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The Advantages of TURP in Patients with an Elevated/Rising PSA, Mild/Moderate LUTS, Bladder Outlet Obstruction and Negative Prostate Cancer Imaging/Prostate Biopsies. A Prospective Analysis in 105 Consecutive Patients

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Abstract

Aim: To investigate elevated/rising PSAas a marker for BOO (Bladder Outlet Obstruction) in patients with minor LUTS (Lower urinary tract Symptoms) and without prostate cancer.

Methods: 105 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 (I-PSS (International Prostate Symptom Score) 0-19)) and without suspicion for prostate cancer were included. All patients had BOO, shown by full urodynamics, and underwent TURP. Resected tissue was histologically examined and PSA/IPSS 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 cm H_2O. The mean resected volume 52 g and the mean prostatebiopsyrate1.8. 83/105 patients (79%) had no malignancy and were diagnosed with BOO due to BPH (Benign Prostatic Hyperplasia) (subgroup 1). Their mean PSA decreased from 9.2to 0.7ng/ml and 0.9 ng/ml after 6 and 12 months post-op respectively. The mean IPSS declined from 11 to 3 after 6 months and12months. 16/105 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. 6/105 Patients (5.7%) had active surveillance (subgroup 3).

Conclusion: BOO can cause an elevated/rising PSA in patients with minor LUTS and negative screening for prostate cancer. TURP is an adequate treatment for these patients.

Core tip: Patients referred to the urologist because of an elevated/high PSA-value, are a common problem in the daily practice. After excluding prostate cancer or urinary tract infection, patients are reassured. But what has to be done when the PSA-level rises? Our hypothesis suggests that BOO (bladder outlet obstruction) can cause an elevated/high PSA in patients with minor LUTS (I-PSS 0-19) and negative findings for prostate cancer. We describe our findings in 105 consecutive, prospectively enrolled patients and also describe the benefits of a TURP in these patients.

Keywords: PSA; BOO; TURP; PdetQmax; Prostate cancer

Abbreviations: BOO: Bladder Outlet Obstruction; LUTS: Lower Urinary Tract Symptoms; I-PSS: International Prostate Symptom Score; BPH: Benign Prostatic Hyperplasia; DRE: Digital Rectal Examination; TRUSP: Transrectal Ultrasound of The Prostate; ICS: International Continence Society; SPSS: *Statistical Package for Social Sciences*

Introduction

Patients presenting with a rising and/or elevated PSA-value are a common problem in the daily, urology practice. Patients without signs of urinary tract infection and minor obstructive LUTS, are usually investigated by digital rectal examination (DRE), followed by imaging (transrectal ultrasound of the prostate (TRUSP)). 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 DRE 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, which may 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), soy beans (isoflavones) or green thee (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) [2,4].

We subjected this subgroup of patients to a full urodynamic investigation and those with a proven BOO, underwent a 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/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 regulation (approval number 06.06/uro06.01).

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) and/or rising PSA (PSA velocity (PSAV) ≥ 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 and/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 DRE and/or TRUS/MRI were considered after at least one set of negative 12-core prostate biopsies. Prostate biopsies were performed with a spring-loaded automatic biopsy gun (Bard magnum) fitted with an 18-gauge Tru-cut needle guided by a side firing transrectal probe ultrasound 7.5 MHz biplanar. Six laterally targeted biopsies, two 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 (ICS) 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 cm *H20*were considered obstructed those with a PdetQmax < 20 cm *H20 unobstructed and patients with a PdetQmax between 20 and 40 were considered equivocal. When BOO was proven, patients underwent TURP and the prostatic tissue was histologically examined by one referee pathologist. Endoscopic procedures were performed under loco-regional an aesthesia 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 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-operatively 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 (SPSS) 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* $p < 0.05$.

Results

General characteristics: 105 Patients satisfied the inclusion criteria, as described above and were included in this study. The baseline characteristics are shown in Table 1.

Characteristics	
Mean age	64.9 ± 7.4
Mean follow-up	38.2 ± 1.2
Mean PSA (ng/ml)	8.91 ± 4.2
Mean PSAV (ng/ml/j)	2.2 ± 2.03
Mean PSA-ratio	17.7% ± 6.8
Mean I-PSS	11.1 ± 5.7
Mean PdetQmax	93.6 ± 35.4
Mean Qmax	11.8 ± 6.1

Table 1: Baseline Characteristics. Qmax = maximal flow rate.

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 PSAV 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 cm H_2O, 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. Different subgroups were defined, according to the outcome of the histology assessment.

Subgroup 1: Consists of patients without prostate cancer (BPH-group).

Subgroup 2: Consists of patients in active surveillance for prostate cancer and subgroup 3 of patients who were actively treated for prostate cancer. The characteristics of the different subgroups are shown in Table 2.

