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Diagnosis of prostate adenoma and the relationship between the site of prostate adenoma and bladder outlet obstruction

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INTRODUCTION The objective of this study was to evaluate the accuracy of using intravesical prostatic protrusion (IPP) as a parameter for the diagnosis of prostate adenoma (PA), as well as to determine the relationship between the site of PA and bladder outlet obstruction. IPP was determined with the use of transabdominal ultrasonography (TAUS).
METHODS A total of 77 consecutive adult men aged 30–85 years with haematuria or undergoing checkup for bladder tumour were enrolled. International Prostate Symptom Score (IPSS), and the results of uroflowmetry, TAUS and cystourethroscopy were assessed. All cases of IPP were classified into grades 0 (no IPP), 1 (1–5 mm), 2 (6–10 mm) or 3 (> 10 mm). PA diagnosis was confirmed using flexible cystourethroscopy. The sites of PA were classified as U0 (no adenoma), U1 (lateral lobes), U2 (middle lobe) or U3 (lateral and middle lobes).
RESULTS Of the 77 patients, 11 (14.3%) had no IPP. PA was confirmed using cystourethroscopy for all patients with IPP and for 7 of the 11 patients without IPP. Of the 37 patients with prostate volume < 20 g, 29 (78.4%) had IPP. Sensitivity, specificity, as well as positive and negative predictive values for diagnosing PA using only IPP were 90.4%, 100.0%, 100.0% and 36.4%, respectively. Higher sensitivity (95.9%) and negative predictive value (50.0%) were obtained when PA was used together with peak urinary flow rate (Qmax) < 20.0 mL/s. The mean Qmax of patients classified as U1 (n = 39) was 16.0 mL/s, while the mean Qmax in those classified as U2 (n = 12) and U3 (n = 22) was 11.9 mL/s and 8.9 mL/s, respectively.
CONCLUSION All patients with IPP had PA, and PA in the middle lobe was more obstructive than those in lateral lobes. Patients without IPP may still have PA.

Keywords: benign prostate hyperplasia, intravesical prostatic protrusion, prostate adenoma, transabdominal ultrasonography

INTRODUCTION

While benign prostatic hyperplasia (BPH) is common worldwide, its definition remains controversial. The International Consultation on Benign Prostatic Hyperplasia suggested that the term BPH be restricted to histological diagnosis, and that the term benign prostatic enlargement (BPE) be used to define the clinical entity.[1] However, in our clinical experience, there are many exceptions which suggest that BPH still exists as a clinical entity, causing symptoms and obstruction even when small and not enlarged.[1,2] We therefore propose that 'prostate adenoma' (PA) would be a more accurate term for the entity, which is similar to fibroadenoma of the breast.

In McNeal's classical paper on the pathology of BPH, the histology of BPH was described as benign nodular hyperplasia.[3] The fundamental concept is that BPH is a disease affecting the transitional and periurethral zones of the prostate, and is not diffused hyperplasia affecting the zones uniformly. However, as a nodular adenomatous hyperplasia, BPH gives rise to definite nodules, and more commonly, multiple nodules joined together forming an adenomata (Fig. 1) – a feature seen on open or endoscopic enucleation of BPH (Fig. 2). As the adenomata is nodular, the obstruction and symptoms that arise may be due to its location (site) rather than its size. For instance, a PA situated at the submucosal region of the bladder neck could give rise to significant obstruction and symptoms, even if it is small. Conversely, if the PA is located deeper in the stroma of the transitional zone, it would need to grow to a much bigger size before it causes obstruction and symptoms.

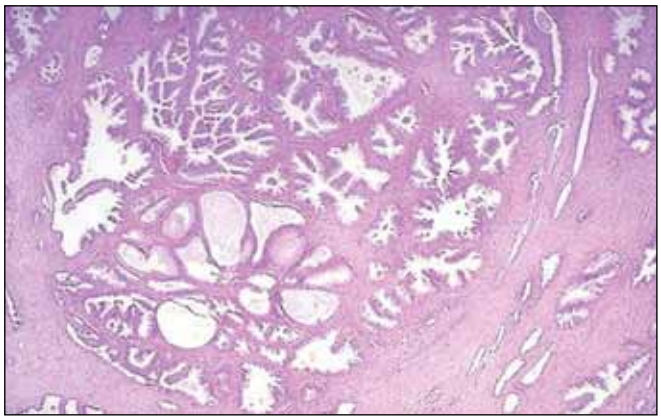

Fig. 1 Photomicrograph shows the histopathology of benign prostatic hyperplasia and its nodular nature (Haematoxylin & eosin, × 40).

