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UROLOGY - REVIEW

A new algorithm in patients with elevated and/or rising prostate-specific antigen level, minor lower urinary tract symptoms, and negative multisite prostate biopsies

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Abstract Patients with elevated and/or rising prostate-specific antigen (PSA), minor lower urinary tract symptoms (LUTS), and no evidence for prostate cancer on (multiple) extended prostate biopsies are a regularly encountered problem in urological practice. Even now, patients are seen with no objective explanation of this persistent elevated and/or rising PSA. So far, many strategic proposals have been elaborated and published to deal with this specific population including the use of different PSA derivates; applying different biopsy schemes—strategies—biopsy target imaging; diagnostic use of prostate cancer genes; and many more. In this review, we propose a new algorithm in which an urodynamic evaluation should be included since bladder outlet obstruction (BOO) can be expected. Once BOO is confirmed, a transurethral resection of the prostate (TURP) can be offered to these patients. This procedure will result in subjective and biochemical improvement and allows extensive histological examination. Current literature was reviewed with regard to this specific population. This research was performed using the commercially available Medline online search tools and applying the following search terms: "diagnostic TURP"; "elevated PSA"; and "prostate biopsy". Furthermore, subsequent reference search was executed on retrieved articles.

Keywords Benign prostatic hyperplasia (BPH) · Bladder outlet obstruction (BOO) · Prostate cancer · Transurethral resection of the prostate (TURP) · Elevated prostate-specific antigen (PSA)

Introduction

Twenty-five percent of men over 50 years old have lower urinary tract symptoms (LUTS). LUTS may be caused by benign prostatic hyperplasia (BPH), one of the most common diseases among ageing men and the second most common cause of surgery in men over 60 years old [1]. Another condition that might be accompanying LUTS could be prostate cancer (PCa), which has become the most common cancer in men in several developed countries, especially in Western populations and particularly among the black population of the United States.

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Since the concept of prostate-specific antigen (PSA) has been introduced in clinical practice [2], many patients are referred to an urologist because of elevated and/or rising PSA levels. To find the cause of these elevated and/or rising PSA levels, often extended prostate biopsies are taken. If cancer cells are discovered in the biopsies, therapy is usually straightforward. If, however, prostate biopsies are negative for cancer cells, numberless diagnostic strategies have been put forward. When PSA levels remain high or rise even more, new extended prostate biopsies are usually taken, eventually with different methods. When PSA levels keep on rising and when extended prostate biopsies remain negative in this group of patients, uncertainty will grow for patients, as well as for general practitioners and last but not least for urologists. More specifically, this will be the case if the patient suffers only minor LUTS. We have previously shown that this group of patients (patients with elevated/and or rising PSA levels, minor LUTS and no signs of prostate cancer) are likely to have bladder outlet obstruction (BOO) on pressure flowmetry according to Abram–Griffiths definition [3, 4]. Despite minor to no LUTS, transurethral resection of prostate (TURP) is a therapeutic option that can be offered to patients resulting in (super)normalisation of PSA levels, symptomatic benefit, and improvement of the quality of life. Additionally, this technique allows extended histological examination, which will reveal in few cases prostate cancer that can be aggressive and need further treatment. Since patients with elevated and/or rising PSA, minor LUTS, and (multiple) negative extended prostate biopsies can be expected to have BOO, we elaborated a new algorithm in which we propose to consider urodynamic evaluation as well as the possibility of performing a TURP in this group of patients.

What are urologists doing today with patients presenting with elevated and/or rising PSA levels, minor LUTS, and no signs of prostate cancer on (multiple) extended prostate biopsies?

Strategies related to PSA evaluation

If PSA is elevated and/or rising in a patient with minor LUTS, no signs of prostate cancer on digital rectal examination and/or transrectal ultrasound (TRUS), and eventually on extended prostate biopsies, different PSA derivates have been proposed. A first PSA derivative that can be used is age-related PSA levels [5]. However, the use of age-specific PSA cut-off values can result in missing up to 60% of cancers in men older than 60 years of age [6]. Borer concluded that age-specific PSA references did not safely eliminate the need for prostate biopsies in a population aged 60–79 years [7].

