New Laser Treatment Approaches for Benign Prostatic Hyperplasia

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The recent introduction of higher power 100 W holmium: yttrium-aluminum-garnet (Ho:YAG) and 80 W potassium titanyl phosphate lasers for rapid incision and vaporization of the prostate has resulted in renewed interest in the use of lasers for treatment of benign prostatic hyperplasia (BPH). Although long-term studies are still lacking, short-term results demonstrate that these procedures are at least as safe and effective in relieving BPH symptoms as transurethral resection of the prostate and may provide reduced morbidity. Other laser techniques, such as interstitial laser coagulation and contact laser vaporization of the prostate, have lost popularity due to complications with increased catheterization time, irritative symptoms, and infection rates. Although Ho:YAG laser enucleation of the prostate is more difficult to learn and a slower procedure than potassium titanyl phosphate laser vaporization, the Ho:YAG laser is currently the most proven laser technique for BPH treatment. This article reviews the latest developments in laser treatment of BPH over the past 2 years and provides a view toward the future of lasers in the treatment of BPH.

Introduction

Benign prostatic hyperplasia (BPH), or enlargement of the prostate gland, is a common benign disease that occurs with increasing age in the male population. Because surgery in the form of an open prostatectomy is associated with significant morbidity, transurethral resection of the prostate (TURP) has become the gold standard for minimally invasive treatment of BPH. However, numerous new thermal therapy technologies, such as lasers, therapeutic ultrasound, and microwave thermal therapy, have recently been introduced as alternatives to TURP for minimally invasive treatment of BPH as well.

These thermal technologies can broadly be divided into two categories based on their mechanisms of thermal interaction with prostate tissue: coagulative and ablative. Coagulative technologies, such as microwave, therapeutic ultrasound, and interstitial laser coagulation (ILC), provide deep volumetric heating of the prostate gland. Heating of the prostate gland to temperatures above approximately 50°C results in thermal denaturation, coagulative necrosis, and sloughing of the tissue during the wound healing process. Ablative technologies, such as holmium:yttrium-aluminum-garnet (Ho:YAG) and potassium titanyl phosphate (KTP) lasers, provide direct removal of the tissue through either incision or vaporization by elevating the tissue temperature well above 100°C. During tissue vaporization using the Ho:YAG and KTP lasers, residual heating of the tissue adjacent to the ablation crater through thermal diffusion results in a small thermal coagulation zone sufficient for hemostasis.

This article focuses on reviewing the latest results with laser technologies for either ablation or coagulation of the prostate. There are currently several laser therapies for treatment of BPH: visual laser ablation of the prostate (VLAP) using the neodymium:YAG (Nd:YAG) or KTP laser; ILC using the Nd:YAG or diode laser; and Ho:YAG laser resection or enucleation of the prostate [1,2]. A summary of the specifications for current clinical lasers used in the treatment of BPH are provided in Table 1 and Figure 1.

Visual Laser Ablation of the Prostate (VLAP)

Early VLAP studies utilized Nd:YAG laser radiation with a wavelength of 1064 nm, delivered via a side-firing optical fiber through a standard cystoscope for noncontact laser ablation of the prostate tissue. The wavelength of the Nd:YAG laser has the deepest optical penetration depth of any medical laser system used in urology (Fig. 2). As a result, direct vaporization of prostate tissue can be achieved combined with deep coagulative necrosis and hemostasis, resulting in tissue necrosis and sloughing. However, when VLAP was compared with TURP, it was found that TURP produced more reduction in prostate volume and improved symptom score and flow rate. Furthermore, long-term results with VLAP showed increasing reoperation rates and complications with long-term retention and

Table 1. Technical specifications for lasers used in treatment of benign prostatic hyperplasia

Laser Parameters	Holmium	KTP	Diode
Name	VersaPulse	GreenLight	Indigo
Manufacturer	Lumenis, Inc. (Santa Clara, CA)	Laserscope (San Jose, CA)	Ethicon Endo-Surgery, Inc. (Cincinnati, OH)
Procedure	Enucleation	Vaporization	Coagulation
Wavelength, *nm*	2120	532	800–850
Average power, *W*	100	80	20
Operation mode	Long-pulse	Quasi-CW	CW
Pulse length, *µs*	500	—	—
Repetition rate, *Hz*	5–550	—	—
Electrical specs	220 V, 30 A	220 V, 50 A	110 V, 5 A
Cooling specs	Internal water	External water	Air
Weight, *kg*	155	104	13

CW—continuous wave; KTP—potassium titanyl phosphate.
Data from Lumenis, Inc. (Santa Clara, CA); Laserscope (San Jose, CA); and Ethicon Endo-Surgery (Cincinnati, OH).

