

# Effects of prostatectomy in patients with elevated serum prostate specific antigen levels and lower urinary tract symptoms: A prospective study

Şenol Adanur<sup>a,\*</sup>, Hasan Rıza Aydın<sup>b</sup>, Tevfik Ziypak<sup>a</sup>, Erdem Koç<sup>a</sup>, Turgut Yapanoğlu<sup>a</sup>, İsa Özbey<sup>a</sup>, Özkan Polat<sup>a</sup>

<sup>a</sup>Department of Urology, Medical Faculty, Ataturk University, Erzurum, Turkey

<sup>b</sup>Department of Urology, Akçaabat Haçkalı Baba Hospital, Trabzon, Turkey

**Abstract.** Our aim is to determine the impact of prostatectomy on serum prostate specific antigen levels in patients with Lower Urinary Tract symptoms (LUTS), but negative multicore prostate biopsy results and higher serum prostate specific antigen levels.

100 patients were referred to our clinics with lower urinary system symptoms without any evidence of suspect prostate carcinoma in digital rectal examination, and transurethral ultrasound (TRUS). Patients with histopathologically benign diagnoses in prostatic biopsy because of higher serum prostate specific antigen (PSA) levels (PSA>4ng/ml) were retrospectively evaluated. The association between preoperative and postoperative 3 and 6 month serum PSA levels were statistically evaluated in patients who had undergone transurethral resection of the prostate (TUR-P) or open prostatectomy resection with the diagnosis of benign prostatic hyperplasia (BPH), and also correlation between changes in serum PSA levels and histopathologic diagnosis was analysed.

The preoperative mean total PSA (tPSA) and free PSA (fPSA) values were 16.89 ng/mL and 3.65ng/mL, respectively. Postoperative 3 month- mean tPSA and fPSA values were 1.34 and 0.4ng/mL, while postoperative 6 month mean tPSA and fPSA values were determined as 1.59 and 0.56ng/mL, respectively. Postoperative histopathologic evaluation of the surgical specimens of the patients revealed BPH in 84%, BPH + prostatitis in 12%, and prostate cancer 4% of the cases, respectively.

BPH surgery can be performed safely on patients with symptomatic BPH and increased PSA levels without any evidence of prostate carcinoma. Favourable and comforting results can be achieved with BPH surgery, which improves symptoms and normalises PSA values.

Key words: Prostate specific antigen, benign prostatic hyperplasia, prostatectomy

## 1. Introduction

The most frequently employed biochemical parameter in clinical practice used in the differential diagnosis of Benign Prostatic Hyperplasia (BPH) and prostate carcinoma is the level of serum prostate specific antigen (1). The upper limit of serum PSA is acknowledged as 4.0ng/ml. A strong correlation has been demonstrated between BPH patients, PSA levels,

and prostate volume (2). Following prostatectomy operations such as TUR-P or open enucleation, the transitional zone which harbours PSA secreting epithelial cells are resected, and after a while a decrease in PSA levels is anticipated in proportion with the amount of resected tissue (3).

Patients with increased serum PSA levels without any biopsy-proven disease are frequently encountered problematic cases in our urology practice. Patients with negative biopsy results are monitored closely, many of them are re-biopsied, and in particular certain cases with presumptive diagnosis of prostatitis are re-evaluated after a course of anti-biotherapy (4). In spite of all of these, urologists remains in difficult situation if the pathology can not be put forth which explains increased PSA levels. This uncertainty

\*Correspondence: Dr. Şenol Adanur  
Department of Urology, School of Medicine Ataturk  
University 25240 Erzurum, Turkey  
Phone: +90442 3166666-7627  
Fax: +90442 3166688  
E-mail: s.adanur61@hotmail.com  
Received: 02.10.2013  
Accepted: 21.11.2013

complicates the diagnostic decision-making process.

Aim of this study is to investigate the effects of prostatectomy on serum PSA levels in BPH patients with increased serum PSA levels, lower urinary tract symptoms and negative multi-site biopsy.

