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BPH: Latest Update

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Benign prostatic hyperplasia (BPH) is a major cause of lower urinary tract symptoms(LUTSs) in men, especially in individuals over the age of 50 years[1].Currently, the maintreatment options for BPH include pharmacological therapysuch as—αadrenergic blockers and5α-reductase inhibitors or surgerysuch as transurethral resection of the prostate (TURP),transurethral incision of the prostate and open simple prostatectomy[2].Ineffective or unwillingto accept medical intervention, BPH patients with LUTS may finally need surgical treatment.

Although TURP is the current 'gold standard' treatment for moderate-to-severe LUTSsecondary to BPH[3,4]. However, TURP has its own limitations. The rate of complicationsfollowing TURP, including infections, urethral strictures, sexual dysfunction, urinary incontinence, urinary retention and the development of transurethral resection (TUR) syndrome, is almost 20%[5,6].On the other hand, a lot of elderly BPH patients are using long-term anticoagulationmedicine for their cardiac and cerebrovascular problems. When they are treated with TURP, asudden interruption of medicines in these patients creates a paradox situation in whichcompeting risks of thrombosis and haemorrhage must be managed.These disadvantages ofTURP have stimulated the development of new alternative surgical procedures for BPH.

In recent years, photoselective vaporisation of the prostate (PVP) has become a promising alternative to TURP[7–11]. PVP uses a high-powered potassium-titanyl-phosphate laser or a lithium triborate laser that emits light at a wavelength of 532 nm, which is in the green portion of the light spectrum[7,8,12].It is because this wavelength is absorbed strongly by haemoglobin but not by water when it is applied to vascularized prostatic tissue, that the laser lightis absorbed instantly by the blood, which is then quickly vaporized and removed, thus, creatinga prostate cavity with minimal blood loss, postoperative discomfort and hospital stay[13,14].

With PVP, promising outcomes have been observed in reduction of bleeding riskin medicallycomplicated patients on anticoagulant and/or antiplatelet therapy[15,16] .Its safety inmen using anticoagulation and efficacy in treating symptomatic BPH have been well reported[15,16].However, due to high cost associated with the use of Green light laser, the use of PVP getsrestricted.

Bipolar enucleation of prostate can be a good alternative to PVP. First suggested by Gillings et al, the technique has undergone multiple modifications. After making an incision close toverumonatum marking, the distal edge of the prostate lobes, the incision is deepened until the surgical capsule of the prostate is reached. Then, the prostate gland is peeled off from thesurgicalcapsule in retrograde fashion towards the bladder neck using the resectoscope tipcombined witha loop or a button electrode. The use of a cutting loop or a button electrode helpscoagulate thedenuded supply vessels and haemorrhagic spots on the capsule surface.Thus, the prostaticlobes are sub-totally enucleated and devascularized but remain stillconnected to the bladderneck by a narrow pedicle. The enucleated adenoma can be either resected in pieces rapidly andbloodlessly with the bipolar resection loop or can be morcellated using a morcelloscope.

In a study by Xiao-Nan Mu etal[23], they compared the safety and the efficacy of bipolar transurethral enucleation of the prostate (TUEP) versus 160-W lithium triborate laser (LBO) photoselective vaporization of the prostate (PVP) for treating benign prostatic hyperplasia >70 ml. Both, bipolar TUEP and 160-W LBO PVP, were found safe and effective in treating benign prostatic hyperplasia >70 ml. Bipolar TUEP offers a more complete removalof prostatic adenoma than 160-W LBO PVP. Final results at a 12-monthfollow-up indicated that
the clinical efficacy of bipolar TUEP was more durable and favourable than 160-W LBOPVP[23].

Epidemiology:

With the increasing population of aging males in the world, benign prostate hyperplasia

(BPH) is becoming one of the most common diseases in elderly men due to its high morbidity[24]. BPH is a common problem that affects the quality of life in approximately one third of men older than 50 years. BPH is histologically evident in up to 90% of men by age of 85 years. Worldwide, approximately 30 million men have symptoms related to BPH[25].The prevalence of BPH rises markedly with increased age. Autopsy studies haveobserved a histological prevalence of 8%, 50%and 80% in the 4th, 6th and 9th decade of life, respectively[26]. Observational studies from Europe, US and Asia have also demonstratedolder age to be a risk factor for clinical BPH onset and progression[27,28,29]. Furthermore, the prostate volume increases with age based on data from the Krimpen and BaltimoreLongitudinal Study of Aging suggesting a prostate growth rate of 2.0%–2.5% per year in older men[30,31]. Continued prostate growth is a risk factor for LUTS progression and larger prostatesare associated with benign prostatic enlargement (BPE) and increased risks of clinical BPH progression, urinary retention and a need for prostate surgery[32].

Pathophysiology:

The precise aetiology of BPH is not well understood. It is characterised by an increase number ofstromal and epithelial cells in the periurethral area of prostate. The increase in number may bedue to the increased proliferation of epithelial and stromal cells or due to the decreased programmedcell death. Either mechanism can lead to cellular accumulation.

Androgen Pathway:

Androgens are critical for the development of BPH. However it is not testosterone butits active metabolite dihydrotestosterone (DHT) that causes growth. Testosterone is convertedto dihydrotestosterone (DHT) by 5-alpha reductase[33].However, the pathogenesis of BPH goesbeyond just DHT. Androgen receptors in the prostate appear to be critical for the developmentof BPH. In fact, there is animal data to suggest that estrogens sensitize the prostate to theeffects of androgens[34].

