Benign Prostatic Hyperplasia (BPH)
Lower Urinary Tract Symptoms (LUTS)

Lower Urinary Tract Obstructive Syndrome

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Clinical case – 1 65 yrs old male

«Doctor…

- ✓ ***In the last two of years my urinary flow has not been as good as it used to be (weak urinary stream) and sometimes it stops and starts again (intermittency).***
- ✓ ***I need to go to the toilet more frequently than I used before. Even at night, I have to get up once.***

What's going on? Is this normal?»

Clinical case – 2

«Doctor, doctor help me please!

- ✓ *I have to go the toilet frequently (pollakiuria - frequency) and sometimes I can't even postpone urination (urgency) .*
- ✓ *Sometimes holding back urine is impossible (urge incontinence).*
- ✓ *My urinary stream is so weak and intermittent.*
- ✓ *Sometimes, I also have troubles starting urination (urinary hesitancy) and, when I am finished, I have the sensation of a not empty bladder (incomplete emptying) .*
- ✓ *I get up 3-4 times per night to urinate (nocturia)*

My life is too much conditioned by all this ….

Clinical case – 3

«Doctor,

- ✓ ***Despite the medication that you have recommended, my urinary symptoms have not improved and are now no longer tolerable .***
- ✓ ***Moreover, I've experienced in some cases a burning pain during micturition (strangury) with associated fever.***

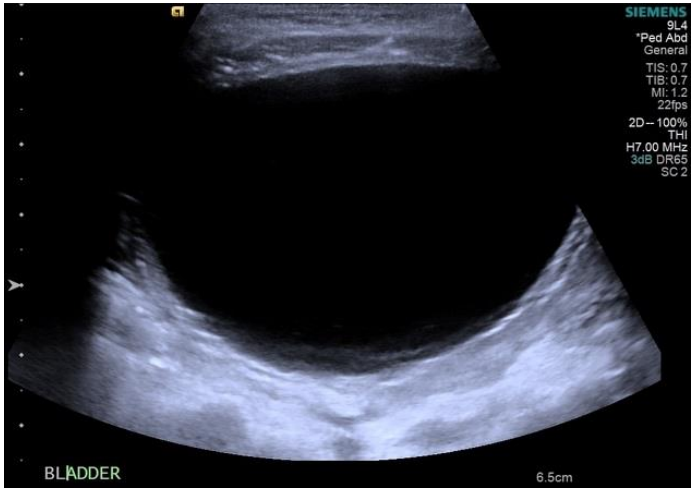
… what are we going to do now?»

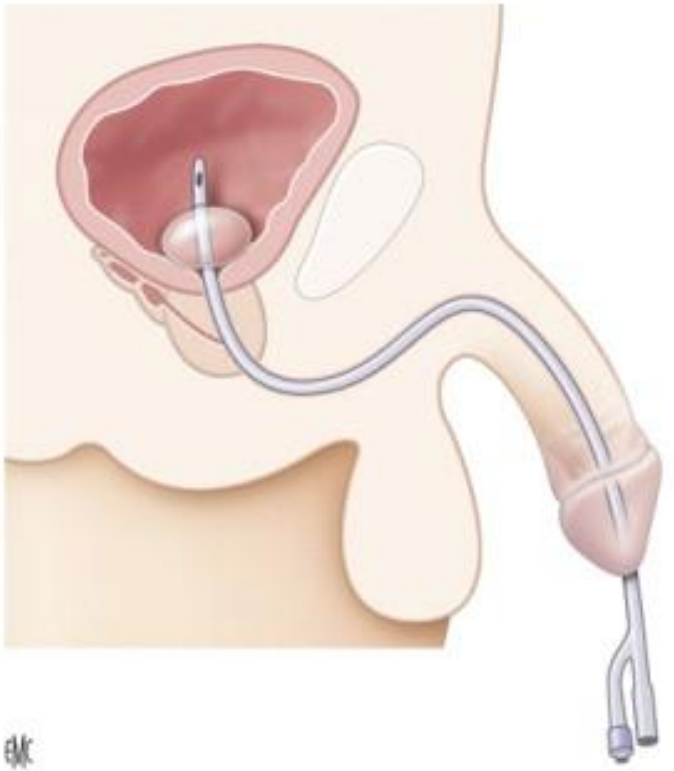
Caso clinico – 4

«Doctor help me…

Yesterday, I suddenly became unable to pass urine (acute urinary retention) … I had to go to the Emergency Department, where doctors placed me a urinary catheter

What am I supposed to do now?»



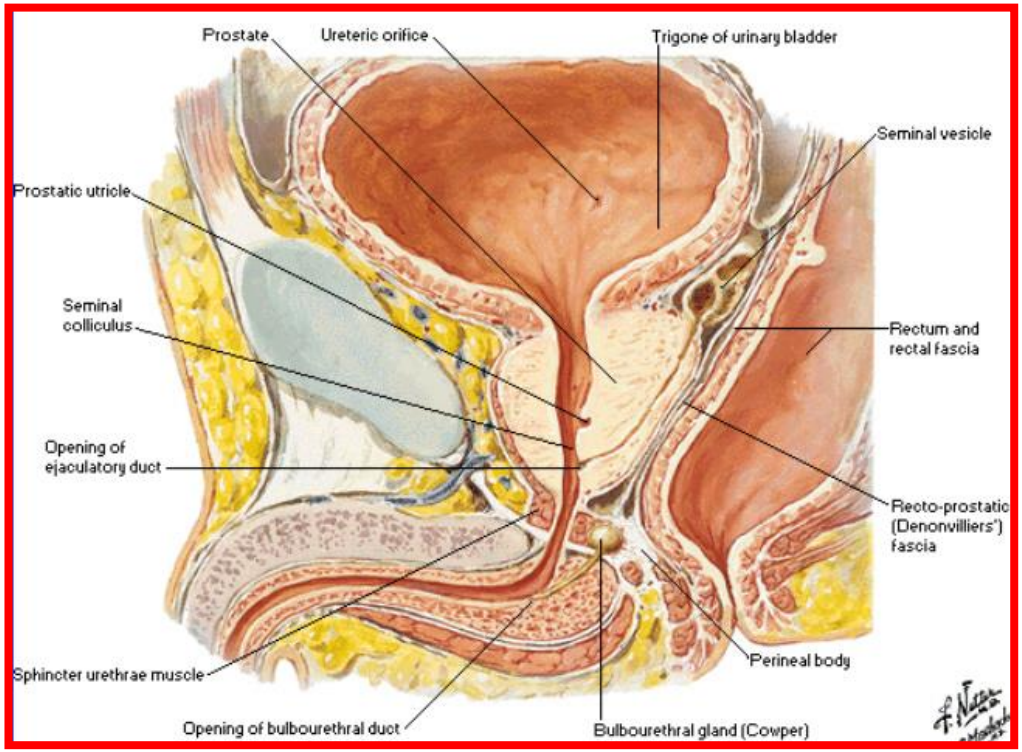


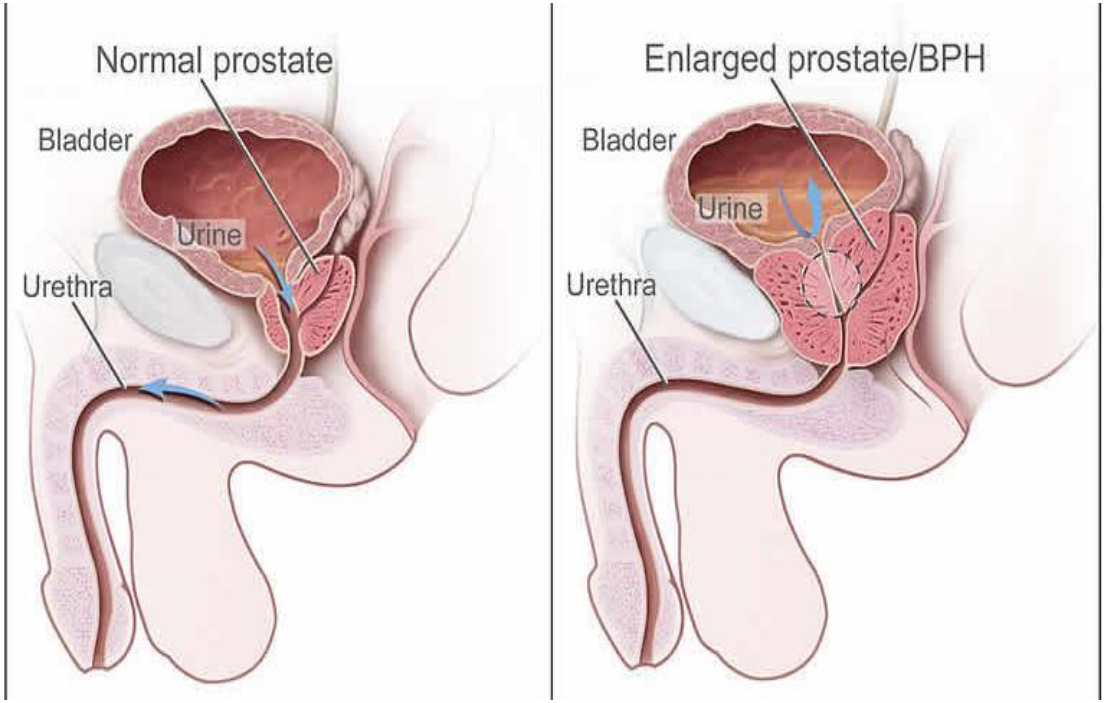
Prostate

- The prostate is a gland of the male reproductive system

- The gland

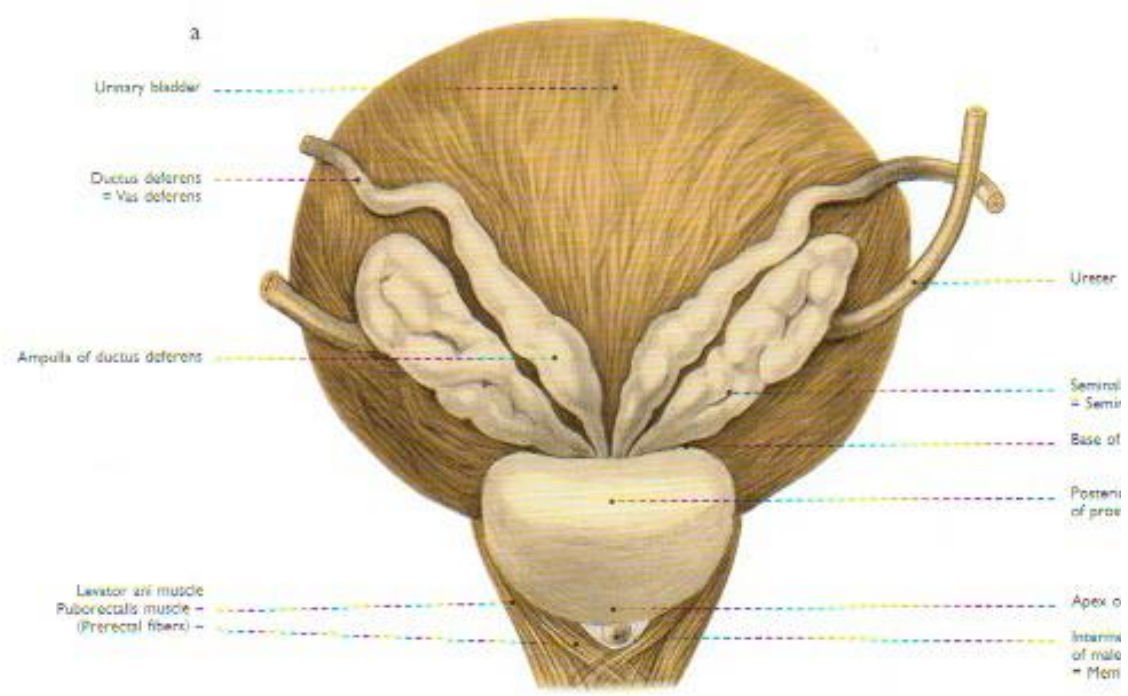
1. produces and
2. secretes into the urethra during ejaculation a fluid which becomes part of the semen.

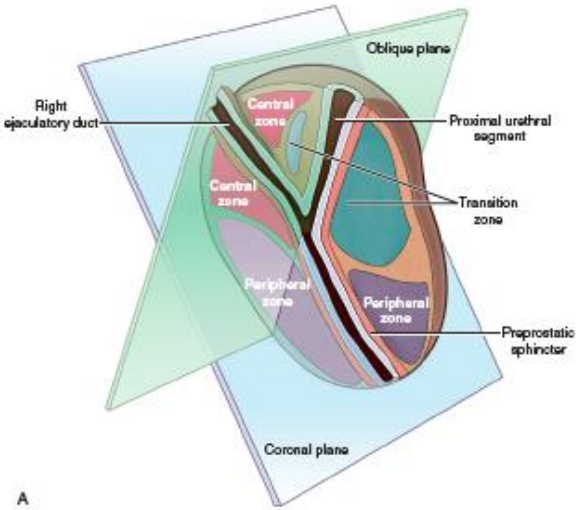


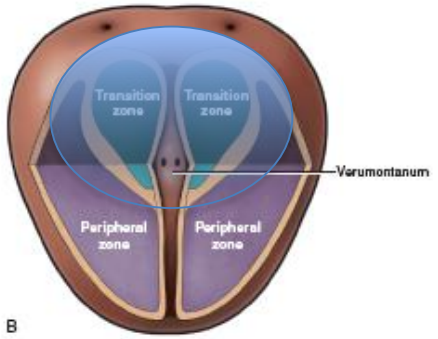


- ✓ At birth and before puberty , the gland is tiny and weighs a few grams.
- ✓ When testosterone levels rise during puberty, the prostate grows rapidly and doubled its size by the age of 20, approximately to 20 grams.
- ✓ In the fifth decade a second growth peak tipically occurs in the periurethral zone.

Anatomy of the Prostate





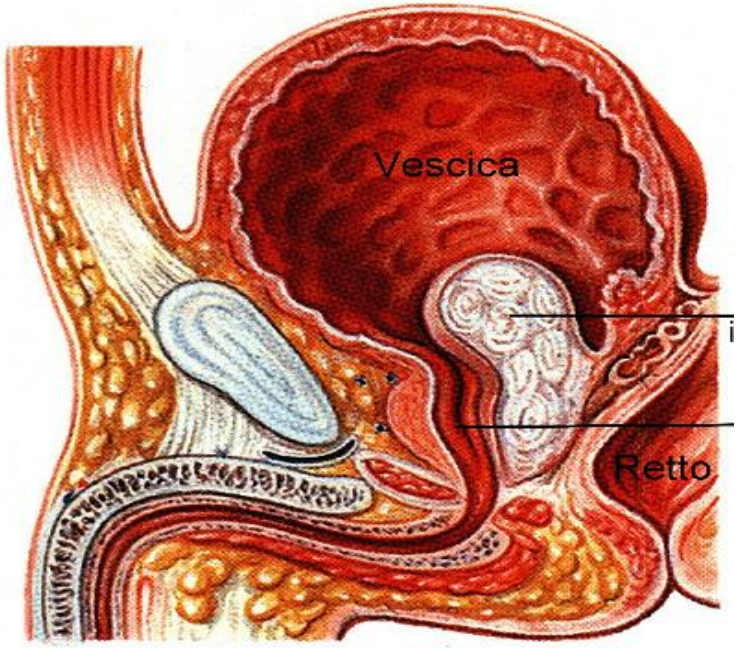


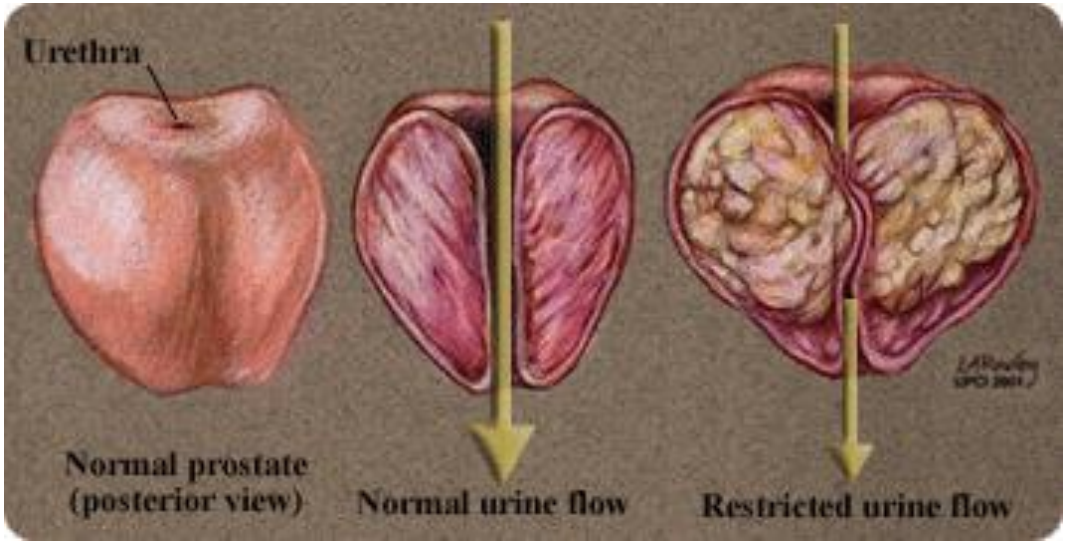
The McNeal Prostate - 4 zones:

- ✓ Peripheral zone (PZ)
- ✓ Transition zone (TZ)
- ✓ Central zone (CZ)
- ✓ Anterior fibromuscular stroma (AFMS)

Benign Prostatic Hyperplasia (BPH)

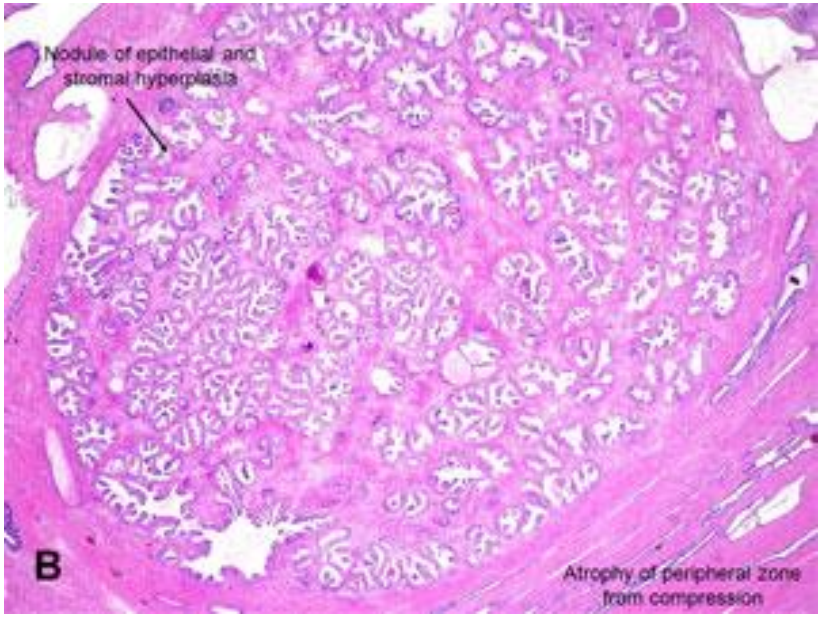
Transition zone (TZ) increases in size and gradually takes over the other prostatic zones.





