This document was amended in January 2022 to reflect literature that was released since the last update in February 2021. This document will continue to be periodically updated to reflect the growing body of literature related to this topic.

BENIGN PROSTATIC HYPERPLASIA

KEYWORDS: Prostatic hypertrophy, prostatic hyperplasia, PSA, voiding dysfunction, lower urinary tract symptoms (LUTS).

At the end this unit, the medical student will be able to:

1. Identify and name the major anatomic and histologic features of the prostate gland
2. Identify the predominant location in the prostate where BPH develops and describe how this fact relates to the symptoms and signs of BPH
3. Define BPH
4. Describe the distinctive epidemiological features and natural history of BPH
5. List the symptoms and signs of BPH
6. List the important components of the history when interviewing a patient with BPH
7. List the important components of the physical exam of a patient with BPH
8. Summarize the laboratory, radiologic, or urodynamic tests, if any, that should be ordered in a patient with BPH
9. List the indications for treatment of BPH
10. List the medical and surgical treatment options for BPH.
11. Describe when a patient with BPH should be referred to a urologist

PROSTATE ANATOMY

There are 4 basic anatomic zones of the prostate, as illustrated in **Figure 1**: the anterior zone, the peripheral zone, the central zone, and the transition zone. The anterior zone is entirely fibromuscular and non-glandular, and it appears to have little significance in prostatic function or pathology. This area comprises approximately 20% of the bulk of prostatic tissue. The peripheral zone is composed entirely of acinar tissue. It comprises the posterior surface of the prostate, including the apical, lateral, posterolateral and anterolateral portions of the prostate. The peripheral zone and anterior zone, together, represent approximately 70% of glandular volume in the normal adult prostate. The vast majority of prostatic carcinomas arise in the peripheral zone of the prostate. The central gland is composed of the proximal urethra, the prostate tissue around the posterior urethra and the smooth muscle of the internal urethral sphincter. It forms the central portion of the prostate and extends from the base of the prostate to the verumontanum. The transition zone surrounds the urethra, and although this region accounts for only 10% of prostate glandular tissue in young men, it exhibits significant growth with age. Indeed, it is in the transition zone is where benign prostatic hyperplasia (BPH) develops.

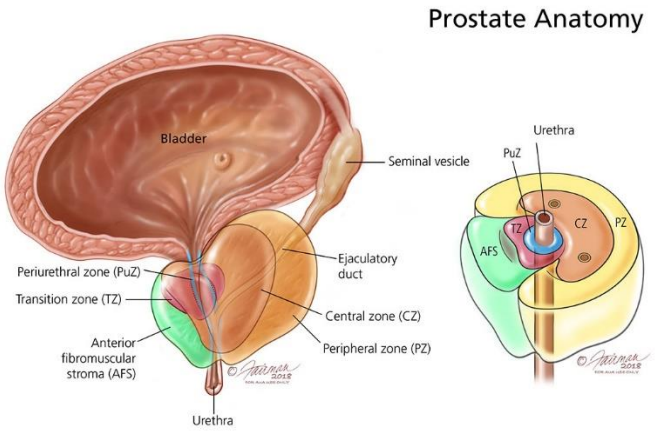


Figure 1. The zones of the normal prostate.

BENIGN PROSTATIC HYPERPLASIA-DEFINITION

Benign prostatic hyperplasia (BPH) refers to the proliferation of epithelial and smooth muscle cells within the transition zone of the prostate (**Figure 2**). Other terms for BPH include benign prostatic hypertrophy and benign prostatic enlargement (BPE). The term has been used to describe a constellation of voiding symptoms that occurs in men with aging. These symptoms are generally referred to as obstructive in nature, as the hyperplastic tissue leads to a narrowing of the prostatic urethra. Such symptoms include decreased force of stream, hesitancy, straining, incomplete bladder emptying, and nocturia. Irritative symptoms are also associated with BPH and include urinary frequency, urgency, and occasionally dysuria.

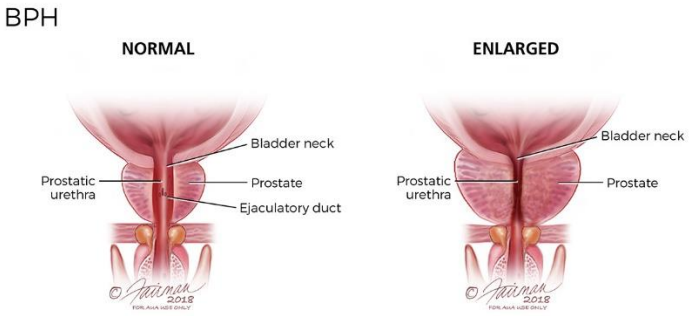


Figure 2. Diagram of a normal and enlarged prostate.