Inflammatory Pathway:

There has also been a consideration that inflammation may be related to the genesis ofBPH[35].Cytokines (IL-2, IFN alfa, IL-6, IL-8 and IL-15) have been identified in areas offibromuscular prostatic growth. Prostatic inflammation is associated with overall clinicalprogression and an increased risk of urinary retention and the need for surgery. Furthermore, apositive association between high plasma C-reactive protein levels and the odds of reportingmoderate to severe LUTS was reported as well[36, 37].

Age-Related Tissue Remodelling:

Aging and androgens are the two established risk factors for the development ofBPH/BPE[38].In addition, local para- and luminocrine pleiotropic mechanisms/factors areimplicated in the prostatic tissue remodelling process as exemplified in a review by Untergasseret al[39].Prostate tissue remodelling in the transition zone is characterized by-

(1) Hypertrophic basal cells; or
(2) Altered secretions of luminal cells leading to calcification, clogged ducts and Inflammation; or
(3) Lymphocytic infiltration with production of pro-inflammatory cytokines; or
(4) Increased radical oxygen species production that damages epithelial and stromal cells; or
(5) Increased basic fibroblast and TGF-β production leading to stromal proliferation,transdifferentiation and extracellular matrix production; or (6) Altered autonomous innervation that decreases relaxation and leads to a high adrenergic tonus; or
(7) Altered neuroendocrine cell function and release of neuroendocrine peptides[39].

Metabolic Factors-

Results from multiple pre-clinical and clinical studies indicate that several age-relatedmetabolicaberrations (metabolic syndrome, obesity, dyslipidaemia and diabetes) are importantdeterminants in both the development and the progression of BPH/LUTS[40]. Metabolicsyndrome and its related comorbidities, such as sex steroid alterations and low-gradeinflammation, have been related to BPH/LUTS development and progression. In the BaltimoreLongitudinal Study of Aging cohort, each 1 kg/m2 increase in body mass index (BMI)corresponds to a 0.4-mL increase in prostate volume. Obese (BMI > 35 kg/m2) participants had a 3.5-fold increased risk of prostate enlargement compared to non-obese(BMI < 25 kg/m2) participants[41]. Most established aspects of the metabolic syndrome arelinked to BPH/BPE. The presence of metabolic syndrome is associated with a higher annualBPE growth rate, increased sympathetic activity and LUTS. The underlying pathophysiologicmechanisms involved in the association of metabolic factors with BPH/BPE/LUTS are notcompletely understood, but

systemic inflammation, pelvic ischemia and increased sympathetic activity may play a role[40].BPH or histological hyperplasia in itself does not require treatment and is not thetarget of therapeutic intervention. BPH does, however, in many men lead to an enlargement ofthe prostate called benign prostatic enlargement (BPE). The onset of the enlargement is highlyvariable as is the growth rate, though a 5% increase in volume has been shown in longitudinalstudies of placebo treated patients[42]. Clearly not all men with BPH will develop any evidenceof BPE. The prostate gland may cause eventually obstruction at the level of the bladder neck,which in turned is termed benign prostatic obstruction (BPO), assuming a noncancerousanatomy. It is important to realize that not all men with BPE will develop obstruction or BPOjust as not all men with BPH will have BPE. To complicate matters further,obstruction mayalso be caused by other conditions referred to as BOO. Thus, BPO is a subset of BOO.LUTS increase in frequency and severity with age and are divided into those associated with storage of urine and with voiding or emptying. In addition, there are othersymptoms following urination (e.g. post void dribbling). The enlarged gland has been proposedto contribute to the male LUTS complex via at least two routes: 1) Direct BOO/BPO from enlarged tissue (static component), and 2) From increased smooth muscle tone and resistance within the enlarged gland (dynamic component). This complex of storage symptoms is oftenreferred to as overactive bladder (OAB). In men, OAB may be the result of primary detrusoroveractivity/underactivity or develop secondary to the obstruction induced by BPE and BPO[43].

It is important to recognize that LUTS are non-specific, occur in men and women with similar frequency, and may be caused by many conditions, including BPE and BPO. Histological BPH is common and may lead to BPE. BPE may cause BPO. According to AUA, LUTS secondaryto BPHis referred to as "LUTS attributed to BPH" to indicate LUTS among older men forwhom an alternative cause is not apparent after a basic evaluation.

"Evaluation of "LUTS attributed to BPH"- Diagnostic evaluation starts with a complete medical history and a clinical examination. Amedical history aims to identify the potential causes of LUTS as well as any relevant comorbidities the patient may have. It further allows the treating clinician to review the patient's current medication and lifestyle habits.The history will also inquire about associatedsymptoms such as gross hematuria or urinary tract infections. Voiding symptoms are most common but storage symptoms are most bothersome[44]. To assess the severity of LUTS multiple validated symptom score systems are available. EAU guidelines[45] mention The International Prostate Symptom Score (IPSS), The International Consultation on Incontinence Questionnaire (ICIQ-MLUTS) and the Danish Prostate Symptom Score (DAN-PSS). Of these available questionnaires, IPSS is the one most commonly used. The IPSS is an 8-itemquestionnaire, consisting of seven symptom questions and one QoL question[46]. The IPSS scoreis categorised as 'asymptomatic' (0 points), 'mildly symptomatic' (1-7 points), 'moderatelysymptomatic' (8-19 points), and 'severely symptomatic' (20-35 points). Limitations includelack of assessment of incontinence, post-micturition symptoms, and bother caused by eachseparate symptom. A minimum of three point changes is considered as a clinically meaningfulimprovement. Physical examination along with digital rectal examination (DRE) should beperformed in all the patients. DRE is the simplest way to asses prostate volume but the correlationis poor. Underestimation of prostate volume by DRE increases with increasing TRUS volume.