Benign prostatic Hyperplasia

Histology



Nodules of epithelial (glandular tissue) and stromal (fibrous tissue) hyperplasia

Benign Prostatic Hyperplasia
Macroscopic patterns

BILOBED
BPH

MEDIAN LOBE
BPH

DIFFUSE
BPH

Different definitions for the same clinical condition

BPH : (benign prostatic hyperplasia)

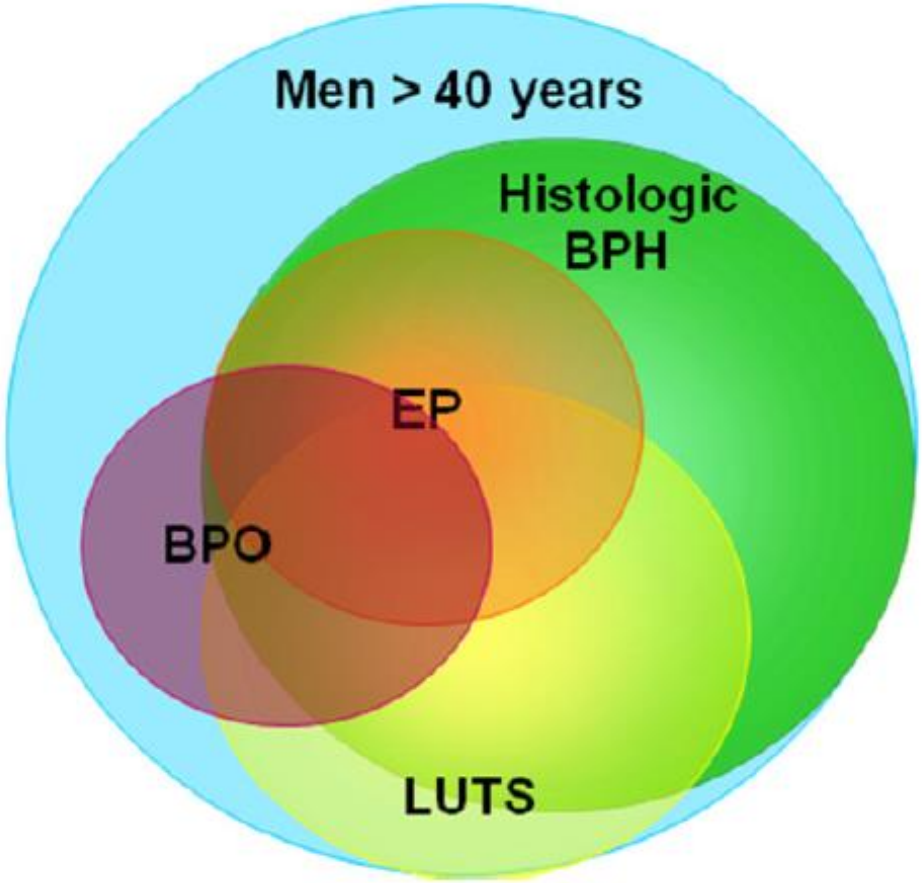
(enlarged prostate)

BOO: (bladder outlet obstruction)

LUTS: (Lower Urinary Tract Symptoms)

Epidemiology

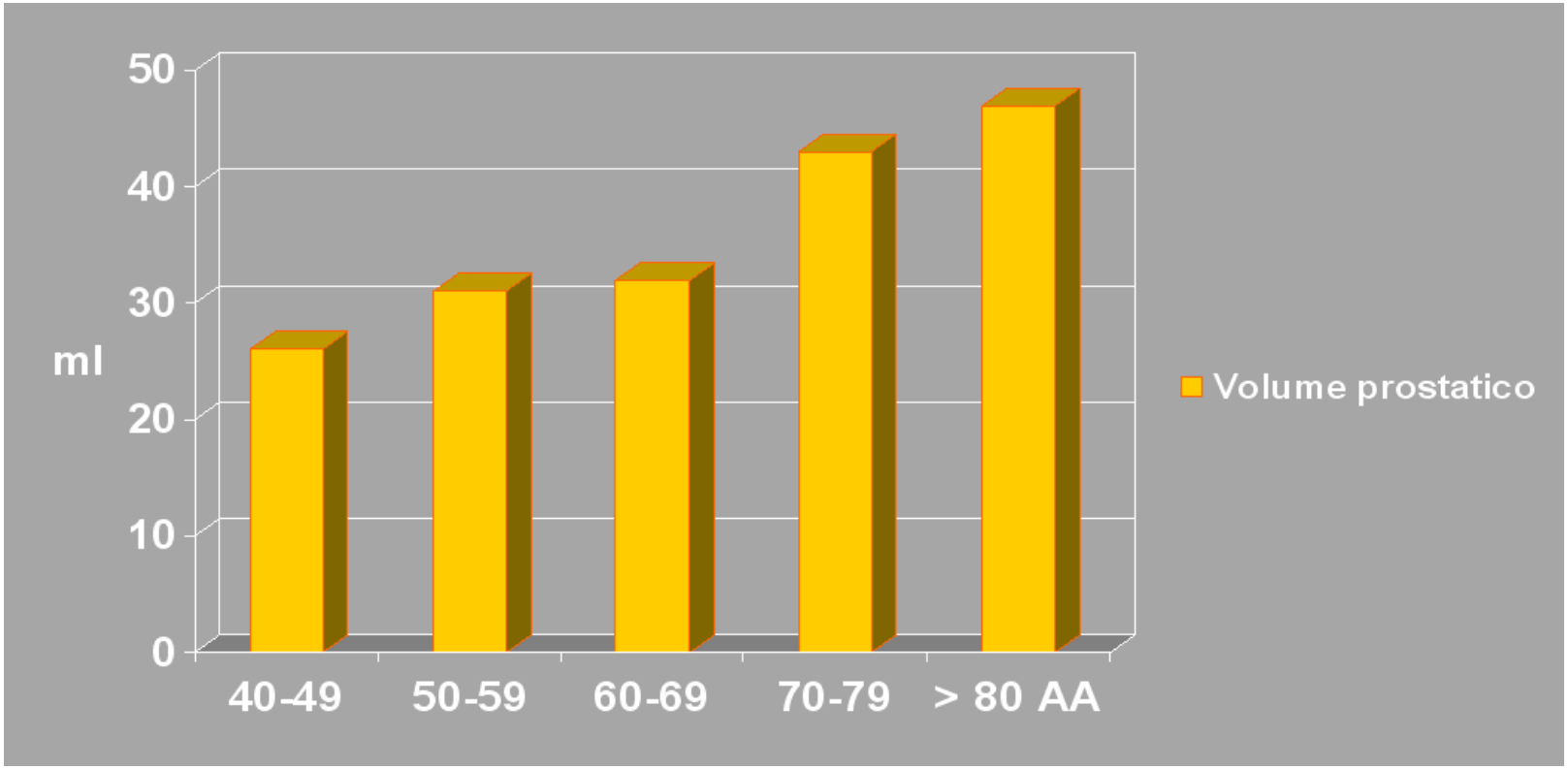
The association between BPH (histologic), LUTS, EP (Prostate Enlargement) and BOO (bladder outlet obstruction)



Roehrborn CG. Med Clin North Am. 2011, 95(1): 87-100

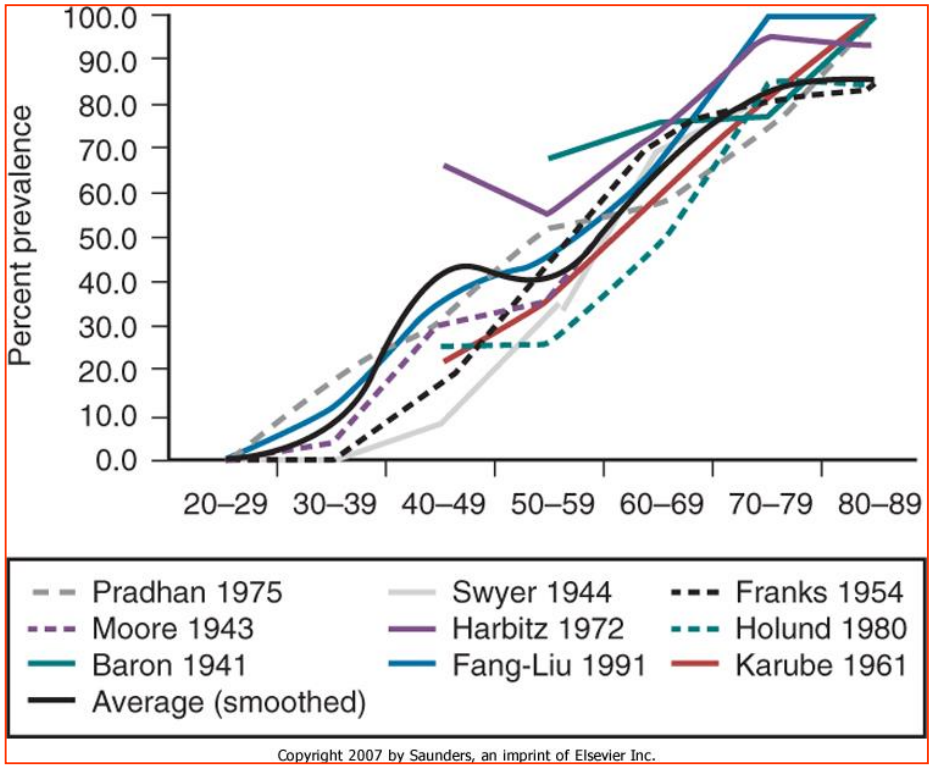
EPIDEMIOLOGY of BPH

BPH
Epidemiology



Relationship between
age and prostate volume

BPH
Epidemiology



Age-stratified prevalence of histologic BPH > 80% in the eight decade

Campbell-Walsh Urology, 10th Edition

Lower Urinary Tract Symptoms Prevalence

Urinary symptoms	Age (years) ≤39	40-59	≥60	All ages
Storage				
Any storage symptom	38	51	74	51
Nocturia at least once a night	34	48	72	49
Urgency	7	9	19	11
Frequency	5	6	11	7
Any urinary incontinence	2	5	10	5
Voiding				
Any voiding symptom	20	24	37	26
Intermittency	6	8	14	8
Slow stream	4	7	19	9
Strain	4	7	10	7
Terminal dribbling	12	13	19	14

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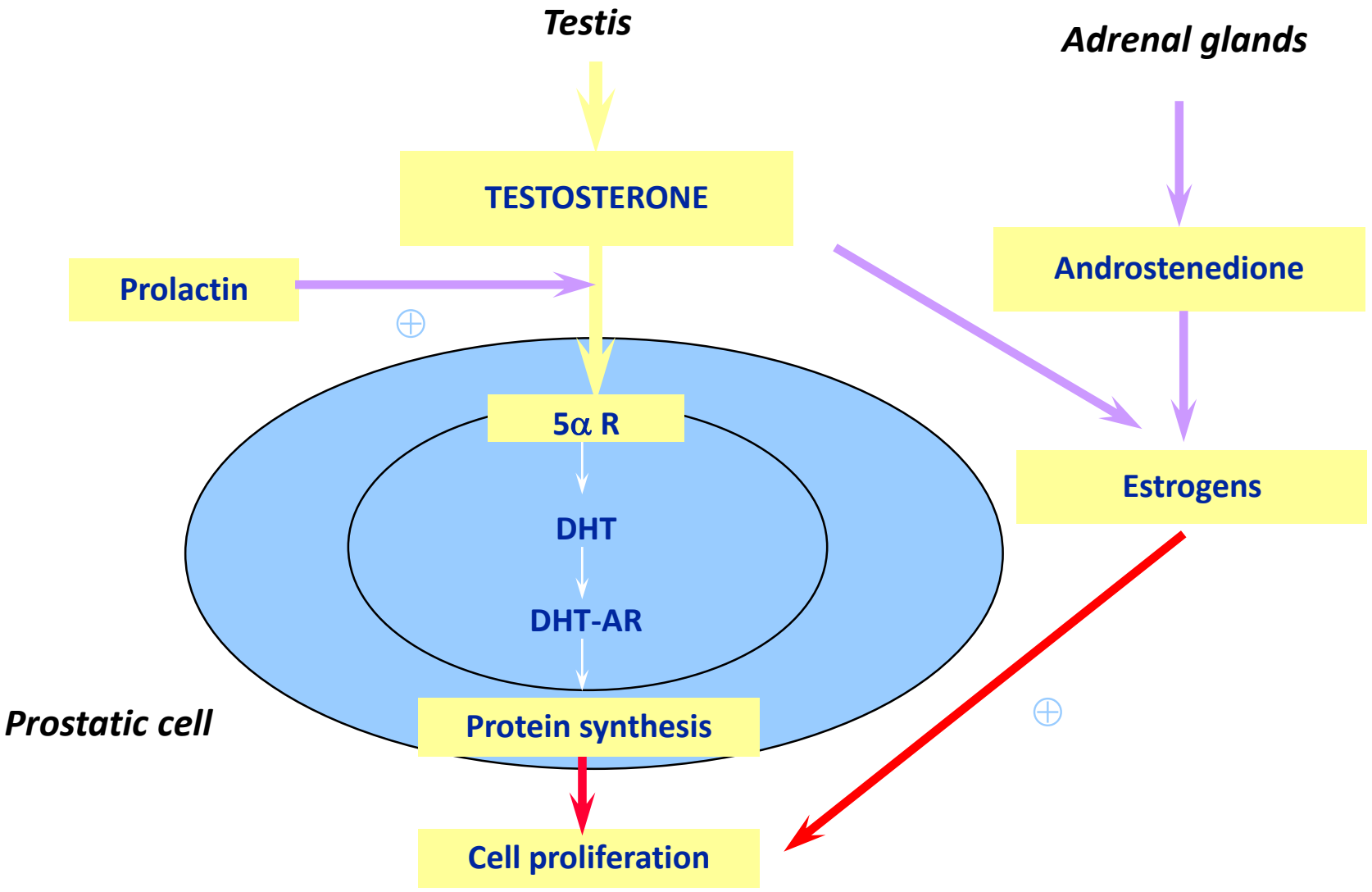
BPH
Aetiology

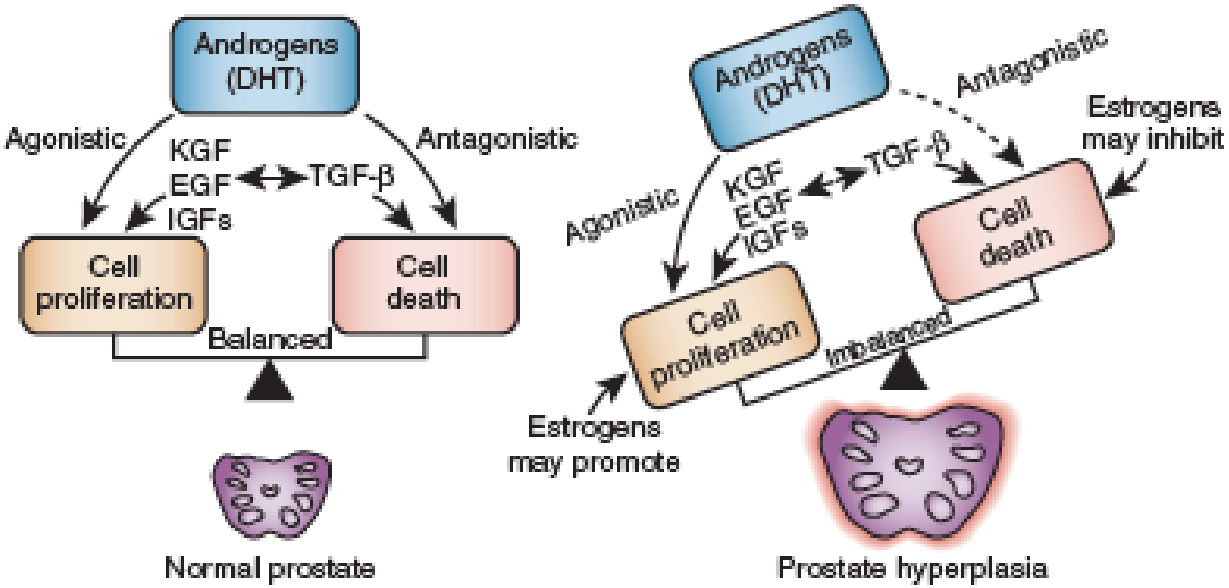
Aetiological factors in BPH

- ✓Hormonal disorders
- ✓ Inflammation
- ✓Metabolic syndrome

Prostate hormone regulation



Molecular control of prostate growth



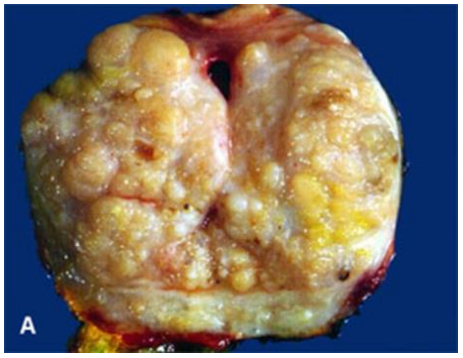
An increased agonistic activity of testosterone
…probably estrogen-mediated

Epitelial proliferation

Campbell-Walsh Urology, 10th Edition

Aetiology of BPH
Inflammation

- The role of inflammation as a key component in the progression of BPH has been reported since 1937.
- BPH is histologically characterized by a varying combination of epithelial and stromal hyperplasia
- Presence of intense lymphocytic infiltration has been frequently reported in BPH nodules, which are mainly composed of chronically activated T cells and macrophages
- These infilitrating cells are responsible for the production of cytokines which may support prostatic fibromuscular growth



Kramer and Marberger, Curr Opin Urol 2006, 16:25-9
Steiner et al, J Urol 1994, 151:480-4
Untergasser et al, Exp Gerontol 20052005, 40:121-8

Inflammation and BPH

CELL	ROLE IN BPH PATHOPHYSIOLOGY	REFERENCES
T cells	Stimulation of stromal cells growth	Kramer et al, 2002
	Prostate specific antigen recognition	Alexander et al, 2004 Klyushnenkova et al, 2004
	Phenotypic characterization of prostate gland	Theyer et al, 1992 Bierhoff et al, 1997
CD8+ linf T citotossici	Prostatic cell lysis in advanced stage	Blumenfeld et al, 1992
CD8+ linf T soppressori	Maintenance of Immune tolerance	El.Demiry et al, 1985 Vyskhovanets et al, 2005
CD4+ T helper 1	Epithelial and stromal cells growth stimulating factors T-cell recruitement	Kramer et al, 2002 Deshpande et al, 1989
CD4+ T helper 2	Increase of prostatic activated-androgen production	Gingras et al, 1999
Linfociti T helper 17	IL-17, IL-6 e IL-8 synthesis	Steiner et al, 2003
	Stimulation and secretion of pro-inflammatory cytokines	McKenzie et al, 2006
Linfociti B, mast cells	Function: poorly understood	Ablin et al, 1971
Macrofagi	Antigen presentation or epithelial COX-2 expression focal upregulation	Taoka et al, 2004 Wang et al, 2004

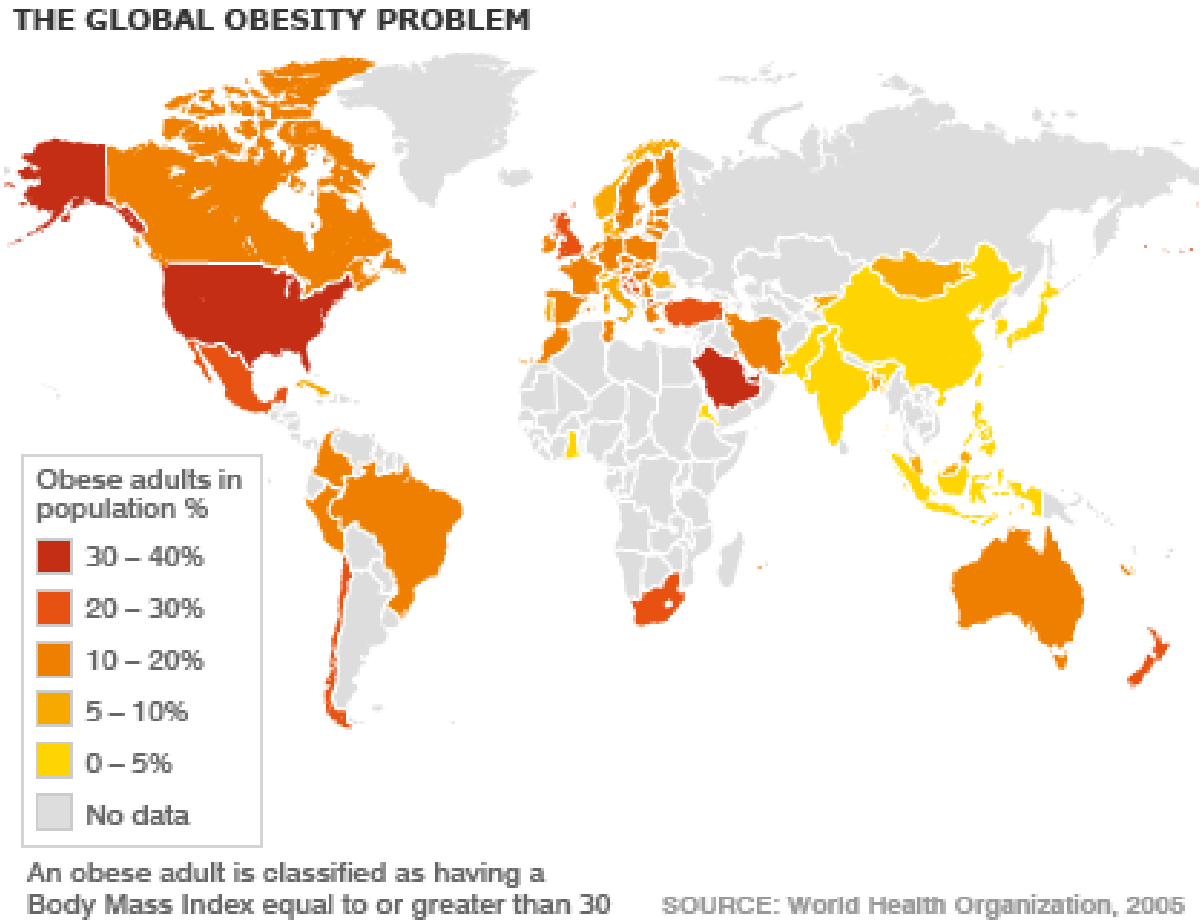
Aetiology of BPH
Metabolic Syndrome

Metablic syndrome : Group of risk factors involved in heart disease and other health problems, such as diabetes, stroke and also BPH