A second PSA derivate that is regularly used is PSA density. When a cut-off value of 0.078 is used for PSA density, the sensitivity for detection of prostate cancer is 95% [5]. Especially in intermediate PSA levels, PSA density nomograms allow a more precise determination than age-related PSA levels [8].

A third very frequently used PSA derivative, which is related to PSA kinetics, is PSA velocity. Despite its frequent use, caution is required as different methods exist to calculate PSA velocity [9]. The best way to calculate PSA velocity is by performing linear regression. However, in routine practice urologists often use the rate of PSA change using the first and last value. The arithmetic equation of PSA change should not be recommended [9]. Carter [10] proposed a cut-off value of 0.75 ng $ml^{-1}year^{-1}$ for PSA velocity. Since the use of this cut-off value has been shown to result in missing 48% of prostate cancers, Loeb [11] advised in men younger than 60 years to use a cut-off value of 0.4 ng $ml^{-1}year^{-1}$. Additionally, Berger [12] showed that PSA velocity increases in the years before diagnosis of prostate cancer, which correlates well with the pathological stage and with Gleason scores.

Another PSA derivate that can be used is the PSA ratio. The use of this parameter with a cut-off value of 25% results in sensitivity of 95% in prostate cancer diagnosis [5]. Catalona [13] proved that the use of PSA ratio can reduce the number of unnecessarily performed biopsies in men with elevated PSA levels on the condition that cut-off values are well defined. An additional PSA-derived parameter was investigated by Froehner who evaluated the value of complexed PSA in comparison with total PSA [14]. Using this parameter, a statistical advantage was detected. However, clinical relevance remains unclear.

Several authors investigated the use of "benign" PSA [15–18]. BPSA is a "benign" form of free PSA that seems to be increased in patients with BPH. A correlation was found with transition zone volume and total prostate volume. However, as is the case

with some other PSA derivatives, more studies are needed to confirm its clinical utility.

In addition to these PSA-derived parameters, molecular assays are a new tool that can be used to refine difficulties in PSA interpretation. A well-described and commercially available molecular assay is the PCA3 assay [19]. PCA3 is a very prostate cancer-specific gene also called DD3. When a cut-off value of 35 is used, sensitivity amounted 58–65% with a specificity of 66–72% (PSA specificity of 47%) [19–21]. Haese and colleagues [22] conducted a prospective, multicentre study including 463 patients with one or two negative biopsies who were scheduled for a repeat biopsy. Aim of the study was to compare the diagnostic accuracy of PCA3 with fPSA%. With a cut-off value of 35 for PCA3, the probability of a positive repeat biopsy was greater if PCA3 was higher. Deras et al. [23] found PCA3 to be independent of prostate volume, serum PSA, and number of previous biopsies. Although these assays are promising, there are some disadvantages related to these tests. First of all, it should be emphasised that they cannot be used in a routine screening as they are far more expensive. Secondly, these tests can also give false-negative and false-positive results. Therefore, more evidence confirming the use and the outcome of these assays is required. Last but not least, in addition to these molecular assays, common extended prostate biopsies are still needed to prove possible prostate cancer.

Strategies related to technique and prostate biopsy regimen

Numerous publications have been made on techniques of prostate biopsies. Hodge [24] started with ultrasound guided, 6-core random biopsies. Subsequently, Eskew [25] proved 5-region prostate biopsies to be superior to sextant biopsies, resulting in an increasing diagnostic yield. A few years later, a 10-core protocol with laterally directed biopsies together with sextant biopsies was developed by Gore [26]. Arnold [27] extended the biopsy technique to a 12-core regimen. This extension resulted in a 13.5% increased detection rate of prostate cancer in comparison with sextant biopsies combined with transition zone biopsies [28]. Additional techniques were developed by Matsumoto [29], who described a technique where special attention was taken for deep apical biopsies and Lui [30], who advised on more specific attention for transition zone biopsies. However, other authors have shown that biopsies of transition zone and seminal vesicles resulted in low additional yield in the diagnosis of prostate cancer [31–33]. Recently, Guichard [34] proposed a 21-core biopsy protocol. Compared to sextant biopsies, a 22% improvement in prostate cancer detection rate was observed with a 12-core biopsy. When using a 21-core protocol, the cancer detection rate was further increased to 42.5% compared to 38.7% with 12-core biopsies. Scattoni et al. [35] reviewed the literature on extended and saturation prostate biopsies and concluded extended biopsies should be performed at first biopsy, saturation biopsies at repeated biopsies. However, Ashley [36] evaluated the diagnostic yield of saturation biopsies. In these latter biopsy protocols, 24 or more biopsy cores are taken. Ultimately, they proved that saturation biopsies did not detect more abnormal pathology than standard biopsies [36].

