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Original Article

Prostatic urethral length as a predictive factor for surgical treatment of benign prostatic hyperplasia: a prospective, multiinstitutional study

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ABSTRACT

Background: We hypothesized that prostatic anatomical factors may affect the progression of benign prostatic hyperplasia (BPH) and analyzed whether prostatic anatomical factors could be predictive of the risk of surgery.

Materials and methods: From February to October 2014, 679 men older than 40 years who had lower urinary tract symptoms and enlarged prostates were enrolled from five medical centers. Patients' medical characteristics, serum prostate-specific antigen levels, transrectal ultrasound (TRUS) results, and uroflowmetry were analyzed. Using TRUS in all patients, the total prostate volume, transitional zone volume, prostatic urethral length, transitional zone urethral length, intravesical prostatic protrusion, and prostatic urethral angle were measured. Logistic regression analysis was used to determine factors associated with the risk of surgery. Receiver operating characteristic curves were used to determine cutoff values for significant variables.

Results: Of 679 patients, 37 (5.4%) underwent BPH-related surgery. Prostatic urethral length and transitional zone urethral length were independently associated with the risk of surgery. Age, serum prostate-specific antigen levels, peak flow rate, postvoid residual urine, and other anatomical factors determined by TRUS were not statistically significant with respect to the risk of surgery. Using receiver operating characteristic curve–based predictions, the best cutoff values for prostatic and transitional zone urethral length were 4.53 cm (sensitivity: 83.3%, specificity: 61.6%) and 3.35 cm (sensitivity: 83.3%, specificity: 77.9%), respectively.

Conclusions: This study showed that patients with BPH with longer prostatic and transitional zone urethral lengths had a higher risk of surgery. Prostatic and transitional zone urethral length may be useful predictive factors for medical treatment failure in patients with BPH.

1. Introduction

Lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) are present in more than 50% of men older than 50 years.[1,2] In the past, BPH was considered an acute surgical condition and was typically managed by urethral catheterization or surgery. However, development of drugs such as alpha-adrenergic receptor antagonists and 5-alpha reductase inhibitors has resulted in medical, rather than surgical, approaches for the initial treatment of BPH.[3] Nonetheless, certain BPH cases remain refractory to medical therapy and must still be managed surgically.

Current indications for BPH-related surgery include severe and complicated conditions such as acute urinary retention, recurrent or persistent urinary tract infection, bladder stones, and medical refractory gross hematuria or LUTS.[4] In addition, age, postvoid incomplete bladder emptying, impaired flow rate, large prostate volume, and elevated serum prostate-specific antigen (PSA) levels are considered risk factors for surgery.[5] However, in addition to these traditional risk factors for surgery, still there has been a significant problem to determine surgery for the patients who did not respond to medical therapy. Because the degree of LUTS does not

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always correlate with large prostate size or high PSA level, a small prostate with detrusor underactivity also can cause severe LUTS. Although a differential diagnosis can easily be made between bladder outlet obstruction and detrusor underactivity using pressure flow studies in patients with BPH, pressure flow studies are not commonly performed because of their invasiveness and time-consuming nature.

Several studies have aimed to determine whether there is a correlation between the degree of LUTS and other prostate anatomical factors such as the transitional zone volume (TZV), the presence and degrees of intravesical prostatic protrusion (IPP), and the prostatic urethral angle (PUA).[6–11] Recently, prostatic urethral length (PUL) was also suggested to be associated with the degree of LUTS.[12] Although several studies showed significant correlations between some of these anatomical factors and the degree of LUTS, there remains no consensus about the predictive value of these factors for BPH-related surgery.

Recently, endoscopic equipment such as bipolar electrocautery and various laser modalities have been developed, allowing for minimally invasive surgery. Current surgical treatment for patients with BPH is more often curative with a lower risk of perioperative complications. Therefore, it has become increasingly important to distinguish high-risk patients who will ultimately need surgery and offer surgical treatment earlier to relieve bothersome LUTS and give a higher possibility of cure. It is necessary to be able to detect risk factors for surgery using clinically easily approachable, less-invasive modalities. Herein, we hypothesized that prostatic anatomical factors, which can be measured by transrectal ultrasound (TRUS), may affect the progression of BPH and analyzed whether these factors could be predictive for risk of surgery in patients with BPH.