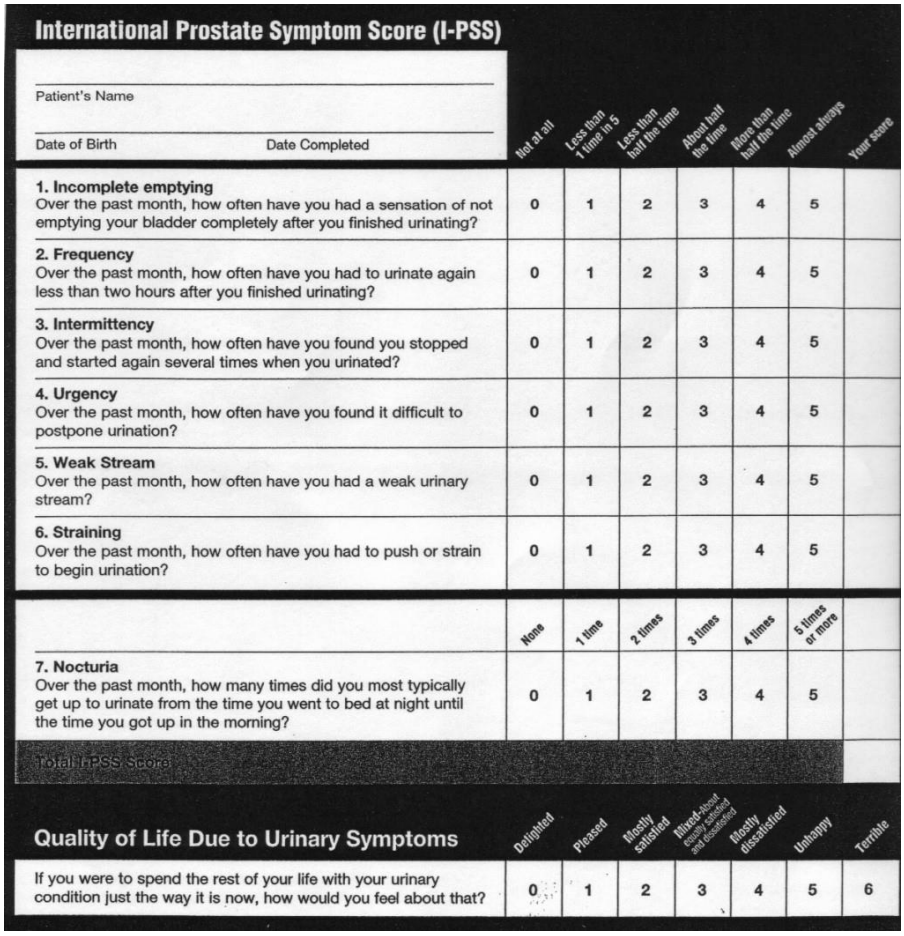
BPH has been used synonymously with "prostatism" and "bladder outlet obstruction", implying that obstruction to urinary outflow, secondary to prostatic enlargement, is the cause of such symptoms. More recently, it has been recognized that prostatic enlargement is not necessary for such symptoms. Furthermore, women may experience similar symptoms with age. Thus, "lower urinary tract symptoms" (LUTS) is currently the preferred term to describe this complex of obstructive and irritative urinary symptoms that occur in both sexes with age.

Voiding dysfunction in the aging male may be due to a variety of factors including changes in the bladder, prostate and/or urethra. Intrinsic changes in the bladder, such as bladder instability, decreased bladder compliance and decreased bladder capacity may all lead to LUTS. However, in many men these symptoms are due to BPH. With age, the prostate exhibits glandular enlargement, increased smooth muscle tone and decreased compliance secondary to altered collagen deposition; these changes can lead to altered urinary symptoms due to outlet obstruction. Urethral stricture and bladder neck contracture are other forms of obstruction or blockage that can present with similar symptoms.