Although prostate biopsies are a standard technique, one has to be aware of the possible complications of this procedure, which are excellently reviewed by Raaijmakers [37]. Minor complications such as haematuria, hemospermia, etc. are frequently seen. Severe complications occur less frequently: fever (3.5%), acute urinary retention (0.4%), and hospitalisation (0.5%).

Another dilemma with prostate biopsies is how many repeat biopsies should be taken. Djavan [38, 39] investigated the cancer detection rate in repeat biopsies. He observed that prostate cancer detection rate in a first biopsy was 24%. In a second biopsy, the cancer detection rate lowered to 13%. Prostate cancers found in first and second biopsies were comparable in terms of PSA, grade, stage, and cancer volume. Cancer detection rate in biopsies three and four were far less, 5 and 4% respectively.

What to do if extended prostate biopsies remain negative and PSA keeps on rising?

In case prostate biopsies remain negative and PSA keeps on rising at the same time, many urologists treat these patients with antibiotics. However, several authors noticed that inflammation seems to have no effect on PSA [40–42], putting the antibiotic treatment in question. Another frequently used strategy is an attempt to normalise PSA with dietary

manipulation [43–45]. However, these data do not support the hypothesis that dietary manipulation protects against prostate cancer. For example, Eastham [46] showed that fat intake was not associated with PSA levels. Therefore, advocating functional foods or supplements explicitly for cancer control purposes would currently be premature.

What has been suggested so far to deal with those patients?

Several authors [47–50] showed that PSA can be seen as a marker for BOO, as a predictor of future prostate growth and as a marker for risk of acute urinary retention in patients with LUTS. Furthermore, a correlation was found with an elevated need for surgical treatment of BPH in symptomatic patients [50].

However, the challenging problem are patients with elevated and/or rising PSA, minor LUTS, normal digital rectal examination (DRE) and/or TRUS, and (multiple) negative extended prostate biopsies. This problem is well recognised in literature [51, 52].

A first attempt to deal with this problem was described by Rovner [53]. He showed that a transurethral sampling of at least four quadrant chips together with prostate biopsies in patients with elevated and/or rising PSA levels and negative prostate biopsies did not significantly improve prostate cancer diagnosis. Kitamura [54] evaluated 139 consecutive patients with negative prostate biopsies. These patients received TURP for relief of LUTS implying that these patients were symptomatic. Because four of these patients were revealed to have prostate cancer during the follow-up period, the authors concluded that the role of TURP in these patients remained unclear. Zigeuner [55] performed a retrospective analysis in patients with LUTS. All patients had (multiple) negative extended prostate biopsies. Another important characteristic in this group of patients was that besides an elevated PSA level, 21.8% of these patients had an abnormal DRE. After TURP, prostate cancer was detected in 7.9% of all cases and in 5.5% of the patients with a normal DRE. Zigeuner [55] concluded that detection rate was low and that diagnostic yield in asymptomatic men remained unknown.

Özden [56] evaluated 64 patients with LUTS and normal DRE presenting with elevated PSA levels and negative extended prostate biopsies. When TURP was performed, BPH was encountered in 63 patients, and in 1 patient prostatic intraepithelial neoplasia was detected. Six months after TURP, 7 of 64 patients still had an elevated PSA level. In 3 of these 7 patients, prostatitis was suggested to be the reason of PSA elevation; 1 patient seemed to have prostate cancer; and the remaining 3 patients were diagnosed having BPH. The long-term follow-up in these 7 patients was unclear.