PA, which can be suspected in patients with lower urinary tract symptoms (LUTS) and impaired urinary flow rate, is

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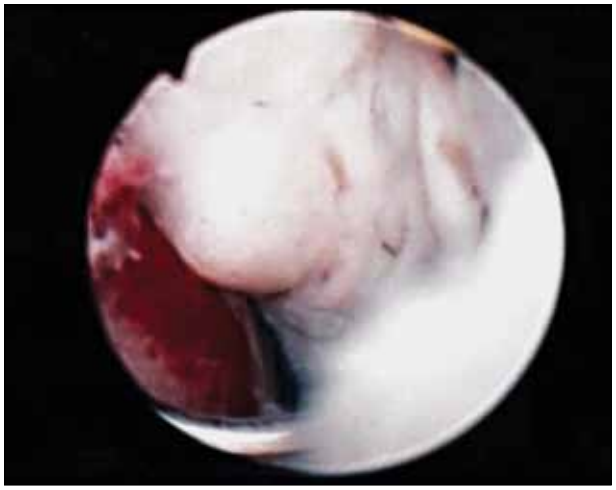

Fig. 2 Endoscopic image shows the appearance of prostatic adenoma during transurethral enucleation and resection of the prostate (TUERP).

confirmed on cystourethroscopy. When the tip of the flexible scope is placed at the verumontanum of patients without PA blocking the prostatic urethra, the bladder cavity can be seen in the distance. However, in patients with PA blocking the prostatic urethra, the view would be distorted. Although it is accepted that bladder outlet obstruction (BOO) can only be diagnosed or confirmed on pressure flow study, flexible cystourethroscopy would be able to assess the presence or absence of PA, which could be causing varying degrees of obstruction.

LUTS is a common clinical problem in ageing males. However, not all patients with LUTS have PA.[4] Therefore, it is important to first determine whether a patient with LUTS has PA. However, diagnosing PA can be challenging, not only because LUTS is found in conditions other than PA, but also because prostate volume correlates poorly with obstruction and the symptoms of PA.[5-7] PAs that cause marked obstruction may also be seen in patients with a small prostate. Furthermore, a small group of patients with PA may develop chronic retention associated with renal impairment because they have no symptoms.[8] Although PA is routinely diagnosed by pathologists, it is important that a clinical diagnosis of PA be made possible, and that the diagnosis can be made in a simple and non-invasive manner.

The use of transabdominal ultrasonography (TAUS) to measure prostate size and intravesical protrusion of the prostate (IPP) has been shown to be useful for the assessment of patients with LUTS suggestive of BPH.[9,10] IPP occurs as the PA enlarges into the bladder, along the plane of least resistance. The enlargement of either the middle or lateral lobes or even both lobes may cause IPP. This can be seen and easily measured and classified on TAUS. Previous studies on IPP have focused on its ability to predict the obstruction or progression of clinical BPH (i.e. PA).[11-14]

The primary objective of the present study was to determine the accuracy of noninvasive TAUS measurement of IPP for the diagnosis of PA. Flexible cystourethroscopy was

