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The role of transurethral resection of the prostate for patients with an elevated prostate-specific antigen

Hee Ju Cho, Soon Cheol Shin, Jeong Man Cho, Jung Yoon Kang, Tag Keun Yoo

Department of Urology, Eulji General Hospital, Eulji University School of Medicine, Seoul, Korea

Purpose: The aim of this study was to define the clinical significance of transurethral resection of the prostate (TURP) in patients with benign prostate hyperplasia (BPH) and an elevated prostate-specific antigen (PSA) level.

Methods: We retrospectively evaluated patients with BPH, lower urinary tract symptoms (LUTS; International Prostate Symptom Score [IPSS] ≥ 8), an elevated serum PSA level (≥ 4 ng/mL), and previous negative transrectal ultrasonography (TRUS) guided prostate biopsy. The PSA level after TURP was monitored by long-term follow-up. The tumor detection rate on resected prostate tissue, IPSS, maximal urinary flow rate (Qmax), and postvoid residual urine (PVR) were analyzed.

Results: One-hundred and eighty-six patients were enrolled. Histological examination of resected tissue by TURP revealed prostate cancer in 12 of these patients (6.5%). Among 174 patients without prostate cancer, the mean PSA level and the PSA normalization rate in 112 patients followed up at postoperative day (POD) 3 months were 1.26 ± 0.13 ng/mL and 94.6%, respectively. The mean PSA level and the PSA normalization rate were 1.28 ± 1.01 ng/mL and 95.7% in 47 patients at 1st year, 1.17 ± 0.82 ng/mL and 97.1% in 34 patients at second years, and 1.34 ± 1.44 ng/mL and 97.2% in 36 patients at third years of TURP. One patient showed a dramatic increase in the PSA level was diagnosed with prostate cancer at 7 years after TURP. IPSS, quality of life, Qmax, and PVR were improved significantly at POD 3 months compared to baseline ($P < 0.05$), respectively.

Conclusions: TURP significantly reduced the serum PSA level, which was maintained for at least 3 years. This could be helpful to screen the prostate cancer using PSA value in the patient with previous negative biopsy and elevated PSA. In addition, TURP improves IPSS, Qmax, and PVR in patients with BPH, moderate LUTS, and an elevated PSA level.

Keywords: Transurethral resection of prostate, Prostate-specific antigen, Prostate neoplasms

INTRODUCTION

The serum prostate-specific antigen (PSA) level allows for the early diagnosis and a chance for successful treatment of prostate cancer. However, PSA is not a cancer-specific marker, and other factors can increase its level as well [1]. While patients with an elevated PSA level and a positive prostate biopsy are treated by radical prostatectomy, radiotherapy, or hormonal therapy, treatment methods are not defined for patients with an elevated or rising serum PSA level despite previous negative prostate biopsy. Although the % free-PSA, PSA density (PSAD), PSA velocity, and age-specific PSA are useful clinical parameters, they are not sufficient to prevent misdiagnosis [2]. In addition, the accuracy of the prostate biopsy diagnosis is enhanced by increasing the number of biopsy cores and changing the biopsy target zone [3]; however, although repeated and extended biopsies were negative, the anxiety by the elevated or rising PSA does not disappear.

Studies have shown an α-blocker and a 5-α reductase inhibitor (5-ARI) to improve lower urinary tract symptoms (LUTS)

Corresponding author: Tag Keun Yoo
Department of Urology, Eulji General Hospital, Eulji University School of Medicine, 68 Hangeulbiseok-ro, Nowon-gu, Seoul 139-711, Korea
E-mail: ytk5202@eulji.ac.kr / Tel: +82-2-970-8305 / Fax: +82-2-970-8517
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and to block the progression of BPH [4,5]. However, the α-blocker cannot reduce the PSA. Although the 5-ARI reduces the PSA, quantification of the PSA level may be inaccurate because the response of PSA to 5-ARI is heterogeneous [6,7]. In addition, the previous studies that concerned increasing of the high grade prostate cancer incidence after 5-ARI treatment [8] give another difficult issue to the doctor in the treatment of the BPH with the elevated or rising PSA.

The aim of this study was to define the clinical significance of transurethral resection of the prostate (TURP) in patients with BPH and an elevated PSA level in terms of PSA value, oncologic and functional outcomes.