BPH is one of the most frequent diagnoses leading to urology referral. It begins to develop before age 30 with almost 10% of men having histologic evidence of BPH by 40 years of age, and 50% of men showing evidence by age 60. Overall, nearly 80% of men will develop BPH, and as many as 30% will receive treatment for it. In studies that examine the natural history of BPH, the incidence of acute urinary retention or the development of a significant post-void residual urinary volume is 2% per year. Although BPH is seldom life-threatening, it significantly impacts patient quality of life. Thus, the burden of BPH on the healthcare system is substantial.

BENIGN PROSTATIC HYPERPLASIA-DIAGNOSIS

In the initial evaluation of LUTS possible due to BPH, clinicians should obtain a medical history, conduct a physical exam, utilize the International Prostate Symptom Score (IPSS), and collect a urinalysis. After excluding other causes of LUTS, both objective and subjective parameters are used to decide whether or not treatment is indicated. Objective parameters include determination of prostate size, measurement of urinary flow rate and determination of the post-void residual urine volume. Although several subjective instruments are available to quantify the severity of LUTS, the IPSS is widely used to quantify the severity of LUTS and its impact on the quality of life. (**Figure 3**). This questionnaire consists of 7 items that determines the severity of irritative and obstructive voiding symptoms.



International Prostate Symptom Score (I-PSS)

Patient's Name

Date of Birth Date Completed

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	
7. Nocturia Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Total IPSS Score							

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly satisfied	Mixed-about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Figure 3. Validated objective survey instrument for voiding symptoms.

Symptom severity related to urinary frequency, nocturia, weak urinary stream, hesitancy, intermittency, incomplete bladder emptying and urinary urgency is assessed, as well as its effect on quality of life. On a scale of 0-35, mild symptoms exist with scores of 0-7, moderate symptoms with scores of 7-15 and severe symptoms with a score of >15. This index demonstrates predictive validity, reliability and internal consistency. There is some correlation between the objective and subjective measures in that the lower the peak of urinary flow rate, the more severe the urinary symptoms and the larger the prostate. Using the IPSS and the information from the clinical evaluation, the patient should be counselled on management options including lifestyle and behavioral modifications, medical therapy, and/or surgical options. The treatment options can be reviewed, as outlined in Figure 4.

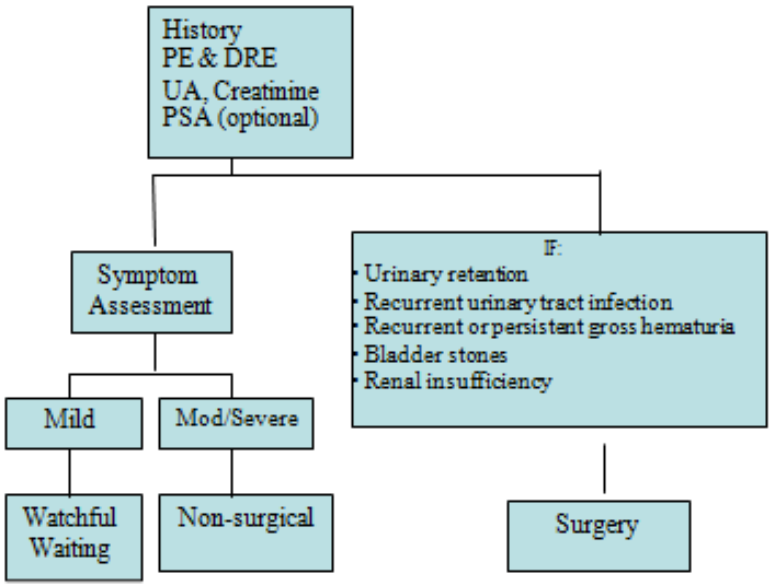


Figure 4. Diagnostic and treatment algorithm of BPH.

Importantly, there are several signs or symptoms that may coexist with voiding symptoms that can alter the treatment algorithm. If the patient has urinary retention, an acute condition in which urine is unable to be voluntarily voided, then immediate treatment is indicated, and may include surgical intervention. A trial of Foley catheter or clean intermittent catheterization (CIC) and alpha blocker medication may avoid surgical treatment in the future in about 80% of cases in which urinary retention coexists with LUTS. Recurrent urinary tract infections, persistent or recurrent gross hematuria, renal insufficiency due to BPH, and bladder stones are also coexisting conditions that may necessitate surgical rather than medical treatment.