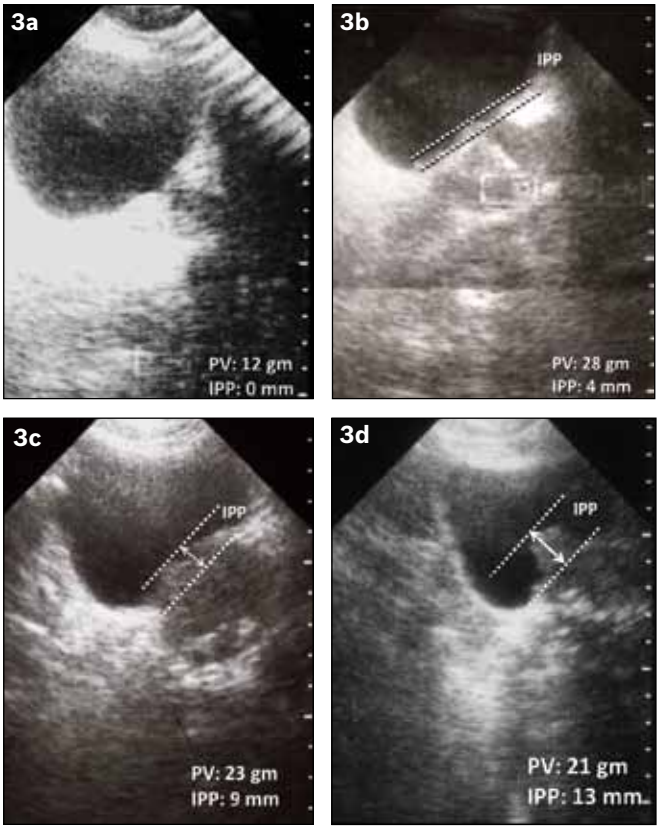

Fig. 3 Transabdominal ultrasonography images show (a) grade 0, (b) grade 1, (c) grade 2, and (d) grade 3 intravesical prostatic protrusions.

used to determine the absence or presence of PA, as well as the site of the PA. A secondary endpoint was to determine the relationship between the site of PA and BOO, as assessed by uroflowmetry.

METHODS

This prospective study included 77 consecutive adult men (age range 30–85 years) with haematuria or undergoing investigations for bladder tumours at the Department of Urology, Singapore General Hospital, Singapore, between December 2009 and June 2010. Patients with active urinary tract infections, neurological diseases, diabetes mellitus, urethral stricture and previous surgery on the prostate or bladder neck were excluded.

Initial evaluation consisted of the International Prostate Symptom Score (IPSS), quality of life (QOL) score, urinalysis and a complete physical examination that included digital rectal examination (DRE). The bladder and prostate were then assessed by TAUS (Aloka SSD-1700; Hitachi Aloka, Tokyo, Japan) with a comfortably full bladder (capacity 150–250 mL). Prostate volume was determined using the prolate ellipsoid formula in the transverse plane. IPP was measured from the tip of the protruding prostate to the base of the prostate at the circumference of the bladder in the sagittal plane.[13] IPP was classified according to the various degrees: grade 0 (no IPP), grade 1 (1–5 mm), grade 2 (6–10 mm) or grade 3 (> 10 mm) (Fig. 3). After TAUS assessment, peak urinary flow

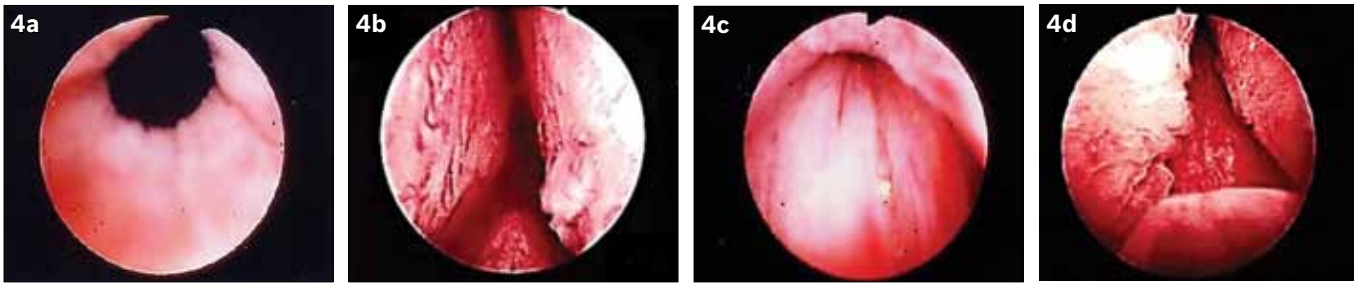

Fig. 4 Cystouretheroscopy images show (a) no enlargement, (b) lateral lobe enlargement, (c) middle lobe enlargement, and (d) lateral and middle lobes enlargement of the prostate.