– Visceral obesity
– High blood pressure
– Hyperglycemia
– High serum tryglicerides
– Low serum high-density lipoprotein

Meigs JB. *Am J Manag Care* 2002; Hu G. *Arch Med Int* 2004

Metabolic syndrome and BPH



Metabolic syndrome and BPH

Increased Risk of BPH and LUTS			
STUDY	OUTCOME MEASURE (RISK FACTOR)	REFERENCE CATEGORY	OR (95% CI)
BLSA	LUTS:		
	Diabetes	No diabetes	2.80 (1.10-7.10)
	Fasting glucose >110 ng/dL	Fasting glucose ≤110 ng/dL	2.60 (1.01-6.70)
	Prostate ≥40 mL:		
	BMI >35 mg/kg^2	BMI <25 kg/m^2	3.52 (1.45-8.56)
	Diabetes	No diabetes	2.25 (1.25-4.11)
	Fasting glucose >110 ng/dL	Fasting glucose ≤110 ng/dL	2.98 (1.70-5.23)
Flint Men's Health Study	LUTS:		
	Diabetes	No diabetes	1.95 (1.49-2.57)
	Hypertension	No hypertension	1.29 (1.04-1.61)
Health Professionals Follow-up Study	BPH surgery (waist circumference >109 cm)	Waist circumference <89 cm	2.38 (1.42-3.99)
	LUTS (waist circumference >109 cm)	Waist circumference <89 cm	2.00 (1.47-2.72)
Hunt-2	LUTS:		
	BMI 40 mg/kg^2 or less	BMI less than 25	1.79 (0.90-3.56)
	Diabetes	No diabetes	1.25 (1.04-1.49)
	Waist/hip ratio 0.94 or less	Waist/hip ratio 0.85 or less	1.32 (1.15-1.50)
NHANES III	LUTS:		
	Diabetes	No diabetes	1.67 (0.72-3.86)
	Hypertension	No hypertension	1.76 (1.20-2.59)
	Increase in BMI between age 25 yr + highest BMI ever	No increase	1.90 (0.89-4.05)
	Waist circumference >102 cm	Waist circumference <94 cm	1.48 (0.87-2.54)

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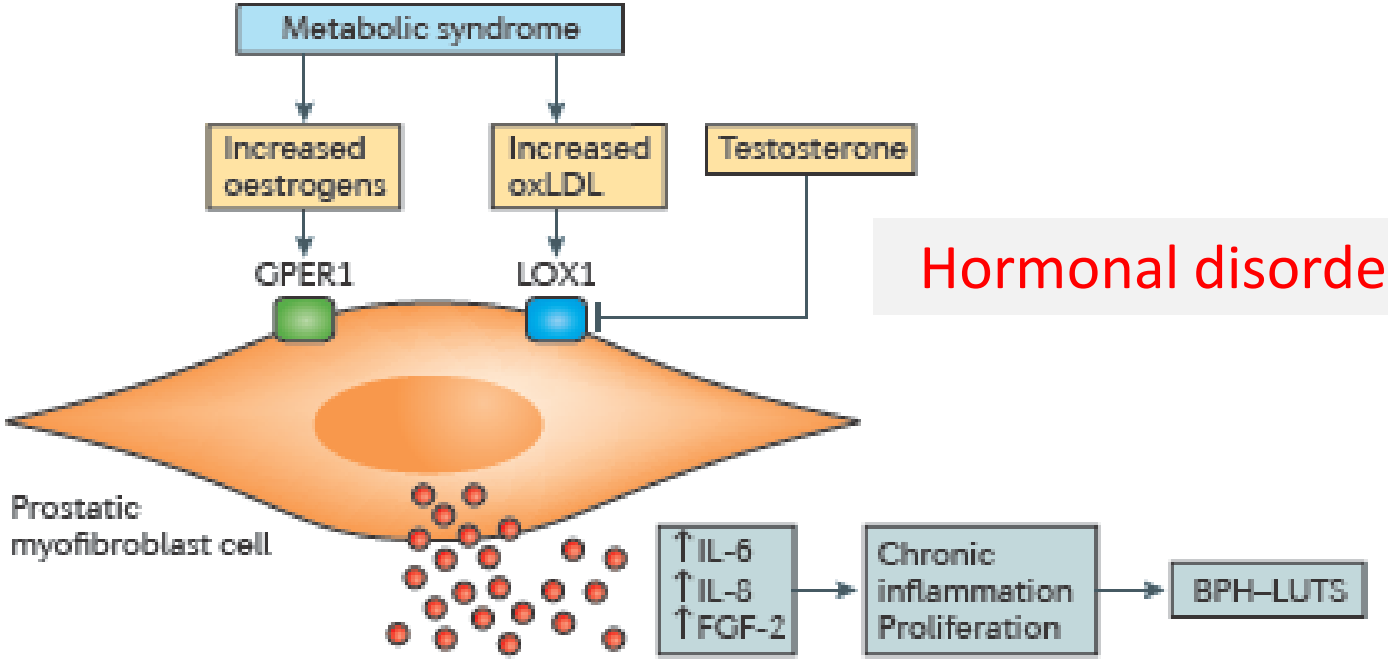
Metabolic syndrome and BPH

Molecular mechanisms underlying the association of metabolic syndrome with intracellular signaling pathways responsible for prostatic inflammation



Hormonal disorders

Pro-inflammatory state

Vignozzi L et al. Nat Rev Urol 2016

Impact of autonomic hyperactivity and metabolic syndrome on prostate enlargement and LUTS

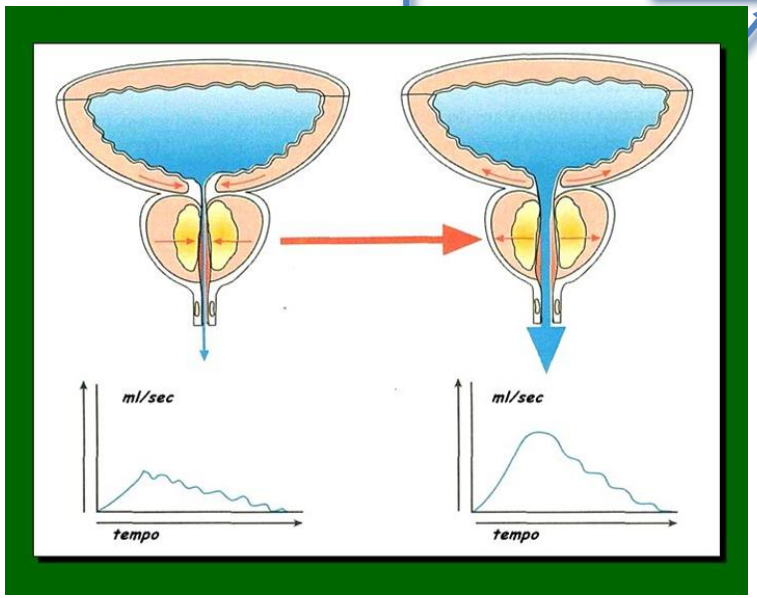
Obesity-BMI

Hypertension

Hyperinsulinemia

Age

INCREASED SYMPATHETIC TONE



BPH

BOO, BPH

LUTS

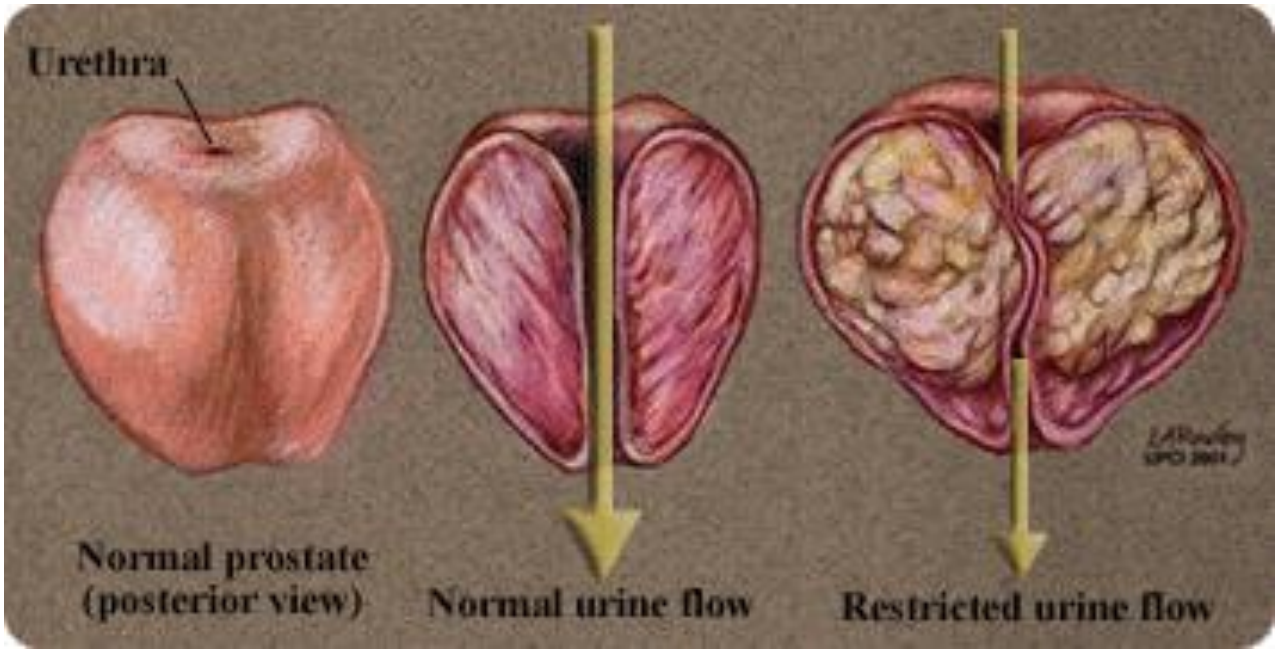
BPH
Signs – Symptoms and Pathophysiology

LUTS: Lower urinary Tract Symptoms

VOIDING SYMPTOMS (OBSTRUCTIVE)

- ✓ Poor stream
- ✓ Intermittency
- ✓ Incomplete voiding
- ✓ Hesitancy
- ✓ Terminal dribbling

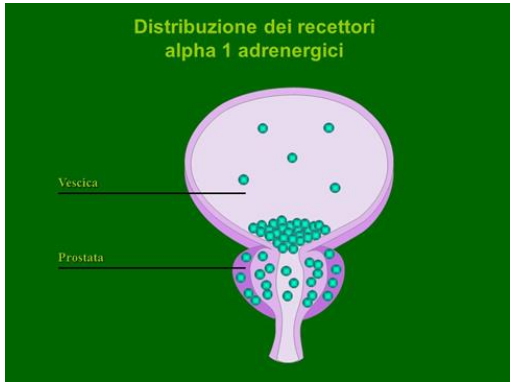
Obstructive symptoms (voiding)



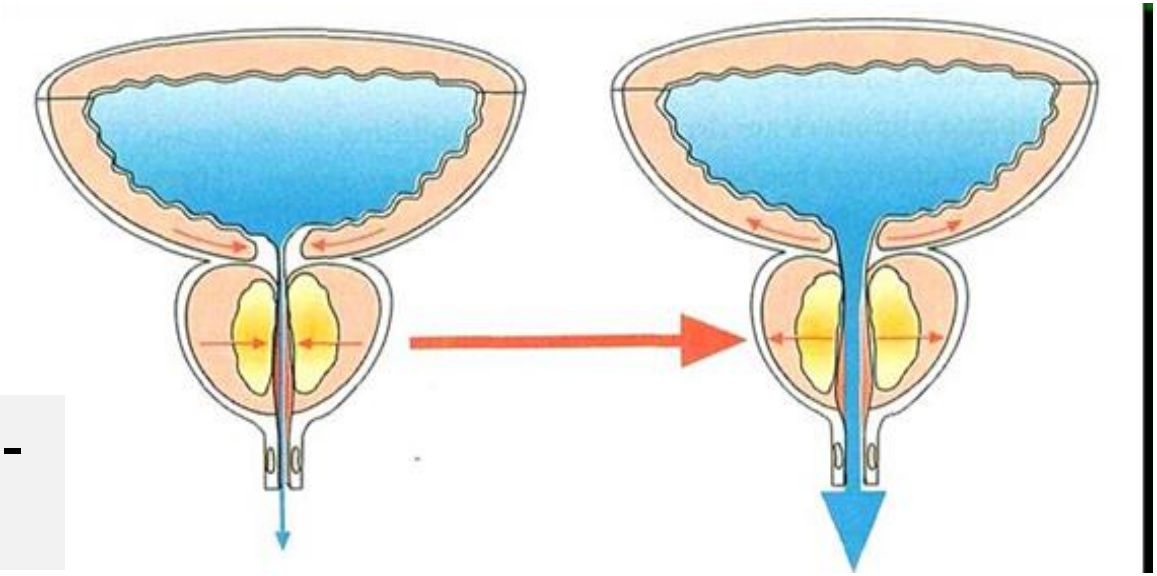
Mechanical obstruction

caused by benign prostatic hypertrophy

Obstructive symptoms (voiding)



Over-expression of α1-adrenergic receptors



Dynamic obstruction

(dynamic component of BOO)

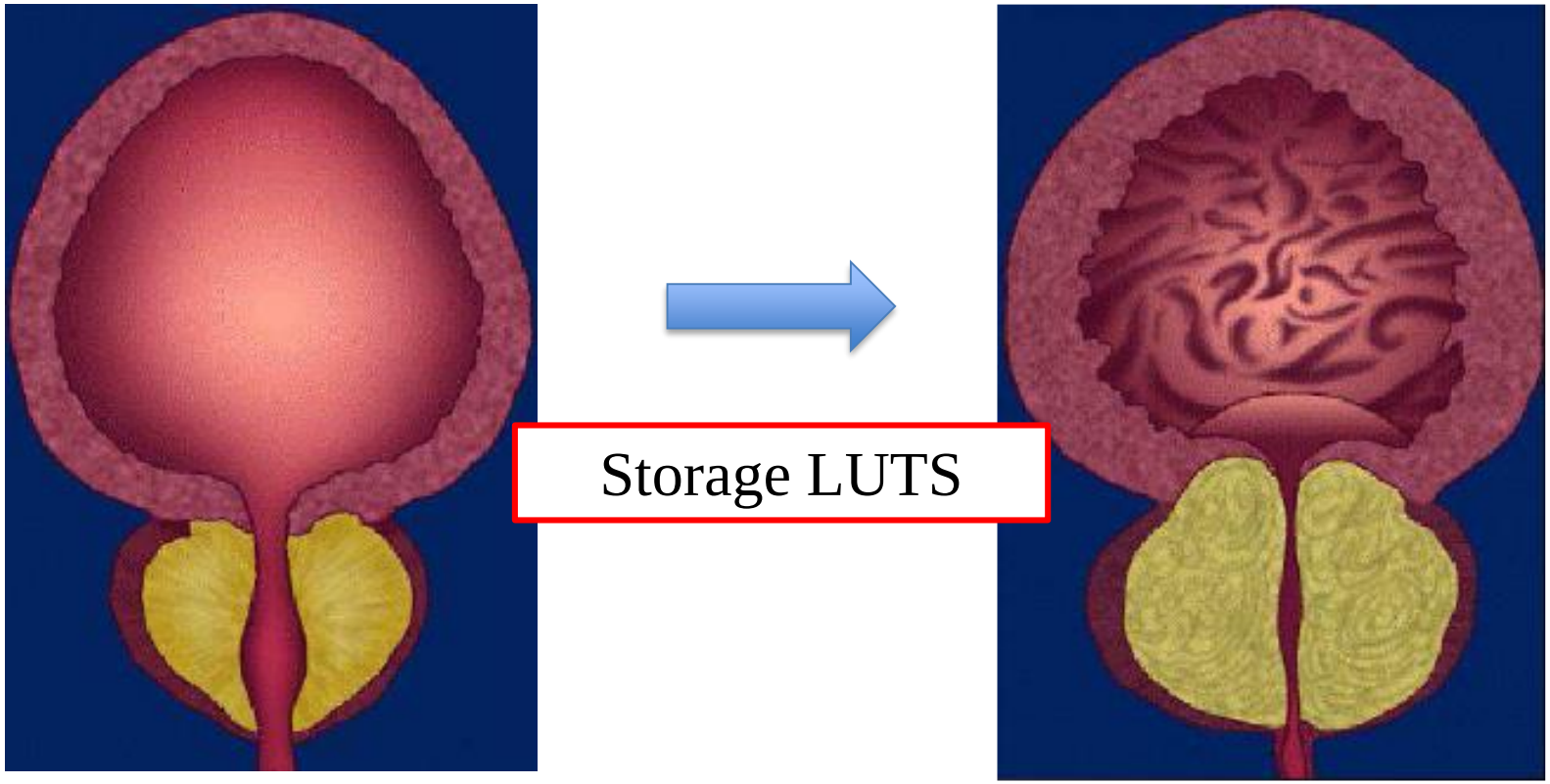
Adrenergic hypertonia responsible for overactive bladder, which prevents the relaxation of bladder neck muscular fibers and urethra during micturition

LUTS: Lower urinary Tract Symptoms

FILLING OR STORAGE SYMPTOMS (IRRITATIVE)

- ✓ **Pollakiuria** : frequent daytime urination
- ✓ **Nicturia**: frequent night time urination
- ✓ **Urgency**: urgent necessity to urinate
- ✓ **Urge incontinence**: urinary incontinence secondary to urgency

BPH and Storage Symptoms



- ✓ **Hypertrophy of detrusor muscle**
- ✓ **Over-expression of β3 M2-M3 muscarinic receptors**
- ✓ **Muscarinic hyperactivity responsible for overactive bladder**

Static component

Prostatic enlargement

Dynamic component

Increase of the adrenergic tone in the smooth muscle

Bladder outflow obstruction

Voiding symptoms

Bladder modifications

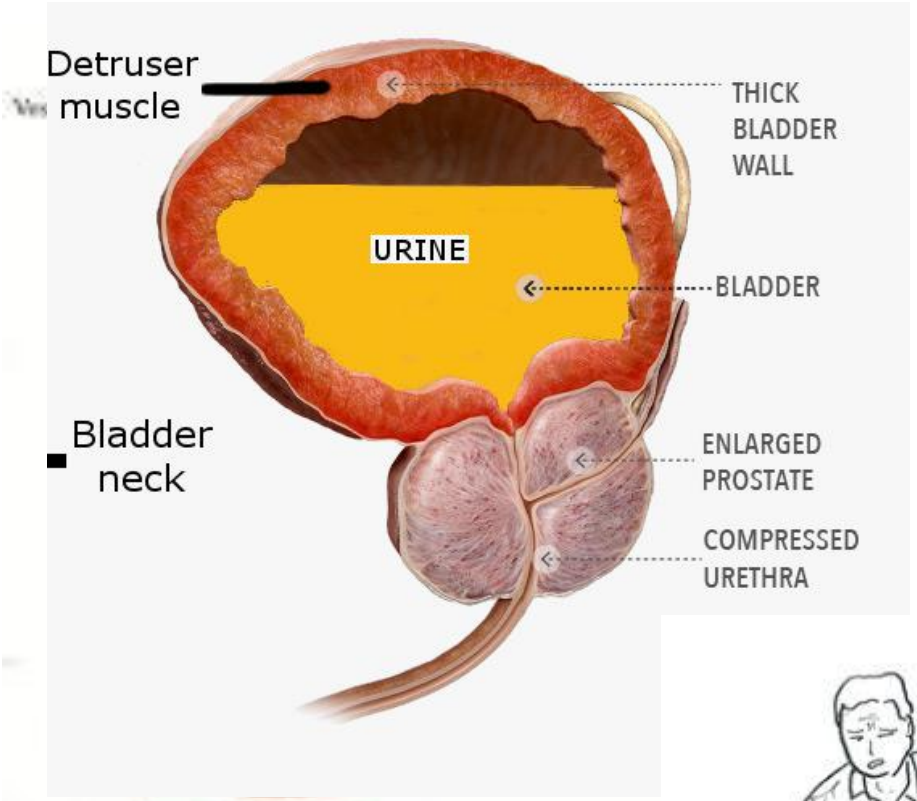
- Detrusor instability with spontaneous contractions