BENIGN PROSTATIC HYPERTROPHY-TREATMENT

Watchful waiting

Before initiating medical or surgical treatments, conservative options can help curtail mild LUTS. Avoiding decongestants or antihistamines, decreasing fluid intake at bedtime and decreasing caffeine and alcohol intake can all reduce and often delay the need for other treatments.

Drug Therapy

The medical therapy algorithm outline is below (Figure 5). The medical therapy for BPH attempts to shrink or stop the growth of the prostate or relaxes the urethral channel within the prostate, without using surgery. The FDA has currently approved multiple drugs to relieve the symptoms associated with an enlarged prostate.

The alpha-1-adrenergic receptor blockers (alpha blockers) are considered the first-line therapy for BPH. They improve urine flow and improve LUTS symptoms by relaxing the smooth muscle of the prostate and bladder neck. This class includes terazosin, doxazosin, tamsulosin, and alfuzosin. They all have found to be equally efficacious in multiple phase III RCTs, Phase IV studies, and systematic reviews with an expected improvement in IPSS score of 5-8 points.

Another class of drugs used for treating BPH is the 5-alpha-reductase inhibitors (5-ARIs). They help shrink the prostate by decreasing the production of dihydrotestoterone (DHT) hormone, which is responsible for growth of the acinar glands of the prostate. These include Finasteride, FDA-approved in 1992, and dutasteride, FDA-approved in 2001. These are normally used in combination with alpha blockers for men with enlarged prostate of >30cc on imaging, a PSA >1.5ng/dL or palpably enlarged prostate on DRE, as the combination therapy has been shown to be more effective in reducing the risk of urinary retention and need for future prostate-related surgery. 5-ARIs can also be used as monotherapy in men with aforementioned prostatic enlargement profile.

Another class of drugs that can be used for BPH related LUTS are phosophodiesterase-5-inhibitors (PDE5i). These medications are normally used for erectile dysfunction. In this class, only Tadalafil (Cialis) has been FDA approved for the treatment of LUTS, as it has been shown to be equally efficacious in improving LUTS symptoms as Tamsulosin in a clinical trial while improving concomitant erectile dysfunction.

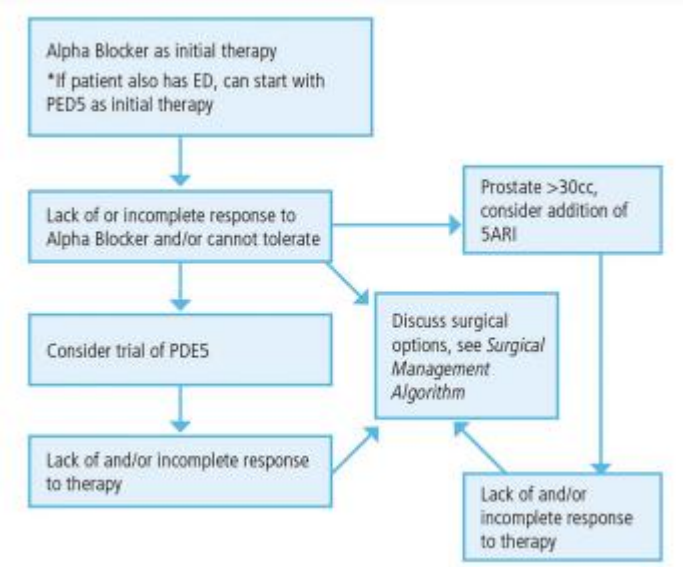


Figure 5. Trial of Medical therapy algorithm

Conventional Surgical Therapy

When selecting the best surgical treatment, the optimal option is often based on the size of the prostate and surgeon preference **(Figure 6).**