Further, the recommended tests for primary management of BPH have beenrecommended by both the AUA and the EAU, which are as follows-

1. Urinalysis: It must be included in the primary evaluation to identify conditions such asurinary tract infections, micro-hematuria and diabetes mellitus.
2. Frequency volume chart and bladder diaries: It should be used in patients withprominent storage symptoms and nocturia. When done, it should be done for atleast 3days.
3. Renal function tests: Assess renal function if renal impairment is suspected based onhistory and clinical examination or in the presence of hydronephrosis; or whenconsidering surgical treatment for male LUTS.
4. Serum prostate specific antigen (PSA): Should be measured in patients who have more than 10 years of life expectancy to detect any associated prostate cancer.
5. Post void residual (PVR) urine: In both, the MTOPS and ALTESS studies, a highbaseline PVR was associated with an increased risk of symptom progression[47, 48].PVR should be measured if chronic urinary retention is suspected.
6. Uroflowmetry: Key parameters of uroflowmetry are Q-max and flow pattern. It shouldpreferably be evaluated with a voided volume of > 150 ml. A

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threshold Q-max of 10mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for BOO.According to EAU guidelines, it should be performed prior to medical or invasivetreatment.

7. Imaging: Upper urinary tract ultrasound should be performed in cases withhaematuria, UTI,renal insufficiency, urolithiasis and history of upper tract surgery.Evaluation of prostate volume is usually done with transabdominal USG or TRUS. Itis also important prior to treatment with 5-alpha reductase inhibitors.It is recommendedto do prostate imaging when considering for surgical treatment.

8. Urethrocystoscopy: It can be done in patients with microscopic or gross haematuria,urethral stricture or bladder cancer, h/o prior lower tract surgery (TURP) and in case of surgical and invasive therapy to help surgeon determine the most appropriate technical approach.

9. Urodynamics: Pressure flow studies are the basis for the definition of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. Bladder outlet obstruction/BPO has to be differentiated from detrusorunderactivity (DUA), which signifies decreased detrusor pressure during voiding incombination with decreased urinary flow rate due to its invasive nature and thusit is offeredonly if conservative treatment fails.

Apart from the pressure flow studies, newer non-invasive tests are available for the diagnosis of bladder outlet obstruction in patients with LUTS, which are as follows-

• Prostatic Configuration using Presumed Circle Area Ratio (PCAR): The PCARevaluates how closely the transverse US image of the prostate approaches a circularshape. The ratio tendstoward one as the prostate becomes more circular. Thesensitivity of PCAR is 77% for diagnosing BPO when PCAR is > 0.8, with 75%specificity [97].

• Intravesical Prostatic Protrusion: Ultrasound measurement of IPP assesses thedistance between the tip of the prostate median lobe and bladder neck in themidsagittal plane using a supra-pubically positioned US scannerwith a bladdervolume of 150-250 mL; further, grade I protrusion is 0-4.9 mm, grade II is 5-10 mm andgrade III is > 10 mm.

• Bladder wall thickness (BWT): BWT of >5 mm at the anterior bladder wall with abladder filling > 150 ml differentiates between patients with or without BOO.

• Detrusor wall thickness (DWT): DWT of > 2 mm at the anterior bladder wall with abladder filling > 250 ml has a PPV of 94% and specificity of 95% for BOO.

• Ultrasound-estimated bladder weight: It may identify BOO with a diagnostic accuracyof 86%at a cut off value of 35gm.

Overall, although the majority of studies have a low risk of bias, data regarding thediagnostic accuracy of these non-invasive tests is limited by the heterogeneity of the studiesin terms of the threshold values used to define BOO, the different urodynamic definitions ofBOO used across different studies and the small number of studies for each test. It was foundthat specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable.Therefore, even though several tests have shown promising results regarding non-invasivediagnosis of BOO, invasive urodynamics remains the modality of choice[49].

Management of Patients with BPH:

Management of BPH includes conservative treatment in the form of watchful waiting,pharmacologicaltreatment and surgical treatment.

Watchful Waiting (WW):

Men with mild-moderate uncomplicated LUTS with no troublesome symptoms are suitable for WW. Components of medical management includes [50]-

Education and Reassurance

• Discuss the causes of LUTS, including normal prostate and bladder function.

• Discuss the natural history of BPH and LUTS, including the expected future symptoms.

• Reassure that no evidence of a detectable prostate cancer has been found.

Fluid Management

• Advise a daily fluid intake of 1500 to 2000 mL (minor adjustments made for climate and activity).

• Avoid inadequate or excessive intake on the basis of a frequency volume chart.

• Advise fluid restriction when symptoms are most inconvenient (e.g., during long journeys or when out in public).

• Advise evening fluid restriction for nocturia (no fluid for 2 hours before retiring).Caffeine and Alcohol

• Avoid caffeine by replacing with alternatives (e.g., decaffeinated or caffeine-free drinks).

• Avoid alcohol in the evening if nocturia is bothersome.

• Replace large-volume alcoholic drinks (e.g., pint of beer) with small-volume alcoholic drinks (e.g., wine or spirits).

Concurrent Medication

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• Adjust the time when medication with an effect on the urinary system is taken, to improve LUTS at times of greatest inconvenience (e.g., during long journeys and when out in public).
• Replace antihypertensive diuretics with suitable alternatives with fewer urinary effects (via the patient's general practitioner).
Types of Toileting and Bladder Retraining:
• Advise men to double-void.
• Advise urethral milking for men with post-micturition dribble.
• Advise bladder retraining. Using distraction techniques (predetermined mind exercise,perineal pressure or pelvic floor exercises), aim to increase the minimum time between voids to 3 hours (daytime) and/or the minimum voided volume to between 200 and 400 mL (daytime). The urge to void should be suppressed for 1 minute, then 5 minutes, then 10 minutes, and so on, increasing on a weekly basis. Use frequency-volume charts to monitor progress.