Storage symptoms

Progression of BPH and Bladder Outlet Obstruction

- ✓ **Late clinical signs**
- ✓ **Complications**

Disease progression and complications
Urinary Retention



- ✓ Chronic Urinary Retention.
- ✓ Acute Urinary Retention

Disease progression and complications

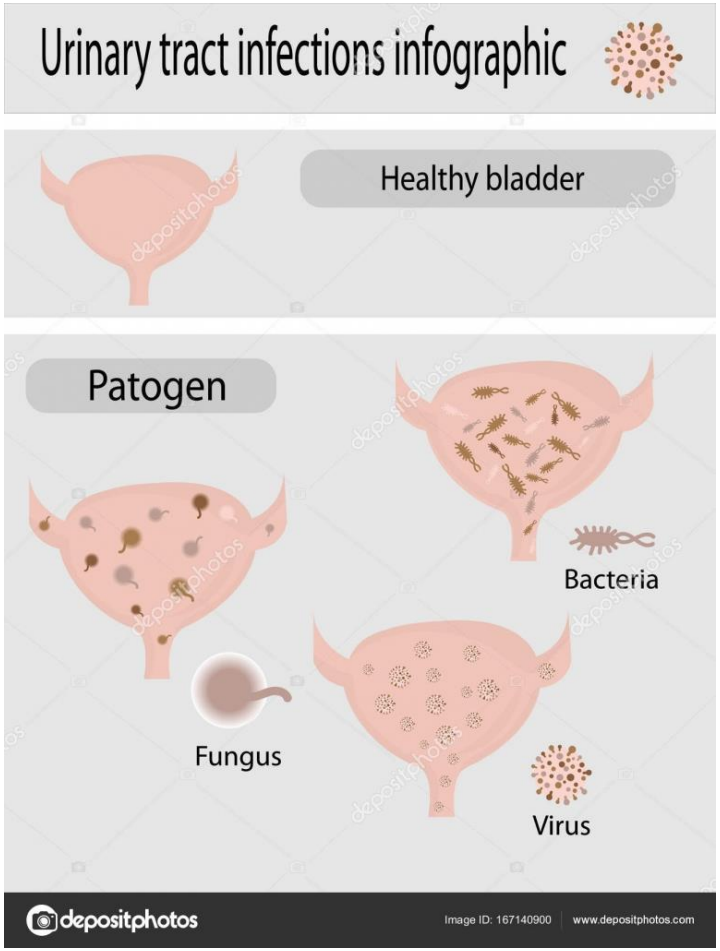
BLADDER DIVERTICULA

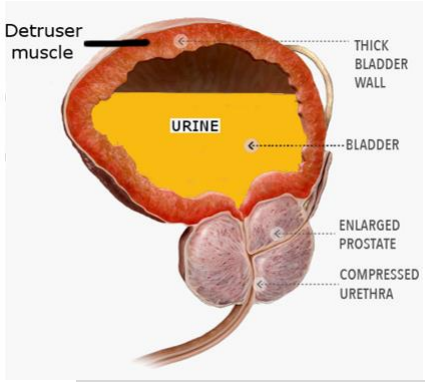
BLADDER STONES

«I will not use the knife, even upon those suffering from stones, but I will leave this to those who are trained in this craft..»

Hippocrates' Oath.

Disease Progression
Infections

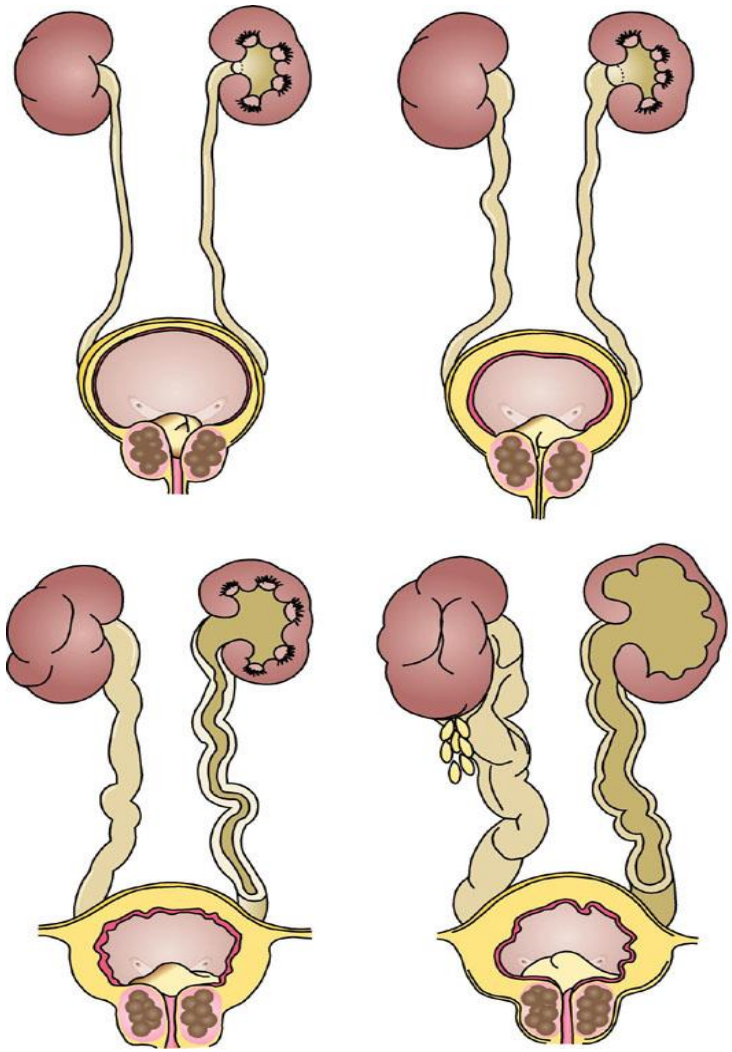




- ✓ **Recurrent Urinary Infections**
- ✓ **Acute Prostatitis**

Please study in deep causes, symptoms and signs

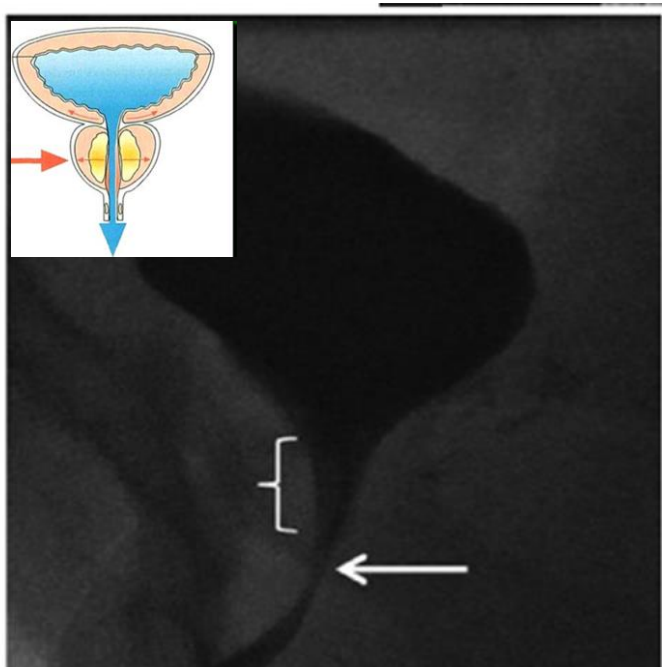
Disease Progression



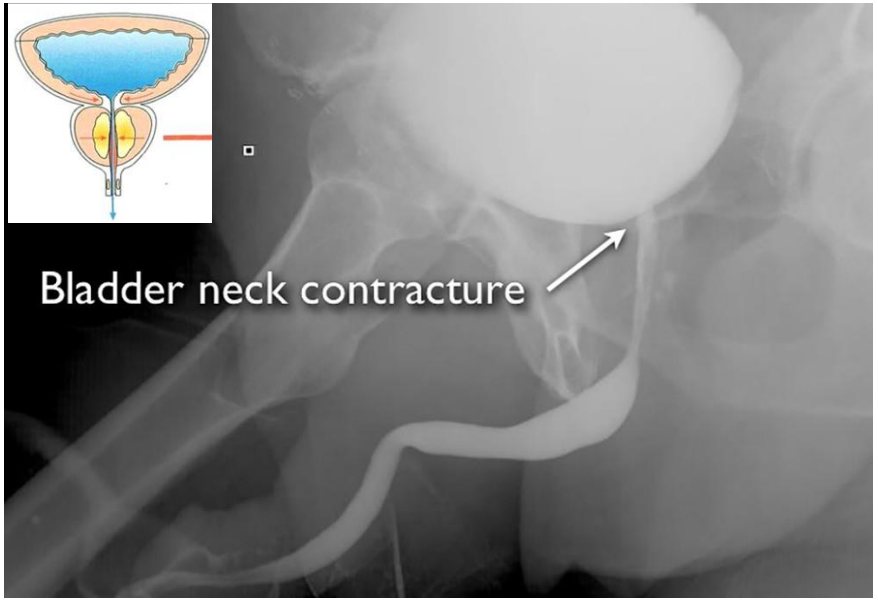
- ✓ CHRONIC RENAL FAILURE
- ✓ ACUTE RENAL FAILURE

Other conditions of Bladder Outlet Obstruction <u>not related</u> to BPH

- **Functional Bladder Neck Obstruction**



Normal funnel distension of the bladder neck during micturition

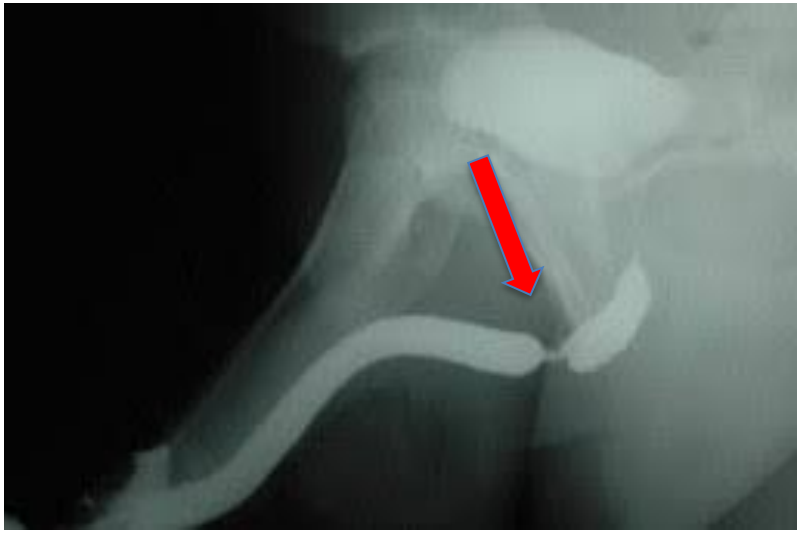


Increased Sympathetic Tone
Functionl bladder neck contraction during micturition

Other conditions of Bladder Outlet Obstruction not related to BPH

- **Urethral Strictures**

Penile urethra (anterior) stricture



Bulbar urethra (posterior) stricture

DIAGNOSIS
and
Diagnostic Tools for BPH

LUTS
Diagnostic Tools

Level 1

- Anamnesis
- Validated Questionnaries (IPSS)
- Clinical examination
- Digital Rectal Exam (DRE)
- Post-void residual volume (PVR)
- Clinical urine tests
- PSA

Level 2

- Transrectal US
- Uroflowmetry
- Urinary tract US
- Urodynamic studies (UDS)
- Cystoscopy

Anamnesis

Medical history helps identifying the nature (voiding vs storage), frequency and intensity of symptoms.

An adequate anamnesis possibly identifies **other than BPH** potential causes of LUTS and relevant comorbidities, such as**:**

- Medical condition (diabetes, renal failure, cardiovascular diseases)
- Neurological disease (Parkinson, Multiple Sclerosis, cerebrovascular disease, spinal cord injury, or prolapsed intervertebral disc impinging on the spinal cord).

	LE	GR
A medical history must always be taken from men with LUTS.	4	A*

EAU Guidelines 2016

Validated Questionnaires

- ✓ Validated symptom score questionnaire should be used for the assessment of male LUTS in all patients
- ✓ Validated questionnaires are widely used to objectify urinary symptoms
- ✓ Useful tool to drive treatment options and let the patient play an active part in the disease management

➢ **The International Prostate Symptom Score (IPSS)**

	LE	GR
A validated symptom score questionnaire with QoL question(s) should be used for the routine assessment of male LUTS in all patients and should be applied for re-evaluation of LUTS during treatment.	3	B

EAU Guidelines

IPSS questionnaire

Over the past month, how often have you...	Never	Very Rare	Rare	Medium	Frequent	Always	YOUR SCORE
Incomplete voiding	0	1	2	3	4	5	
Pollakiuria	0	1	2	3	4	5	
Intermittency	0	1	2	3	4	5	
Increased urgency	0	1	2	3	4	5	
Poor stream	0	1	2	3	4	5	
Hesitancy	0	1	2	3	4	5	
Nocturia	None	Once	Twice	3 times	4 times	5 times or more	
						TOTAL	

URINARY SYMPTOMS

f your life with your urinary condition the way it is now, how would you feel about that?

What if you stay like now?	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied & dissatisfied	Mostly dissatisfied	Unhappy	Terrible
	0	1	2	3	4	5	6

The International Prostate Symptom Score (IPSS)

IPSS 0-7: MILD symptoms / obstruction

IPSS 8-19: MODERATE symptoms / obstruction

IPSS 20-30 SEVERE symptoms / obstruction

Take Home Message

Nocturia is the least specific symptom of BPH

Nocturia as the only or dominant LUTS must be investigated for other causes,

since prostatic disease is unlikely to exist in the absence of other voiding symptoms.

NOCTURNAL POLIURIA

Chronic heart failure, obstructive sleep apnea syndrome (OSAS), Drugs (ex: diuretic)

Physical examination and Digital Rectal Exam

- ✓ **Suprapubic/Hypogastric** region to rule out bladder distention (vesical globe)
- ✓ **External genitalia** to detect such conditions which may cause or contribute to LUTS (ex. Urethral disease, phimosis, stricture of urethral meatus, penile cancer)
- ✓ **The perineum and lower limb** examination provides information on sensory and motor functions

	LE	GR
Physical examination including DRE should be a routine part of the assessment of male LUTS.	3	B

EAU Guidelines

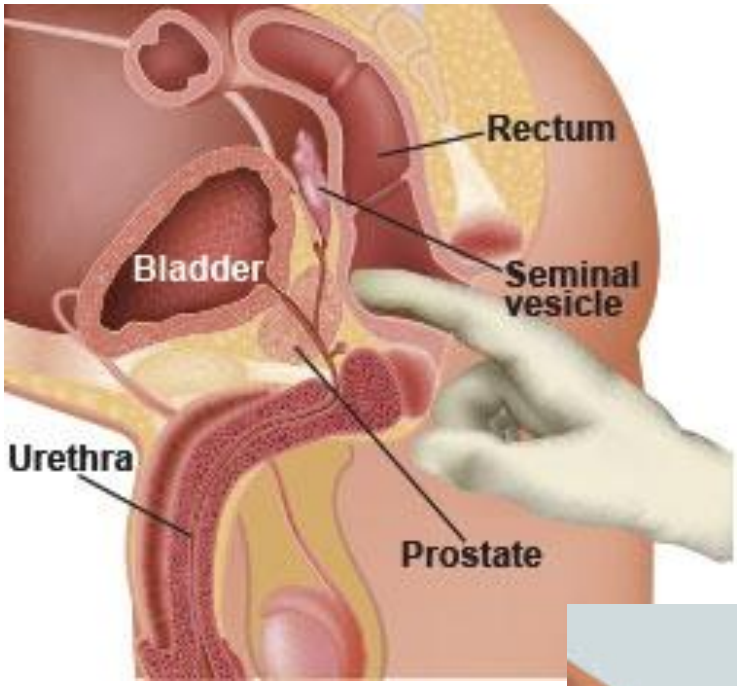
Physical examination and DRE

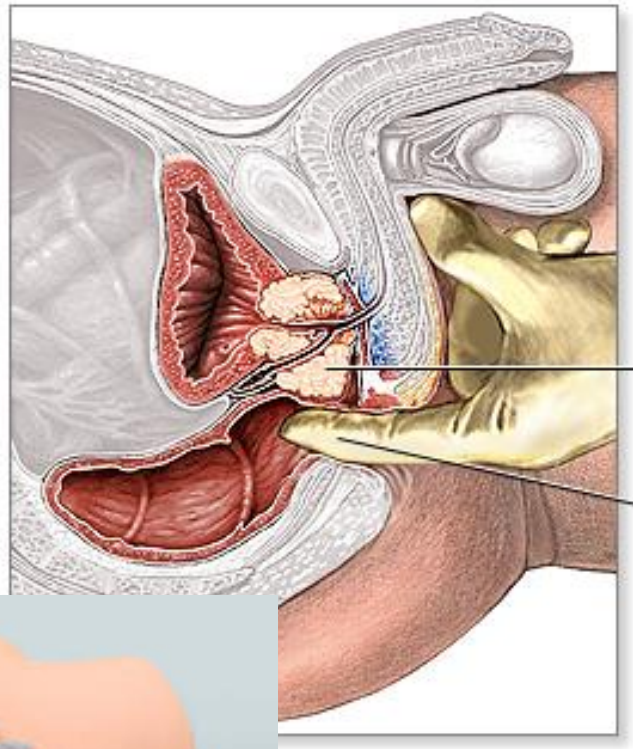
- ✓ A digital rectal examination (DRE) is a simple procedure that doctors use to examine the lower rectum and other internal organs.
- ✓ A DRE also provides information on prostate size, shape and consistency.
- ✓ A DRE does not give any information regarding indication to any treatment modality

	LE	GR
Physical examination including DRE should be a routine part of the assessment of male LUTS.	3	B

EAU Guidelines

Physical examination and DRE





A.D.A.M.