MATERIALS AND METHODS

Patients who came to the hospital for LUTS from March 2003 to August 2010 were included in this study. Except for those who were previously treated by TURP, patients received 5-ARI, underwent transurethral instrumentation or catheterization, and showed acute urinary retention (AUR) within the past 6 weeks. A prostate biopsy was performed when the serum PSA level was >4 ng/mL. After exclusion of patients with prostate cancer in previous prostate biopsy, patients who had indications for TURP such as persistent (LUTS) despite medical treatment, recurrent acute AUR or bladder stone etc., were underwent surgery, and the medical records of these patients were examined retrospectively.

All prostate biopsy was performed by transrectal ultrasonography (TRUS) guided prostate biopsy. In this hospital, eight core biopsies, including two transitional zone and six standard core biopsies [9], were performed from 2003 to 2007. Fourteen core biopsies, including 12 cores and two transitional zone biopsies, were performed from 2008. Before TURP, a urodynamic study (UDS) was performed in selected patients, and the bladder outlet obstruction index (BOOI = detrusor pressures at peak flow–2 maximal urinary flow rate) was calculated [10]. Under spinal or general anesthesia, TURP was performed with a mono- or bipolar loop resectoscope. The experienced pathologist histologically examined the resected prostate tissue. Three months after TURP, the serum PSA level, maximal urinary flow rate (Qmax), postvoid residual urine (PVR), and IPSS (International Prostate Symptom Score) were determined. The serum PSA level was measured at 3- or 6-month intervals for 3 years. The ethics committee approved this study.

RESULTS

One-hundred and eighty-six patients were enrolled based on inclusion criteria. Table 1 lists the preoperative variables. Twelve patients (6.5%) were diagnosed with prostate cancer by TURP (one patients, Gleason score of 8; five patients, Gleason score of 7; five patients, Gleason score of 6; and one patient, Gleason score of 4). Except for 12 patients with prostate cancer, 174 patients were analyzed. The preoperative serum PSA level of the 12 patients with prostate cancer and the 174 patients without cancer was 7.15±2.36 and 8.47±4.16 ng/mL, respectively. The PSAD was 0.13±0.04 and 0.14±0.1, respectively. There was no significant difference in the PSA and PSAD compared to patient with prostate cancer (Table 1).

The average serum PSA level was 1.26±1.13 ng/mL in 112 patients followed up at 3 months after TURP, 1.28±1.01 ng/mL in 47 patients at 1 year, 1.17±0.82 ng/mL in 34 patients at 2 years; and 1.34±1.44 ng/mL in 36 patients at 3 years (Fig 1).

Table 1. Preoperative clinical variables

Variable	All patients (n=186)	Patients without cancer (n=174)	Patients with cancer (n=12)
Age (yr)	71.4±8.12	71.3±8.1	72.9±8.1
PSA (ng/mL)	8.48±4.1	8.69±4.62	7.15±2.36
Prostate volume (mL)	71.5±27.4	72.2±27.6	60.0±21.5
Transitional volume (mL)	43.7±37.2	44.3±38.1	34.5±18.2
PSAD	0.14±0.10	0.14±0.98	0.13±0.44
Resected weight (g)	27.7±17.6	27.5±17.5	30.2±18.7
BOOI	56.3±29.9	56.3±30.4	64.4±31.0
Qmax (mL/sec)	8.69±3.89	8.6±3.9	9.84±3.27
PVR (mL)	132.3±198.9	129.3±197.3	178.4±242.2
Total IPSS	20.1±8.1	20.1±8.0	19.3±10.0
QoL	4.3±1.27	4.28±1.19	3.4±2.0

Values are presented as mean±standard deviation.
PSA, prostate specific antigen; PSAD, PSA density; BOOI, bladder outlet obstruction index; Qmax, maximal urinary flow rate; PVR, postvoid residual urine; IPSS, international prostate symptom score; QoL, quality of life.

The PSA normalization rate at the third month, and first, second, and third year after TURP was 94.6% (106/112), 95.7% (45/47), 97.1% (33/34), and 97.2% (35/36), respectively (Table 2). Of the 112 patients followed up at 3 months after TURP, 40, 28, and 31 patients continued to be followed for first, second, and third years after TURP, respectively. During three years follow-up, the serum PSA level increased by >1 ng/mL in three patients. One of these three patients did not show PSA normalization and presented with atypical small acinar proliferation after three consecutive prostate biopsies. Another patient was diagnosed with prostate cancer 7 years after TURP. During the initial visit, the patient had a serum PSA level of 15.7 ng/mL; however, it decreased to 1.69 ng/mL after TURP. Seven years after TURP, the PSA level increased again to 8.12 ng/mL, and the patient was diagnosed with prostate cancer by TRUS guided biopsy. Robot-assisted laparoscopic radical prostatectomy was performed, and the cancer was staged as T3cN0M0 with a Gleason score of 4+3.