Miscellaneous:
• Avoid constipation in men with LUTS.
Pharmacological treatment:
The ideal candidate for medical therapy should have symptoms that are bothersome and negatively affect quality of life so that the patient is willing to make a long-term commitment to medical therapy, providing the drug is effective and adverse experiences are minimal. And patients with absolute indications for intervention should be discouraged from selecting medical therapy.
Medical treatment options available are α blockers, 5- α reductase inhibitors, anti-muscarinics,phosphodiesterase inhibitors and beta3 agonist.

1. α Blockers-
Class of α blocker Drug
Non-selective Phenoxybenzamine
α1
Prazosin,Alfuzosin,Indoramin
Long acting α1
Terazosin,Doxazosin,Alfuzosin SR
α1 selective
Tamsulosin,Silodosin,Naftopidil

Of the all abovementioned— α-blocker, alfuzosin, tamsulosin and silodosin are the ones which are in clinical use present day. Prazosin was the first to be identified for the treatment of LUTS and BPH. However, due to its short half-life, it does require frequent dosing.

Phenoxybenzamine ,a nonselective α-blocker, became out of favour because of the adverse clinical events associated with it. Terazosin and Doxazosin came into market with the promise of being long-acting but terazosin was associated with a greater fall in blood pressure in patients with untreated hypertension or poorly controlled medically treated hypertension.

Similarly, Doxazosin was found to be associated with clinically significant hypotension in hypertensive patients. Naftopidil α1D blocker is more effective in patients with storage symptoms as compared to voiding symptoms. Mechanism of action of α-blocker is to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO[51].Tamsulosin is α1 blocker that exhibits some modest degree of selectivity for the α1A versus the α1B adrenoceptors and no selectivity for the α1A versus the α1D adrenoceptors, while Silodosin shows 162:1 selectivity for α1Aadrenoceptors versus α1B adrenoceptors.

α1-blockers can reduce both storage and voiding LUTS. Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of less than one year but α1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies[52-55]. In addition, α1-blockers neither reduce prostate size nor prevent AUR in long term studies[53-55]. Nevertheless, IPSS reduction and Q-max improvement during α1-blocker treatment appear to be maintained for over at least four years. The most frequent adverse eventsassociated with α1-blockersare asthenia, dizziness, orthostatic hypotension and retrogradeejaculation. It is also been found to be associated with intra-operative floppy iris syndrome.EAU guidelines recommends α1-blockers to men with moderate to severe LUTS[45].

2. 5- α reductase inhibitors-

Two 5-ARIs are available for clinical use: dutasteride and finasteride. Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits 5α-reductase types 1 and 2 with similar

potency (dual 5-ARI). 5α-reductase inhibitors act by inducing apoptosis of prostate epithelial cells[56] leading to prostate size reduction of about 18-28% and a decrease in circulating PSA levels of about 50% after six to twelve months of treatment[57]. 5α-reductase inhibitors, but not α1-blockers, reduce the long-term (> one year) risk of AUR or need for surgery[58-60]. In the PLESS study, finasteride treatment reduced the relative risk of AUR by 57%, and surgery by 55% at four years, compared with placebo[59]. In the MTOPS study, a significant reduction in the risk of AUR and

surgery in the finasteride arm compared with placebo was reported (68% and 64%, respectively)[58]. A pooled analysis of randomised trials with two-year follow-up data, reported that treatment with finasteride significantly decreased the occurrence of AUR by 57% and surgical intervention by 34%, in moderately symptomatic LUTS[61]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. According to EAU guidelines, 5α-reductase inhibitors are recommended for men who have moderate-to- severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).While prescribing 5α-reductase inhibitors patient should also be counselled about the onset of action of 5α-reductase inhibitors i.e. 3- 6 months.

3. Combination of α-blocker & 5α-reductase inhibitors-Combination therapy consists of an α1-blocker together with a 5-ARI. The α1-blocker exhibits clinical effects within hours or days, whereas the 5-ARI needs several months to develop full clinical efficacy. Long-term data (four years) from MTOPS, and Combination of Avodart and Tamsulosin (CombAT) studies showed that combination treatment is superior to monotherapy for symptoms and Q-max, and superior to α-blocker alone in reducing the risk of AUR or need for surgery[54,55,58]. EAU guidelines recommend to offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL)[45].

4. Muscarinic receptor antagonists-

Muscarinic receptor antagonists licensed for treating OAB/storage: darifenacin hydrobromide (darifenacin),fesoterodine fumarate (fesoterodine), oxybutynin hydrochloride (oxybutynin), propiverine hydrochloride (propiverine),solifenacin succinate (solifenacin), tolterodine tartrate (tolterodine),trospium chloride. According to EAU guidelines, muscarinic receptor antagonists should be used in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. Do not use antimuscarinic overactive bladder medications in men with a post-void residual volume > 150 mL[45].

5. β3-agonists-

β3-adrenoceptors are the predominant β receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation. Mirabegron 50 mg is the first clinically available β3-agonist with approval for use in adults with OAB. The most common treatment-related adverse events of mirabegron are hypertension, UTI, headacheand nasopharyngitis[62-65]. Mirabegron is contraindicated in patients with severe uncontrolledhypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg,or both). Presently there is no study which evaluated Mirabegron in the treatment of OABsymptoms in patients with BOO. EAU guidelines mention it as weak strengthrecommendation for men with moderate-to-severe LUTS who mainly have bladder storage symptoms.

