The Advantages of Transurethral Resection of the Prostate in Patients with an Elevated or Rising Prostate Specific Antigen, Mild or Moderate Lower Urinary Tract Symptoms, Bladder Outlet Obstruction and Negative Prostate Cancer Imaging or Prostate Biopsies: A Prospective Analysis in 105 Consecutive Patients

Evert Baten Koenraad van Renterghem

UZ Leuven, KU Leuven, Leuven, Belgium

Key Words

Prostate Specific Antigen • Bladder outlet obstruction • Transurethral Resection of the Prostate • PdetQmax • Prostate cancer

Abstract

Objective: To investigate elevated or rising prostate specific antigen (PSA) as a marker for bladder outlet obstruction (BOO) in patients with minor lower urinary tract symptoms (LUTS) and without prostate cancer. **Materials and Methods:** One hundred and five consecutive patients were prospectively analyzed between 2005 and 2013. All patients were referred to the principal investigator by their general practitioner as a result of an elevated and/or rising PSA. Only patients with minor LUTS [International Prostate Symptom Score (I-PSS) 0–19] and without suspicion for prostate cancer were included. All patients had BOO, shown by full urodynamics, and underwent transurethral resection of the prostate. The resected tissue was histologically examined

and PSA and I-PSS were evaluated after 3, 6 and 12 months and later on yearly. **Results:** Mean pre-operative PSA and I-PSS values were 8.8 ng/ml and 11.1, respectively. The mean detrusor pressure at maximum flow was 93.6 cmH₂O. The mean resected volume was 52 g and the mean prostate biopsy rate was 1.8. Eighty-three of 105 patients (79%) had no malignancy and were diagnosed with BOO due to benign prostate hyperplasia (subgroup 1). Their mean PSA decreased from 9.2 to 0.7 ng/ml and 0.9 ng/ml after 6 and 12 months post-operation, respectively. The mean I-PSS declined from 11 to 3 after 6 and 12 months. Sixteen of 105 patients (15%) were treated for prostate cancer (subgroup 2). Radical prostatectomy was performed in 11 patients, brachytherapy in 3 patients and external beam radiotherapy in 2 patients. Six of 105 patients (5.7%) had active surveillance (subgroup 3). **Conclusion:** BOO can cause an elevated or rising PSA in patients with minor LUTS and negative screening for prostate cancer. Transurethral resection of the prostate is an adequate treatment for these patients.

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Introduction

Patients presenting with a rising or elevated prostate specific antigen (PSA) value are a common problem in the daily, urology practice. Patients without signs of urinary tract infection and minor obstructive lower urinary tract symptoms (LUTS) are usually investigated by clinical examination, followed by imaging (transrectal ultrasound of the prostate). The next step is usually taking prostate biopsies or further imaging by MRI scan.

When pT1c prostate cancers are excluded and no significant lesions are seen on MRI, patients can be reassured and further follow-up by PSA and digital rectal exam is maintained. However what has to be done when PSA keeps on rising, despite previous negative investigations?

One can regularly follow-up the rising PSA value, although it can lead to anxiety in the patient. This can negatively influence quality of life (QoL), sexual function and be a cause of uncertainty in the general practitioner/urologist [1]. Antibiotics, like fluoroquinolones, are frequently used to lower the PSA value. Antibiotics however, have no effect on the PSA level and are the cause of significantly more frequent urinary tract infections with fluoroquinolone-resistant bacteria [2].

Dietary supplements as tomatoes (selenium), soybeans (isoflavones) or green tea (polyphenols) can be recommended but no sound theoretical base exists [3]. One can repeat prostate biopsies but only 13% of the repeated biopsies are positive for cancer. Prostate biopsies are also a stressful procedure for the patient, with risk of severe complications (urosepsis, hematuria, urinary tract infection) [2].

We subjected this subgroup of patients to a full urodynamic investigation and those with a proven bladder outlet obstruction (BOO), underwent a transurethral resection of the prostate (TURP). A supernormalisation of the PSA value was observed afterwards. This supernormalisation of the PSA value after TURP, was much more distinct than can be explained by reduction of prostate volume alone. BOO can cause a chronic irritation of the prostate gland due to the high detrusor pressure at maximal voiding (PdetQmax), with disruption of the normal prostatic epithelium and as such cause an elevated/rising PSA.