Radhakrishnan [57] described a retrospective analysis in 14 patients undergoing TURP after at least two negative extended prostate biopsies. In 21% of the subjects, aggressive prostate cancer was encountered. In 50% of the subjects, PSA values returned to normal after TURP. In 1 patient, repeated prostate biopsies revealed prostate cancer after TURP. Philip [58] presented results in 11 patients with prostate cancer diagnosed in TURP after negative extended prostate biopsies with 24–48 cores. Out of these 11 patients, 5 patients underwent a radical retropubic prostatectomy in which organ-confined cancer was found, especially located anteriorly. Additionally, in this group of patients TURP was performed to resolve LUTS. Important to notice in this group of patients is that prostate cancer was mainly located anteriorly.

Puppo [59] described the role of TURP together with biopsies of the peripheral zone in the same session in the diagnosis of prostate cancer after repeated negative biopsies. In this study, a group of 43 patients with at least two negative extended prostate biopsies is described. In 35 of the 43 patients, further PSA elevation was shown and these patients underwent new prostate biopsies. In 7 of 35 patients, prostate cancer was shown after repeated prostate biopsies. Additionally, 3 patients were lost during the follow-up period and 4 patients had a severe co-morbidity and hence were unable to undergo TURP. The remaining 21 patients were offered TURP together with prostate biopsies of the peripheral zone regardless of BOO. In this group of 21 patients, 14 patients accepted to undergo TURP. In 8 of these 14 patients, prostate cancer was diagnosed and these patients underwent a radical prostatectomy. The remaining 6 patients had no cancer in TURP specimen and were followed with a median follow-up

of 9 months. Persistently rising PSA values were noted for 2 of these 6 patients. However, on repeated prostate biopsies, no signs of prostate cancer were detected. Puppo [59] concluded that TURP together with lateral extended prostate biopsies had a high diagnostic power in patients with previously negative extended prostate biopsies and rising PSA levels.

Several authors investigated the value of new imaging techniques that can possibly be used for targeted biopsies. A first new emerging and promising technique is contrast-enhanced ultrasound of the prostate (CEUS). This technique overcomes classical limitations of conventional ultrasonography in the B-mode imaging of parenchymal disease. With CEUS, the blood flow in the prostate can be investigated which will result in a better detection of abnormal micro- and macro-vascular lesions. Applying CEUS targeted biopsies, more cancers can be detected in comparison with systematic ultrasound guided biopsies [60–62]. In a multicentre European study, this technique was further evaluated [63]. Cancer was visualised and localised in 78%. However, further studies to confirm these results have to be initiated. Other authors performed research on real time elastography (RTE). With this technique, tissue stiffness is investigated as this is related to cancer high cell density. Additionally, RTE can be used for targeted biopsies. However, also for this technique further studies are needed to approve the value in prostate cancer imaging and targeted biopsies [64–68]. Another innovative technique in prostate cancer imaging and targeted biopsies is magnetic resonance (MR) and MR-guided biopsies of the prostate. This technique is well discussed in a recent review by Pondman et al. [69]. However, this technique also needs further evaluation.