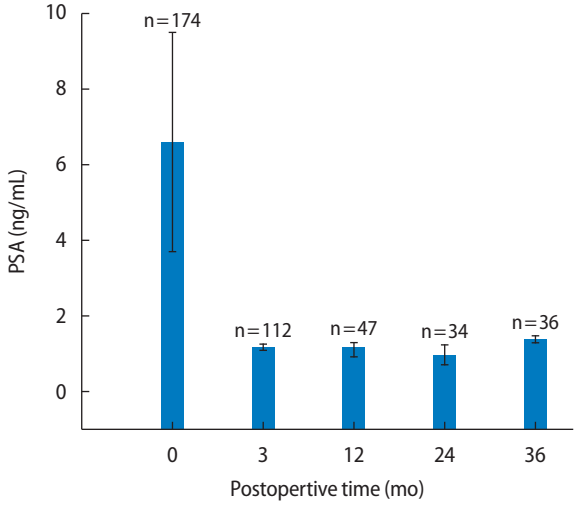

Fig. 1. The serum prostate specific antigen (PSA) level at baseline and postoperative months 3, 12, 24, and 36 after transurethral resection of prostate.

Of the 115 patients who received preoperative UDS, the preoperative PSA level and the PSAD of 80 patients with BOOI ≥ 40 were 8.81 ± 4.48 and 0.13 ± 0.07 ng/mL, respectively. There were no significant differences between these values and those of 35 patients with BOOI < 40 (9.24 ± 5.90 and 0.1 ± 0.17 ng/mL; P = 0.703 and P = 0.085). Seventy-nine patients who received preoperative UDS was measured postoperative PSA level at 3 months after TURP. Among these patients, the aver-

Table 2. Mean PSA and PSA normalization rate after transurethral resection of prostate

	Postoperative time (mo)			
	3	12	24	36
PSA normalization, n (%)	106/112 (94.6)	45/47 (95.7)	33/34 (97.1)	35/36 (97.2)
PSA (ng/mL), mean ± SD	1.26 ± 1.13	1.28 ± 1.01	1.17 ± 0.82	1.34 ± 1.44

PSA, prostate specific agent; SD, standard deviation.

Table 3. Characteristics in the patients[a] without prostate cancer according to the presence of urodynamic bladder outlet obstruction

Variable	Obstructive pattern (AG NO > 40, n = 55)	Nonobstructive pattern (AG NO ≤ 40, n = 24)	P-value
PSA (ng/mL)	9.37 ± 5.00	9.38 ± 5.96	0.996
Prostate volume (mL)	76.38 ± 24.34	65.18 ± 21.01	0.044
Transitional volume (mL)	42.69 ± 19.32	53.94 ± 85.7	0.531
PSAD	0.14 ± 0.08	0.18 ± 0.19	0.338
BOOI	67.5 ± 31.3	26.4 ± 10.9	< 0.001
Resection weight (g)	31.3 ± 17.3	23.7 ± 12.5	0.034
RPWR	0.59 ± 0.16	0.61 ± 0.27	0.700
Qmax (mL/sec)	8.71 ± 3.66	9.97 ± 4.03	0.223
PVR (mL)	181.2 ± 232.6	57.4 ± 51.7	0.016
Total IPSS	20.2 ± 7.9	18.7 ± 8.4	0.521
QoL	4.42 ± 1.20	3.95 ± 1.32	0.185
Extent of the PSA decrement at 3 months after TURP (ng/mL)	8.09 ± 4.96	8.09 ± 5.85	0.997

Values are presented as mean ± standard deviation.
AG NO, Abrams-Griffiths nomogram; PSA, prostate specific antigen; PSAD, PSA density; BOOI, bladder outlet obstruction index; RPWR, residual prostatic weight ratio, calculated as the prostate weight after TURP divided by the initial weight; Qmax, maximal urinary flow rate; PVR, postvoid residual urine; IPSS, international prostate symptom score; QoL, quality of life; TURP, transurethral resection of prostate.
[a]Seventy-nine patients underwent urodynamic study among 112 patients who followed up at 3 months postoperatively.

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age PSA decrement at the third month of the operation in 55 patients with BOOI ≥ 40 and 24 patients with BOOI < 40 were 78.09 ± 4.96 and 8.09 ± 5.85 ng/mL respectively (P = 0.997) (Table 3).

