Medical and surgical management of BPH

Medical Management Of BPH

- Medical therapy plays a major role in the management of patients with LUTS.
  - α-adrenergic blockers (α1-blockers)
  - 5α-Reductase Inhibitors(5ARIs)
  - Antimuscarinic drugs
  - Phosphodiesterase type 5 inhibitors (PDE5Is)
  - β3-agonists
  - Numerous plant extracts
- Different combinations of medical compounds play a relevant role in the management of LUTS.

Classification of α-Adrenergic Blockers and Recommended Doses

CLASS OF α-BLOCKERS	AVAILABLE FORMULATION	RECOMMENDED DAILY DOSE	RECOMMENDED ADMINISTRATION[a]
NONSELECTIVE			
Phenoxybenzamine	10-mg capsule	10 mg bid	No longer indicated for LUTS treatment
SELECTIVE			
Prazosin	0.5[c]-, 1-, 2[d]-, 5[d]-mg capsule	2 mg bid	No longer indicated for LUTS treatment
Indoramin	20-mg capsule	20 mg bid	No longer indicated for LUTS treatment
Terazosin	1[d]-, 2-, 5-, 10[d]-mg capsule	5 or 10 mg qd	Initial dose is 1 mg at bedtime. The dose should be titrated up to 5 or 10 mg.
Doxazosin IR	1-, 2-, 4-mg capsule	2–8 mg qd	Initial dose is 2 mg at bedtime. The dose should be titrated up to 4 or 8 mg.
Doxazosin SR	4-, 8-mg capsule	4 or 8 mg qd	Initial dose is 4 mg after breakfast, eventually increased to 8 mg.
UROSELECTIVE			
Alfuzosin ER[b]	10-mg capsule	10 mg qd	Initial dose is 10 mg with the same meal each day.
Tamsulosin	0.4-, 0.8[d]-mg capsule	0.4–0.8 mg qd	Initial dose is 0.4 mg with the same meal each day.
Silodosin	4-, 8-mg capsule	8 mg qd	Initial dose is 8 mg with the same meal each day.
Naftopidil	25-, 50-mg capsule	25–75 mg/day	Marketed only in Asian countries

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Therapy With α1-Adrenergic Blockers

- α1-Blockers are the first-line treatment for patients with moderate to severe LUTS.
- The uroselective α1-blockers tamsulosin, silodosin, and alfuzosin showed the best tolerability profile.
- Uroselective α1-blocker has demonstrated the highest selectivity for the α1a-AR subtype

- The blockade of α1-ARs leads to the relaxation of smooth muscle tissue at both sites, with a decrease of the sympathetic baseline muscle tone and the consequent relief of symptoms.

Gup et al., 1989; Lepor et al., 1988

- The effect of α1-blockers on bladder detrusor function has not yet been clarified.

- Because of the nonselectivity of the molecule, blocking both α1 and α2 receptor subtypes, serious cardiovascular AEs were observed, and the drug was no longer used to treat LUTS/BPH.

- α1-blockers should be carefully administered in patients taking antihypertensive medications.

- The concomitant use of α1-blockers with other α-blocker compounds is not recommended.

- The odds of reporting ejaculation disorders was significantly higher for silodosin (odds ratio, 32.5; $P < 0.001$) than for tamsulosin (odds ratio, 8.57; $P = 0.006$).

Gacci et al., 2014

- Physicians should warn patients regarding a risk for first-dose hypotension with α1-blockers.

- Intraoperative floppy iris syndrome (IFIS) was firstly reported after the intake of tamsulosin.

Chang and Campbell, 2005

- Discontinuation of the use of drug before cataract surgery does not significantly reduce the risk for IFIS.

Androgen Manipulation

- Prostate tissue is androgen dependent, and both testosterone and dihydrotestosterone (DHT) play a key role in the development of BPH.