Laboratory tests

First level

- ✓ **Urine** (UTI, Hematuria)
- ✓ **PSA** (inflammation and early diagnosis of prostate cancer)

Second level

- ✓ **Urine cytology** (Irritative symptoms)
- ✓ **Urine culture test**
- ✓ **Serum creatinine test** (renal failure)

Urine laboratory analysis

Urine analysis does not give any information for the diagnosis and treatment of BPH ..

but

- ✓ LUTS may indicate non BPH-related conditions, such as UTI or bladder cancer
- ✓ Urinalysis is crucial to establish a differential diagnosis among other possible causes (diabetes, UTI) and to detect abnormalities (hematuria, proteinuria, presence of ketones, sugar, nitrites and/or leukocyte)

	LE	GR
Urinalysis (by dipstick or urinary sediment) must be used in the assessment of male LUTS.	3	A*

EAU Guidelines

Prostate-specific antigen (PSA)

✓ PSA is a a serum test for the diagnosis of Prostate Cancer

✓ PSA measure should be always performed in BPH patients affected by LUTS to exclude Prostate Cancer

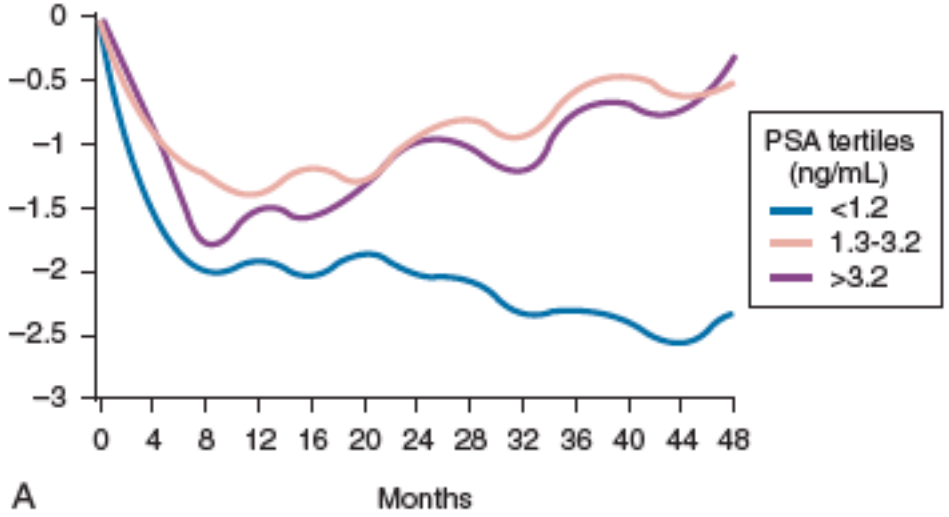
Campbell-Walsh Urology, 10th Edition

	LE	GR
PSA measurement should be performed only if a diagnosis of PCa will change the management or if PSA can assist in decision-making in patients at risk of progression of BPE.	1b	A

EAU Guidelines

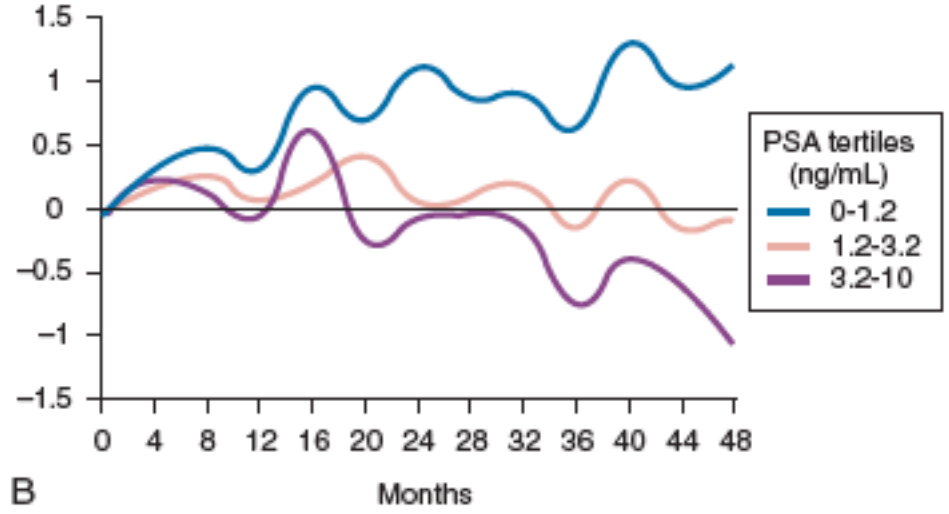
Prostate-specific antigen (PSA)

Symptoms score changing over time in untreated patients



A

Peak flow rate over time in untreated patients



B

In addition, the PLESS study showed that **PSA also predicted the changes in symptoms, QoL/bother, and maximum flow rate (Qmax) and was a significant predictor of clinical progression**

Campbell-Walsh Urology, 10th Edition

LUTS
Diagnostic tools

Level 1

- Anamnesis
- Surveys (IPSS)
- Clinical examination
- Digital Rectal Exam (DRE)
- Post-void residual volume (PVR)
- Clinical urine tests
- PSA

Level 2

- Transrectal US
- Uroflowmetry
- Urinary tract US
- Urodynamic studies (UDS)
- Cystoscopy

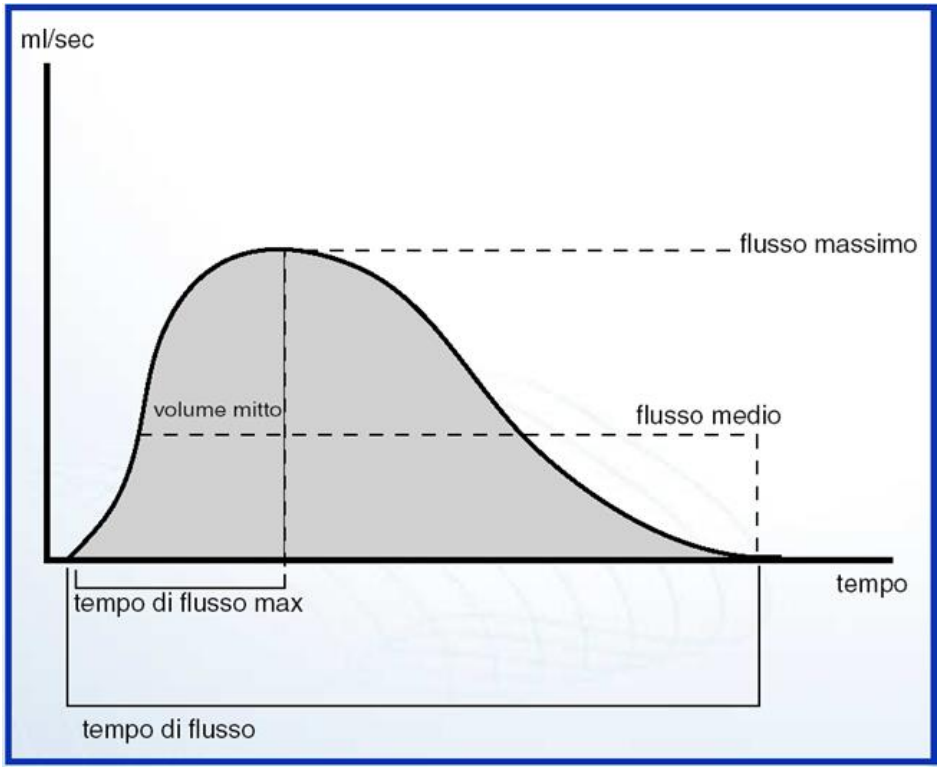
Uroflowmetry

Urinary flow rate assessment is a basic noninvasive urodynamic test that is widely used to evaluate the flow-rate

	LE	GR
Uroflowmetry in the initial assessment of male LUTS may be performed and should be performed prior to any treatment.	2b	B

Uroflowmetry

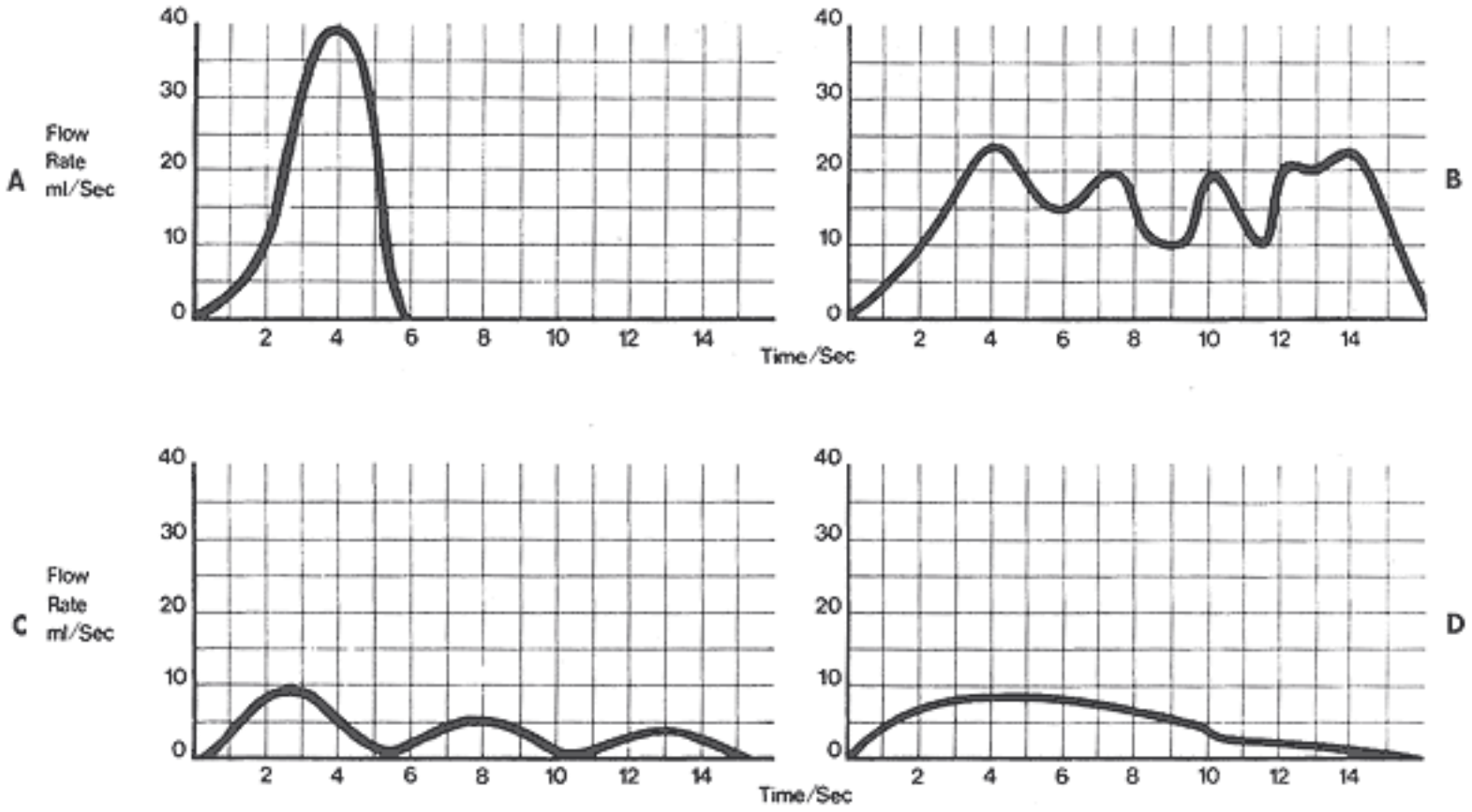
- ✓ Evaluable parameters are Qmax (maximum flow = KEY PARAMETER), voided volume, and flow pattern
- ✓ Uroflowmetry parameters should ideally be evaluated when the voided volume is >150 ml



	LE	GR
Uroflowmetry in the initial assessment of male LUTS may be performed and should be performed prior to any treatment.	2b	B

EAU Guidelines

Uroflowmetry



Graphic representation of various uroflow patterns. **A,** Superflow commonly seen with poor urethral resistance. **B,** Intermittent multiple-peak pattern. **C,** Intermittent interrupted pattern. **D,** Abnormal flow rate characteristic of detrusor outlet obstruction.

Post-void residual urine volume (PVR)

- PVR is the amount of urine retained in the bladder after a voluntary void and is used as a diagnostic tool

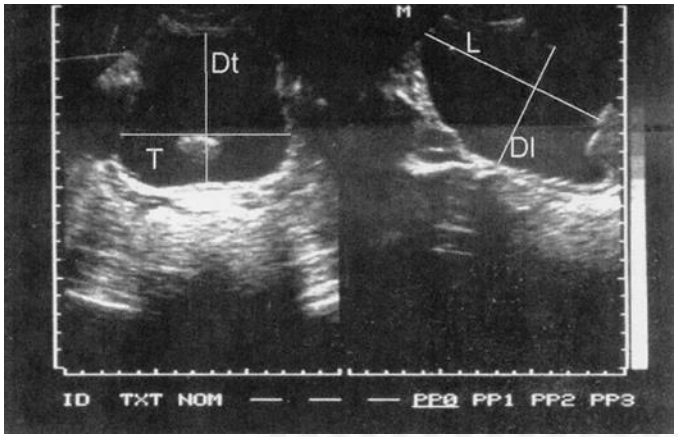
- High residual volume (> 100 cc) is and indicator of severe obstraction

	LE	GR
Measurement of post-void residual (PVR) in male LUTS should be a routine part of the assessment.	3	B

EAU Guidelines

Post-void residual urine volume (PVR)

Post-void residual urine (PVR) can be measured by transabdominal ultrasonography, a bladder scan, or catheterisation



Post-void residual urine

High PVR indicates bladder dysfunction, poor response to treatment and an increased risk of acute urinary retention

Imaging
Prostate Ultrasounds

Is it necessary to have and ultrasound study of the prostate in the diagnosis of BPH?

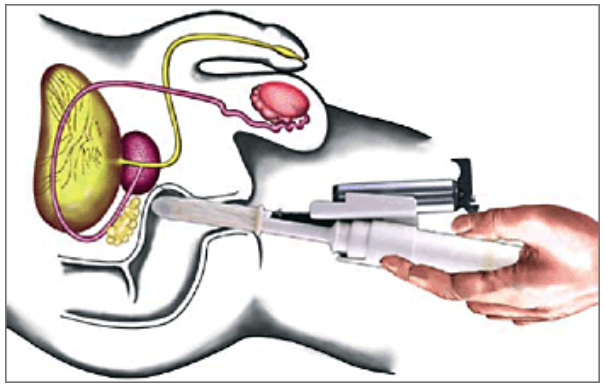
NOT for the diagnosis!

US is not able to differentiate between BPH an Cancer

YES FOR THE SELECTION OF TREATMENT

Ultrasound has only the role of measuring prostatic volume.
Treatment option depend on prostatic volume

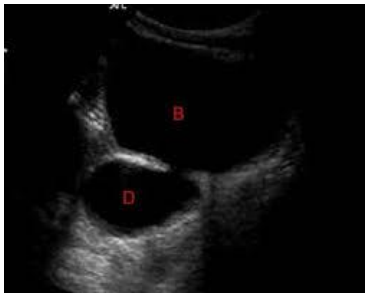
TRANS RECTAL PROSTATIC US



SOVRAPUBIC PROSTATIC US

Urinary tract ultrasound

Urinary tract sonography is a simple, non invasive procedure that offer several usefull pieces of information



- ✓ Prostatic volume
- ✓ Post-voinding redidual
- ✓ Bladder diverticula
- ✓ Bladder stones
- ✓ Study of the upper urinary tract

	LE	GR
Imaging of the upper urinary tract (with US) in men with LUTS should be performed in patients with a large PVR, haematuria or a history of urolithiasis.	3	B

TREATMENT OF BPH

Treatment of LUTS secondary to BPH

1) SUPPORTIVE MANAGEMENT

- Watchful waiting/behavioural treatment – most suitable for those with low symptom scores, which are less bothersome and have a low risk of progression
- Selection of patients who might benefit from active therapy (medication / surgery)
- Education, reassurance & periodic monitoring
- Lifestyle advice

2) MEDICAL THERAPY

3) SURGICAL TREATMENT

EAU Guidelines

CONSERVATIVE TREATMENT: Watchful Waiting

- ✓ Many men with LUTS are not troubled enough by their symptoms to need drug treatment or surgical intervention.
- ✓ Watchful Waiting is a viable option for many men with non-bothersome LUTS as few will progress severe sympthoms, to urinary retention or other complications complications.

EAU Guidelines

IPSS QUESTIONNAIRE

IPSS Score is a key tool for monitoring symptoms, choosing those patients who really need treatment and evaluating how fast the disease is likely to progress.

	LE	GR
Men with mild symptoms are appropriate for watchful waiting	1b	A
Men with LUTS should always be offered lifestyle advice prior to or concurrent with treatment	1b	A

EAU Guidelines

Conservative treatment

Behavioural and dietary modifications

- ✓ Weight Loss
- ✓ Physical Activity

Glycemic control

Management of blood pressure

EAU Guidelines

Pharmacological treatments

- α1-Adrenoceptor antagonists (α1-blockers)
- 5α-Reductase inhibitors
- Muscarinic receptor antagonists
- β-3 agonists
- Phosphodiesterase 5 inhibitors
- Plant extracts – phytotherapy
- Vasopressin analogue - desmopressin

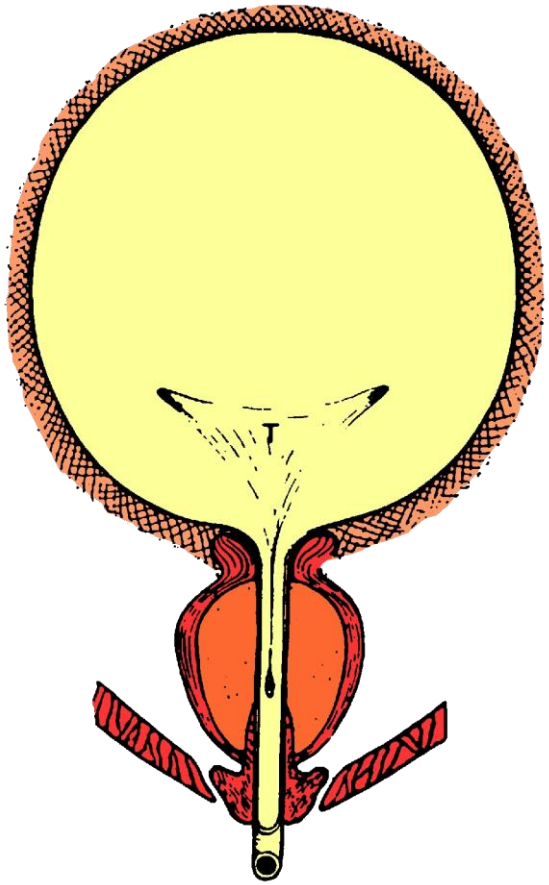
Drug therapy: different options

- **Targeting the bladder**

  Antimuscarinics/Beta-3 agonists:

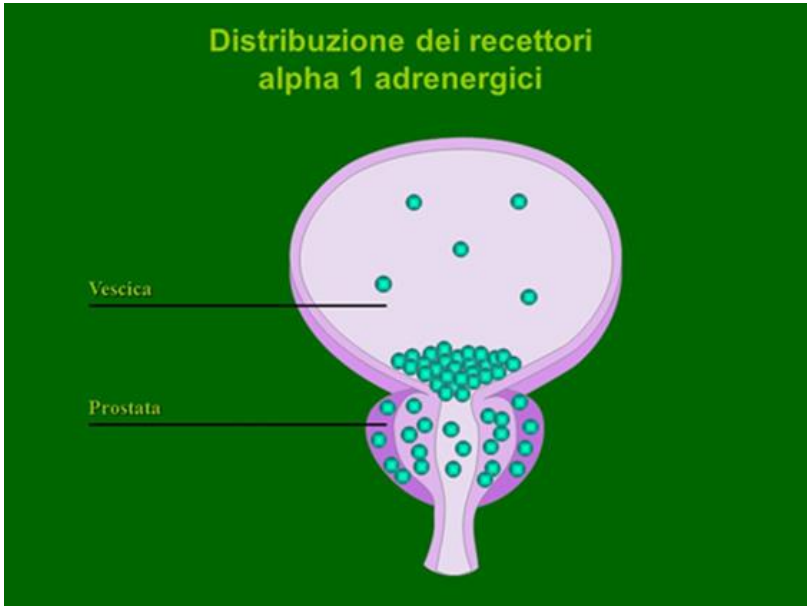
  Symptom control OAB (storage) component of LUTS

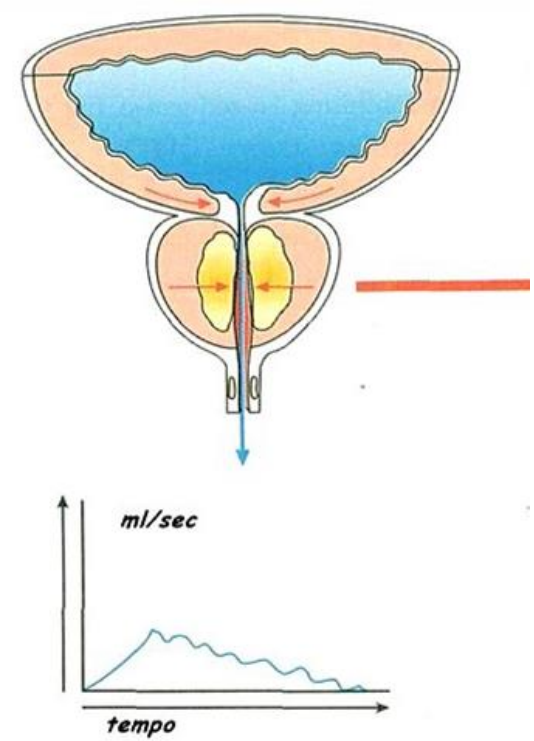
- **Targeting the prostate**
  - **α-blockers:**
    - **Symptom control**
  - **5-ARIs**
    - **Disease modification**



α1-Adrenoceptor antagonists Mechanism of action

Increased Symphatetic tone is a major cause of Bladder Outlet Obstruction and LUTS in BPH





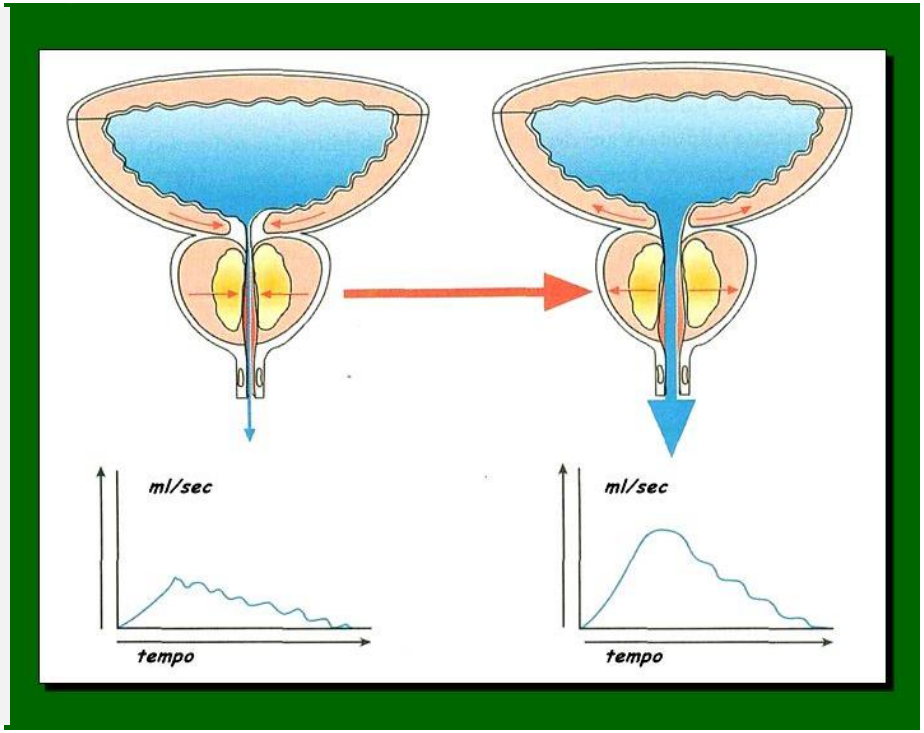
α1-Adrenoceptor antagonists
Mechanism of action