In our series of studies [4, 70–72], we included a population with very specific characteristics that are notwithstanding regularly encountered in a urological practice. Therefore, we investigated patients with elevated and/or rising PSA, minor LUTS, negative DRE and TRUS, and (multiple) negative extended prostate biopsies. In this group of patients, we found that BOO is extremely likely to occur [4]. In a retrospective analysis of 82 patients [71], 74 patients were shown to suffer from BPH after TURP. In these 74 patients, only 3 patients (4.1%) had an equivocal $PdetQ_{max}$ (detrusor pressure at maximum flow) according to Abram–Griffiths [3], while nearly all patients (95.9%) were clearly obstructed with a mean $PdetQ_{max}$ of 89.5 cm H_2O (range 20–200 cm H_2O). In a prospective group of 33 patients, mean $PdetQ_{max}$ was 80.3 cm H_2O (range 40–150 cm H_2O) [72]. When TURP was performed in patients with these characteristics, this resulted in a symptomatic benefit (international prostate symptoms score [IPSS]/quality of life) and (super)normalisation of PSA levels both in our retrospective and prospective study [71, 72]. Most of the patients seemed to have BPH (retrospective study: 74/82 = 90.2%; prospective study: 27/33 = 81.8%). However, a few subjects suffered aggressive prostate cancer (taking into account the age of the subject, the Gleason score, and the amount of cancer cells) that needed further treatment [73, 74]. This was the case in 7 of 8 non-BPH patients in the retrospective analysis ($n = 82$) [71] and in 2 of 6 non-BPH patients in our prospective analysis ($n = 33$) [72]. On the other hand, in 1 of 8 non-BPH patients ($n = 82$) [71] and in 4 of 6 ($n = 33$) non-BPH patients [72], unaggressive prostate cancer was found. For these patients, watchful waiting was proposed. These results were confirmed in a long-term follow-up analysis with a mean follow-up of 61.5 months. In the same analysis, we found 1 patient (out of 36) who had a persistently rising PSA that resulted in positive extended prostate biopsies 4 years after TURP. This patient received further treatment with radical retropubic prostatectomy and has a tumour-free follow-up of 36 months [71].

As already mentioned, in our series of studies, most patients proved to have BPH after TURP (90.2% retrospective series; 81.8% in prospective series; 93.9% in prospective series with no aggressive cancer, only small amount of cancer cells or BPH). This implies that in this particular group of patients, even PCA3 testing, saturation prostate, biopsies, CEUS, RTE, and MR-guided biopsies will remain negative, since there is no cancer to be found. When in this group of patients' PSA remains elevated or even rises, confusion will increase and patients cannot be submitted for ever to high-tech, cumbersome, expensive new investigations such as PCA3, CEUS, RTE, or MR. Additionally, it should also be emphasised that even new technologies have false-positive and false-negative result. Last but not least, most of these new investigations have to be investigated more thoroughly in the future. Considering these remarks, no clear answer will be found in this

group of patients explaining the elevated and/or rising PSA levels. Moreover, it should be emphasised that we found in our series that in patients who underwent a radical prostatectomy, cancer was mainly located anteriorly in the peripheral zone, which is not easily accessible for prostate biopsies regardless of the targeting technique.

Proposal of a new algorithm in patients with elevated and/or rising PSA, minor LUTS, normal DRE and/or TRUS, and (multiple) negative extended prostate biopsies

Patients showing abnormal screening parameters, but with a negative cancer screening result, can be terrified because there is no answer for their abnormal values [75–77]. For example, Katz [51] showed that men with abnormal values observed during prostate cancer screening, have an increased cancer-related worry and show more problems with sexual function despite their negative biopsy results. Furthermore, we know that medical treatment has no effect on PSA levels (in case of α1 blockers) or a heterogeneous effect on PSA levels (in case of 5α reductase inhibitors) [78, 79]. Concerning 5α reductase inhibitors, Brawer [78] showed "the multiply by two rule" is not correct.

We also know that if BOO is not treated, patients are at increased risk of detrusor decompensation and/or renal insufficiency [80, 81]. Taking into account the economic aspects of the different treatments for BPH [82–84] and knowing that TURP should no longer be seen as an invasive treatment [85–89], offering TURP to these patients can be a valuable alternative strategy after BOO was proven with urodynamic evaluation, since pressure-flow studies can exclude patients who will not benefit from TURP. Moreover, the pressure-flow studies provide great predictive value of clinical improvement after TURP. The worse the degree of BOO, the higher the efficacy of TURP seemed to be [90–93]. Therefore, we suggest that in these patients with elevated and/or rising PSA level, and/or abnormal PSA velocity, and/or abnormal PSA density, and/or abnormal PSA ratio together with minor LUTS and negative DRE and TRUS, extended prostate biopsies should be taken with at least 12 cores (Fig. 1). Special attention should be taken for lateral and anterior peripheral biopsies as well as transition zone biopsies. If patients suffer from mild LUTS (IPSS 0–7), at least one series of repeated extended prostate biopsy should be taken