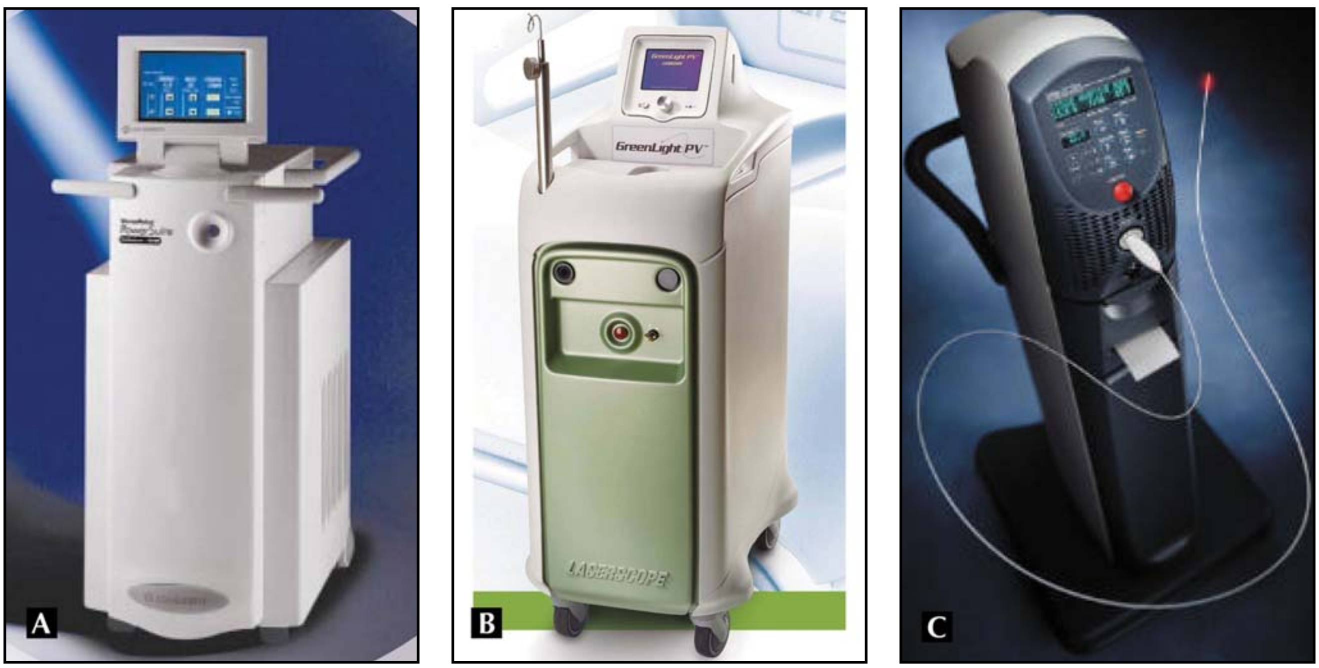

Figure 1. Examples of the current surgical lasers used in urology. **A,** VersaPulse holmium:YAG laser (Lumenis, Inc., Santa Clara, CA); **B,** GreenLight frequency doubled neodymium:YAG or KTP laser (Laserscope, San Jose, CA); **C,** Indigo diode laser (Ethicon Endo-Surgery, Inc., Cincinnati, OH). *Images courtesy of* Lumenis, Inc. (Santa Clara, CA); Laserscope (San Jose, CA); and Ethicon Endo-Surgery (Cincinnati, OH); with permission.

extended catheterization (Table 2). As a result of these complications, VLAP using the Nd:YAG laser has lost popularity in recent years and is no longer being performed on a wide scale.