α1-Adrenoceptor antagonists

Inhibition of the effect of endogenously released noradrenaline on smooth muscle cells in the prostate

✓ Prostate and bladder neck tone reduction

✓ BOO reduction



α1-Adrenoceptor antagonists Mechanism of action

Five α1-blockers are currently in use

- ✓Doxazosina
- ✓Terazosina
- ✓Alfuzosina
- ✓Tamsulosina
- ✓Silodosin

Greater affinity for prostate receptors

	LE	GR
Alpha$_1$-blockers can be offered to men with moderate-to-severe LUTS	1a	A

EAU Guidelines

α1-Adrenoceptor antagonists Mechanism of action

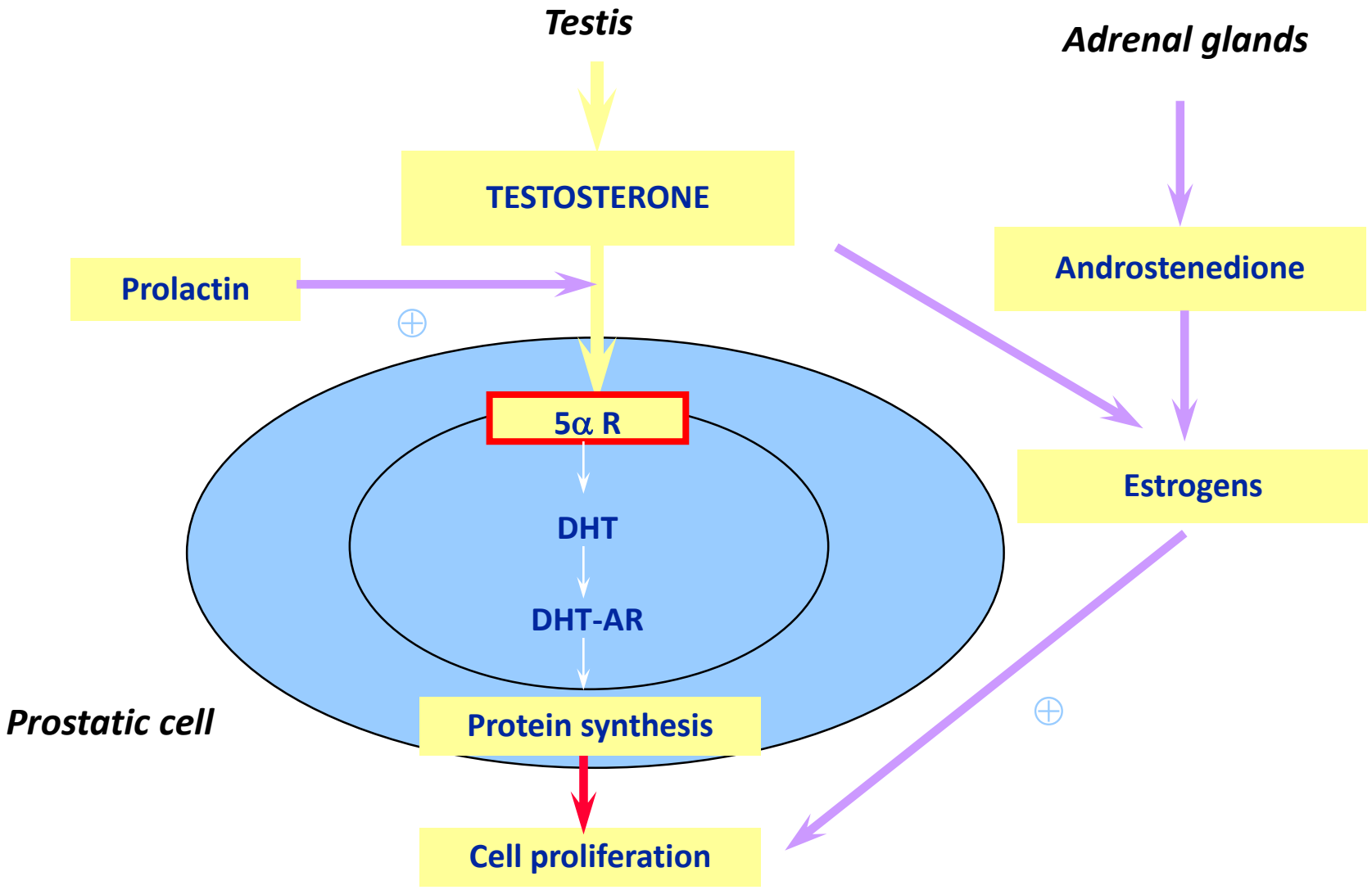
- ✓ All α1-blockers have a **similar efficacy** in appropriate doses
- ✓ α1-blockers can reduce **both storage and voiding LUTS**
- ✓ However, α1-blockers **neither reduce prostate size nor prevent acute urinary retention** in long-term studies
- ✓ Effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days
- ✓ Controlled studies show that α1-blockers typically **reduce IPSS** by approximately **30-40%** and **increase Qmax** by approximately **20-25%**

Alfa-blockers: side effects

- ✓ Asymptomatic postural hypotension
- ✓ Symptomatic postural hypotension
- ✓ Severe postural hypotension: syncope
- ✓ Asthenia (dizzines)
- ✓ Nasal congestion
- ✓ Retrograde ejaculation

Roehrborn, Pharmacotherapy 2009

5α-Reductase Inhibitors



5α-Reductase Inhibitors

5α-reductase inhibitors induce epithelial and prostatic cells apoptosis, **reducing**:

- ✓ **Prostate size:** 18-28%
- ✓ **PSA serum level**: approximately 50%

After 6-12 months of treatment

FINASTERIDE: inhibits only 5-alfa-reductase type 2

DUTASTERIDE: inhibits 5-alfa-reductase type 1 and 2

EAU Guidelines 2016

Effects of 5ARI therapy on BPH

	FINASTERIDE[1] (n : 3440, 48 mo)		DUTASTERIDE[2] (n: 4325, 24 mo)	
	Finasteride	Placebo	Dutasteride	Placebo
Prostate Volume	- 18%	+ 14%	- 26%	- 2%
IPSS	- 3.3	- 1.3	- 4.5	- 2.3
Qmax	+ 1.9	+ 0.2	+ 2.2	+ 0.6
Acute Urinary Retention ⇓	57%		57%	
Surgery risk ⇓	55%		48%	

5α reductase inhibitors reduce the risk of Acute Urinary Retention and Surgery in BPH

5ARI - Tolerability

- Reported adverse events typically related to sexual dysfunction and include:
  - Reduced libido
  - Erectile dysfunction
  - Ejaculation disorders (less commonly)

- Gynaecomastia develops in ~1–2% of patients

Implications for practice and recommendations

Treatment with 5α-reductase inhibitors should be considered only in men with moderate-to-severe LUTS and an enlarged prostate (>40 mL)

Their effect on the serum PSA concentration needs to be considered for prostate cancer screening.

	LE	GR
5α-Reductase inhibitors can be offered to men who have moderate-to-severe LUTS and an enlarged prostate (>40 mL)	1b	A
5α-Reductase inhibitors can prevent disease progression with regard to acute urinary retention and the need for surgery	1b	A

The effects of combination therapy with 5α-Reductase inhibitors and α1-blockers

TAMSULOSIN + DUTASTERIDE

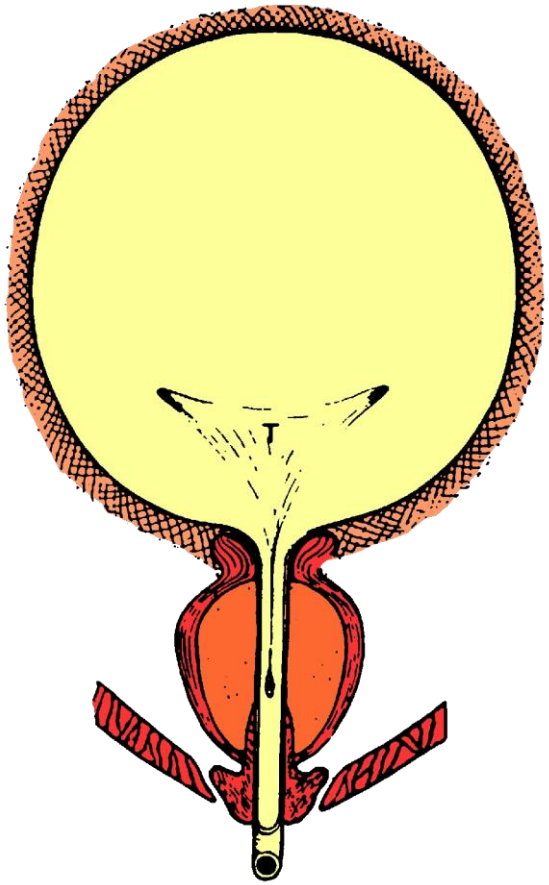
Combination therapy was significantly superior in reducing the risk of acute urinary retention in patients with high volume prostate and IPSS>20 (severe obstruction)

CombAT Study

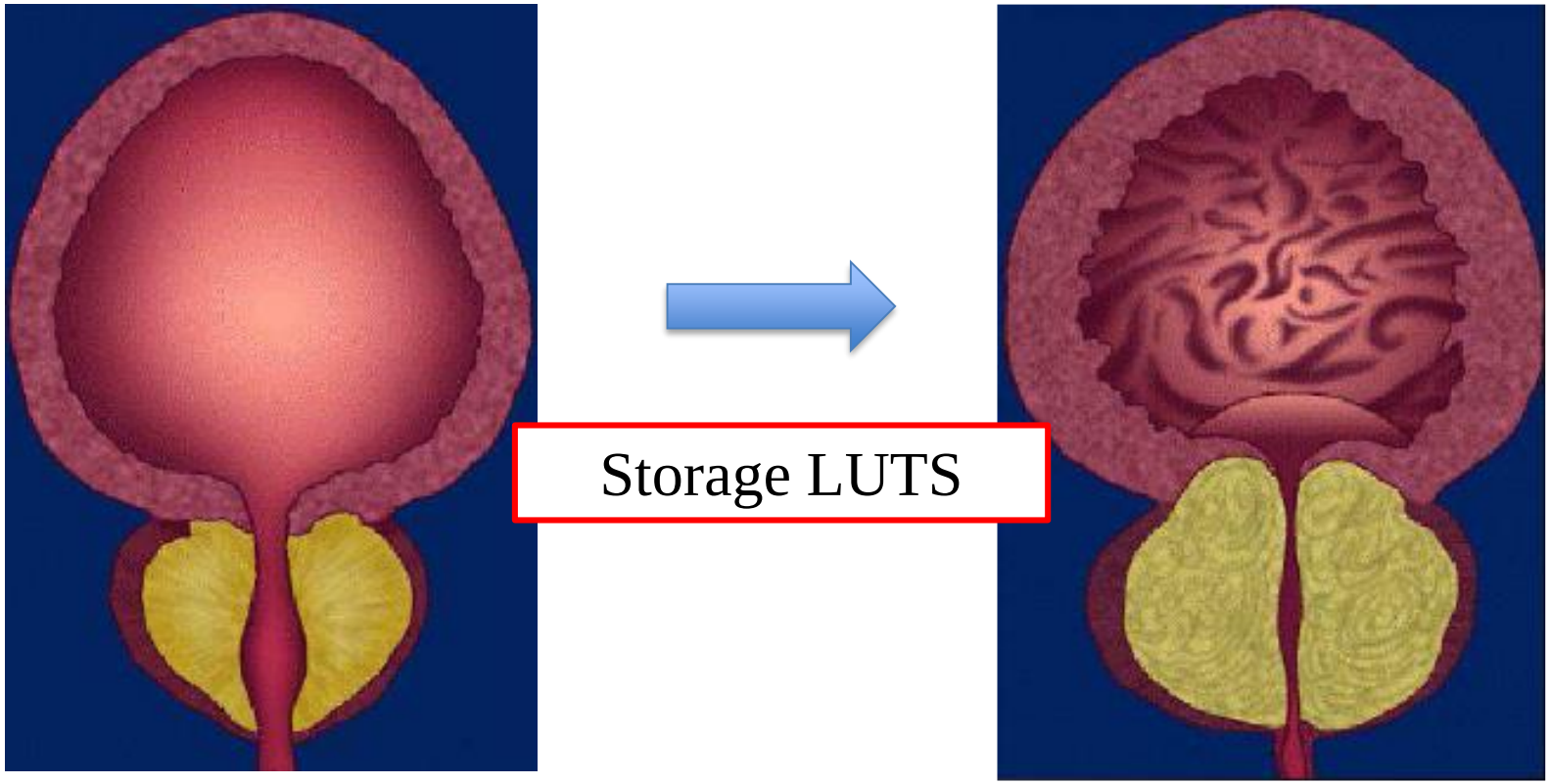
Recommendation	LE	GR
Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and risk of disease progression (e.g. prostate volume > 40 mL).	1b	A

Pharmacological treatment options

- **Targeting the bladder**
  - **Antimuscarinics/Beta-3 agonists:**
    - **Symptom control OAB (storage) component of LUTS**
- **Targeting the prostate**
  - **α-blockers:**
    - **Symptom control**
  - **5-ARIs**
    - **Disease modification**



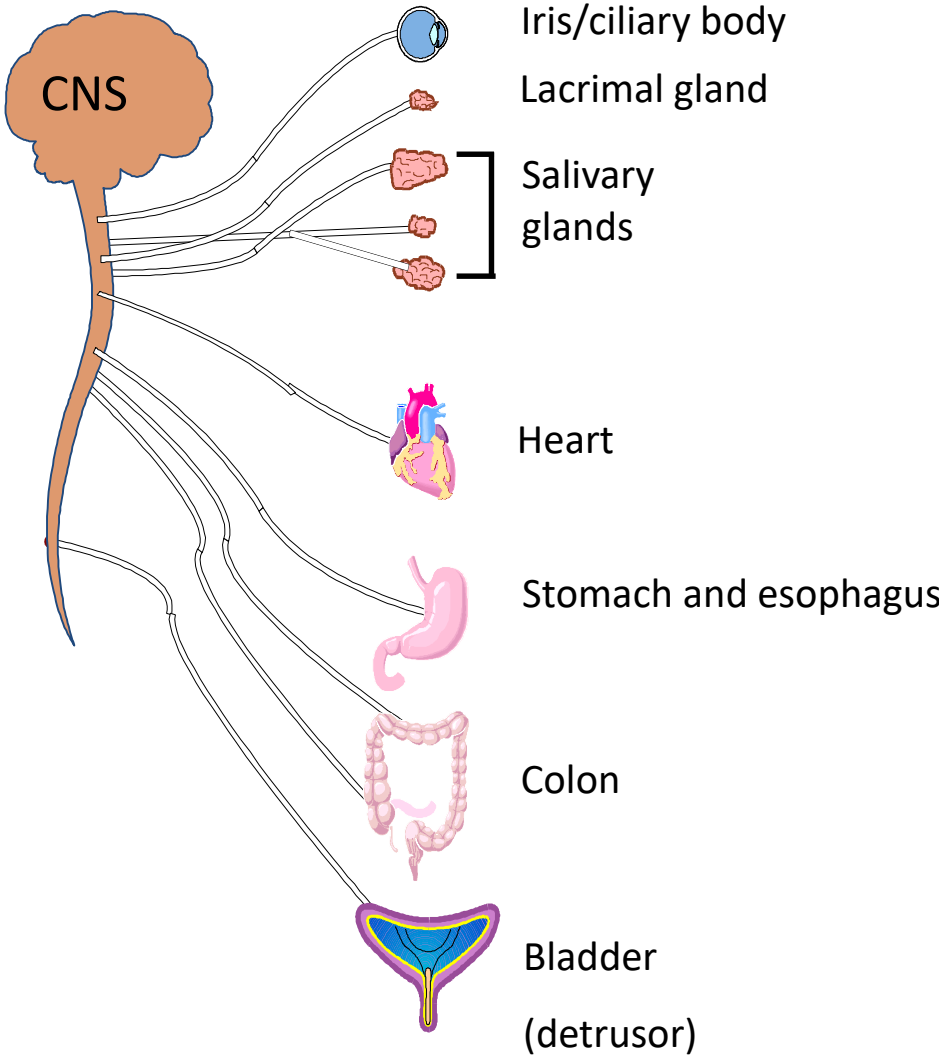
BPH and Storage Symptoms



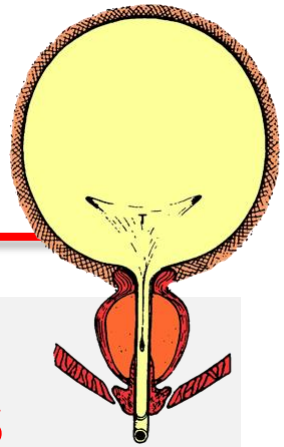
- ✓ **Hypertrophy of detrusor muscle**
- ✓ **Over-expression of β3 M2-M3 muscarinic receptors**
- ✓ **Muscarinic hyperactivity responsible for overactive bladder**

Muscarinic receptor antagonists

- Five muscarinic receptors have been described (M_1–M_5)
- Expressed in the bladder, salivary glands, and synapses in the CNS
- M_2 and M_3 are most predominant in the bladder
- Only M_3 is involved in bladder contractility
- Inhibition of muscarinic receptors reduce smooth cell contractions of the bladder



COMBINATION TREATMENT



ANTIMUSCARINICS + ALFA- BLOCKERS

Only in combination!

For patients with severe storage symptoms
(Increased urgency, urge incontinence)

RISK OF URINARY RETENTION!

Recommendations	LE	GR
Use combination treatment of an α1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug.	1b	B
Prescribe combination treatment with caution in men with a PVR volume > 150 mL.	2b	B

Plant extracts - phytotherapy

A large number of different plants are used for the preparation of extracts, the most widely used being:

- *Cucurbita pepo (pumpkin seeds)*
- *Hypoxis rooperi (South African star grass)*
- ***Pygeum africanum** (bark of the African plum tree)*
- *Secale cereale (rye pollen)*
- ***Serenoa repens** (syn. Sabal serrulata; berries of the American dwarf palm, saw palmetto)*
- *Urtica dioica (roots of the stinging nettle)*

Serenoa repens/Sabal serrulata

A recently updated Cochrane report summarized the clinical results of 30 randomized trials comprising 5,222 men.

The report concluded that *Serenoa repens* **was not superior to placebo, with regard to IPSS improvement, Qmax, or prostate size reduction.**

The combination treatment **with *Serenoa Repens*, Lycopene (Ly), and Selenium (Se) and tamsulosin** was more effective than single therapies (SeR-Ly-Se or Tamsulosin) in improving IPSS and increasing Qmax in patients with LUTS at 12 months.