The biopsy results of resected tissue by TURP were as followed; 91 patients with nodular hyperplasia, 75 patients with chronic inflammation, eight patients with low-grade prostatic intraepithelial neoplasia (PIN) and 12 patients with adenocarcinoma. There was no significant difference in the preoperative PSA level, PSAD and the level of the PSA decrement at 3rd months of TURP between patients with different histologic characteristics. At third months after TURP, the IPSS decreased from 19.2 ± 8.0 to 7.5 ± 5.5 (P = 0.006) and the quality of life decreased from 4.2 ± 1.2 to 1.5 ± 1.1 (P = 0.04). The Qmax increased from 8.7 ± 4.0 to 15.6 ± 6.6 mL/sec (P = 0.04) and the PVR decreased 131.8 ± 201.0 to 30.0 ± 44.8 mL (P = 0.001).

Among 12 patients with prostate cancer, four patients with Gleason score < 7 were treated with active surveillance and four patients with Gleason score ≥ 7 were conducted hormonal therapy. Each of two patients with Gleason scores 6 and 7 requested surgical treatment and the biopsy result of these patients showed remnant prostate cancer less than 3% of specimen without overgraded cancer.

DISCUSSION

In BPH patients who were suspected as prostate cancer despite previous negative prostate biopsy, TURP normalized dramatically and maintained the PSA level for an extended period of time. TURP also could be helpful for diagnosis of clinically significant prostate cancer in transition zone, which was undetected in previous biopsy.

Approximately 20%–30% of prostate cancers are found in the transition zone or anterior portion of the prostate where it is difficult to obtain a TRUS biopsy [11]. Presently, magnetic resonance imaging (MRI) is the best modality to localize, monitor, and stage tumors. Studies have shown modern MRI techniques, including dynamic contrast-enhanced MRI, 3T-diffusion-weighted imaging and functional MRI, to increase the rate of tumors detected [12-14]. Other reports have examined prostates for suspicious lesions by MRI or MRI combined with a real-time TRUS-guided prostate biopsy [15,16]. Despite these advance, clinicians still have challenging issues in determining the additional prostate biopsies or the direction of future treatment in cases where the serum PSA level remains elevated.

TURP is another method that is useful in the detection of prostate cancer [17-20]. Yates et al. [19] report that the cancer detection rate in previous biopsy-negative patient was higher in receiving TURP and saturation prostate biopsy (SBx, 38.9%) than in receiving SBx alone (27.1%). Ploussard et al. [20] describe similar results, namely, a 28.5% increase in the cancer detection rate in 113 patients that underwent TURP plus 21-core biopsies compared to 21-core biopsies alone. In this study, 6.5% of previous biopsy-negative patients (12/186) were diagnosed with prostate cancer after TURP, and six of these patients had a Gleason score of ≥ 7. Taken collectively, these results indicate that TURP is invaluable in the detection of prostate cancer and building of treatment plan such as active surveillance for low grade cancer and surgical or hormonal therapy for aggressive cancer.

TURP can reduce PSA level in patient with BPH. Ploussard et al. [20] report that the serum PSA level normalized in 57% of patients after TURP. In addition, the average preoperative PSA level in patients without prostate cancer decreased from 10.4 to 4.2 ng/mL 1 month after TURP, and this level was maintained at 1 year after the procedure. Furthermore, van Renterghem et al. [21] report the cancer detection rate and the long-term monitoring of the PSA after performing the TURP in 82 consecutive patients with more than 4 ng/mL of the PSA and the negative previous prostate biopsy; the average PSA level of the 74 cancer free patents decreased from 8.2 to 0.9 ng/mL 1 year after TURP. Ninety-seven point two percentage of the patients (35/36) showed the permanent normalized PSA (< 4 ng/mL). In this study, the PSA level normalized in 95.5% of patients (106/112) at 3 months after TRUP (mean PSA, 1.26 ± 1.13 ng/mL), and this level was maintained in 97.2% of patients (35/36) 3 years after TRUP.