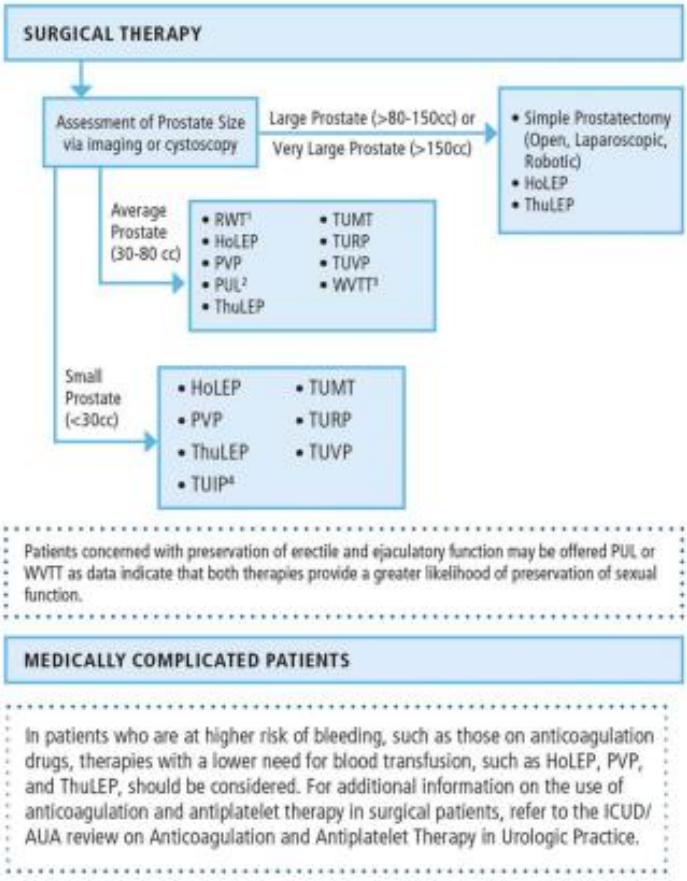


Figure 6. Surgical Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia Algorithm.

Transurethral resection of the prostate (TURP): Surgical therapy with transurethral resection of the prostate (TURP) has traditionally been the "gold standard" treatment for men with BPH. In 1986, it was estimated that TURP accounted for 24% of the professional workload for practicing urologists in the U.S. In this type of surgery, no external incision is needed. After giving anesthesia, the surgeon reaches the prostate by inserting an instrument called a resectoscope through the urethra (**Figure 7)**. The resectoscope is about 12 inches long and 1/2 inch in diameter, contains a light, valves for controlling irrigating fluid, and an electrical loop that cuts tissue and seals blood vessels. During the 60-90-minute operation, the surgeon uses the scope's wire loop to remove the obstructing tissue one piece at a time. The pieces of tissue are carried by the fluid into the bladder and then flushed out at the end of the operation. A TURP is used for approximately 90% of all prostate surgeries for BPH. In most patients, before TURP is performed, consideration has already been given to medical therapy. In general, TURP is reserved for very symptomatic men or those who develop complications including urinary tract infection, bladder stones, or gross hematuria as mentioned above.

A variation of the TURP procedure is called transurethral incision of the prostate (TUIP),which is only recommended in men with prostates ≤30cc. Instead of removing tissue, as with TURP, this procedure widens the urethra by making a few small cuts in the bladder neck, where the urethra joins the bladder, and in the prostate gland itself. Although some people believe that TUIP gives the same relief as TURP with less risk of side effects such as retrograde ejaculation, its advantages and long-term side effects have not been clearly established.

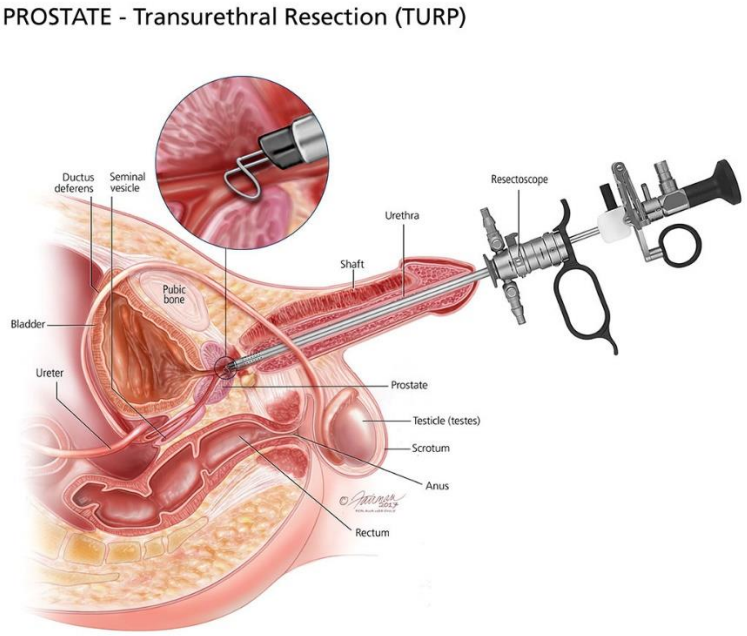


Figure 7. Diagram of Transurethral Resection (TURP).