2. Materials and methods

2.1. Patient enrollment

This study was approved by the local institutional review board (13-0496-082), and six urologists from five tertiary general hospitals participated in patient enrollment using the same protocol. From February to October 2014, a total of 679 consecutive male patients older than 40 years who had LUTS due to enlarged prostates and completed follow-up for more than 12 months were enrolled from the five medical centers. All patients were evaluated by taking medical history, including international prostate symptom score (IPSS) and physical examination. Patients also underwent TRUS, uroflowmetry, and tests for serum PSA levels. Patients with prostate or bladder cancer, previous prostate surgery or pelvic radiation, urethral stricture, neurogenic bladder disease, and active urinary tract inflammation were excluded.

Every patient was initially managed with medical therapy, including alpha-adrenergic receptor antagonists, 5-alpha reductase inhibitors for the patients with larger prostate (>30 cc), and anticholinergic drugs if patients have urgency. All patients were followed up every 4 weeks, and their symptom improvements were evaluated. The decision to perform surgery for BPH was made by following general indications such as acute urinary retention, recurrent or persistent urinary tract infection, medically refractory gross hematuria, bladder stones, renal insufficiency, or LUTS refractory to medical therapy. Age, serum PSA levels, and prostate size were not considered in this decision. Effectiveness of medical therapy was assessed by patients' subjective reporting of symptoms, the IPSS, results of uroflowmetry, and postvoid residual urine volume measurement. Each surgeon decided the operation method, considering patient characteristics and the surgeon's preferences.

2.2. Ultrasound measurement

TRUS was performed by a single urologist in each hospital. Before beginning patient enrollment, all urologists standardized the measurement of ultrasonography-based variables. Prostate volume (PV), TZV, PUL, transitional zone urethral length (TZUL), presence and length of IPP, and PUA were measured in a single session by TRUS. The PV and TZV were calculated by measuring the maximal height, width, and length of the total prostate and transitional zone for the transverse and sagittal sections and then applying the ellipsoid formula (height × width × length × 0.52). The IPP was defined by measuring the distance from bladder circumference at the prostate base to the tip of the protruding prostate gland in the sagittal plane. The PUL was measured by continuous tracing of the route of the prostatic urethra, which runs from the base to the apex of the prostate. The TZUL was measured similarly to the PUL by continuous tracing of the route from the base of the prostate to the distal end of the transitional zone. The PUA was defined as the angle formed by two rays of both the proximal and distal prostatic urethra. The PUL, TZUL, and PUA were measured from the midsagittal image, which was taken when the pressure from the rectal probe was minimized (Fig. 1).

2.3. Statistical analysis

Patients were divided into two groups, the surgery group and the nonsurgery group. The correlation between performance of BPH-related surgery and clinical parameters, including age, serum PSA levels, peak flow rate, and postvoid residual urine, and anatomical factors measured by TRUS, such as PV, TZV, PUL, TZUL, IPP, and PUA, was analyzed. Logistic regression analysis was performed to identify risk factors associated with surgical treatment. After confirming the risk factors for surgery, a receiver operating characteristic curve was drawn, and the best cutoff point was determined based on the sensitivity and specificity. Finally, we selected the same number of patients from nonsurgery group to pair with the patients of the surgery group by SPSS case–control matching in condition of the age and prostate volume. Cox regression analysis was used for these pairs. Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL), and a P value < 0.05 was considered significant.

3. Results

Of 679 patients, 37 patients (5.4%) underwent BPH-related surgery. Transurethral resection of the prostate (TURP) using a

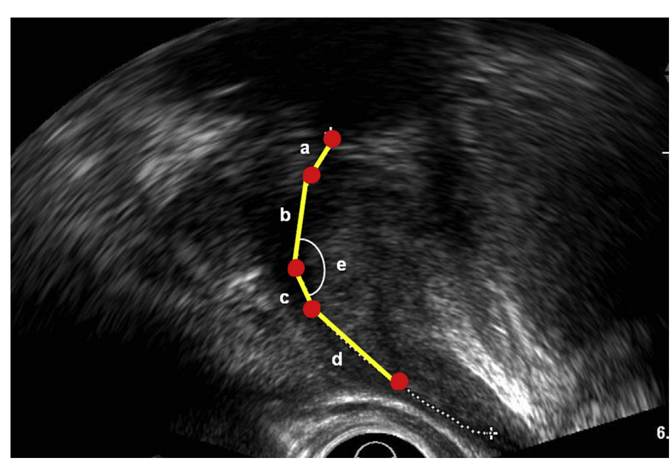

Fig. 1. Ultrasonographic measurements of prostatic urethral length (a + b + c + d), transitional zone urethral length (a + b + c), and prostatic urethral angle (e) in a midsagittal image of a transrectal ultrasound.

bipolar electrocautery system was performed in 34 patients. Transurethral holmium laser enucleation of the prostate (HoLEP) and open retropubic prostatectomy were performed in two and one cases, respectively. The mean time between the initial visit and the operation was 74.4 days (range: 33–200 days). LUTS refractory to medical therapy was the most common indication for surgery, accounting for 26 of 37 patients, whereas nine and two patients underwent surgery because of acute urinary retention and bladder stones, respectively.