6. Phosphodiesterase 5 inhibitors-

Phosphodiesterase 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Although clinical trials of several selective oral PDE5Is have been conducted in men with LUTS, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS. Phosphodiesterase 5 inhibitors are contraindicated in patients using nitrates, the potassium channel opener nicorandil, or the α1-blockers doxazosin and terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (< three months) or stroke (< six months), myocardial insufficiency (New York Heart Association stage > 2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is. The meta-regression suggested that younger men with low body mass index and more severe LUTS benefit the most from treatment with PDE5Is[66]. Several RCTs have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS, and improve QoL. However, Q-max did not significantly differ from placebo in most trials. EAU guidelines recommend use of phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction[45].

Surgical Management-

According to AUA indications for surgical management of BPH are patients who have renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections (UTIs), recurrent bladder stones or gross haematuria due to BPH and/or with LUTS attributed to BPH refractory to and/or unwilling to use other therapies.

Various available options are[45]-

• Transurethral resection of the prostate (TURP),

• Transurethral incision of the prostate (TUIP),
• Transurethral microwave therapy (TUMT),
• Transurethral needle ablation (TUNA), and
• Open simple prostatectomy.

• Lasers-
o Laser vaporisationincludes—GreenLight, thulium, and diode lasers vaporisation, whereas
o Laser enucleationincludes— holmium and thulium laser enucleation,
• Prostatic stents,
• Prostatic urethral lift (PU lift),
• Intraprostatic injections.

• Newer techniques under investigations-
o Minimal invasive simple prostatectomy,
o iTIND,
o Aquablation: image guided robotic waterjet, ablation: AquaBeam;
o Convective water vapour energy (WAVE), ablation: The Rezum system;
o Prostatic artery embolization.
Of all the available options, the choice of modality depends on the patient factors,gland size and available resources.

Transurethral Incision of Prostate (TUIP):

It involves incising the bladder outlet without tissue removal. It is indicated especially in prostate sizes < 30 cc without middle lobe. Risk of TUR syndrome associated with TUIP is negligible. A meta-analysis comparing TUIP with TURP after a minimum follow-up of 6 months identified a lower rate of RE (18.2% versus 65.4%) and a need for blood transfusion (0.4% versus 8.6%) as the key advantages of TUIP versus TURP[67]. A RCT (n=86, data reported for 80 completers) conducted in Egypt that compared TUIP to TURP in men with small prostates (≤30g) was identified[45]. Mean age of 14 participants was 65 years, and baseline I-PSS was 19. Baseline prostate size was 28g. Follow-up was 48 months. In men with small prostates, long-term mean change from baseline in IPSS was similar between the TUIP and TURP groups (WMD: 0.5; CI: -0.2, 1.2). Need for reoperation and blood transfusion was similar between the TUIP and TURP groups. In terms of sexual side effects, ED was reported for 8% of TUIP participants compared to 20% for TURP participations, though this difference was not significant (RR: 0.4; CI: 0.1, 1.3). There was, however, a significant difference in reports of RE with a total of 30 participants experiencing RE (9 in the TUIP arm and 21 in the TURP arm). So, in today's time, various guidelines do mention TUIP as a standard option for surgical treatment of moderate-to-severe LUTS in men with prostate size < 30 mL, without a middle lobe.

Transurethral Resection of Prostate (TURP): Monopolar/BipolarTURP remains the historical standard by which all the other subsequent surgical approaches totreatment of BPH are compared and serves as the reference group for all other techniques.Transurethral resection of the prostate removes tissue from the transition zone of the gland.

Various reported techniques are gland resection are- Maurmayers technique, Nesbit technique,Holtgrewe modification of Nesbit technique, Barnes technique, Richard Notley Method,Milner technique, Alcock and Flocks technique, etc. Monopolar and Bipolar are the two energy sources available for TURP. Contrary to M-TURP, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed locally; energy is confined between an active (resection loop) and a passive pole situated on the resectoscope tip ("true" bipolar systems) or the sheath ("quasi" bipolar systems). Prostatic tissue removal is identical to M-TURP; however, B-TURP requires less energy/voltage because there is a smaller amount of interpolated tissue. Energy from the loop is transmitted to the saline solution,resulting in excitation of sodium ions to form plasma; molecules are then easily cleaved underrelatively low voltage enabling resection. During coagulation, heat dissipates within vesselwalls, creating a sealing coagulum and collagen shrinkage. While monopolar TURP requiresthe use of either iso-osmolar solutions of sorbitol, mannitol, or glycine, bipolar TURP may beperformed in 0.9% NaCl solution. This reduces (if not eliminates) the risk for acute dilutionalhyponatremia during prolonged resection, which may lead to the so-called TUR syndrome.

Regarding the comparative efficacy, effectiveness, and safety of monopolar versus bipolar TURP, there are five systematic reviews and meta-analyses published between 2009 and 2015 that compared bipolar TURP to monopolar TURP[68-72]. None of the authors found significant differences in terms of IPSS improvement at 12 months or improvements in peak urinary flow rates, the main efficacy parameters of interest. However, there were differences regarding safety parameters. Length of stay and dilution hyponatremia both favoured bipolar TURP. TUR syndrome occurred less frequently in the group that received bipolar TURP[69-72].

Bleeding and drops in haemoglobin seem to favour bipolar TURP, risk reduction for clot retention favoured bipolar TURP. Both AUA and

EAU recommends B-TURP for surgical treatment of moderate-to-severe LUTS in men with prostate size of 30-80 ml.