NO GRADE OF RECOMMENDATION IS AVAILABLE

SURGICAL TREATMENT

BPH

Indications for surgery

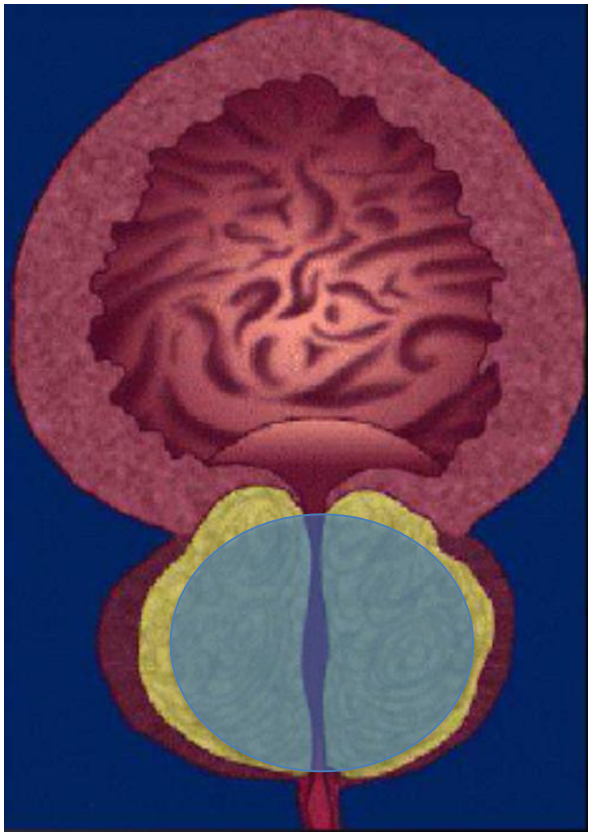
Absolute

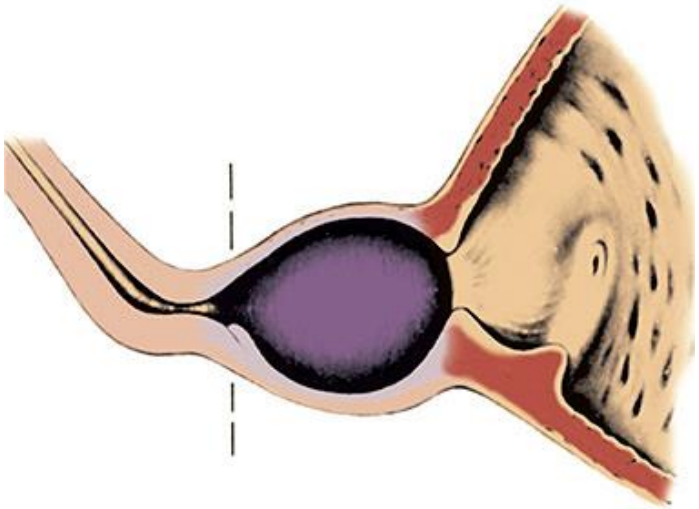
- Acute or chronic urinary retention
- Recurrent UTI
- Renal failure
- Bladder stones
- Large diverticula

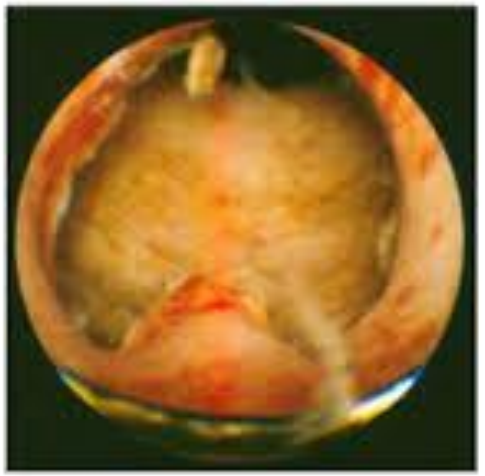
Relative

- Not adequate relief from LUTS using conservative or medical treatments

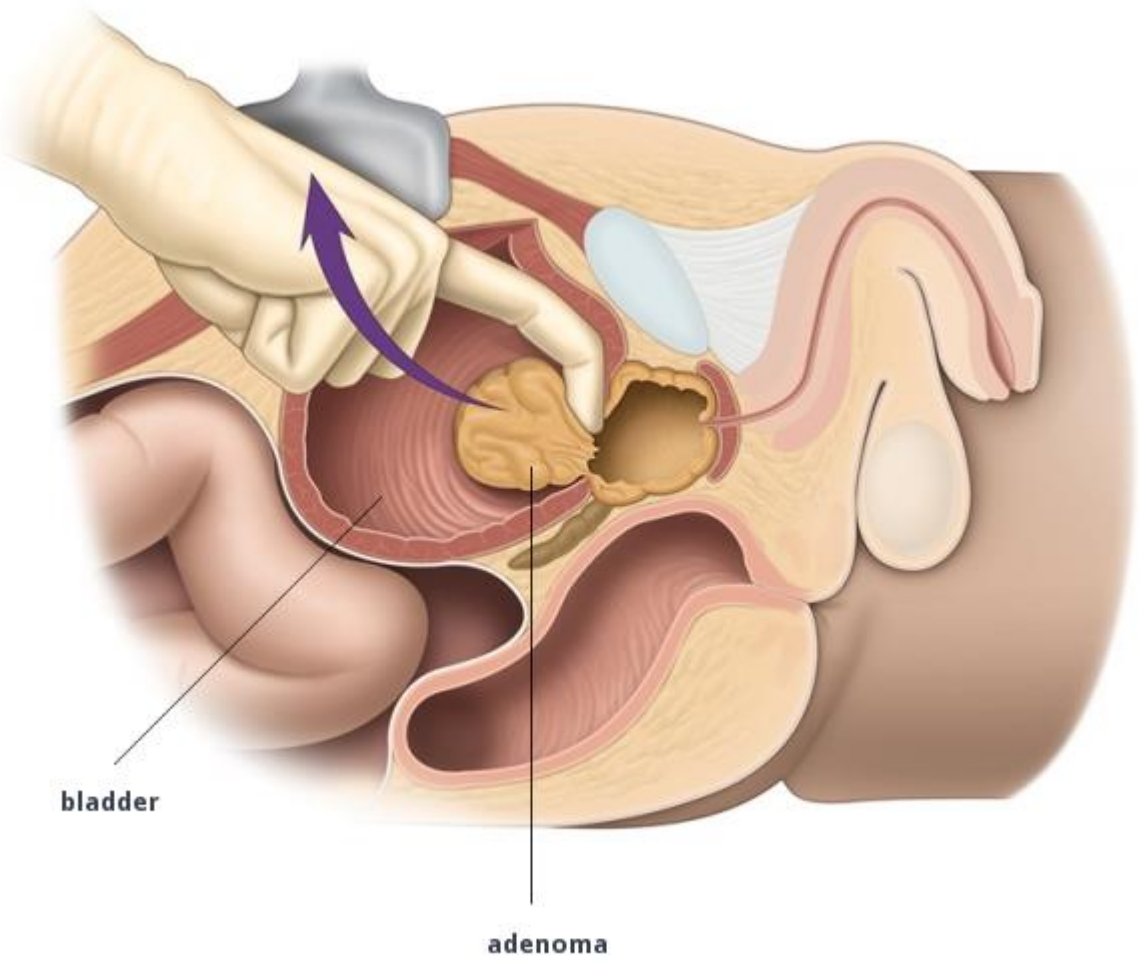
Aims of surgical treatment







Open Simple Prostatectomy



Open Prostatectomy

- Open prostatectomy is still recommended if the prostate is larger than 80 ML because other types of surgery would take more time to achieve the same result.

- It may still be recommend in the presence of bladder stones or bladder diverticulum.

- Today: less than 5% of surgical procedures

Open Prostatectomy

PROs

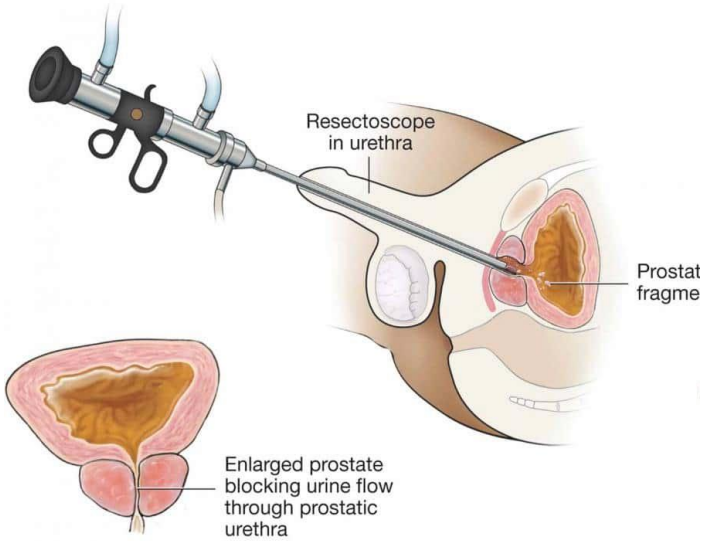
- Optimal and long-lasting improvement of the symptoms
- Very low risk of urinary incontinence

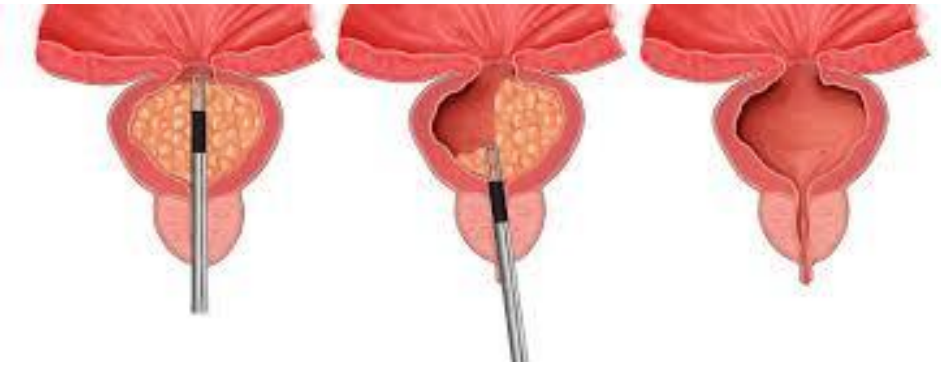
CONs

- Will leave a scar
- Longer hospital stay
- Longer use of catheter
- Significant bleeding may occur
- Risk of bladder neck stricture

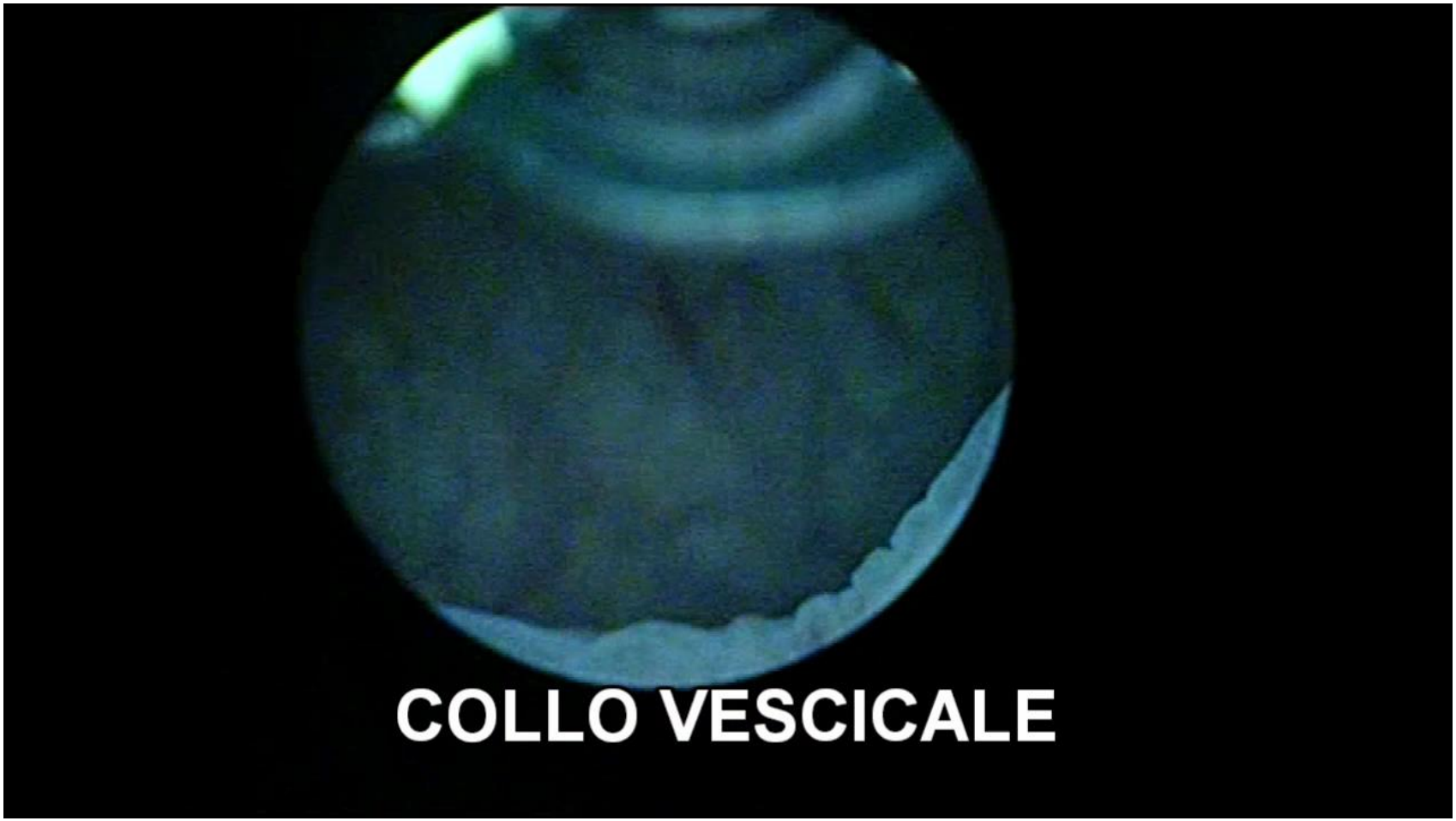
Trans-urethral resection of the prostate (TURP)

- The aim is to remove the hypertrophic part of the prostate which causes obstruction . The procedure is done through the urethra .

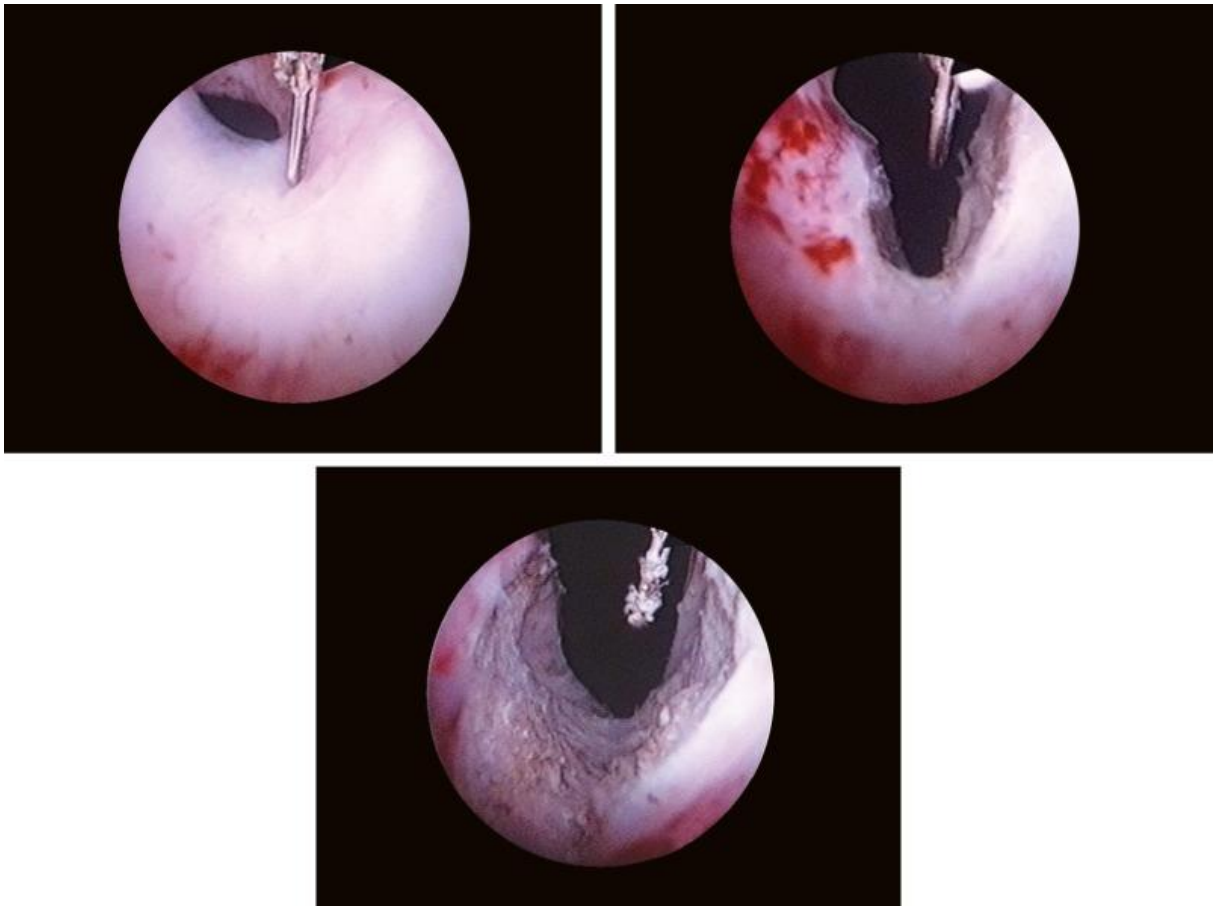




TURP



Trans-urethral incision of the Prostate (TUIP)



Transurethral resection of the prostate (TURP) and incision of the prostate (TUIP)

TURP is still the current surgical gold standard procedure for the treatment of LUTS secondary to BPO in prostates between 30 and 80 mL

TUIP reduces LUTS secondary to BPO by splitting the bladder outlet without tissue removal

This technique may replace TURP as the surgical therapy of choice of treatment in selected men with benign prostate enlargement (BPE), especially men with prostate sizes < 30 mL and without prostate middle lobes.

EAU Guidelines

TURP

PROs

- The procedure is safe and widely used
- Optimal and long-lasting improvement of the symptoms
- Short hospital stay
- **Very low risk of incontinence**

CONs

- Risk of bleeding
- Risk of retrograde ejaculation
- Risk of urethral stricture
- Risk of urinary retention
- Low risk of urinary tract infection and urgency

Practical Considerations

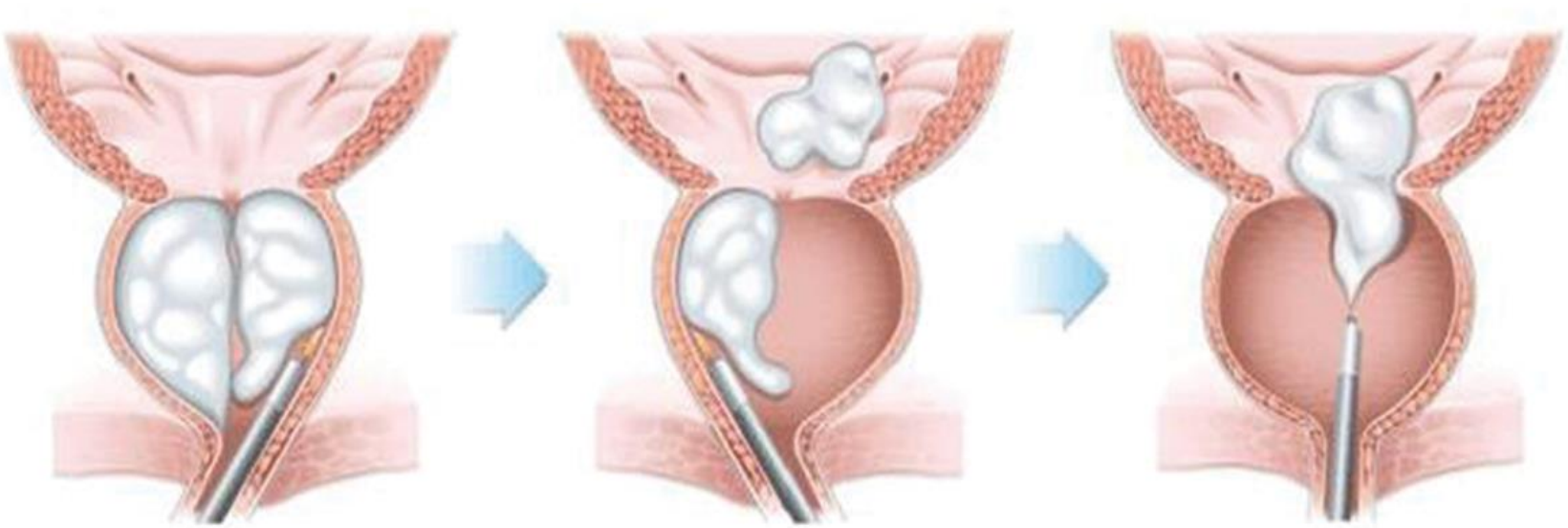
TURP and TUIP are both effective primary treatments for men with moderate-to-severe LUTS secondary to BPO.

The choice between TURP and TUIP should be based primarily on prostate volume, with prostates < 30 mL suitable for TUIP and prostates 30-80 mL for TURP. UTIs should be treated prior to TURP or TUIP.