A prospective study was set up to investigate the influence of BOO on PSA in this subgroup of patients. Our main hypothesis is that BOO alone can be the cause of elevated or rising PSA in patients with minor LUTS and with a proven BOO on full urodynamics.

Methods

This study was approved by the Jessa Ziekenhuis (Hasselt) hospital's Ethic Committee and conducted according to the established good clinical practice and the applicable laws and regulations (approval number 06.06/uro 06.01).

Total 105 consecutive patients were prospectively enrolled between 2005 and 2013. All patients were referred to the principal investigator by their general practitioner as a result of an elevated (≥ 4 ng/ml) or rising PSA (PSA velocity ≥ 0.98 ng/ml/yr). Patients were not referred to our institution because of bothersome LUTS; only patients with minor LUTS (I-PSS 0–19) were included in this study. Patients with urinary tract infections or clinical prostate cancer were excluded from the study. All patients were informed about the potential risks associated with the procedure.

Only patients without suspicion for prostate cancer on digital rectal exam or ultrasound/MRI were considered after at least 1 set of negative 12-core prostate biopsies. Prostate biopsies were performed with a spring-loaded automatic biopsy gun (Bard magnum) fitted with a 18-gauge Tru-cut needle guided by a side firing transrectal probe US 7.5 MHz biplanar. Six laterally targeted biopsies, 2 from the transition zone and four from the lateral peripheral zones were taken in addition to the conventional parasagittal sextant biopsies (at the base, mid-gland and apical regions of the prostate).

After exclusion of pT1c prostate cancer, full urodynamics with pressure flow urometry were performed in all patients. Pressure flow urometry was performed in agreement with the International Continence Society criteria (Abrams-Griffith score). Filling was done standing with a filling speed of 35 ml/min, using a 6 French filling catheter. Urodynamics were performed using Laborie Medical technologies INC/UDS-64-ls. Patients with a PdetQmax > 40 cmH₂O were considered obstructed, those with a PdetQmax < 20 cmH₂O unobstructed and patients with a PdetQmax between 20 and 40 cmH₂O were considered equivocal.

When BOO was proven, patients underwent TURP and the prostatic tissue was histologically examined by one referee pathologist. Endoscopic procedures were done under locoregional anesthesia using an Olympus resectoscope 26 or 28 Charrière, depending on estimated prostate volume. After TURP, resected prostate fragments were weighed and carefully examined. Patients were divided in subgroups according to histology. Patients with BOO due to benign prostate hyperplasia (BPH) (subgroup 1), patients with aggressive prostate cancer (subgroup 2) and patients in active surveillance for prostate cancer (subgroup 3).

The I-PSS was evaluated before and within the first year after surgery. PSA levels were evaluated pre- and post-operatively after 3, 6 and 12 months and later on yearly or more frequent in case of prostate cancer.

Statistical analysis was performed using the routines of the Statistical Package for Social Sciences software. When two successive results were compared on the same patients, the paired samples *t*-test was used for variables for which the normal assumption was accepted. The non-parametric sign test was used for variables with no normal distribution. Two groups of patients were compared using the independent samples *t*-test when the normality assumption was accepted and the Mann-Whitney U test for variables with no normal distribution. The one-way analysis of variance (ANOVA) was used to determine whether there were any significant differences between the means of three or more groups. Data were statistically significant if $p < 0.05$.

Table 1. Baseline characteristics

Variable	Value
Mean age, years	64.9 ± 7.4
Mean follow-up, months	38.2 ± 1.2
Mean PSA, ng/ml	8.91 ± 4.2
Mean PSAV, ng/ml/yr	2.2 ± 2.03
Mean PSA-ratio, %	17.7% ± 6.8
Mean I-PSS	11.1 ± 5.7
Mean PdetQmax, cmH ₂ O	93.6 ± 35.4
Mean Qmax, ml/s	11.8 ± 6.1

PSAV = PSA velocity.