Table I. Evaluation of the accuracy of the use of intravesical prostatic protrusion (IPP) with and without peak urinary flow rate (Qmax) for the diagnosis of prostate adenoma, which was confirmed using flexible cystourethroscopy.

Variable	IPP	IPP + Qmax*
Sensitivity	90.4	95.9
Specificity	100.0	75.0
Positive predictive value	100.0	98.6
Negative predictive value	36.4	50.0

Data is expressed as percentage. *Qmax < 20.0 mL/s.

rate (Qmax) was determined using a uroflowmeter (Urodyn 1000 Medtronic; Medtronic, Skovlunde, Denmark). Post-void residual urine volume (PVR) was also measured using TAUS.

Patients then underwent cystourethroscopy to confirm whether the prostate was normal or had PA. Bladder findings were noted using standard charts for PA configurations. Flexible cystourethroscopy was performed by senior doctors and using a standard cystourethroscope (Olympus CYS-5; Olympus, Tokyo, Japan), with the patients under local anaesthesia. Normal saline drip was used for irrigation, with the bottle placed 1 m above the supine patient and fluid running at full rate. Based on the view from the verumontanum to the bladder neck, the sites of PA were classified as U0 (no adenoma), U1 (lateral lobes), U2 (middle lobe) or U3 (lateral and middle lobes) (Fig. 4).[15]

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows version 13.0 (SPSS Inc, Chicago, IL, USA). Diagnostic measures such as sensitivity, specificity, and positive and negative predictive values were used to evaluate the accuracy of each index for predicting PA. Ethical approval was obtained for the study from the institutional review board (SGH IRB No. CIRB 2009-868-D).

RESULTS

The mean age, IPSS score, QOL score, prostate volume and Qmax of the 77 patients were 61.5 ± 11.4 (range 30–87) years, 6.3 ± 6.2 (range 0–35), 2.4 ± 1.3 (range 0–6), 21.9 ± 11.1 (range 7.6–68.2) g, and 13.7 ± 5.6 (range 4.0–26.8) mL/s, respectively. Of the 77 patients, 66 had IPP (41 with grade 1 IPP, 18 with grade 2, 7 with grade 3). All of these 66 patients were confirmed to have PA on flexible cystourethroscopy. The PAs were detected at different sites, ranging from U1 to U3. Of the 11 patients who had no IPP, 7 had PA (Qmax range 12.5–26.0 mL/s, prostate volume range 7.8–22.3 g) and 4 had normal prostate (Qmax range 19.9–26.8 mL/s, prostate volume range 8.9–21.7 g). Of the 37 patients with prostate volume < 20 g, 29 had IPP. Table I summarises the descriptive statistics of the use of IPP with and without Qmax < 20.0 mL/s for the diagnosis of PA. A total of 73 patients had PA – 39 were situated at U1, 12 at U2, and 22 at U3; the mean Qmax of each of the three types of PAs were 16.0 mL/s, 11.9 mL/s and 8.9 mL/s, respectively. One-way analysis of variance showed statistically significant differences among the Qmax values of patients with the three types of PA ($F = 21.347$, $p = 0.000$) (Fig. 5).

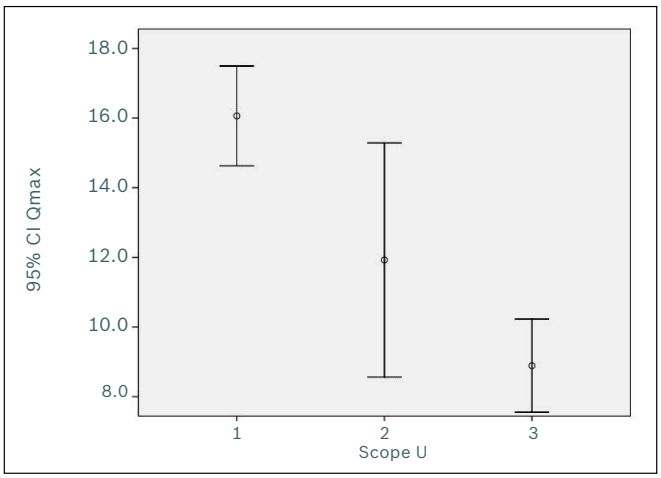

Fig. 5 Qmax of patients with U1 (n = 39), U2 (n = 12) and U3 (n = 22) prostate adenomas. 95% CI: 95% confidence interval; U1: lateral lobe enlargement; U2: middle lobe enlargement; U3: lateral and middle lobe enlargement; Qmax: peak urinary flow rate