Electrosurgical modification of TURP is TUVP i.e. transurethral vaporisation of prostate. TUVP can utilize a variety of energy delivery surfaces including amongst others: a spherical rolling electrode (rollerball), grooved roller electrode (vaportrode), or hemi-spherical mushroom electrode (button). TUVP typically uses saline and is powered with a bipolar energy source. With minimal direct tissue contact (near-contact; hovering technique) and heat production, following the generation of an initial electrical pulse, the bipolar electrode produces a constant plasma field (thin layer of highly ionized particles; plasma corona), allowing it to glide over the tissue and vaporise a limited layer of prostate cells without affecting the underlying tissue whilst achieving haemostasis, ultimately leaving behind a TURP-like cavity[73]. Compared to traditional resection loops, the various TUVP designs hope to improve upon tissue visualization, blood loss, resection speed and patient morbidity. A distinct difference between B-TUVP and its ancestor (monopolar transurethral vaporisation of the prostate) is that B-TUVP displays thinner (< 2 mm) coagulation zones[73], compared to the disproportionate extent of those created by the former (up to 10 mm)[74] that potentially lead to mostly irritative side-effects and stress urinary incontinence[73,75,77] .Various guidelines recommend B-TUVP as an alternative to B-TURP for surgical treatment of moderate-to-severe LUTS in men with prostate size of 30-80 mL.

Photoselective Vaporisation of Prostate:

The Potassium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) lasers work at a wavelength of 532 nm. PVP utilizes a 600-micron side firing laser fiber in a noncontact mode. The laser wavelength is 532nm, which is preferentially absorbed by hemoglobin resulting primarily in tissue ablation/vaporization with a thin layer of underlying coagulation that provides hemostasis. The procedure is generally performed with saline irrigation, eliminating the possibility of TUR syndrome that can occur with non -ionic irrigation. The goal of the procedure is to vaporize the prostate adenoma sequentially outwards until the surgical capsule is exposed and a defect is created within the prostate parenchyma through which the patient may now void. Given the lack of availability of the 80W platform and the superior outcomes as compared to the higher powered lasers, clinicians utilizing PVP should utilize either the 120W or 180W options. In the GOLIATH study[78-80], an international multicentre RCT comparing the 180W PVP to TURP, the recently published 24-month data reported similar adverse events related to urinary incontinence (RR: 1.0; CI: 0.3, 3.28), need for blood transfusion (RR: 0.3; CI: 0.01, 7.9), and overall need for reoperation (RR: 1.4; CI: 0.6, 3.0) between the two modalities. Outcomes at study termination were also similar with regards to PSA, transurethral ultrasound (TRUS)-based prostate volume, PVR, and EF. While the IPSS at 24 months was 5.9 for TURP (compared to 6.9 for PVP), this difference did not meet the non-inferiority criteria in the study (defined as a 3-point difference in the IPSS). In a single center study comparing M-TURP, B-TURP and 120W PVP through 36 months supports the above insofar as there is similar change in IPSS and IPSS-QOL between PVP and the TURP cohorts[81,82]. Apart from KTP/LBO, Diode and Thullium lasers can also be used for vaporisation purpose. Presently various guidelines recommend laser vaporisation of prostate with 120W/180W LBO laser for men with moderate – severe LUTS with prostate size < 80 cc, as an alternative to TURP. It is also recommended for patients on anti-platelet and anticoagulant therapy.

Enucleation of Prostate:

Laser Enucleation:

The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 2,140 nm) is a pulsed solid-state laser that is absorbed by water and water-containing tissues. Tissue coagulation and necrosis are limited to 3-4 mm, which is enough to obtain adequate haemostasis[83]. Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates higher haemostasis and intra-operative safety when compared to TURP and OP. Peri-operative parameters like catheterisation time and hospital stay are in favour of HoLEP. EAU recommends laser enucleation of the prostate using Ho:YAG laser (HoLEP) for men with moderate-to-severe LUTS as an alternative to TURP or open prostatectomy.

Due to the chromophore of water and minimal tissue depth penetration with both holmium andthulium (0.4mm for holmium, 0.2 mm for thulium), these two lasers achieve rapid vaporizationand coagulation of tissue without the disadvantage of deep tissue penetration. They have bettercoagulative properties in tissue than either monopolar or bipolar TURP, and combined withtheir superficial penetration, both thulium and

holmium are reasonable for endoscopicenucleation[84].

Based on four studies reporting long-term follow-up comparing HoLEP to TURP, ranging from 12 to 92 months, mean changes in IPSS (approximately -19) between groups were statistically similar (WMD: -0.5; CI: -1.2, 0.3). Only two studies reported I-PSS-QoL outcomes (mean change approximately -3.5) at follow-up of greater than 12 months, and mean differencesbetween groups were not statistically significant (0.10; CI: -0.05, 0.25)[85,86].

When comparing ThuLEP to TURP, 3 trials reported long-term results in IPSS reduction (mean change approximately -15), ranging from 18 to 60 months (WMD: 0.4 points; CI: -0.9, 1.6). Similarly, there was no significant difference in mean reduction in IPSS-QoL outcomes (mean change approximately - 2.0). At long-term follow-up, the mean difference was - 0.3 (CI: -0.4, 0.9). Qmax at last follow-up after HoLEP and ThuLEP compared to TURP is generally similar. Of the 11 studies reporting Qmax, 9 found the HoLEP and TURP groups to be similar[85-99].Two studies, however, found significantly higher Qmax in the HoLEP groups. In reviewing the need for blood transfusion, either perior post-operatively, likelihood was significantly lower compared to TURP for both HoLEP (RR 0.20; CI: 0.08, 0.47) and ThuLEP (RR: 0.4; CI: 0.1, 0.9).