## **2. Materials and method**

This study included 100 patients referred to our clinics with lower urinary tract symptoms between June 2007, and December 2009 who had undergone prostatic biopsy because of higher PSA levels (PSA>4ng/mL). TUR-P or open prostatectomy was performed on these patients with the indication of BPH whose histopathologic results were reported as cancer-negative. A detailed medical history was obtained from all patients, and the patients were also asked to fill in International Prostate Symptom (IPSS) questionnaire forms. Any medication that the patients were taking for the treatment of BPH was also inquired about. The patients underwent a physical examination, Digital Rectal Examination (DRE), hematologic and biochemical tests, complete urinalysis, uroflowmetric and ultrasonographic tests. Serum samples for PSA analysis were obtained before DRE. Within the previous 4 weeks, any urologic or rectal manipulation such as a rectal examination, cystoscopy, urethral catheterisation, TUR, rectal endoscopic procedures and prostate massage was not performed on the patient.

The PSA levels of the patients were measured using electrochemiluminescent immunometric methods using a Modular E-170 autoanalyser device (Roche, In, USA). Patients with serum PSA levels above 4ng/mL underwent TRUS for the determination of the prostate volume and morphology as well as TRUS guided 14-core prostate biopsy for histopathologic diagnosis was performed. Any case of suspected malignancy and remarkable DRE findings were excluded from the study and a re-biopsy was planned.

TRUS and 14-core biopsy procedures were performed using the Siemens Sano Line-1 (SLE-1) ultrasound device and with a 7.5MHz biplanar transrectal probe. One day before the biopsy all patients started to receive prophylactic oral antibiotics (ciprofloxacin 500mg tablet 2x1), which was maintained for 48-72 hours after the procedure. One hour before the procedure, a rectal enema (Libalaks®) was applied to eliminate artefacts interfering with the image quality. Assuming an ellipsoid configuration for the prostate, prostate volume was estimated using the following formula: Anteroposterior diameter

x transverse diameter x longitudinal diameter x  $\pi$  /6.

An 18G, 22/30 automated Tru-Cut® biopsy needle was used for the biopsy procedure. From all patients, systematic 14-core prostate biopsy materials were retrieved from both sides of the prostate on a sagittal axis (apex, apex periphery, mid-gland, mid-gland periphery, basal, basal periphery and transitional zone). All patients with histopathologic diagnosis of BPH were included in our study. Suprapubic transvesical sub-capsular open prostatectomy or TURP was performed on patients with the indication of clinical BPH.

Indications for prostatic surgery include obstructive urinary symptoms, catheter-dependent acute or chronic retention, refractoriness to medical treatment and post-void residual urine volume of more than 100ml.

According to the preference of the surgeon, the TUR-P operation was performed using a continuous flow 24F or 26F resectoscope (K. Storz or Olympus). As irrigation fluid Resectisol® solution with 5% mannitol was used, and the operation was terminated within an hour, which is considered to be the optimal operative time. At the end of the operation a 20F 3-way prostatectomy catheter was inserted via the transurethral route. Urethral catheters were removed an average of 3 days after TUR-P, and 5 days following open prostatectomies.

The patients were divided in 3 groups based on postoperative histopathologic diagnoses as prostate carcinoma, BPH, and prostatitis + BPH. The patients were called for control visits at months 3 and 6 for the detection of serum PSA levels, and re-evaluation of their health status.

The relationship between preoperative and postoperative 3, and 6 month serum PSA levels were evaluated statistically and correlation of the changes in PSA levels with histopathologic diagnosis was analysed.

Statistical evaluation was performed using the SPSS 11.0 Windows ® software program. Data was expressed as numbers, percentages and means  $\pm$  standard deviation. Normality of data distribution was analysed by using the Kolmogorov-Smirnov test. Preoperative and postoperative 3 and 6 month-fPSA, and tPSA values were compared with Friedman variance analysis. For further analysis Wilcoxon test was used. Difference with a P<0.05 was considered to be statistically significant.

## **3. Results**

Suprapubic transvesical prostatectomy (n=79; 79%), and TUR-P (n=21; 21%) operation were

performed on 100 patients with a diagnosis of clinical BPH. The mean age of the operated patients was  $68.7 \pm 7$  years (age range: 43-82 years). The mean prostate volume was  $77.5 \pm 45.2$  cc (23-261) as detected by TRUS. The mean preoperative IPSS score was  $26.2 \pm 4.35$  (16-35). Patient and operation characteristics are listed in Table 1.