Fig. 1. Evolution of PSA, LUTS (I-PSS) and Qmax of the BPH group during follow-up.**Table 2.** Baseline characteristics

Variable	BPH group	Prostate cancer		p
		Active surveillance	Treated	
Number, n (%)	83 (79%)	6 (5.7%)	16 (15%)	
Mean age, years	64.6 ± 7.2	62.2 ± 4.1	67.1 ± 9.2	0.31
Mean PSA, ng/ml	9.24 ± 4.3	5.44 ± 1.7	7.9 ± 3.3	0.08
Mean PSAV, ng/ml/yr	2.4 ± 2.2	1.67 ± 1.2	2.1 ± 1.9	0.65
Mean I-PSS	11.1 ± 5.7	9.7 ± 3.8	11.8 ± 6.2	0.75
Mean PPBS, n	1.8 ± 1.2	1.9 ± 0.4	1.7 ± 0.7	0.91
Mean volume, g	56.5 ± 28.5	42.2 ± 22.3	32.2 ± 15.8	0.04
Mean Qmax	11.2 ± 4.5	14.4 ± 3.9	13.3 ± 10.5	0.21

PSAV = PSA velocity; PPBS = prostate punction biopsies.

Results

General Characteristics

Total 105 patients satisfied the inclusion criteria, as described above and were included in this study. The baseline characteristics are shown in table 1.

The mean age was 64.9 ± 7.4 years and the mean follow-up 38.2 ± 1.2 months. The mean pre-operative PSA was 8.9 ± 4.2 ng/ml and the mean PSA velocity 2.2 ± 2.03 ng/ml/yr. The mean I-PSS was low with a value of 11.1 ± 5.7 and the mean PdetQmax distinctly elevated with a mean value of 93.6 ± 35.4 cmH₂O, showing a distinct BOO.

The mean resected prostate volume by TURP was 52.3 g and the mean number of prostate biopsies 1.8.

Subgroups

The characteristics of the different subgroups are shown in table 2.

The BPH group was the largest with nearly 80% of the patients. The active surveilled group consisted of 6/105 (5.7) patients and the actively treated group of 16/105 (15%) patients. No statistical significant differences were observed between the different groups, except for the resected amount of prostatic tissue, which was largest in subgroup 1. The evolution of the PSA value, LUTS (I-PSS) and Qmax during follow-up of the BPH group is shown in figure 1.

A supernormalisation of the initial PSA value was observed, with a decrease of 9.24 to 0.96 ng/ml after 6 months, which persisted during the length of follow-up. The mean I-PSS decreased from 11 to 3 after 6 months and was nearly constant during follow-up. A significant, persistent increase of the Qmax was seen with a value rising from 11 to 20 ml/s (fig. 2).

Six patients underwent active surveillance. Four patients had a Gleason 6 (3 + 3) and 2 patients a Gleason 5 (3 + 2) prostate cancer. All patients had a supernor-

Fig. 2. PSA, I-PSS and Qmax according to each subgroup.

malisation of the PSA value (< 1 ng/ml) after TURP and as such no additional imaging or prostate biopsies were performed. They all experienced a distinct improvement in QoL.

Sixteen patients were actively treated for prostate cancer. Three patients had brachytherapy for 1 Gleason 5 (2 + 3), 1 Gleason 5 (3 + 2) and 1 Gleason 6 (3 + 3) tumor. Two patients underwent external beam radiotherapy for a Gleason 7 (4 + 3) tumor and 11 patients had a radical prostatectomy. One patient had a radical prostatectomy for a Gleason 9 (4 + 5) tumor, 1 patient for a Gleason 8 (4 + 4), 6 patients for a Gleason 7 (4 + 3) and 3, relatively young, patients for a Gleason 6 (3 + 3) tumor. All but 2 patients had a good functional outcome; 1 patient needed an artificial male sphincter and 1 patient a penile implant. No biochemical recurrence was observed during follow-up and general patient satisfaction was high (table 3).