Coffey and Walsh 1990; Shapiro 1990

- The potent male sex hormone DHT is a metabolite of testosterone and is synthesized by two isoenzymes
  - Type 1 isoenzyme: present in several organs other than the prostate, such as the liver and the skin
  - Type 2 isoenzyme: mainly expressed at the level of the prostate and genital tissues

- Multicenter RCTs have demonstrated the efficacy of finasteride and dutasteride for the treatment of patients with BPH.

- Finasteride is a selective inhibitor of the type 2, 5α-reductase isozyme.

  Vermeulen et al., 1989

- Dutasteride is a dual inhibitor of 5α-reductase types 1 and 2.
  - Greater decrease of serum DHT levels compared with finasteride.

  Clark et al., 2004

- Therapy with finasteride has been associated with a roughly 20% reduction of PV.

- long-term data have shown a 51% reduction in the risk for either AUR or surgery for patients treated with finasteride.

- long-term (≥6 months) treatment is required to observe a significant reduction of PV and a benefit in terms of symptom relief.

- International clinical guidelines suggest therapy with 5ARIs for patients with an enlarged prostate (>40 mL) and moderate to severe symptoms.

Muscarinic Receptor Antagonists

- Muscarinic receptor antagonists are the mainstay of treatment for patients with OAB syndrome.

- Of the five muscarinic receptor subtypes (M1 to M5), M2 and M3 receptors are predominant at the bladder level.

- The inhibition of these receptors reduces involuntary bladder contractions and alters the contraction threshold, thus resulting in decreased urgency and increased bladder.

Chapple et al., 2002

- Muscarinic receptor antagonists are used for the treatment of patients with BOO presenting with predominant storage LUTS.

- Antimuscarinics can be safely administered in patients with low PVR volume and no history of AUR.

- International clinical guidelines suggest the use of antimuscarinic therapy in patients with moderate to severe LUTS who mainly complain of bladder storage symptoms and present with a baseline PVR volume lower than 200 mL.

McVary et al., 2011; Oelke et al., 2013)

Phosphodiesterase Type 5 Inhibitors

- The biologic mechanisms associated with its inhibition have not been completely clarified.

- The inhibition of PDE5 at the level of the endothelial and smooth muscle cells of blood vessels can lead to increased oxygenation of both the bladder and the prostate.

  Morelli et al., 2010

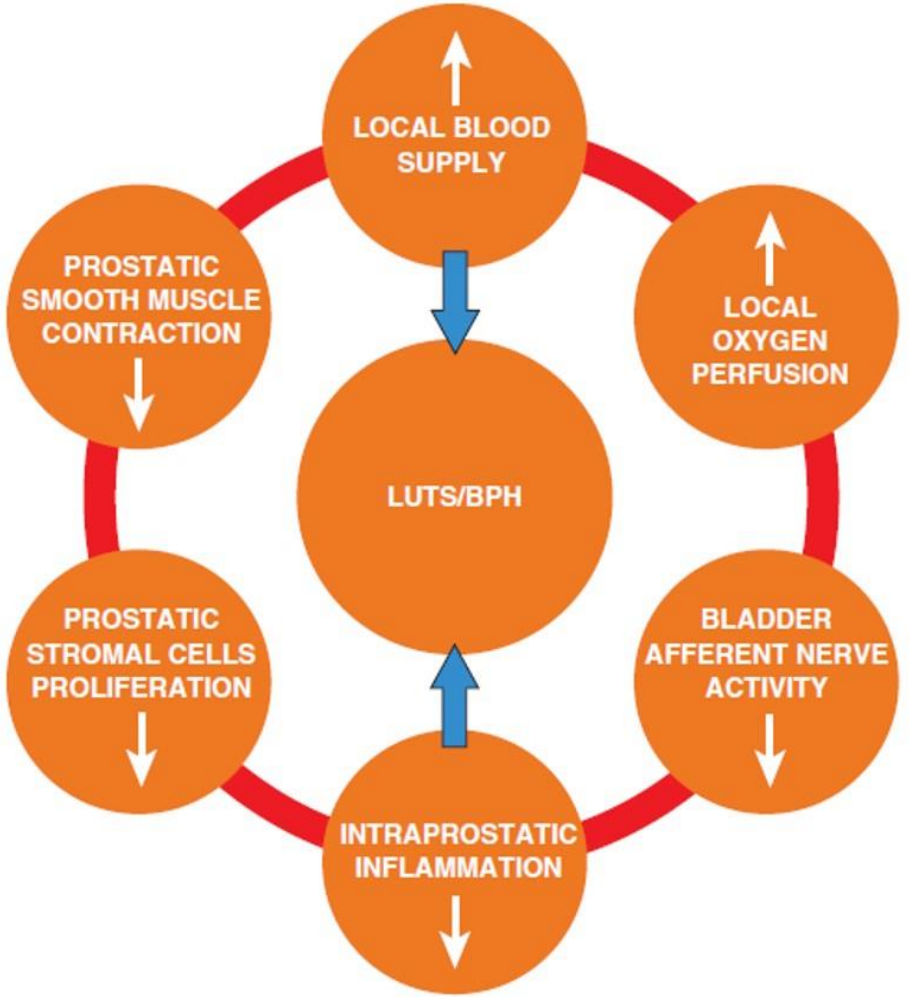
- PDE5Is can relax the prostate and bladder neck smooth muscle.