DISCUSSION

LUTS is a common urinary complaint in men. A study by Eckhardt et al on patients with LUTS suggestive of BPH found that only 53% of the patients had obstruction, and 36% of volunteers above the age of 50 years with no LUTS still had obstruction on pressure flow study.[8] Therefore, it is important and relevant for PA to be clinically diagnosed in order to differentiate patients with LUTS due to PA obstruction from those with LUTS due to other causes. Even if patients display no symptoms, PA can silently cause severe BOO, leading to chronic retention of urine with renal impairment. Some PA patients may even present with haematuria (either microscopic or macroscopic) although their enlarged prostates may not

have led to significant BOO. Thus, accurate diagnosis of PA is important. In previous studies, we demonstrated the correlation of IPP with BOO using pressure flow study, as well as the use of IPP in predicting the progression of benign prostatic obstruction.[11,12] These findings have been validated by studies from other centres.[14,16] In the present study, all patients with IPP were confirmed to have PA on flexible cystourethroscopy.

In general, clinical BPH has been defined as a prostate volume of > 20 g. However, we found that 29 of the 37 (78.4%) patients in our study group with a prostate volume of < 20 g still had IPP, and all patients with IPP in our study were diagnosed with PA. This finding provides further evidence that small prostates may contain PA and may even cause marked BOO.[1,2] Compared to prostate volume, IPP is better able to predict BOO.[17] IPP is a simple parameter to use in diagnosing PA that causes various degrees of obstruction. The use of IPP in the diagnosis of PA is advantageous as it is easily measured at the bedside with ultrasonography and is noninvasive, unlike transrectal ultrasonography and flexible cystourethroscopy.

In our study, we found that IPP had the highest specificity (100.0%) for diagnosing PA. However, as patients with no IPP may also have PA, there was a need to combine IPP with Qmax to ensure higher sensitivity. The sensitivity (95.9%) and positive predictive value (98.6%) were excellent when IPP was combined with a Qmax parameter of < 20.0 mL/s. A high sensitivity ensures that patients who have the disease are not overlooked, thus allowing earlier diagnosis and treatment of such patients. This is especially important for patients with significant BOO and minimum symptoms, as these patients often have chronic retention of urine and kidney impairment. However, a high specificity ensures that patients who do not have the disease are not subjected to unnecessary procedures such as cystourethroscopy and urodynamic studies (UDS), and needless treatment with medications such as 5-alpha reductase inhibitors.

Patients with high-grade IPP and low Qmax do not need flexible cystourethroscopy or UDS to confirm the diagnosis of PA. Only patients with minimal or no IPP and low Qmax need to undergo such procedures. This is because the negative predictive value of IPP, which is low at 50.0%, does not weaken the diagnostic role of IPP, as the subgroup of PA patients without IPP usually has a small prostate volume and good urinary flow rate. However, further investigations need to be conducted if this subgroup of PA patients has poor, instead of good, urinary flow rate and more invasive treatment is planned. This is to rule out other causes of poor urinary flow rate and to confirm the diagnosis.