Surgical "open" prostatectomy: In the few cases when a transurethral procedure is not able to be done, because the prostate is too large, the bladder has been damaged or contains bladder stones, or important identifying landmarks not visible for TURP, open prostatic surgery in indicated. With all open surgical procedures, anesthesia is given and an incision is made. Once the surgeon reaches the prostate capsule, he or she scoops out the enlarged tissue from inside the gland. Importantly, as with other types of surgery and procedures for BPH, the part of the prostate at risk for prostate cancer development is not removed and therefore men who have procedures for BPH are still at risk for developing prostate cancer.

Transurethral laser surgery (Photoselective Vaporization of the Prostate – PVP): This surgical procedure employ side-firing laser fiber to vaporize obstructing prostate tissue to treat BPH. A laser fiber is passed into the urethra near the prostate using a cystoscope and then several bursts of energy lasting 30 to 60 seconds are delivered through the laser fiber. The laser energy destroys prostate tissue and causes shrinkage. As with TURP, laser surgery requires anesthesia and a hospital stay. One advantage of PVP over TURP is that it leads to less blood loss and allows for a quicker recovery. However, it may not be as effective against larger prostates and appears to have higher rates of surgical retreatment.

Laser enucleation: Holmium laser enucleation of the prostate (HoLEP) or thulium laser enucleation of the prostate (ThuLEP) is a minimally invasive technique that can be offered to patients with larger prostate glands. The main benefit of this procedure is that it can be used for

virtually any size prostate including very large (>100 gm) glands. Additionally, these lasers have excellent hemostatic properties, significantly improving blood loss and rates of blood transfusion.

Robotic Waterjet Treatment (RWT): This surgery also requires general anesthesia. It utilizes a robotic handpiece, console, and conformal planning unit (CPU). Here, pre-treatment transrectal ultrasound of the prostate is used to plan the tissue resection, which is then achieved using a water jet from a transurethrally placed handpiece. When compared to TURP, the short-term outcomes appear to be comparable in improving the LUTS symptoms, but the long-term efficacy remains unknown.

Prostate Artery Embolization (PAE): The PAE is technically very challenging ans is usually performed by interventional radiologists. There is insufficient evidence to support routine use of PAE over other BPH surgical modalities for BPH/LUTS. Hence, it is currently only recommended in the setting of clinical trials.

Although these approaches are often successful, some adverse effects may occur. The cutting of prostatic tissue may result in significant bleeding and the absorption of irrigation fluid leading to a life-threatening syndrome of fluid overload and dilutional hyponatremia known as "TUR syndrome." This is less commonly seen now due to improvement in bipolar TURP technology and utilization of 0.9% normal saline as irrigant. Additionally, there is a small risk of damage to the surrounding structures from electrical energy. This includes damage to the internal urethral sphincter, which may cause retrograde ejaculation and possible incontinence, whereas damage to the nerves responsible for erection (which run along the outer rim of the prostate) may result in impotence. It should be noted that laser-based surgeries i.e. PVP, HoLEP, ThuLEP, have excellent hemostatic properties, and as such are recommended for men at higher risk for bleeding.

Minimally Invasive Therapy

A number of minimally invasive procedures have been developed to relieve BPH symptoms, while avoiding general anesthesia and the potential adverse effects listed above. In general, these procedures are less invasive than conventional surgery for BPH.

Prostatic urethral lift (Urolift): Prostatic urethral lift is a transurethral procedure that can be office-based whereby implants are delivered to retract the obstructing prostatic lobes. It is only recommended for men with prostate volume of 30-80cc and verified absence of an obstructive median lobe. Symptom reduction and flow rates for this procedure are less significant as compared to TURP, but this procedure can be offered to patients who are concerned with preservation of ejaculatory and erectile function.

Transurethral microwave procedures: This device uses microwaves to heat and destroy excess prostate tissue. In the procedure called transurethral microwave thermotherapy (TUMT), the device sends microwaves through a catheter to heat selected portions of the prostate to at least 111 degrees Fahrenheit. A cooling system protects the urinary tract during the procedure. The procedure is performed on an outpatient basis in an hour without general anesthesia. TUMT has not been reported to lead to erectile dysfunction or incontinence. Although microwave therapy does not cure BPH, it reduces urinary frequency, urgency, straining, and intermittent flow. It does not correct the problem of incomplete emptying of the bladder. The long-term effects of

microwave therapy are still not clear however.