	LE	GR
M-TURP is the current surgical standard procedure for men with prostate sizes of 30-80 mL and bothersome moderate-to-severe LUTS secondary of BPO. M-TURP provides subjective and objective improvement rates superior to medical or minimally invasive treatments.	1a	A
The morbidity of M-TURP is higher than for drugs or other minimally invasive procedures.	1a	A

TUIP is the surgical therapy of choice for men with prostate sizes < 30 mL, without a middle lobe, and bothersome moderate-to-severe LUTS secondary to BPO.	1a	A

Laser enucleation of the prostate



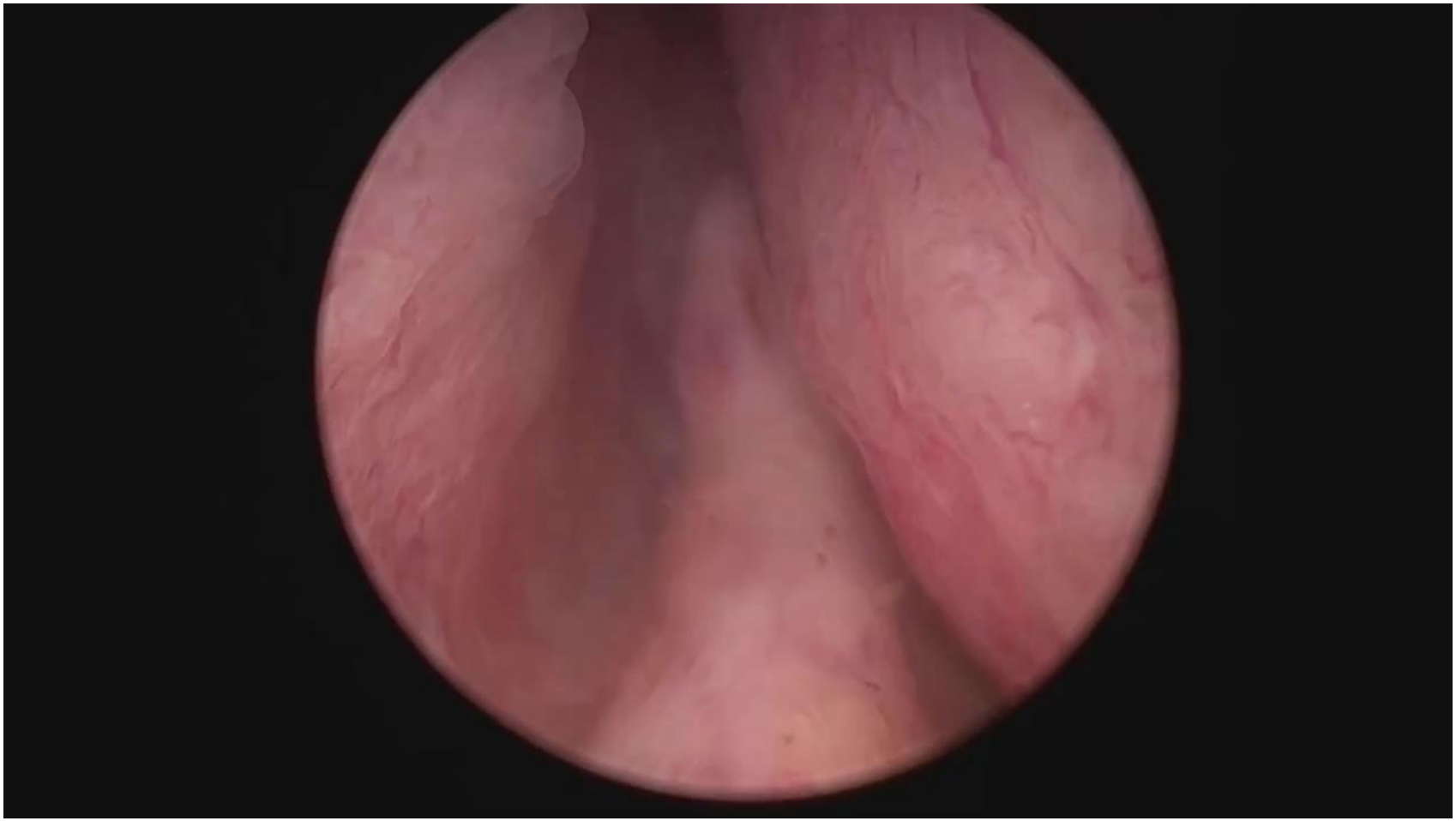
HoLEP: (Holmium)

ThuLEP: (Thullium)

Holmium laser enucleation of the prostate (Holep)

- Laser enucleation is a common treatment option for BPE. The laser uses intensive light to cut the prostate tissue. At the same time, the heat from the laser is used to close blood vessels. This is why only a small amount of blood is lost during this type of surgery.
- If the prostate is over 80 millilitres, laser enucleation may be the best option, because it removes the whole adenoma. This type of surgery is also a good option for men with smaller prostates.
- Laser enucleation is suitable for men who take blood-thinning medication for other conditions.
- It now represents the gold standard, size-independent treatment

HOLEP



Holep - Thulep

PROs

- Immediate improvement of the urine flow
- Short hospital stay
- Shorter period of using a catheter
- Effective for all prostates, especially for large ones

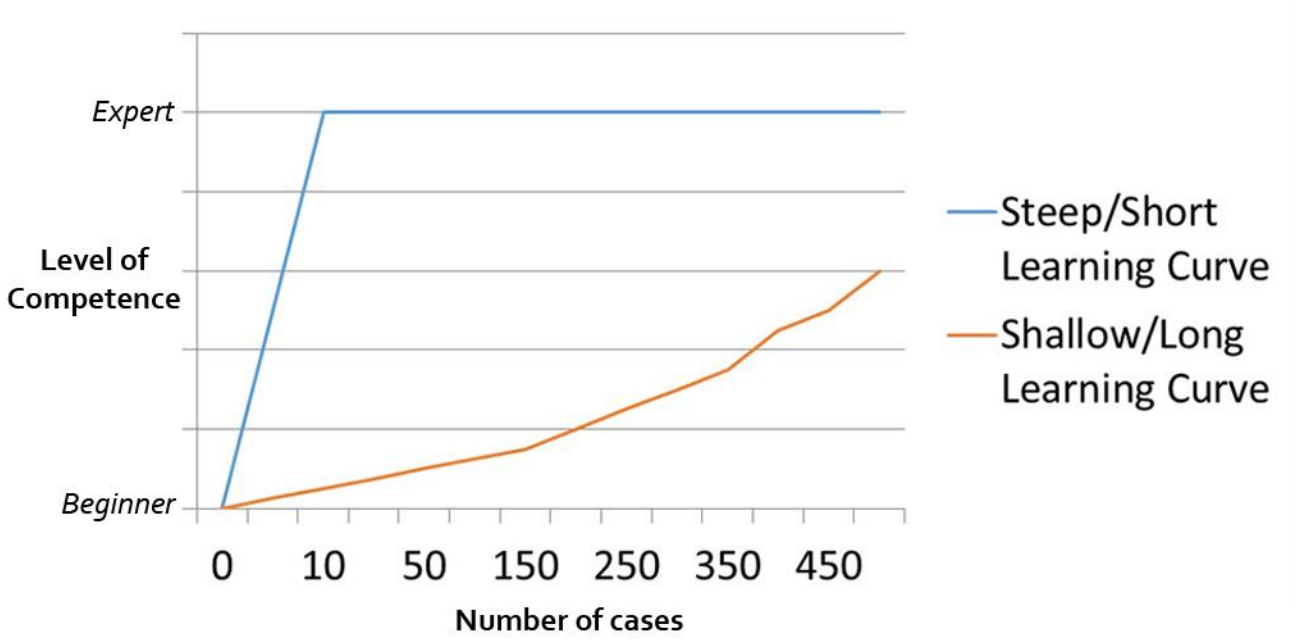
CONs

- Surgery may take longer for small prostates
- Painful urination for some time after the surgery
- Retrograde ejaculation
- Risk of urinary retention, urinary tract infection, and urgency
- Very low risk of urinary incontinence (4-5%)

Holep - Thulep

CONs

HIGHEST SURGICAL LEARNING CURVE

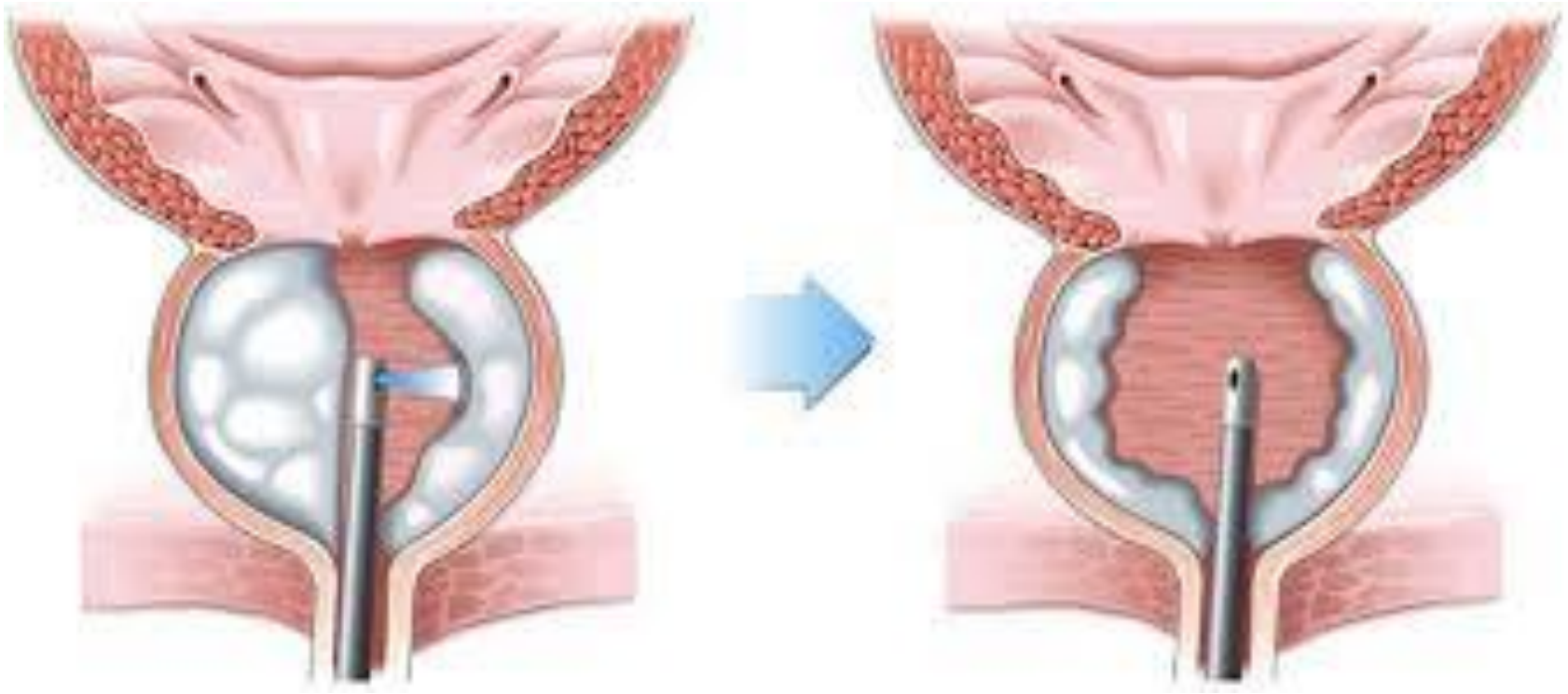


Practical considerations

Holmium laser operations are surgical procedures that require experience and relevant endoscopic skills. The experience of the surgeon was the most important factor affecting the overall occurrence of complications.

Recommendations	LE	GR
HoLEP and 532-nm laser vaporisation of the prostate are alternatives to TURP in men with moderate-to-severe LUTS leading to immediate, objective, and subjective improvements comparable with TURP.	1a	A
The short-term and mid-term functional results of 532-nm laser vaporisation of the prostate are comparable with TURP.	1b	A
The long-term functional results of HoLEP are comparable with TURP or open prostatectomy.	1b	A

Laser vaporization of the prostate



Laser vaporization of the prostate

- ✓ Laser vaporization is a common treatment option for BPE.
- ✓ The laser uses intensive light to vaporize the prostate tissue. At the same time, the heat from the laser is used to close blood vessels. This is why only a small amount of blood is lost during this type of surgery.
- ✓ Laser vaporization can be done with different laser systems. The choice of the laser depends on the expertise of the surgeon.

Laser vaporization of the prostate

PROs

- Immediate improvement of the urine flow
- Short hospital stay
- Shorter period of using a catheter
- Low risk of complications
- No need to stop blood-thinning medication (??)

CONs

- Less effective for very large prostates
- Painful urination for some time after the surgery
- May need another surgery after several years because the prostate continues to grow
- No possibility to analyse the prostate tissue after the surgery
- Risk of retrograde ejaculation
- Risk of urinary retention, urinary tract infection, and urgency
- Very low risk of urinary incontinence

‘Greenlight’ vaporization of the prostate

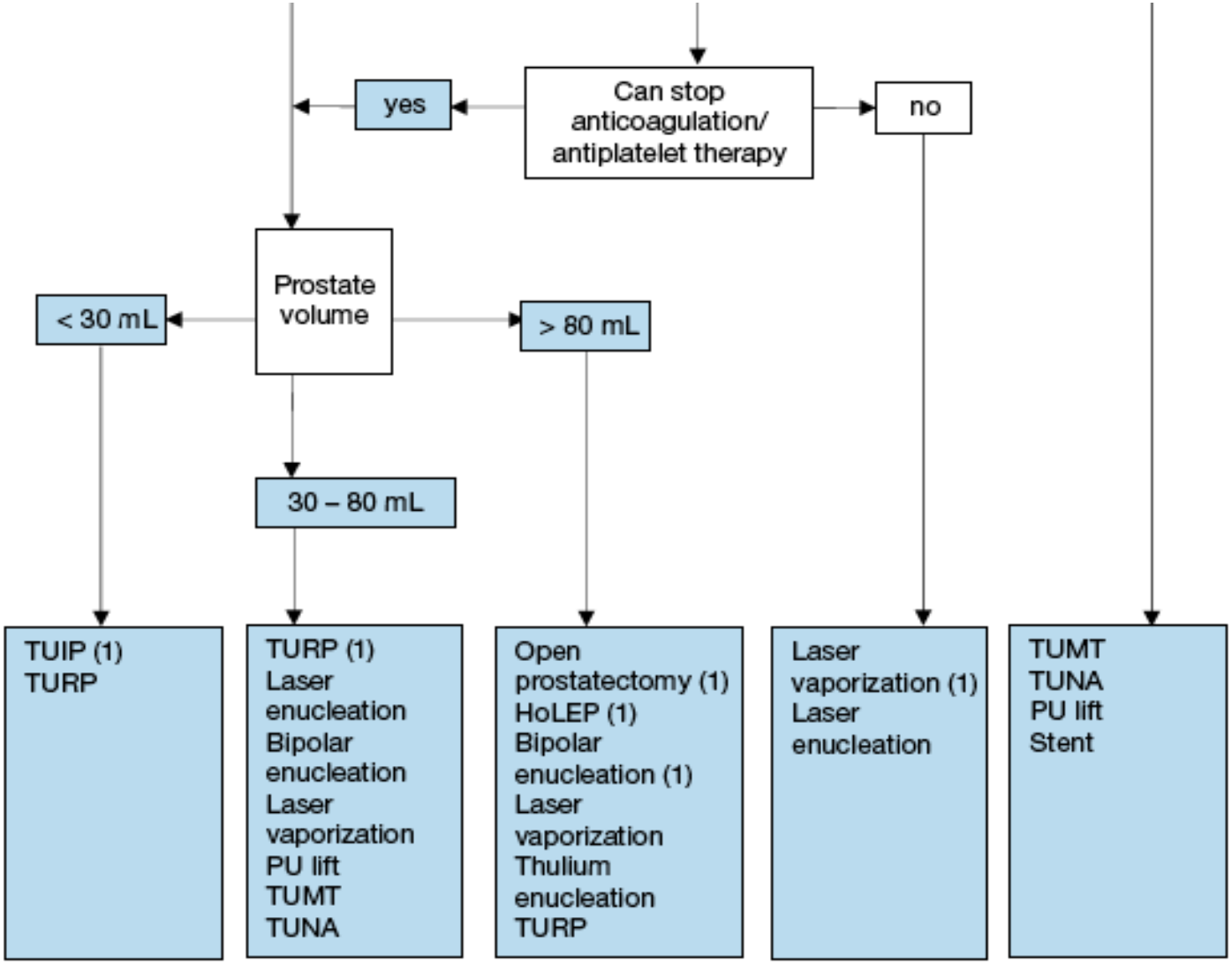
Vaporization leads to immediate removal of prostatic tissue, relief of BPO, and, secondarily, reduction of LUTS.

No differences were found in Qmax and IPSS between PVP and TURP, but only three RCTs provided sufficient 12-month data to be included in the meta-analysis.

Reoperation rate was significantly higher after PVP (11% vs 1.8%; p = 0.04).

With regard to intra-operative safety, 532-nm laser vaporization is superior to TURP.	1b	A
532-nm laser vaporization should be considered in patients receiving anticoagulant medication or with a high cardiovascular risk.	3	B

Surgical treatment



EAU Guidelines

Clinical case - 1

- ✓ My **urinary stream** is not as good as it used to be and **sometimes** it **stops and starts** again several times
- ✓ Why do I need to go to the toilet so often? Especially during the **night**, I have to get up **once** to urinate

Is it normal?»

= 9

Watchful waiting
Behavioural and dietary modifications
Periodical check-ups

Clinical case – 2

- ✓ I have to **go the bathroom continuosly** and sometimes **I can't postpone urination.**
- ✓ Sometimes **holding back urine impossible.**
- ✓ My **stream is filiform** and **inter**
- ✓ I often have to strain to start I have the sensation of bladder.
- ✓ I get up 3-4 times

S = 20

birth: _____ Date completed _____

		Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
	0	1	2	3	4	5	
e had to every two	0	1	2	3	4	5	
ermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 Times	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: ***Mild*** 8-19: ***Moderate*** 20-35: ***Severe***

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	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

Pharmacological management

Alfa-blockers +/- 5α-Reductase Inhibitors

Clinical case – 3

- ✓ **Despite all the medical treatments and drugs you prescribe me, my symptom persist and are unbearable**
- ✓ **Moreover, I often have a f related to pain while urinati**

Drug-resistant LUTS, no relief

Surgery recommended

I-PSS]

ate of birth: _____ Date completed _____

		than 1 in 5 Times	**Less than Half the Time**	**About Half the Time**	**More than Half the Time**	**Almost Always**	**Your score**
	0	1	2	3	4	5	
ave you had to ss than every two ?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: ***Mild*** 8-19: ***Moderate*** 20-35: ***Severe***

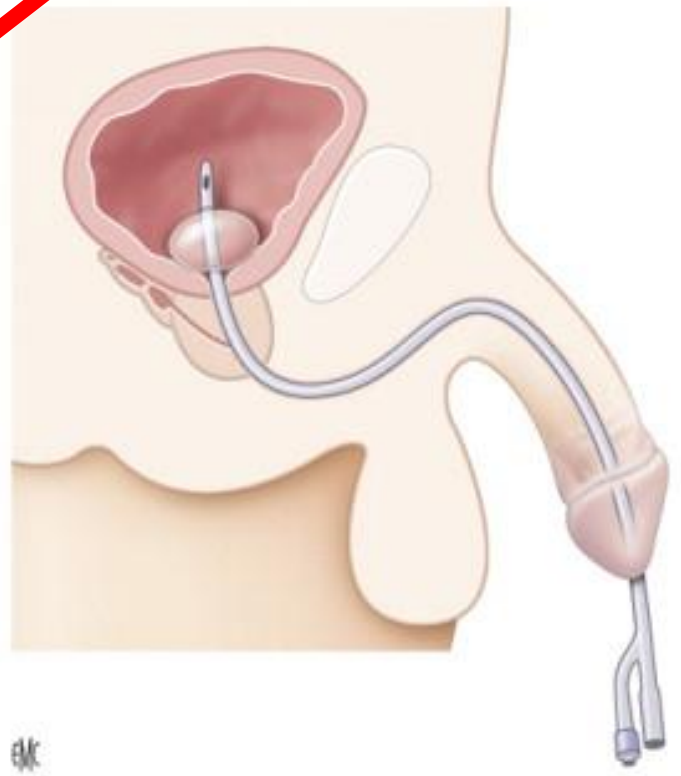
Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Caso clinico – 4

«Doctor help me…

Yesterday I could not urinate anymo
(acute urinary retention) … at th
Emergency Department they
me a urinary catheter

Early surgery!



What am I supposed to do now?»