According to a study by Abrams, a Qmax cutoff of < 15 mL/s is widely accepted as an indicator of BOO that requires treatment.[18] Pernkopf et al performed uroflow nomograms for healthy male adolescents and obtained a mean Qmax of 28.4 mL/s.[19] In another study on healthy young men, the mean Qmax values of the young men when voiding in the standing, sitting and squatting positions were 26.8 mL/s, 31.3 mL/s and 31.0 mL/s, respectively.[20] Hence, although the accepted normal Qmax defined by pressure flow study is > 15 mL/s, many patients with flow rates > 15 mL/s still have PA. Therefore, it is rational that a diagnosis of PA be excluded using a Qmax cutoff value of ≥ 20.0 mL/s. It should be noted, however, that a normal urinary flow rate does not guarantee the absence of PA, as patients with high bladder pressure can maintain high urinary flow rates in spite of PA. It is not surprising for some patients with PA to have a Qmax of > 20.0 mL/s. In such cases, IPP and prostate volume measurements would help to differentiate between these subsets of patients.

Cystourethroscopy provides visual documentation of the appearance of both the prostate and bladder in men with PA. It provides good information on the site of PA, as well as the severity of the obstruction.[15] Although pressure flow studies are able to diagnose the presence or absence of obstruction, cystourethroscopy is better suited to diagnose the presence or absence of PA. When urodynamic diagnosis of the obstruction is equivocal, cystourethroscopy is important to determine whether the obstruction is due to PA or other causes. The presence or absence of a middle lobe and the degree of urethral occlusion by the lateral lobes of the PA can be seen from the verumontanum via cystourethroscopy. In the present study, we found that patients without IPP may still have PA (Qmax range 12.5–26.0 mL/s). While cystourethroscopy is not recommended in the routine evaluation of patients with LUTS due to its invasiveness, patients with poor urinary flow rate but no IPP need to undergo cystourethroscopy and/or UDS for further evaluation, especially if more invasive treatment is being contemplated for them.

It is important for clinicians to be able to accurately determine whether a prostate is normal or whether PA is present in a simple and easy manner, even when the prostatic volume is within normal range, as this has significant impact on the treatment regimen prescribed for the patient. With a more accurate diagnosis, patients with LUTS and other presentations can be properly graded (according to the degree of IPP) and staged (according to the severity of obstruction and the extent to which the symptoms are deemed bothersome) for further management.[21] Proper diagnosis and classification of PA would translate into a more cost-effective management of PA, as the likelihood of over- or undertreatment would be reduced. Indeed, in a previous study conducted by our group, 59% of the 408 enrolled patients with LUTS suggestive of PA could be watched, only 9% required surgical treatment and 32% were on pharmacotherapy.[22]

In the present study, we found that patients with IPP had PA, and propose the combination of IPP evaluation and uroflowmetry as a promising option for the clinical diagnosis of PA. Clinical diagnosis based on IPP and uroflowmetry results is advantageous as the measurement of IPP by TAUS and

Qmax by uroflowmetry is quick and noninvasive. The present study also revealed an interesting relationship between the site of PA and the degree of BOO. PAs located in the middle lobe appeared to be more obstructive than PAs in the lateral lobes, with the former able to cause severe obstruction even if small in size. This observation can be explained using flow dynamics, as distortion of the bladder outlet and prostatic urethra due to the presence of PA in the middle lobe results in greater obstruction than the mere compression that results from PA situated in the lateral lobes. PAs in the middle lobe tend to elevate and distort the funnelling effect of the bladder neck.

The present study was not without limitations. First, observations made on flexible cystourethroscopy were subjective. However, although experience is needed to assess whether the PA is causing significant obstruction, it is relatively easy to determine the presence or absence of an adenoma. Also, as a measure to ensure uniformity and reduce biasness while these assessments were performed, charts displaying the various configurations of PA were used. Second, the present study had a relatively small sample size. Since all of the enrolled patients either had haematuria or were undergoing checkup for bladder tumour, only four patients were found to have a normal prostate in the our study group. If we had recruited a higher number of healthy adult men, the proportion of individuals with normal prostate might have been higher. More extensive studies that include a larger number of patients are needed to confirm our findings.

PA was confirmed in all patients with IPP on flexible cystourethroscopy. PAs located in the middle of the prostatic urethra (middle lobe) were found to be more obstructive than those located in the lateral position (lateral lobes). We propose IPP as a novel parameter for the diagnosis of PA. As PA can also be present in patients without IPP, patients who have poor urinary flow rate in the absence of IPP may need to undergo UDS or flexible cystourethroscopy to determine the cause of poor uroflow.

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