Interstitial Laser Coagulation (ILC)

During ILC, a diode or Nd:YAG laser is used to provide deep heating and coagulative necrosis of the prostate gland without tissue vaporization. ILC is performed via a transurethral route in which the diffusing optical fiber is inserted directly into the prostate gland, and the laser energy is emitted radially into the tissue. The objective is to produce a large volumetric thermal lesion leading to coagulative tissue necrosis and a reduction in the volume of the prostate gland from atrophy. However, the optical penetration depth of the diode and Nd:YAG laser wavelengths is somewhat limited, resulting in thermal lesions that are much smaller than the size of the prostate gland. Thus, from a mechanistic point of view, it is unclear whether this laser technology provides any significant advantage compared with other thermal technologies that

Laser	Ho:YAG	KTP	Diode	Nd:YAG
Wavelength, λ	2120 nm	532 nm	808 nm	1060 nm
Optical penetration depth	0.4 mm	0.8 mm	2 mm	3 mm

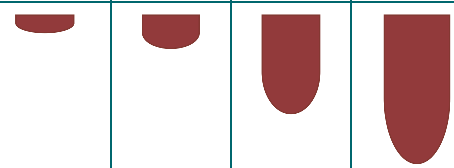

Figure 2. Optical penetration depths (OPD) in prostate tissue at different wavelengths (λ) for common surgical lasers used in the treatment of benign prostatic hyperplasia (BPH). Ho:YAG—holmium: yttrium-aluminum-garnet; KTP—potassium titanyl phosphate; Nd:YAG—neodymium: yttrium-aluminum-garnet.

are capable of much deeper and more uniform volumetric tissue heating, such as transurethral microwave thermal therapy and therapeutic ultrasound.

Although the popularity of ILC has declined over the past few years, several studies have recently been reported [3–6]. These studies found that the main advantage of ILC is that it offers decreased operative morbidity compared with TURP. However, the postoperative complications are higher with ILC, with prolonged catheterization times, greater incidence of irritative symptoms, higher infection rates, and less improvement in peak urinary flow than TURP [3–5] (Table 2). As a result, ILC has become less popular and is only recommended for selected BPH patients who are suffering from coagulation disorders.

KTP Photoselective Laser Vaporization of the Prostate (PVP)

Most recently, the frequency doubled Nd:YAG laser (KTP) has been used as an alternative to the Nd:YAG laser for vaporization of the prostate. The 532 nm wavelength of the KTP laser is more strongly absorbed by blood, resulting in a shallower optical penetration depth in the tissue (approximately 0.8 mm; Fig. 2) and more efficient tissue ablation with a smaller thermal coagulation zone of approximately 1–2 mm. The shorter coagulation depth of the KTP laser prevents the large volume sloughing of necrotic tissue that is seen with the Nd:YAG laser. The KTP laser procedure, pioneered by Hai and Malek [7], is termed photoselective vaporization of the prostate (PVP) because the laser wavelength is not absorbed by water but rather selectively absorbed by hemoglobin in the tissue, resulting in direct vaporization of the prostate [7,8•,9,10]. During PVP, a cavity is created after laser tissue vaporization, which is similar to TURP.

With the recent commercial availability of higher power, 80 W KTP lasers, such as the "GreenLight" laser, higher tissue vaporization rates have been achieved in a virtually bloodless procedure. Operative times have decreased significantly compared with earlier studies with the lower power 40 W and 60 W KTP lasers. As a result, this procedure has recently become one of the preferred methods for laser treatment of BPH. Early results of randomized trials comparing the PVP procedure to TURP show equivalent results [11,12]; however, the long-term effectiveness of the procedure has yet to be determined. There are few long-term clinical studies, but these studies do show lasting improvement of symptom scores and peak flow rates [13,14]. Recent reports have also shown that, due to the excellent hemostatic properties of the KTP laser, it can be used for treatment of BPH in patients receiving anticoagulant therapy as well [15].

A higher power KTP laser, the GreenLight HPS (Laserscope, San Jose, CA), has recently been introduced for use in treatment of BPH and other urologic diseases. Several of the limitations of the previous GreenLight PV (Laserscope, San Jose, CA) laser appear to have been addressed, including limited power delivery and inconvenient electrical and water cooling requirements. The new GreenLight HPS™ laser has increased output power from 80 W to 120 W for more rapid prostate vaporization, can be operated from a single-phase 220 V electrical outlet, and has internal water cooling, thus making it more attractive for use in a clinical setting. Although this laser appears to be a significant improvement, evaluation of its performance has yet to be reported.