Water vapor thermal therapy: This therapy uses heated water to destroy excess tissue in the prostate. A catheter containing multiple shafts is positioned in the urethra so that a treatment balloon rests in the middle of the prostate. A computer controls the temperature of the water, which flows into the balloon and heats the surrounding prostate tissue. The system focuses the heat in precise regions of the prostate, while surrounding tissues in the urethra and bladder are protected. Destroyed tissue either escapes with urine through the urethra or is reabsorbed by the body. This therapy may be offered to patients who are desirous of preserving erectile and ejaculatory function.

Transurethral needle ablation (TUNA). The TUNA system delivers low-level radiofrequency energy through twin needles to burn away selected regions of the enlarged prostate. Shields protect the urethra from heat damage. AUA Guidelines no longer recommend this therapy for the treatment of LUTS attributed to BPH.

High-intensity focused ultrasound (HIFU). The use of low frequency ultrasound waves to destroy prostate tissue is the youngest of the minimally invasive therapies developed for BPH. It appears as safe as other minimally invasive methods but long-term outcome data is not available as of yet.

BENIGN PROSTATIC HYPERPLASIA AND PSA

Prostate Specific Antigen (PSA) is a serine protease produced by benign and malignant prostate tissue. Functionally, PSA is the enzyme responsible for liquefaction of the seminal fluid after ejaculation. Although produced in small amounts in other tissues, it should be considered to be prostate specific. PSA circulates in the serum in both free (unbound) and complexed (bound) forms. In addition to being elevated by BPH and prostate cancer, PSA may also be transiently elevated in cases of prostatic inflammation (prostatitis) or infarction, and after prostatic manipulation by biopsy. However, routine digital rectal examination (DRE) usually has little effect on serum PSA levels. The half-life of serum PSA is 2.2 to 3.2 days. Therefore, one should wait 4 to 8 weeks after prostate manipulation and inflammation (cystoscopy, prostate biopsy, and prostatitis) before obtaining a PSA.

A flawless and standardized interpretation of elevated PSA values has yet to be determined. Although it has been well demonstrated that patients with elevated serum PSA levels are more likely to be harboring aggressive disease. Serum PSA screening **interpreted outside the context of important patient-specific variables** carries with it a significant risk of what has been called over diagnosis: the identification and treatment of patients who might otherwise have lived out the rest of their lives without experiencing any of the terrible symptoms associated with advanced prostate cancer. Since the treatment of prostate cancer is associated with a significant level of patient morbidity (including bowel dysfunction, urinary dysfunction, and impotence), the use of serum PSA as a screening tool has been a topic of significant controversy. In May of 2012, the United States Preventative Services Task Force (USPSTF), released their recommendation against routine PSA screening, stating they have found "fair evidence that [PSA screening] is ineffective or that harms outweigh the benefits." Nevertheless, the AUA recognizes that the interpretation of an asymptomatic patient's PSA level is a nuanced exercise that must be tailored to the patient in question.

Potential screening should be preceded by an informed discussion of the risks and benefits of screening, early diagnosis and treatment. Given the added cost and anxiety associated with PSA screening, in combination with a lack of randomized trials showing that screening decreases morbidity and mortality, such screening is not recommended for everyone. With such information, the patient can make an individual decision regarding PSA screening.

SUMMARY

1. The prostate is composed of several regions and zones: two zones of interest are the peripheral zone, where most cancers arise, and the transition zone, where BPH arises.
2. The diagnosis of voiding dysfunction due to BPH is made based on both subjective and objective findings on clinical evaluation.
3. Medical treatment of BPH involves treatment that relaxes the muscular stromal tissue of the bladder neck and prostatic urethra (alpha-blockers) and reduction in the acinar-glandular volume of the prostate through reduced DHT production (5-alpha-reductase inhibitors). PDE5 inhibitors can also be used as monotherapy, especially for men with concurrent erectile dysfunction.
4. Indications for surgical intervention with BPH includes refractory urinary retention due to BPH, recurrent urinary tract infections, recurrent bladder stones or gross hematuria due to BPH, and renal insufficiency secondary to BPH
5. Serum PSA, a serine protease that liquefies the ejaculate, increases over time with both BPH and prostate cancer, which makes it a difficult diagnostic marker for cancer alone.

REFERENCES

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