  Angulo et al., 2012; Kedia et al., 2009

- Metabolic syndrome has a proven role in BPH pathophysiology
  - Tadalafil was able to reduce prostate inflammation. Morelli et al., 2013
  - PDE5Is may attenuate the negative effect of metabolic alterations on prostatic tissue.

- International clinical guidelines currently suggest PDE5Is as an alternative therapy for men with moderate to severe LUTS, with or without associated erectile dysfunction
  - Tadalafil is currently the only officially licensed PDE5I for the treatment of male LUTS.
    - The recommended dose is 5 mg taken at approximately the same time every day with or without food.

Effects Of Pde5is On The Lower Urinary Tract



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β3-Agonist (Mirabegron)

- The β3 subtype is the predominant form of β-ARs in the bladder.

  Yamaguchi and Chapple,2007

- The stimulation of the β3-AR is responsible for an increase in bladder capacity without a significant change in micturition pressure, PVR volume, and voiding contraction.

  Leon et al., 2008

- Because of previous evidence showing a significant increase of systolic blood pressure among healthy volunteers, mirabegron is not recommended for patients with uncontrolled hypertension.

  Malik et al., 2012

Phytotherapy

- There is no consensus on the efficacy of phytotherapy for LUTS treatment, although encouraging results have been published for the hexane extract of *Serenoa repens* and for the combination of *Serenoa repens* with lycopene and selenium.

Mechanisms of Actions of Plant Extracts

Inhibition of 5α-reductase
Anti-inflammatory action
Interference with growth factors
Antiandrogenic effects
Estrogenic effects
Inhibition of aromatase
Decrease of sex hormone–binding globulin
Alteration of cholesterol metabolism
Action on α-adrenergic receptors
Free-radical scavenging
Alteration of lipid peroxidation
Modulation of prolactin-induced prostatic growth
Protection of bladder and detrusor function
Placebo effect