Holmium Laser Ablation and Resection of the Prostate (HoLAP and HoLRP)

The Ho:YAG laser procedure has evolved in stages over recent years. Initially, Ho:YAG laser vaporization of the prostate (HoLAP) was developed using low-power Ho: YAG lasers, but it was found to be a time-consuming procedure limited to use in smaller prostates [16,17]. Ho:YAG laser resection of the prostate (HoLRP) was then developed, but the technique was difficult to learn [18]. During HoLRP, the Ho:YAG laser (with a wavelength of 2120 nm) is used to provide precise tissue cutting with an optical penetration depth of only 0.4 mm, thus producing a thin coagulation zone (Fig. 2). The prostatic lobes are resected and removed with a syringe or grasping loop. This procedure is also slow, requires long laser irradiation times, and is not practical for large prostates.

Table 2. Comparison of laser procedures for treatment of benign prostatic hyperplasia

Laser (procedure)	Advantages	Disadvantages
Holmium (HoLEP)	Multiple-use laser	Steep learning curve
	Tissue for histology	Cost of laser plus morcellator
	Symptom scores	Operation time
	Peak flow rates	
	Low morbidity	
	Low blood loss	
	Short catheterization	
	Low retreatment rate	
KTP (PVP)	No blood loss	Cost of fibers
	Simple procedure	No tissue for histology
	Symptom scores	
	Peak flow rates	
Diode (ILC)	No surgical morbidity	Symptom scores
		Peak flow rates
		High retreatment rate
		Urinary tract infection
Nd:YAG (VLAP)	No blood transfusions	No tissue for histology
	No strictures	Symptom scores
		Peak flow rates
		Prostate volume
		High retreatment rate
		Long-term retention
		Extended catheterization

HoLEP—holmium laser enucleation of the prostate; ILC—interstitial laser coagulation; KTP—potassium titanyl phosphate; Nd:YAG—neodymium:yttrium-aluminum-garnet; PVP—photoselective vaporization of the prostate; VLAP—visual laser ablation of the prostate.

However, with the recent introduction of higher power Ho:YAG lasers with output powers up to 100 W, HoLAP may be worth re-exploring because procedure times could be reduced compared with earlier studies conducted with lower power Ho:YAG lasers. The recent commercial success of the 80 W KTP GreenLight laser for direct vaporization of the prostate should also renew interest in a similar approach using the Ho:YAG laser. As of yet, however, there are no published studies directly comparing the 80 W KTP and the 100 W Ho:YAG lasers for vaporization of prostate tissue, so it is unclear which technology provides an advantage for this type of procedure.

Further complicating matters, both lasers operate based on different mechanisms of laser-tissue interaction. The KTP laser radiation can be transmitted easily through water in a noncontact mode because the laser radiation is selectively absorbed by the hemoglobin in the tissue. On the contrary, the Ho:YAG laser radiation is highly absorbed by the water in the tissue, and though it can be used in noncontact mode due to the "Moses effect" (a cavitation bubble forms at the end of the fiber tip due to the short laser pulse and effectively "parts the waters"), the efficiency of tissue vaporization may be reduced. However, it is still unclear which laser provides higher tissue vaporization rates based on these differences in the absorption mechanism, and the design of the optical fiber delivery system may also play an important role in the tissue ablation efficiency.

Holmium Laser Enucleation of the Prostate

The most recent evolution of the Ho:YAG laser procedure is termed holmium laser enucleation of the prostate (HoLEP) and was pioneered by Tan et al. [19]. This procedure was developed because it was found that HoLRP was too slow during earlier studies using lower power Ho:YAG lasers. HoLEP involves laser resection of large prostate lobes into chunks that are pushed up into the bladder, mechanically morcellated into smaller pieces, and then flushed out of the urinary system. Unlike HoLRP, this technique can be used on extremely large prostate glands of greater than 70 g to 100 g. Randomized studies comparing HoLEP and TURP have shown that HoLEP provides better relief of bladder outflow obstruction in small prostates, and it is at least equivalent to TURP in improving symptoms and flow rates in larger prostates [20•,21,22]. Recent studies have also demonstrated that the Ho:YAG laser is also effective for treating patients receiving anticoagulant therapy or with bleeding disorders [23]. However, the HoLAP technique requires significant capital investment in a 100 W Ho:YAG laser and a mechanical morcellator. The procedure is also considered more difficult to learn than PVP and has longer procedural times and a longer learning curve. However, unlike the KTP laser, the Ho:YAG laser can be used for other soft and hard tissue procedures, including incision of strictures, ablation of tumors, and laser lithotripsy, thus offsetting some of the capital equipment costs and making the Ho:YAG laser the most versatile laser for use in urology.

A summary of the advantages and disadvantages of each laser technique for treatment of BPH is provided in Table 2.