Bipolar Transurethral Enucleation of Prostate (B-TUEP):

This has come up as cost effective alternative to laser enucleation of prostate in patients with large prostate (> 80 cc). In 2003, Liu etal[100] performed first totally retrograde B-TUEP. Laser enucleation is thought to be superior in terms of less potential risk of haemorrhage, reduced bladder irrigation and catheterization time. In contrast, bipolar enucleation has its own advantage in that the equipment is easily accessible and highly cost-efficient.[100]Apart from laser enucleation, bipolar enucleation has also been compared with PVP. Bipolar Enucleation of prostate can be a good alternative to PVP, in a study by Xiao-Nan Mu etal[101] , they compared the safety and efficacy of bipolar transurethral enucleation of the prostate (TUEP) versus 160-W lithium triborate laser (LBO) photoselective vaporization of the prostate (PVP) for treating benign prostatic hyperplasia >70 ml. Both bipolar TUEP and 160-W LBO PVP were found safe and effective for treating benign prostatic hyperplasia >70 ml. Bipolar TUEP offers more complete removal of prostatic adenoma than 160-W LBO PVP. Final results at 12 months follow-up indicated that the clinical efficacy of bipolar TUEP was more durable and favourable than 160-W LBO PVP. So Bipolar enucleation is good alternative to B-TURP in patients with moderate to severe LUTS with large prostate size.

Simple Prostatectomy:

Open prostatectomy is the oldest surgical treatment for moderatetosevere LUTS secondary to BPO. Obstructive adenomas are enucleated using the index finger, approaching from within the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure). It is used for substantially enlarged glands (> 80-100 mL). Open prostatectomy reduces LUTS by 63-86% (12.5-23.3 IPSS points), improves QoL score by 60-87%, increases mean Q-max by 375% (+16.5-20.2 mL/s), and reduces PVR by 86-98% [102-104]. Efficacy is maintained for up to six years. According to EAU, open prostatectomy or EEP such as holmium laser or bipolar enucleation of the prostate are the first choice of surgical treatment in men with a substantially enlarged prostate and moderate-to-severe LUTS. Open prostatectomy should be offered in the absence of endoscopic enucleation to treat moderate-to-severe LUTS in men with prostate size > 80 mL[45].

Transurethral microwave therapy (TUMT) & Transurethral needle ablation (TUNA):

In the recent EAU & AUA guidelines these two forms of treatment are not presently considered for the management of patients with BPH because of high retreatment rates.

Prostatron (Prostasoft 2.0 and 2.5) and ProstaLundFeedbackare the two devices used for TUMT. A systematic review has shown, Symptom score after TUMT decreased by 65% in twelve months, compared to 77% after TURP. An RCT-based SR[105] found that TURP achieved greater improvement in Q-max (119% vs. 70%) and that TURP patients (1/100 person-years) were less likely to require retreatment for symptoms than TUMT patients (8/100 person-years).

Due to the low peri and post-operative morbidity and lack of need for anaesthesia, TUMT is a true outpatient procedure and an option for (elderly) patients with comorbidities or greater anaesthesia risks[106]. Similarly, Transurethral needle ablation of the prostate can be performed as a day-case procedure without general anaesthesia[107]. Transurethral needle ablation is not suitable for prostates > 75 mL or isolated bladder neck obstruction. In addition, TUNATM cannot

effectively treat prostatic middle lobes. There are also concerns about the durability of the effects achieved by TUNATM.

Prostatic Stents:

Prostatic stents were primarily designed as an alternative to an indwelling catheter but have also been assessed as a primary treatment option in patients without significant comorbidities[108,109]. Permanent stents are biocompatible, allowing for epithelialisation. Temporary stents do not epithelialize and may be either biostable or biodegradable[108,109]. Due to common side effects and a high migration rate, prostatic stents have a limited role in the treatment of moderate-to-severe LUTS. Temporary stents can provide short-term relief from LUTS secondary to BPO in patients temporarily unfit for surgery or after minimally invasive treatment[108,109].

Prostatic Urethral Lift:

PUL was developed in 2004 as a treatment option for LUTS/BPH that works by altering prostatic anatomy without ablating tissue. These permanent trans prostatic implants take the forms of sutures that are delivered by a hand-held device through a cystoscope to mechanically open the prostatic urethra by compressing the prostate parenchyma. The sutures have "T- shaped" bars on the ends of the suture and are spring loaded and placed so that the bars are setwith one outside the prostate capsule and the other within the prostatic urethral lumen. The T-shaped sutures are placed such that there is sufficient tension on them thus pulling the lumenof the prostatic urethra towards the capsule, compressing the tissue, and opening the prostatic urethral lumen. Roehrborn et al(2013)[110] demonstrated with cystoscopy that the implant doesnot encrustand epithelializes within 12 months. Histopathologic analysis of tissue obtainedafter PUL demonstrates a benign response to the implant[111]. Additionally, no changes werenoted in PSA[112]. The available guidelines recommends PU Lift for patients interested inpreserving the ejaculatory function with prostate < 70-80 cc and no middle lobe.

TIND:

It is an emerging device designed to remodel the bladder neck and the prostatic urethra. The TIND is composed of elongated struts and an anchoring leaflet, all made of nitinol. Under direct visualisation the TIND is deployed inside the prostate in expanded configuration. The intended mode of action is to compress obstructive tissue by the expanded device, thereby exerting radial force leading to ischaemic necrosis in defined areas of interest. The TIND is left in position for five days. The resulting incisions may be similar to a Turner Warwick incision. In an outpatient setting the device is removed by standard urethroscopy. Recently, a second generation implant was introduced, the i-TIND, which is comprised of three nitinol elongated struts and an anchoring leaflet, which is again preloaded by crimping it into the delivery system[45]. A single-arm, prospective study of 32 patients was conducted to evaluate feasibility and safety of the procedure[112]. All participants were treated with light sedation, meanoperative time was 5.8 mins and after the twentieth procedure patients were discharged on thesame day of intervention. Median IPSS was 19, mean Q-max was 7.6 mL/s and median IPSSQoL was 3 at baseline. After twelve months, mean improvements relative to baseline valueswere 45% for IPSS and 67% for Q-max. No intra-operative complications were noted.