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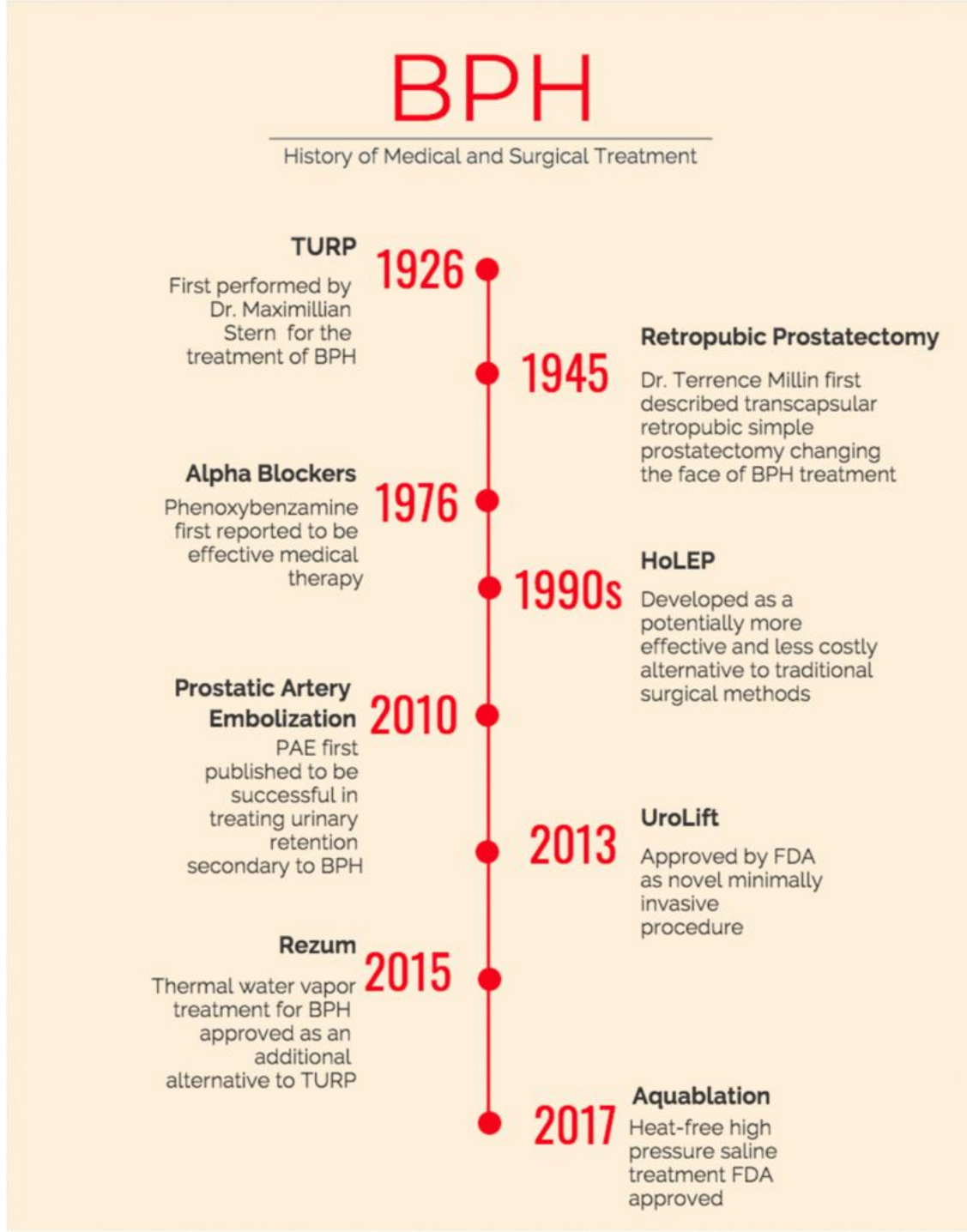
Surgical management of BPH

- Early treatments for BPH centered on open procedures utilizing both suprapubic and perineal approaches.
- These surgeries were prone to profound hemorrhage and led to unacceptable mortality and morbidity.
- The arrival of transurethral resection of the prostate (TURP) offered another option between watchful waiting and open prostatectomy.

- The incorporation of medical management and new technologies has changed which treatment options are selected for the treatment of LUTS/BPH.

- LASER-based treatments are increasingly used, although multiple factors have affected acceptance.

- Multiple factors have changed the usual patient that advances to surgical management of BPH in the preceding decades.