Other Experimental Laser Therapies for Treatment of BPH

Most recently, a solid-state thulium laser has been introduced for clinical use as a potential alternative to the Ho:YAG laser for soft tissue applications [24,25]. The thulium laser operates in continuous-wave mode at a wavelength of 2010 nm (similar to the 2120 nm wavelength of the Ho:YAG laser) and may provide improved tissue cutting and hemostasis without the mechanical damage caused by the pulsed Ho:YAG laser. Like the Ho:YAG and KTP lasers, the power output of the thulium laser has been steadily increased from 50 W to 70 W to provide more rapid tissue ablation. The thulium laser is currently being studied in urology for resection of the prostate [24,25]. However, the clinical use of this technology in urology is very new, and few studies have been published to date, so evaluation of the efficacy of this laser is not yet possible.

Recent advances in fiber laser technology have also resulted in the commercial availability of high-power industrial fiber lasers operating with powers up to 150 W, near the 2-µm Ho:YAG laser wavelength. The thulium fiber laser has several potential advantages over other solid-state lasers such as the Ho:YAG and KTP lasers currently being used for treatment of BPH. The thulium fiber laser wavelength can be chosen to exactly match the 1940 nm water absorption peak in tissue, thus potentially providing more rapid and efficient incision or vaporization of prostate tissue than the Ho:YAG laser. Like the solid-state thulium laser, the thulium fiber laser wavelength can be operated in continuous-wave mode for both tissue vaporization and coagulation or modulated to operate in pulsed mode to provide variable control over the coagulation depth. The thulium fiber laser also has a higher wall-plug efficiency (6%) than the Ho:YAG and KTP lasers (1%–2%), allowing the laser to be smaller, air-cooled, and operate from a standard 110-V outlet at powers up to 50-60 W. Preliminary laboratory experiments using a 110-W thulium fiber laser have demonstrated that it is capable of rapidly vaporizing prostate tissue, ex vivo, while also producing sufficient thermal coagulation zones to achieve hemostasis during the procedure [26]. However, further preclinical studies have to be performed to properly assess the efficacy of this new experimental technology for potential clinical use in treatment of BPH.

The use of photodynamic therapy (PDT) for treatment of BPH has been previously proposed, but few studies have been performed [27,28]. During PDT, which is currently also being tested for treatment of bladder and prostate cancer, a photosensitizing drug is delivered intravenously to the patient. The compound is selectively absorbed by cells, and typically a few days after administration of the drug, the tissue is exposed locally to low levels of laser energy using a light source, resulting in tissue necrosis in the exposed area. Active research in PDT is ongoing on several fronts. Improved photosensitizing drugs are being developed, some of which absorb at longer laser wavelengths, providing deeper optical penetration of the laser radiation in the tissue and thus more uniform treatment of larger tissue volumes such as the prostate. Some of the newer PDT drugs can also be applied locally or clear more rapidly from the body and have fewer side effects (eg, reduced skin photosensitization) as well. Optimization and real-time monitoring of treatment dosimetry is also being conducted to minimize complications from PDT. Early clinical trials are in progress using PDT and an experimental light-activated drug (Lemuteporfin; QLT, Inc., Vancouver, BC, Canada) for treatment of BPH [29].

Conclusions

In summary, the recent introduction of higher power solid-state lasers, such as the 100 W Ho:YAG and 80 W KTP lasers, has resulted in more rapid and efficient incision or vaporization of prostate tissue during treatment of BPH. These lasers are capable of precise tissue ablation, based on selective absorption of either the water or hemoglobin in the tissue, while also providing sufficient thermal coagulation for hemostasis during the procedure. Although initial studies demonstrate that both laser procedures are at least comparable with TURP, ongoing long-term studies will need to confirm these results. Studies have yet to be published directly comparing the Ho:YAG and KTP lasers for BPH treatment. However, such studies would be valuable because financial constraints may prevent the average urologist from purchasing both the Ho:YAG and KTP lasers for their practice. Currently, the Ho:YAG laser may be used for multiple soft and hard tissue applications in urology, making it preferable for urologists who perform a variety of laser procedures other than BPH treatment. On the horizon, even more compact and efficient laser technologies, such as fiber lasers, may replace current solid-state lasers for use in BPH treatment, and PDT may also represent a promising alternative to the photothermal laser ablation techniques currently used in the clinic for treatment of BPH.

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