Recently, the 3-year follow up was published, the change from baseline in IPSS, QoL score and Q-max was significant at every follow-up time point. After 36 months of follow-up, a 41% rise in Q-max was achieved (mean 10.1 mL/s), the median (IQR) IPSS was 12 (6-24) and the IPSS QoL was 2 (1-4)[113]. Randomised controlled trials comparing iTIND to a reference technique are ongoing.

Aquablation – image guided robotic waterjet ablation: AquaBeam—

It uses the principle of hydro dissection to effectively ablate prostatic parenchyma while sparing collagenous structures like blood vessels and the surgical capsule. A targeted high velocity saline stream ablates prostatic tissue without the generation of thermal energy under real-time transrectal ultrasound guidance. After completion of ablation haemostasis is performed with a Foley balloon catheter on light traction or diathermy or low-powered laser if necessary[115]. In the RCT the primary safety end point was the development of Clavien-Dindo persistent grade 1, or 2 or higher operative complications[116].Aquablation was shown to be non- inferior to TURP (26% vs. 42%, p=0.0149). Among sexually active men the rate of anejaculation was lower in those treated with Aquablation compared to TURP (10% vs. 36%, respectively). The first clinical experience provides encouraging results, with a low risk of sexual dysfunction, but further modifications of the AquaBeam system may be necessary. Convective water vapour energy (WAVE) ablation: The Rezum

system It uses radiofrequency power to create thermal energy in form of water vapour, which in turn deposits the stored thermal energy when the steam phase shifts to liquid upon cell contact. Dueto the convective properties of water vapour the steam disperses rapidly and homogenouslythrough the tissue interstices and releases stored thermal energy onto prostatic tissue effectingcell necrosis. The procedure can be performed in an office based setting with minimal painmanagement. Usually, one to three injections are needed for each lateral lobe and one to twoinjections may be delivered into the median lobe. In the initial studies, Safety profile wasfavourable with adverse events documented to be mild to moderate and resolving rapidly. Ofnote, almost 69% received only oral sedation and in contrast to most of the novel minimallyinvasive techniques all critical prostatic zones including the middle lobe were successfully treated. Preservation of erectile and ejaculatory function after convective water vapour thermaltherapy was demonstrated utilising validated outcome instruments such as IIEF and MaleSexual Health Questionnaire Ejaculation Disorder Questionnaire[117]. However further RCTsagainst a reference technique are needed to confirm the first promising clinical results and toevaluate mid- and long-term efficacy and safety of water vapour energy treatment.

Prostatic artery embolization:

Prostatic artery embolization (PAE) can be performed as a day procedure under local anaesthesia with access through the femoral arteries. Digital subtraction angiography displays arterial anatomy and the appropriate prostatic arterial supply is selectively embolised to affect stasis in treated prostatic vessels. The selection of LUTS patients who will benefit from PAE still needs to be defined[118]. Prostatic artery embolization is a technically demanding procedure that can be performed by interventional radiologists with the necessary experience and additional training. It is important to stress, that PAE impacts the entire prostate without the option for focused and controlled action on BOO. This may explain the higher clinical failure rate compared to reference methods like TURP and commonly observed complications like AUR. A multidisciplinary team approach of urologists and radiologists is mandatory as the basis for future RCTs of good quality with long-term follow-up in order to integrate this treatment option into the spectrum of efficient minimally invasive treatment options.

CONCLUSION:

Greenlight laser PVP (HPS) is as effective as B-TURP in symptom reduction, improvement in flow rates and reduction in post-void residual urine.Similarly B-TUEP is as effective as B-TURP in symptom reduction, improvement in flow rates and reduction in post-void residual urine.Overall complication rate were found to be significantly high in patients undergoing B-TURP when compared to Greenlight laser PVP (HPS) and B-TUEP.Rate of transient incontinence were found to be significantly high in B-TUEP grouphowever on long term follow up it was comparable to other groups.

B-TUEP is one good cost-effective alternative toGreenlight laser PVP (HPS) with results comparable to PVP and B-TURP. Also thecomplications with B-TUEP were found to be comparable to PVP and lesser than B-TURP.Also Greenlight laser PVP (HPS) is associated with lesser post-operativecatheterization days as compared to those who underwent B-TURP and B-TUEP.So the surgical outcomes in terms of improvement in IPSS and IPSS

QoL, improvement in Q-max and reduction in PVR were comparable with all 3 modalities of treatment . In such severely co-morbid patients i.e ASA grade 3 and 4, Greenlightlaser PVP (HPS) and B-TUEP is associated with better complication rates when compared toB-TURP.Greenlight laser PVP (HPS) can be considered in patients with BPH with associatedco-morbidities (ASA grade 3 and 4) and gland size of >60cc, with equally efficacious resultsand better complication rates and post-operative catheterization duration.

However B-TUEP being a cost-effective to Greenlight laser PVP (HPS) is a goodalternative with as effective results as B-TURP and Greenlight laser PVP (HPS).

However further, prospective randomised controlled studies are needed to confirm the safety and efficacy of these procedures in patients with ASA grade 3 and 4 comorbidities.

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