Curr Urol Rep. 2020

Surgical Indication

- Acute urinary retention
- Symptomatic prostatism
- Chronic complications
  - Bladder stone/diverticulum
  - Post-void residue
  - Recurrent hematuria
  - Recurrent UTI
  - Renal function impairment

Kaohsiung J Med Sci 2003`

Complication Rates After Endoscopic Benign Prostatic Hyperplasia Procedures

	M-TURP	B-TURP	TUNA	TUMT	HoLEP	PVP	TUVP	TUIP
Transient urinary retention	4.3–6.8[a]	3.3–3.7[b]	23[c]	10–24[d]	2.7–5.9[e]	5.2–9.9[e]	2–9.8[f]	4.9–11.3[g]
UTI	4.1–6.2[a]	2.6–8.4[c]	4[c]	15–20[h]	0.9–2.7[e]	4.2–12[e]	0[f]	IE
Bladder neck contracture	2–3.2[a]	0.5[b]	IE	0[d]	1.2–1.5[e]	1.1–5[e]	0.5–1[f]	IE
Urethral stricture	3.4–4.1[a]	0.5–4.7[i]	0.5[c]	0–2[h]	1.9–4.4[e]	1–6.3[e]	1.9–3.3[f]	2.9–8.8[g]
Incontinence	0.6–1.5[a]	0–1[i]	IE	IE	0.9–1.1[e]	0–0.4[e]	0–2[f]	0.3–1.8[g]
Blood transfusion	2–4.4[a]	1.5–2.3[i]	Very rare	0[d]	0–1[e]	0[e]	0–0.5[f]	1.1[j]
Clot retention	4.9–7.2[a]	2.7–7.9[i]	IE	1[d]	0[k]	0[k]	0–0.5[f]	IE
Postoperative hematuria	3.5–15.7[a]	1[b]	6–28[c]	1–26[d]	0[k]	0.7[k]	0[f]	4.3[l]
Dysuria	0.8[a]	0[b]	8–14[c]	14[d]	1.2[k]	8.5–13.9[e]	2.9[f]	IE
Urgency	2.2[a]	0.2[b]	10[c]	IE	5.6[k]	0[k]	0[f]	IE
Storage symptoms	IE	IE	IE	18–31[d]	IE	IE	21[f]	IE
Reoperation for non-BPE cause	1.1[a]	0.2[b]	0[c]	IE	1.9–2.8[e]	IE	5.4[f]	9.6–18.4[g]
Reoperation for BPE	0.5[a]	0.2[b]	19[c]	4[d]	0[k]	0.7–5.6[e]	2.4[f]	IE
Capsular perforation	0.1[a]	0[b]	IE	IE	0.2[k]	0[k]	0[f]	IE
Conversion to TURP	n/a	0[b]	n/a	n/a	0[k]	3.5[k]	0[f]	IE
TUR syndrome	0.8–2.5[a]	0[b]	0[c]	0[d]	0[k]	0[k]	0[f]	IE
Bladder mucosal injury	0[a]	0[b]	0[c]	IE	3.3[k]	0[k]	0[f]	IE

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Monopolar Transurethral Resection of the Prostate

- Although still considered the gold standard for BPH treatment, the morbidity associated with the procedure has led to the development of many endoscopic alternatives.

- The original M-TURP requires the use of a non-ionic irrigant (glycine, sorbitol) to carry the current through the cutting loop.

- These non-ionic solutions are hypo-osmolar and can lead to acute dilutional hyponatremia (TUR syndrome)