The patients' characteristics and anatomical factors measured by TRUS are summarized in Table 1. In univariate analysis, the surgery group had significantly larger PV (46.0 vs. 34.7 g, $P = 0.011$), TZV (26.7 vs. 16.7 mL, $P = 0.021$), and post-void residual urine (PVR) (129.8 vs. 52.3 mL, $P < 0.001$), longer PUL (4.9 vs. 4.4 cm, $P = 0.002$) and TZUL (3.6 vs. 2.9 cm, $P = 0.006$), higher IPSS (22.5 vs. 16.0, $P < 0.001$) and quality of life (4.0 vs. 3.5 $P = 0.022$), and lower Qmax (9.1 vs. 13.2 mL/s, $P < 0.001$) than the nonsurgery group. Multivariate logistic regression analysis showed statistically significant differences in the PUL and TZUL between surgery and nonsurgery groups (Table 2). According to the receiver operating characteristic curve–based prediction of surgery, the areas under the curve using the PUL and TZUL were 0.702 (95% confidence interval, 0.675–0.782) and 0.765 (95% confidence interval, 0.701–0.809) (Fig. 2), and the best cutoff values of the PUL and TZUL were 4.53 cm (sensitivity: 83.3% and specificity: 61.6%) and 3.35 cm (sensitivity: 83.3% and specificity: 77.9%), respectively. The results of the Cox regression analysis after pairing by age and prostate volume are presented in Table 3. We also observed that PUL and TZUL were significant risk factors for BPH-related surgery. Patients with longer PUL and TZUL had increased odds for surgery when compared with patients with shorter PUL and TZUL.

4. Discussion

Although many patients with BPH can be effectively managed by medical therapy, surgical treatment is still required in some cases. With recent advances in surgical instruments and techniques, determining factors able to predict the risk of surgery has been increasingly emphasized. Traditionally, prostate size was considered one of the important factors related to voiding symptoms and risk of surgery in patients with BPH. However, large prostate size does not always correlate with symptom severity nor does it always require surgical treatment.

Recently, many researchers have performed studies to verify correlations between LUTS and several anatomical factors, such as transition zone index, IPP, PUA, and PUL, which can be measured by TRUS.[6–14] These studies did not assess whether these factors could be risk factors for BPH-related surgery, but we hypothesized that some of them may be predictive of the risk of surgery because our team recently found that structural variations of the prostatic urethra was correlated with the severity of voiding symptoms.[15] As the BPH progresses, the overall prostate volume increases, and other structural changes can occur, such as the presence of IPP, lengthening of PUL, and stiffening of PUA. Surgery for BPH, including prostatectomy, TURP, and holmium laser enucleation of the prostate, can correct these structural changes as well as reduce the overall prostate volume, consequently improving LUTS.

In the 1990s, correlations were reported between the transition zone index and LUTS.[8,10,16] Kaplan et al demonstrated that the TZV and transition zone index strongly correlated with LUTS and peak urine flow.[8] Terris et al also reported that the TZV positively correlated with LUTS and PVR and negatively correlated with Qmax.[10] Moreover, Ohtani et al showed that the TZV and transition zone index correlated with the treatment efficacy of TURP and suggested that the TZV and transition zone index could be useful predictive factors for surgical treatment of BPH.[17] However, although the TZV and transition zone index remain important factors for decision-making in relation to surgery, the need for

Table 1
Comparison of patient characteristics between BPH-related surgery and nonsurgery groups.