Discussion

A rising/elevated PSA value in patients with minor LUTS and negative investigations for prostate cancer, are still a challenging problem in the daily, urology practice. We suggest performing urodynamics after excluding an infectious or oncologic cause of the elevated PSA, to look for BOO. We hypothesize that BOO can be a reason for elevated/rising PSA in this subset of patients. A TURP was performed in patients with proven BOO and a supernormalisation of the PSA value was observed. This supernormalisation of the PSA value after TURP was much more distinct than can be explained by reduction

Table 3. Characteristics of patients with actively treated prostate cancer

Classification	Patient number
Radical prostatectomy	11
Gleason score (4 + 5)	1
Gleason score (4 + 4)	1
Gleason score (4 + 3)	6
Gleason score (3 + 3)	3
External beam radiotherapy	2
Gleason score (4 + 3)	2
Brachytherapy	3
Gleason score (3 + 3)	1
Gleason score (3 + 2)	1
Gleason score (2 + 3)	1

of prostate volume alone. The high detrusor pressure at maximal voiding (PdetQmax) can cause, in our opinion, a chronic irritation of the prostate gland, with disruption of the normal prostatic epithelium and as such be a cause for an elevated/rising PSA.

The patients in our study all have a relatively low pre-operative I-PSS. This can be explained by the distinct mean PdetQmax of 93 cmH₂O, which enhances the flow despite the BOO. All patients experienced however a major improvement of their LUTS and QoL post-operatively. The I-PSS declines with more than 50% after TURP, which suggests that the I-PSS in this specific group of patients should be considered more as a relative value over time instead as an absolute value.

A TURP has several advantages for this group of patients, with minor LUTS on I-PSS, in comparison with conservative management. BPH is a progressive disease which can lead to detrusor hypertrophy and at long term to detrusor fatigue and post-renal insufficiency [5]. When treated on time it can be a reversible disease, which can be cured by a proper performed TURP. Another advantage of TURP is a dramatic drop of the PSA value afterwards. This supernormalisation of the PSA, together with the extensive tissue sampling which shows only benign prostatic tissue, reassures the patient and increases his QoL.

Arguments in favor of performing a TURP instead of starting medical therapy are the fact that alpha-blockers have no/minimal effect on the PSA value and no histological analysis can be performed as well, which is important in this subset of patients with an elevated or rising PSA. 5-Alpha-reductase inhibitors do have an effect on the PSA value, however this effect is heterogeneous

and as such difficult to interpret [6]. Moreover there is an artificial drop in the PSA value, without explaining the high, initial PSA value. A TURP furthermore is a good choice on the long term, considering medico-economic effects of BPH compared with (expensive) 5-alpha-reductase inhibitors [7].

A TURP can also be considered as a safe procedure with excellent long-term results regarding effect on LUTS and QoL, making some authors suggest if a TURP still has to be considered as an invasive procedure [8].

We also showed that TURP has an important diagnostic value in these patients, diagnosing 21% of these patients with prostate cancer whereas previous investigations were negative. This can be explained by the fact that these tumors were located anteriorly or in the transition zone of the prostate and as such difficult to reach by biopsy [4].

We've encountered some high-risk tumors which could possibly have been spotted by a pre-operative MRI. Our study started however in 2005, when MRI was not as frequently used as nowadays and as such only a minority of our patients had a pre-operative MRI. MRI is undoubtedly a useful tool but its role in prostate cancer diagnosis is still controversial, especially its use before taking biopsies. A recent meta-analysis showed that ultrasound

is still the preferred investigation pre-biopsy [9]. It has also a low sensitivity for Gleason 6 and small Gleason 7 prostate cancers, which might be clinically relevant, especially in younger patients [2]. MRI is also an expensive investigation, making it not suitable for every patient with an elevated/rising PSA. Its limited availability and inter-reader variability are also reasons for concern [10].

A TURP should however not be used as a primary tool for diagnosis in patients with an elevated or rising PSA but only performed after exclusion of prostate cancer by clinical examination and imaging (ultrasound/MRI) in patients with a proven BOO on full urodynamics.

Conclusion

An elevated/rising PSA can be caused by BOO. After excluding prostate cancer, full urodynamics can be performed to look for BOO. A TURP should be proposed to patients with proven BOO. A supernormalisation of PSA and improvement of QoL can be expected. A TURP can be considered as a feasible, economic, less-invasive surgery with excellent long-term results and important diagnostic features.

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