	BPH-Group	Pca: Active Surveillance	Pca: TreatedP-Value
Number (n)	83 (79%)	6 (5.7%)	16 (15%)
Mean age (yrs)	64.6±7.2	62.2±4.1	67.1±9.20.31
Mean PSA (ng/ml)	9.24±4.3	5.44±1.7	7.9±3.30.08
Mean PSAV (ng/ml/yr)	2.4±2.2	1.67±1.2	2.1±1.90.65
Mean I-PSS	11.1±5.7	9.7±3.8	11.8±6.20.75
Mean PBS (n)	1.8±1.2	1.9±0.4	1.7±0.70.91
Mean volume (g)	56.5±28.5	42.2±22.3	32.2±15.80.04
Mean Qmax	11.2±4.5	14.4±3.9	13.3±10.50.21

Table 2: Characteristics of the Different Subgroups. *PBS = prostate biopsies.*

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.

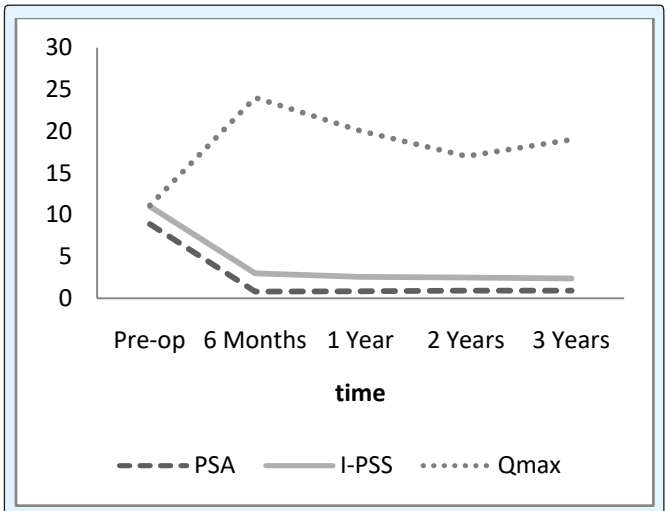

Figure 1: Evolution of PSA, LUTS (I-PSS) and *Qmax of the BPH-group during follow-up.*

A super normalisation 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.

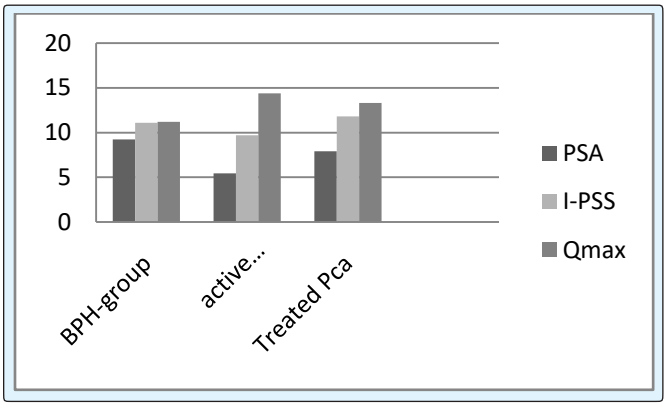

Figure 2: PSA, I-PSS and Qmax according to each subgroup.

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

16 Patients were actively treated for prostate cancer. 3 Patients had brachytherapy for 1 Gleason 5 (2+3), 1 Gleason 5 (3+2) and 1 Gleason 6 (3+3) tumor. 2 Patients underwent external beam radiotherapy for a Gleason 7 (4+3) tumor and 11 patients had a radical prostatectomy. 1 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 two 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.

Treatment	Number	Gleason score
Radical prostatectomy	11	Gs (4+5)
		Gs (4+4)
		Gs (4+3) (6 patients)
		Gs (3+3) (3 patients)
External Beam radiotherapy	2	Gs (4+3)
Brachytherapy	3	Gs (3+3)
		Gs (3+2)
		Gs (2+3)

Table 3: Characteristics of Patients with Actively Treated Prostate Cancer.

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 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 cm H2O, which enhances the flow despites the BOO. All patients experienced however a major improvement of their LUTS and QoL post-operatively. The I-PSS declined 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 in this subset of patients are the minimal effect of alpha-blockers on the PSA-value and the loss of histological analysis of the prostate tissue. 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 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 where located anteriorly or in the transition zone of the prostate and as such difficult to reach by biopsy [9].

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 pre-biopsy investigation [10]. 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 [11].

A TURP should however not be used as a primary tool for diagnosis in patients with an elevated/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.

Our study is unique because of the high number of prospectively, enrolled patients confirming previous findings that BOO can cause an elevated PSA in a subset of patients [4,9]

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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