Parameters	Surgery (n = 37)	Nonsurgery (n = 642)	*P*
Age (y)	71.5	68.2	0.328
PSA (ng/mL)	5.7	1.1	0.036
IPSS	22.5	16.0	<0.001
QoL	4.0	3.5	0.022
Peak flow rate (mL/s)	9.1	13.2	<0.001
Postvoid residual urine (mL)	129.8	52.3	<0.001
Prostate volume (g)	46.0	34.7	0.011
Transitional zone volume (g)	26.7	16.7	0.021
Prostatic urethral length (cm)	4.9	4.4	0.002
Transitional zone urethral length (cm)	3.6	2.9	0.006
Presence of IPP	8 (21.6%)	117 (18.2%)	0.077
Length of IPP (cm)	1.1	0.9	0.163
Prostatic urethral angle (°)	145.1	143.0	0.890

BPH, benign prostatic hyperplasia; IPP, intraprostatic protrusion; IPSS, international prostate symptom score; PSA, prostate-specific antigen; QoL, quality of life.

Table 2
Multivariate logistic regression analysis to determine the predictive factors for BPH-related surgery.

Parameters	Odds ratio (95% CI)	*P*
PSA	1.115 (1.031–1.532)	0.131
IPSS	1.492 (0.351–2.937)	0.668
QoL	1.249 (1.085–3.654)	0.227
Peak flow rate	0.726 (0.503–1.050)	0.089
Postvoid residual urine	0.995 (0.977–1.013)	0.578
Prostate volume	1.132 (0.970–1.320)	0.116
Transitional zone volume	0.843 (0.661–1.075)	0.168
Prostatic urethral length	1.038 (1.002–1.821)	0.037
Transitional zone urethral length	2.289 (1.536–2.459)	0.043

BPH, benign prostatic hyperplasia; CI, confidence interval; IPSS, international prostate symptom score, PSA, prostate-specific antigen; QoL, quality of life.

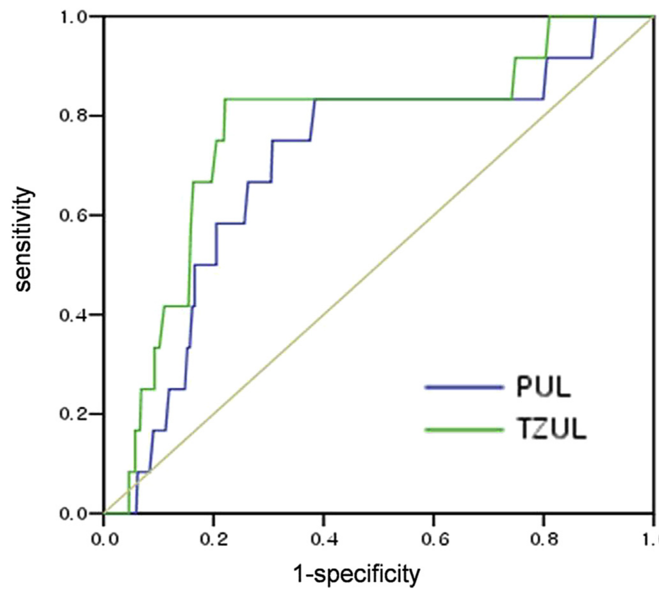

Fig. 2. Receiver operating characteristic curves for prostatic urethral length (AUC = 0.702) and transitional zone urethral length (AUC = 0.765). AUC, area under the curve; PUL, prostatic urethral length; TZUL, transitional zone urethral length.

Table 3
Odds ratio and 95% confidence interval for the risk of surgery in matched cohort (1:1 pairing).

Parameters	Surgery (n = 37)	Nonsurgery (n = 37)	*P*	Odds ratio (95% CI)
Age (y)	71.5	71.2	0.988	1.153 (1.102–1.311)
PSA (ng/mL)	5.7	6.4	0.877	1.010 (0.741–1.325)
IPSS	22.5	18.1	0.056	1.274 (0.885–1.845)
QoL	4.0	3.5	0.086	1.288 (1.008–2.134)
Peak flow rate (mL/s)	9.1	11.1	0.130	0.820 (0.541–1.212)
Postvoid residual urine (mL)	129.8	80.0	0.085	1.186 (0.911–2.315)
Prostate volume (g)	46.0	46.3	0.961	1.124 (1.101–1.322)
Transitional zone volume (g)	26.7	23.6	0.526	1.381 (0.794–1.957)
Prostatic urethral length (cm)	4.9	4.1	0.017	2.115 (1.745–3.241)
Transitional zone urethral length (cm)	3.6	2.8	0.028	3.816 (2.142–6.514)
Presence of IPP	8 (21.6%)	12 (32.4%)	0.483	1.215 (0.987–2.014)
Length of IPP (cm)	1.1	0.9	0.464	0.788 (0.341–1.214)
Prostatic urethral angle (°)	145.1	139.4	0.277	1.238 (0.956–1.874)

BPH, benign prostatic hyperplasia; CI, confidence interval; IPP, intraprostatic protrusion; IPSS, international prostate symptom score; PSA, prostate-specific antigen; QoL, quality of life.

surgery due to large TZV has decreased since 5-alpha reductase inhibitors have become widely used. With early detection of BPH and steady use of 5-alpha reductase inhibitors, further anatomical factors beyond TZV have been considered and studied as predictors of BPH-related surgery.