Mean values for total PSA were also determined as  $16.89 \pm 16.85$  ng/mL before the operation, and  $1.34 \pm 1.27$  ng/mL in 3rd months and  $1.59 \pm 1.44$  ng/mL in 6th months after the operation. Mean tPSA measured at 6th postoperative month was detected substantially decreasing ( $15.30$  ng/mL; 90%) ( $P=0.0001$ ). Mean tPSA measured at 6th postoperative month increased ( $0.25$  ng/mL; 18.6%) relative to postoperative 6th month estimates. ( $P=0.0001$ ). Table 2 shows statistical comparisons among mean fPSA, and tPSA values before and 3rd and 6th months after the operation.

Preoperative (Pre-op-fPSA), postoperative 3rd and 6th month mean free PSA values were detected as  $3.65 \pm 5.87$  ng/mL,  $0.40 \pm 0.27$  ng/mL and  $0.56 \pm 0.29$  ng/mL, respectively. An 89% ( $3.25$  ng/mL) decrease was found in fPSA levels measured at postoperative 3rd months in comparison with preoperative mean fPSA values. ( $P=0.0001$ ). In addition, an 85% ( $3.09$  ng/ml) reduction was noted in postoperative 6th month mean fPSA levels when compared with preoperative fPSA levels ( $P=0.0001$ ). The mean free PSA level at postoperative 6th month was increased 40% ( $0.6$  ng/ml) relative to postoperative 3rd month estimates ( $P=0.0001$ ).

Among patients included in the study, one TUR-P, and 2 open prostatectomy patients had higher than normal ( $4.0$  ng/mL) serum PSA values at 3rd and 6th postoperative months. These patients were included in the postoperative follow-up protocol consisting of assessments by DRE, PSA measurements, and TRUS.

Histopathologic evaluation of the resected materials was reported as BPH (84%), BPH + prostatitis (12%), and prostate carcinoma (4%). In all patients with prostate carcinoma, PSA values at postoperative 3rd and 6th months were below  $4$  ng/mL.

#### 4. Discussion

It has been acknowledged that PSA is not a specific marker for prostate carcinoma, but its levels also increase in BPH, prostatitis and after urologic procedures such as cystoscopy, prostate biopsy and digital rectal examination (5). Owing to the specialised structure of the prostatic glandular epithelium of the basal membrane and its barrier function, only a very small proportion of higher concentrations of PSA in ductal and glandular lumen are detected in plasma, and the average serum PSA levels in healthy individuals rarely exceed  $4$  ng/mL (6).

Higher serum PSA values in prostate carcinoma relative to BPH can be explained by disruption of the prostate–blood barrier. Therefore, in conditions impairing normal prostate histopathology, increases in PSA values are anticipated. BPH and inflammatory conditions of the prostate belong to this category. Increased

Table 1. Patient and operative characteristics

Number of patient	100
Mean age	$68.7 \pm 7$ (43-82)
Mean preoperative TRUS (cc)	$77.5 \pm 45.2$ (23-261)
Mean preoperative IPSS score	$26.2 \pm 4.35$ (16-35)
Mean preoperative total PSA (ng/mL)	$16.89 \pm 16.85$
Mean preoperative PSA (ng/mL)	$3.65 \pm 5.87$
Type of operation	
Suprapubic transvesical prostatectomy (%)	79 (79)
TUR-P	21 (21)
Postoperative histopathology (%)	
BPH	84
BPH+Prostatit	12
Prostat Ca	4

Table 2. Pre-operative, postoperative 3 and 6 month mean free, and total PSA levels, and their statistical comparisons

	Preoperative	Post.op 3month	Post.op 6month	p- value
Free PSA (ng/ml)	$3.65 \pm 5.87$	$0.40 \pm 0.27$	$0.56 \pm 0.29$	0.0001
Total PSA (ng/ml)	$16.89 \pm 16.85$	$1.34 \pm 1.27$	$1.59 \pm 1.44$	0.0001

prostate volume has been stated as an important factor inducing elevations in PSA concentrations (7). Following TUR-P or open prostatectomy, resection of the transitional zone, which contains PSA secreting epithelial cells, a decrease in PSA levels is anticipated after a while in proportion with the amount of prostate tissue removed (3). In adenomectomized BPH patients, a sudden drop in serum PSA levels associated with the amount of the resected prostate gland was reported. Although estimates differ with the screening method used, for every 1g of BPH tissue resected, a 0.1-0.3ng/mL decrease in serum PSA levels was reported (7). In a study performed by Aus et al. (8) the investigators detected an approximately 70% decrease in mean serum PSA levels from preoperative 6ng/ml to 1.9ng/ml at postoperative 3rd months. Furuya et al. (9) revealed a 67% decrease in mean serum PSA levels from preoperative 6.2ng/ml to 2ng/ml. In our study a 92% decrease in mean tPSA, and an 89% drop in fPSA levels was observed at postoperative 3rd months relative to preoperative values.

