised and local advanced disease, upgrading, downgrading, positive surgical margin and GS between groups (Table II).

DISCUSSION

Prostate cancer is one of the most common cancers and the second leading cause of cancer-related death in males in the United States of America.[9] The most established tumor marker is PSA for the diagnosis, staging, and monitoring of PCa patients. The risk of PCa increases with rising PSA levels; and the cut-off value for prostate biopsy is 4 ng/ml was accepted in most of the studies. Although widespread use of PSA testing for prostate biopsy, 30-35% of the patients have PCa in males with PSA less than 10 ng/ml.[10] D'Amico risk classification is the most widely used criteria for localised PCa classification.[11] This classification criteria include PSA level, GS, and clinical T stage. PSA levels are divided into three groups as <10, 10-20 and >20 ng/ml.

Radical prostatectomy is the gold standard treatment in young patients diagnosed with organ confined PCa.[9] Unfortunately, only 66% of males have localised PCa with PSA level between 4-10 ng/ml. Dariane *et al*. reported that 74.9% of the patients with PSA level between 4-10 ng/ml had localised disease at final pathology.[9] In another study from Japan, the authors investigated the small number of patients (n=29) and reported the rate of organ confined disease at final pathology as 66.7%.[12] Jeong *et al*. reported the localised PCa rate with PSA level <10 ng/ml among Korean, Caucasian and African-American population was 72.7%, 88.1% and 86.3%, respectively.[13] The authors found

that 84% of the patients with PSA level 4-10 ng/ml had organ confined disease after robot-assisted radical prostatectomy.[14] In this study, the localised disease rate was detected as 81.65% of the patients with PSA level between 4-10 ng/ml.

In a review of patients with PCa, Singh *et al*. found that 80.4% of males with PSA level between 10 and 20 ng/ml had organ confined disease after robot-assisted radical prostatectomy.[14] In another study, the authors reported the rate of organ confined PCa was 44% in the patients with PSA 10-20 ng/ml after open radical prostatectomy.[15] In the present study, 84.09% of the patients had organ confined disease. Interestingly, this rate is higher than the patients with PSA level 4-10 ng/ml without the statistically significant difference (p=0.721).

The Gleason grading system is the most commonly used grading system for PCa.[16] Concordance of GS is mandatory for preoperative estimation of the disease and planning the treatment. However, the biopsy GS has been reported to have been undergraded in 18-60% and overgraded in 6-25% of the patients after radical prostatectomy. High PSA level, older age, more positive cores, greater maximum percentage involvement of biopsy core, and small prostates are associated with risk of upgrading.[17] The authors found that GS upgrading was 35.8% of males with PSA level between 4 and 10 ng/ml.[9] In another study from Japan consisting 1,629 patients, 21.9% and 16.1% of the patients were upgraded and downgraded, respectively.[16] Hong *et al*. reported that 39.9% and 42.17% of the patients with PSA level of <10 and 4-10 ng/ml, respectively have upgraded.[18] The authors from Korea and USA investigated the upgrading for Korean, Caucasian and African-American patients with PSA level less than 10 ng/ml, cT1 and GS 6, and found the upgrading rate was 59.4%, 30.2% and 26.2% of the patients, respectively. In the present study, 29.35% of the patients were upgraded in the PSA level of 4-10 ng/ml. In patients with PSA level of 10-20 ng/ml, the upgrading rate was 31.81% and there was no significant difference between groups (p=0.764). The downgrading was detected in 3.66% and 9.09% of the patients with PSA level of 4-10 and 10.01-20 ng/ml in the current study (p=0.174).

The positive surgical margins (PSMs) after radical prostatectomy means incomplete cancer resection, leading the surgeon to decide treatments such as: active surveillance, adjuvant radiotherapy or androgen-deprivation therapy.[19] In a contemporary series, the incidence of PSM after radical prostatectomy was reported in 11-38% of the patients. Patients younger than 50 years, older than 70 years of age, PSA $\geq$10 ng/mL, GS $\geq$7 at final pathology, pathologic stage $\geq$T2b, tumor volume $\geq$10% of specimen's total volume, and presence of capsular and perineural invasion are associated with occurrence of PSMs. Authors from Brazil, reported that 66% and 86% of the patients with PSA level of <10 ng/ml and 10-20 ng/ml had PSMs after final pathology.[19] Dariane *et al*. reported that 15.6% of the patients were reported PSM with PSA level between 4 and <10 ng/ml.[9] In the current study, PSMs were positive in 8.25% and 6.81% of the patients in group 1 and 2, respectively.

The current study had some limitations. First, patients treated in single institution might not be representative of the general population. Second, this was a retrospective study consisting small number of the patients. Third, data is lacking for biochemical recurrence and survival in follow-up period. Apart from these limitations, to our knowledge, this is the first study of comparing the radical prostatectomy results of the patients with PCa, according to the PSA levels (4-10 and 10.01-20 ng/ml).

CONCLUSION

The present study showed that serum PSA level at the diagnosis was unrelated to poor pathological outcomes. Additional studies, including large number of patients from multiple centres, are needed to define the relationship between PSA level and pathological outcomes such as stage, upgrading, positive surgical margin and GS at radical prostatectomy.

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