Since Chia et al and Tan et al introduced IPP as a parameter for bladder outlet obstruction in 2003,[18,19] many investigators have studied the significance of IPP in patients with BPH.[9,11,20,21] IPP is a morphological change in the lateral and median lobes of the prostate and is defined as the protrusion of the prostatic adenoma into the bladder during the process of prostatic enlargement.[14] This can be noninvasively and easily measured by TRUS and can be corrected by surgical treatment. Indeed, Kim et al reported that longer IPP was one of the independent risk factors for bladder stones in patients with BPH. Considering bladder stone in patients with BPH is one of the absolute indications for surgery, IPP can be a potential risk factor for surgery. However, there have been no definite studies that proved significant correlation between IPP and the risk of surgery. IPP was not a statistically significant independent risk factor for surgery in our study. Although it is not considered that IPP itself is a predictor of BPH-related surgery, moderate-to-severe IPP can cause longer PUL and TZUL. In addition, progression of IPP can also induce anatomical change of bladder outlet, which aggravates voiding symptoms. Therefore, further studies related to the resection of IPP and change of LUTS will be needed.

PUA was first proposed by Cho et al as an influencing factor in LUTS.[22] The prostatic urethra has a bent tube shape and can increase urethral resistance during voiding. Theoretically, this resistance may increase if the angle of the bent prostatic urethra becomes more acute. Several recent studies demonstrated a correlation between PUA and the severity of LUTS.[6,7,14] However, Ku et al reported no significant correlation between PUA and LUTS severity or Qmax, although they suggested that PUA correlated with bladder outlet obstruction in patients with BPH.[23] PUA is usually measured in patients at rest, but PUA can be altered during micturition. Moreover, PUA can also be differed during measurement by TRUS because of compression of prostate by the probe. Therefore, PUA may not be entirely reflective of true voiding state. There have been limited studies on PUA as a risk factor for surgery in patients with BPH, and our results showed that PUA was not significantly correlated.

Ko et al suggested that the PUL is associated with the severity of LUTS.[12] PUL can be measured noninvasively by TRUS. We hypothesized that the energy loss of urine flow might worsen due to elevated frictional force with increased PUL because the prostatic urethra is a narrow bent tube and more structural change can occur with prostatic enlargement. In addition, we included TZUL as a parameter in this study because transitional zone structural changes can have more effects on LUTS. Indeed, most parameters evaluated in this study including PV, TZV, PVR, IPSS, quality of life, PUL, and TZUL were significantly higher in the surgery group than in the nonsurgery group in univariate analysis. However, multivariate logistic regression analysis showed only PUL and TZUL to be significant independent risk factors for surgery.

There were several limitations of this study. First, a relatively fewer patients were included in the surgery group. This is likely due to the development of drugs for BPH reducing the need for surgical treatment and the fact that we tried to follow absolute indications for surgery to best confirm parameters as risk factors for surgery. To compensate this limitation, we performed further analysis with the matched cohort (1:1 pairing with surgery and nonsurgery group) in condition of age and prostate volume. It showed significantly higher odds in the surgery group than in the nonsurgery group. Second, long-term follow-up results, postoperative outcomes, and postoperative changes in PUL were not assessed. We did not include postoperative follow-up data because this study was originally designed to analyze risk factors for surgery. However, including postoperative outcomes may be valuable and will be a topic of future research. Despite these limitations, this study showed the possibility of using PUL and TZUL as independent predictive factors for surgery in patients with BPH and uncovered other potential anatomical factors related to the risk of BPH-related surgery.

The results of this study showed that patients with BPH with longer PUL and TZUL had a higher risk of surgery. These findings suggest that PUL and TZUL measured by TRUS may predict medical treatment failure in patients with BPH.

Conflicts of interest

All authors have no conflict of interest to declare.

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