Bipolar Transurethral Resection of the Prostate

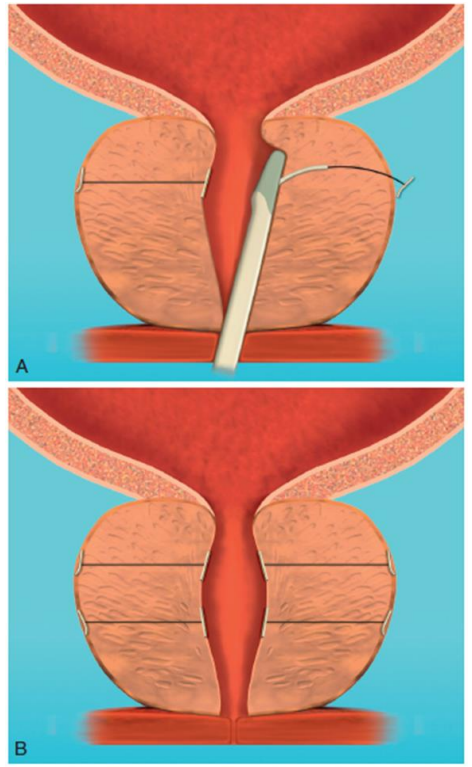
- B-TURP utilizes a specialized resecting loop that incorporates both the active and the return portions of the circuit on the same electrode.
- Bipolar technology is the ability to perform the resection in an ionic iso-osmolar solution.
- This technology will likely replace M-TURP as the gold standard for treatment of BPH in the coming years.

Prostatic Urethral Lift

- These permanent transprostatic implants take the form of sutures through a cystoscope by compressing the prostate parenchyma.

- The advantages of this technology
  - Low rates of local symptoms along with minimization of impact on sexual factors like ED and ejaculatory problems.

- It is not suited for men with a gland larger than 80 g.



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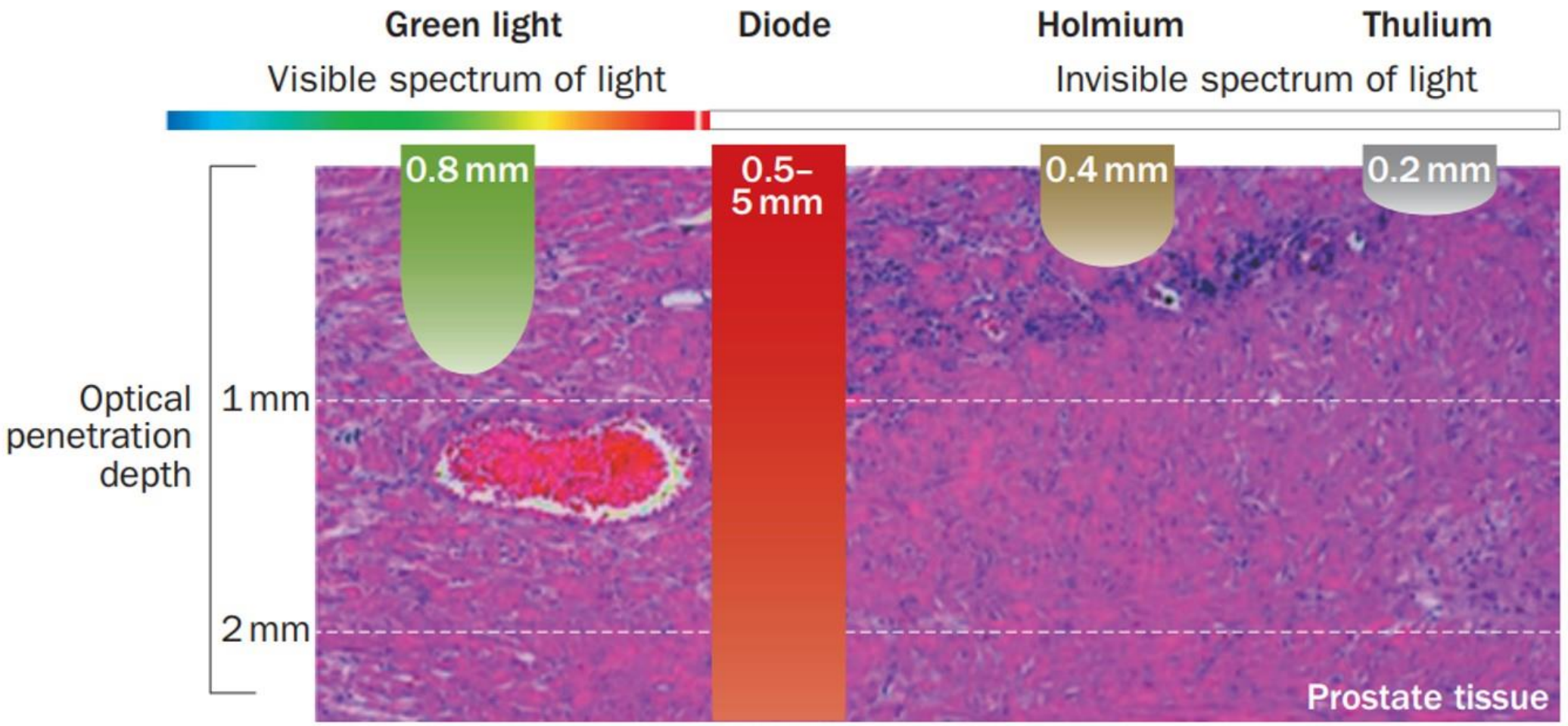
LASER Treatments