Marks et al. (10) reported that mean serum PSA levels dropped from preoperative 4.6ng/mL to 0.7ng/mL at postoperative 6th months and remained at the same level for 5 years after the operation. Fonseca et al. (11) reported a 71% decrease in mean tPSA levels from preoperative 6.19ng/mL to 1.79ng/mL measured at post-TUR-P 6th months. We also detected 90.5% and 85% decreases in mean tPSA, and fPSA levels at post-TUR-P 6th months when compared with the preoperative values.

Marks et al. (10) detected similar PSA levels 6 months and 5 years after prostatectomies, and reported PSA velocities nearing zero. In a study by Renterghem et al. (12) during 2 years of follow-up after TUR-P, a significant change in serum PSA levels was not reported at postoperative 1st and 2nd years. However, in our study, when compared with postoperative 3rd month measurements, a statistically significant increase in serum PSA levels was found at 6th months. In addition, an increase in the incidence of infection can be seen within 6 months after cessation of 2 months of postoperative anti-biotherapy. We supposed that the increase in serum PSA levels detected at postoperative 6th months might be attributed to the termination of anti-biotherapy.

In the literature, it was reported that higher preoperative serum PSA levels should return to normal ranges during the postoperative follow-up period of patients who had had TUR-P and open prostatectomy operations with the indication of BPH. Following a complete TUR-P operation,

higher preoperative PSA levels in 90% of the patients dropped below 4ng/ml as indicated in some literature studies (8). In a study by Renterghem et al. (12) higher preoperative PSA levels returned to normal after TUR-P operation in all patients with a clinical diagnosis of BPH without any histopathologic evidence of malignancy in biopsied specimens (12). However, in a separate study the same author observed significant decreases in serum PSA levels of BPH patients within one year after TUR-P operations. In most of the cases, PSA levels were below 1ng/ml. In the abovementioned study at postoperative 1year one patient and at 2 years two cases had serum PSA levels above 4ng/mL (13). Furuya et al. (9) reported that serum PSA values of 9 out of 94 study patients remained at higher levels (>4ng/mL) even after 3 months after the prostatectomy operations, and 7 of these 9 patients underwent a TUR-P operation. In our study one TUR-P and 2 open prostatectomy patients had higher serum PSA (>4.0ng/mL) levels at 3rd and 6th postoperative months.

In a literature study performed on 131 BPH patients with normal DRE findings, and PSA values above 4ng/ml, focal acute prostatitis, chronic prostatitis, prostatic infarct areas abscess formation and prostate stones were detected in 64% of the patients after histopathologic examination of TUR-P or retro pubic adenomectomy specimens, which were significantly related to elevation of PSA levels (14). In a study by Nadler et al. (15) the effect of prostate volume, inflammation, suspect TRUS results and prostate stones on PSA was analysed and in conclusion the authors reported that the most important factors inducing PSA elevation in patients without prostate carcinoma were increased prostate volume and inflammation. In a literature study encompassing 30 patients with increased preoperative PSA values who had later undergone TUR-P operation, histopathologic diagnoses of chronic prostatitis plus BPH, and BPH were reported in 40% and 60% of the patients, respectively (11).

In spite of the information mentioned above, some studies reported that higher serum PSA levels were not associated with prostatitis. In a study performed on 66 patients with BPH, biopsy results were examined with respect to their relationship with PSA levels. The authors reported that subclinical inflammation of the prostate was not related to increased PSA levels, and they were unable to find a significant correlation between prostatic inflammation and serum PSA levels (16). In a study conducted by Renterghem et al. (13) although in postoperative

histopathologic examination of only 5 out of 74 BPH patients, inflammation, and prostatitis were detected, although the authors did not suggest inflammation as the fundamental underlying cause of increased PSA levels. In our case, postoperative histopathologic examination of 100 cases revealed chronic prostatitis associated with BPH in 12% of the patients, and we obtained results similar to those suggesting lack of any correlation between higher PSA levels, and prostatitis.