In study by Ploussard et al. [20], additional 21-core prostate biopsy was performed to the patients who did not show normalization of the PSA level after TURP. Six of the 30 patients (20%) were diagnosed as prostate cancer. In this study, we performed additional TRUS biopsy to the patients who showed increased PSA level after TURP. The PSA level increased by > 1 ng/mL in three patients during 3 years follow-up period; one of these three patients did not show PSA normalization for entire follow-up period and had one atypical small acinar proliferation in three consecutive prostate biopsies. Another two patients did not have the evidence of prostate cancer. The PSA level of another patient, who had PSA normalization after TURP, showed dramatically increased again to 8.12 ng/mL at 7 years after TRUP. Following a TURS biopsy, robot assisted laparoscopic radical prostatectomy was performed. These studies support that the TURP could normalize and maintained the PSA level persistently unless new prostate cancer newly developed. This could help prostate

cancer screening with PSA level easily performed and reduce the anxiety of prostate cancer for clinician and patients if PSA is not increased again.

The PSA level can increase due to many causes [1]. The PSA level is directly linked with bladder outlet obstruction (BOO), prostate volume, and BPH-related events. Laniado et al. [22] show an association between a high PSA level and urodynamically-defined BOO in patients with a PSA level < 10 ng/mL and LUTS. Van Renterghem et al. [21] also show a correlation between the urodynamically defined BOO and the PSA level before surgery, and they suggest that this is the reason for the increase in the PSA level in patients with a negative prostate biopsy. However, in this study, there was no significant difference of PSA and PSAD between the urodynamic obstructed group (BOOI ≥ 40) and the equivocal or unobstructed group (BOOI < 40). We thought that if the degree of BOO is strong cause of elevated PSA, the extent of PSA decrement after resolving of BOO could be correlated with PSA decrement. The residual prostatic weight ratio was between both groups but there is no significant difference; therefore, we could not prove the relationships between the urodynamically defined BOO and the elevated PSA.

Chronic inflammation without prostate cancer is one of the most frequent causes of an elevated PSA level. Kandirali et al. [23] report that the extent and aggressiveness of inflammation correlated positively with the serum PSA level and PSAD. Serretta et al. [24] show that the PSA level normalized in 59.6% of patients after using antibiotics for three weeks. When the PSA remained high even after the antibiotics treatment, there was a two-fold increase in the prostate cancer detection. In this study, 40.3% of patients (75/186) presented with chronic inflammation. However, there were no significant differences in the PSA level and PSAD in patients with chronic prostatitis or low-grade PIN, nodular hyperplasia and even adenocarcinoma. Under the hypothesis that reduction of prostate tissue presented an inflammation or abnormal cell could influence the extent of PSA decrement, we compared extent of the PSA decrement at 3 months after TURP between the patients with nodular hyperplasia and with chronic prostatitis but there was no significant difference. In the presence of low-grade PIN or prostate cancer, there was a little more decrease in the PSA level 3 months after TURP but was not statistically significant. We did not find the correlation between PSA and histologic feature of prostate.

While we did not show a correlation between the BOO level or histological features and PSA, we thought these factors are strong influencing factor of elevated PSA level. Prostate volume is also one of the solid reasons for elevated PSA level [25,26]. The prostate volume in the aforementioned several studies was 30–50 mL. But the average prostate volume of the patients enrolled in this study was 71.5 mL which is almost double the number of the average prostate volume (36.9 mL) of Korean male patients with LUTS [27]. Thus, a large prostate volume in present study may mask the effect of BOO and histologic feature on the increase of PSA level. In the clinical practice, elevated PSA despite negative prostate biopsy gives the doctor many difficulties to determine the direction of treatment. Furthermore, in patients with larger prostate, clinicians have more ambiguity for evaluating the reason of elevated PSA and there is a greater chance of missing the cancer by a TRUS biopsy compared to the patients with smaller prostate. Therefore, TURP followed by careful monitoring of the PSA level is the good method to detect undiagnosed prostate cancer and easily screen the newly developed prostate cancer without the anxiety for the elevated PSA.

There are several limitations in this study. This was a retrospective study, and data on the PSA level are missing in many cases after 1 year of TURP. But dramatic deceasing of PSA level was confirmative with large number of followed up patients at 3 months after TURP and this trend was persistently maintained up to 3 years. Additional prospective study with large number of patient is necessary to reveal definite conclusion and that will be helpful for further evaluation of the role of PSAV and PSAD for predicting newly occurrence of prostate cancer during follow up after TURP.

In conclusion, TURP can improve prostate cancer detection and effectively normalize the serum PSA level in long-term follow-up. It is thought that TURP makes the prostate screening using PSA level easier in patients with an elevated PSA level and a negative previous biopsy. We recommend that monitoring of PSA value and a TRUS biopsy on patients with an increased serum PSA level after TRUP. Further prospective study of a larger population and longer follow-up are necessary.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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