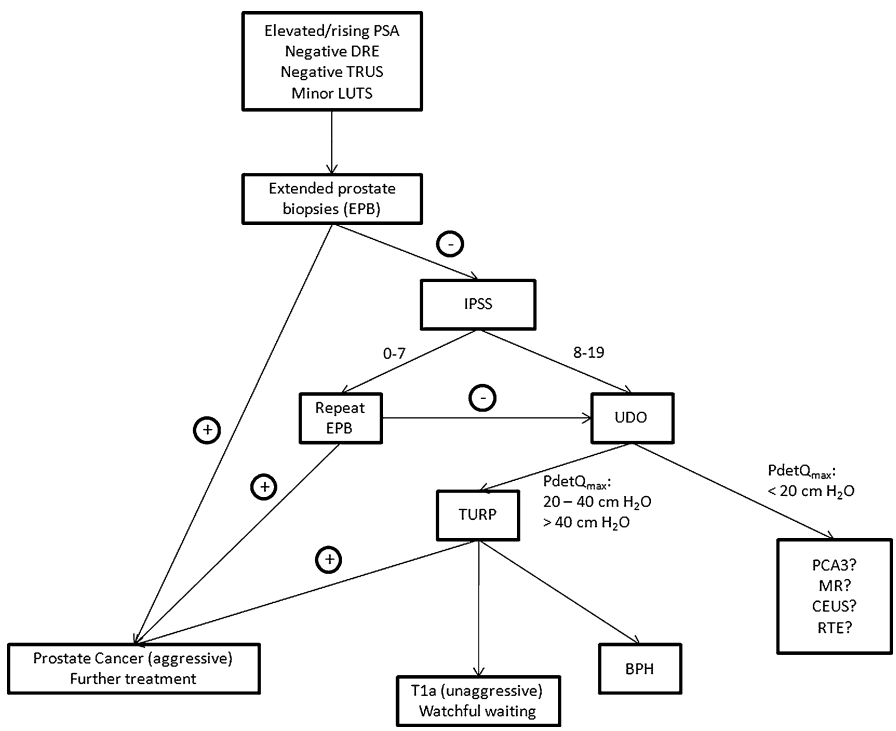

Fig. 1 Algorithm in patients with elevated and/or rising PSA, minor LUTS, normal DRE and/or TRUS, and (multiple) negative extended prostate biopsies. *PSA* prostate-specific antigen, *DRE* digital rectal examination, *TRUS* transrectal ultrasound, *LUTS* lower urinary tract symptoms, *EPB* extended prostate biopsies, *IPSS* international prostate symptoms score, *UDO* urodynamic observations, $PdetQ_{max}$ detrusor pressure at maximum flow, *TURP* transurethral resection of prostate, *BPH* benign prostatic hyperplasia

(Fig. 1). In patients with moderate LUTS (IPSS 8–19), one well-performed extended prostate biopsy should be sufficient ($P = 0.012$, [76]). If extended prostate biopsies remain negative, patients should be offered an urodynamic examination with pressure-flow analysis (Fig. 1). One can expect these patients to have an obstructive pressure-flow value (or at least equivocal). In that case, TURP can be discussed and proposed (Fig. 1). Performing TURP, special attention should be given to the anterior prostate zone.

Conclusion

Patients with elevated and/or rising PSA, minor LUTS, normal DRE and/or TRUS, and (multiple) negative extended prostate biopsies are a conundrum. We showed that in these patients, urodynamics with pressure flowmetry should be performed since BOO can be expected. In this population, we proposed a "diagnostic" TURP with special attention for the anterior prostate. This will probably result in a (super)normalisation of PSA levels and symptomatic benefit, suggesting that BOO, even with minor LUTS, can be seen as a discomfort for patients. However, histological examination will reveal prostate cancer in few cases. This prostate cancer might be aggressive needing further treatment.

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