- LASER prostate treatments rely on the prostate interacting with the light energy and converting it to local thermal energy.

- Vaporization occurs when the tissue is heated above the vaporization (boiling) temperature, which leads to intracellular water vaporization and quick tissue destruction.

- LASER treatments are the fastest-growing option in treatment of LUTS/BPH but should be used as part of a “culture of safety” in the operating room.

Optical Penetration Depth Of Different Lasers In Prostate Tissue



Nat. Rev. Urol. 11, 142–152 (2014)

Laser Types And Techniques For Laser Prostatectomy

Wavelength (nm)	Mode of operation	Optical penetration depth (mm)	Predominant surgical technique	Brand name, manufacturer
Ho:YAG				
2,140	Pulsed	0.4	Enucleation	VersaPulse® PowerSuite™, Lumenis (Palo Alto, USA); Auriga® XL, StarMedTech (Starnberg, Germany)
Tm:YAG				
2,000	Continuous	0.2	Enucleation; vapoenucleation	RevoLix®, LISA Laser (Katlenburg, Germany)
1,900	Continuous	0.2	Enucleation; vapoenucleation	Vela® XL, StarMedTech (Starnberg, Germany)
Green light				
532	Quasicontinuous; continuous	0.8	Vaporization	GreenLight™ KTP, HPS and XPS, all American Medical Systems, (Minnetonka, USA); Greenlaser, Realton (Beijing, China)
Diode				
980, 1,318 or 1,470	Continuous	0.5–5.0	Vaporization; enucleation	Diolas, Limmer Laser (Berlin, Germany); Ceralas®, Biolitec (Jena, Germany); Eraser, Rolle and Rolle (Salzburg, Austria)

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Holmium LASER Enucleation Of The Prostate (HoLEP)

- HoLEP is a very effective treatment option with excellent results that are often comparable to those historically seen with OP.

- There is a significant learning curve associated with the procedure, and catastrophic complications (mostly caused by the morcellator) have been observed.

- Complication profiles show HoLEP, with a lower rate of transfusion and similar rates of bladder neck contracture and urethral stricture to TURP.

Photoselective Vaporization (PVP)

- The GreenLight™ laser operates at a wavelength of 532 nm (green light) at which the energy of the laser is strongly absorbed by haemoglobin, but not by water.

- The PVP technology has been viewed to have a forgiving learning curve with a favorable safety profile.

- The excellent hemostasis of the PVP have allowed for the treatment of many challenging patients, such as those on anticoagulation.

Thulium

- The thulium (Tm:YAG) LASER is a continuous wave of 2013-nm energy and has recently been introduced for the treatment of BPH.

- Like other LASER technologies, thulium may be used to either vaporize or incise tissue.

- It appears that there is potentially an improvement in tissue removal rate compared with other technologies because of the combined vaporization/incision.

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