Renterghem et al. (13) performed TUR-P operation on 82 patients who had undergone prostatic biopsy because of higher PSA levels. Only in 9.8% of these patients, postoperative histopathologic examination revealed evidence of prostate carcinoma (13). In addition, Marks et al. (10) detected prostate carcinoma in 7.3% of their 82 patients during 5 years of follow up after a TUR-P operation. Mean PSA velocities in patients who developed prostate carcinoma after BPH surgery were found to be significantly higher when compared with those. (TUR-P, 0.38–0.06ng/mL/year; open prostatectomy, 0.47–0.13ng/mL/year;  $p < 0.05$ ). They reported that PSA velocities could be used during post-BPH monitorization (17). In our study, prostate carcinoma was detected in 4 (4%) out of 100 patients, and in all of these 4 cases postoperative 3 and 6 month-PSA values were below 4ng/mL. These patients were treated in compliance with the treatment principles of the European Association of Urology (EAU).

## 5. Conclusion

In conclusion, symptomatic BPH patients with higher serum PSA levels, but negative histopathologic results can undergo BPH surgery. Comforting and favourable results can be obtained in terms of symptomatic improvement and normalization of PSA levels. If postoperative histopathologic results indicate a benign course, these patients can be followed up without discarding the possibility of prostate carcinoma.

## References

1. Catalona WJ, Riehle JP, Ahmann FR et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial. *J Urol* 1994; 151: 1283-1290.
2. Roehrborn CG, McConnell JD, Lieber M et al. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. *Urology* 1999; 53: 473-480.
3. Wolff JM, Boekels O, Borchers H et al. Altered prostate specific antigen reference range after transurethral resection of the prostate. *Anticancer Res* 2000; 20: 4977-4980.
4. Van renterghem K, Van Koeveringe G, Achten R, Van Kerrebroeck P. Clinical relevance of transurethral resection of the prostate in "asymptomatic" patients with an elevated prostate-specific antigen level. *Eur Urol* 2007; 52: 819-826.
5. Dew T, Coker C, Saadeh F et al. Influence of investigative and operative procedures on serum prostate-specific antigen concentration. *Ann Clin Biochem* 1999; 36: 340-346.
6. Coker CB, Coptcoat MJ, Mulvin D et al. The release of free prostate specific antigen into the circulation during transurethral resection of the prostate: kinetics and interaction with serum protease inhibitors. *Br J Urol* 1998; 81: 105-108.
7. Stamey TA, Yang N, Hay AR et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987; 317: 909-916.
8. Aus G, Bergdahl S, Frösing R et al. Reference range of prostate-specific antigen after transurethral resection of the prostate. *Urology* 1996; 47: 529-531.
9. Furuya Y, Akakura K, Tobe T et al. Changes in serum prostate-specific antigen following prostatectomy in patients with benign prostate hyperplasia. *Int J Urol* 2000; 7: 447-451.
10. Marks LS, Dorey FJ, Rhodes T et al. Serum prostate specific antigen levels after transurethral resection of prostate: a longitudinal characterization in men with benign prostatic hyperplasia. *J Urol* 1996; 156: 1035-1039.
11. Fonseca RC, Gomes CM, Meireles EB et al. Prostate specific antigen levels following transurethral resection of the prostate. *Int Braz J Urol* 2008; 34: 41-48.
12. Van Renterghem K, Van Koeveringe G, Van Kerrebroeck P. Rising PSA in patients with minor LUTS without evidence of prostatic carcinoma: a missing link? *Int Urol Nephrol* 2007; 39: 1107-1113.
13. Van Renterghem K, Van Koeveringe G, Achten R et al. Clinical relevance of transurethral resection of the prostate in "asymptomatic" patients with an elevated prostate-specific antigen level. *Eur Urol* 2007; 52: 819-826.
14. Ferrero Doria R, Pérez Flores D, Terrer Artes C et al. Impact of prostatic benign hyperplasia and prostatic inflammation on the increase of prostate specific antigen levels. *Actas Urol Esp* 1997; 21: 100-104.
15. Nadler RB, Humphrey PA, Smith DS et al. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. *J Urol* 1995; 154: 407-413.
16. Irani J, Levillain P, Goujon JM et al. Inflammation in benign prostatic hyperplasia: correlation with prostate specific antigen value. *J Urol* 1997; 157: 1301-1303.
17. Helfand BT, Anderson CB, Fought A et al. Postoperative PSA and PSA velocity identify presence of prostate cancer after various surgical interventions for benign prostatic hyperplasia. *Urology* 2009; 74: 177-183.