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Thulium fiber laser utilization in urological surgery: A narrative review

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The thulium fiber laser (TFL) is a novel technology under active investigation as an conceivable alternative to the Holmium:yttrium-aluminum-garnet (Ho:YAG) laser, which is currently the gold standard for an array of urologic procedures. The purpose of this review is to discuss the existing literature on the functionality and effectiveness of TFL in urological practice. We conducted a search of the PubMed, Medline, Web of Science Core Collection, SCOPUS, Embase (OVID), and Cochrane Databases for all full articles and systematic reviews on the TFL. We found a total of 35 relevant pieces of literature. The early research findings pertaining to the TFL exhibit numerous potential advantages over the Ho:YAG laser. *In vitro* and *ex vivo* studies have highlighted the TFL's ability to utilize smaller laser fibers, obtain faster stone ablation rates, and achieve less retropulsion when tested against the Ho:YAG laser in lithotripsy. Currently, there is limited *in vivo* research that investigates the utilization of the TFL. The *in vivo* results that are available, however, look promising both for laser lithotripsy and soft tissue ablation. Indeed, the existing literature suggests that the TFL has great potential and may possess numerous technological advantages over the Ho:YAG laser, especially in laser lithotripsy. Although these early studies are promising, randomized control trials are needed to assess the full applicability of the TFL in urology.

Keywords: Laser therapy; Lithotripsy; Surgical endoscopy; Thulium; Urology

INTRODUCTION

The use of medical lasers during urologic surgery has become increasingly ubiquitous. Most commonly, they are used for laser lithotripsy in the treatment of urolithiasis. Additionally, they have several soft tissue applications such as upper tract urothelial tumor ablation, endopyelotomy, and prostate enucleation. Currently, the gold standard of laser systems utilized in laser lithotripsy is the holmium:yttrium-aluminum-garnet (Ho:YAG) laser [1-3]. Though the Ho:YAG laser has been transformative in the field of urology, it has several notable limitations. For example, Ho:YAG lasers cannot support fibers smaller than 150 µm in diameter [4], which may limit the surgeon's ability to access lower pole calyces while using the laser during pyeloscopy. If smaller laser fibers were feasible, it would allow for better irrigation through existing ureteroscopes and potentially allow for the development of smaller ureteroscopes and instruments. Furthermore, due to the water cooling requirements of newer high-power Ho:YAG lasers [5], the generators have become larger and more complex in size and build, making transfer between individual operating theatres challenging.

Accordingly, there has been great interest in improving the existing laser technology employed by urologic surgeons.

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The thulium fiber laser (TFL) is a novel laser type which has shown early promise and may offer several advantages over Ho:YAG lasers. Indeed, in a prior review, Traxer and Keller [6] evaluated the early literature on TFLs and potential advantages in experimental models. Though the literature on TFLs remains limited, there have since been several *in vivo* studies published. In this review, we discuss the physics of TFLs, and review the existing literature on the use of TFLs, both in experimental laboratory studies (i.e. *in vitro* and *ex vivo*) and *in vivo*.

METHODS

In July 2020, we conducted a search of the PubMed, Medline, Web of Science Core Collection, SCOPUS, Embase (OVID), and Cochrane Databases for all papers containing both the phrases "Thulium Fiber" and "Urology." We reviewed all accepted and published English language full articles and review articles. Notably, TFL is a different technology than the thulium:yttrium-aluminum-garnet (Tm:YAG) laser, and thus we excluded studies on Tm:YAG lasers. Additionally, conference papers, abstracts, editorials, and letters were excluded. In sum, 35 relevant papers were included in our literature review. Our paper selection process in summarized in Fig. 1. Due to the relative novelty, heterogeneity, and sparsity of available literature on TFLs, our findings are presented as a narrative literature review.

THULIUM FIBER LASER–PHYSICS AND THEORETICAL ADVANTAGES

To fully appreciate the theoretical advantages of TFLs in urologic surgery, an appraisal of the physical properties of aqueous media, laser generators, and laser fibers is necessary. We begin with a brief overview of the current gold-standard: Ho:YAG lasers. Ho:YAG lasers are solid-state lasers in which light from a flashlamp is passed through a YAG crystal doped with Holmium ions [7]. The holmium ions become excited in a pulsed fashion and upon returning to their resting quantum state release photons at a wavelength of 2,120 nm [8]. These photons then oscillate between mirrors within the laser generator, further exciting the holmium ions and in turn generating additional photons. An aperture within the laser generator is then opened allowing the release of these photons as a laser beam [7]. The laser beam is then transmitted via a long and thin silica fiber to the surgical site. In urologic surgery, water commonly serves as the laser chromophore and it is the thermal expansion and vaporization of water that leads to ablation [9].

The Ho:YAG laser has demonstrated numerous advantages with its establishment as the gold standard laser in urology across the past two decades [2]. In laser lithotripsy, the Ho:YAG laser has been documented as effective in ablating all stone compositions [10]. Additionally, other studies have demonstrated that the laser also has great clinical utility in soft tissue ablation within the upper and lower urinary tract [11,12]. Importantly, the laser has a good, time-

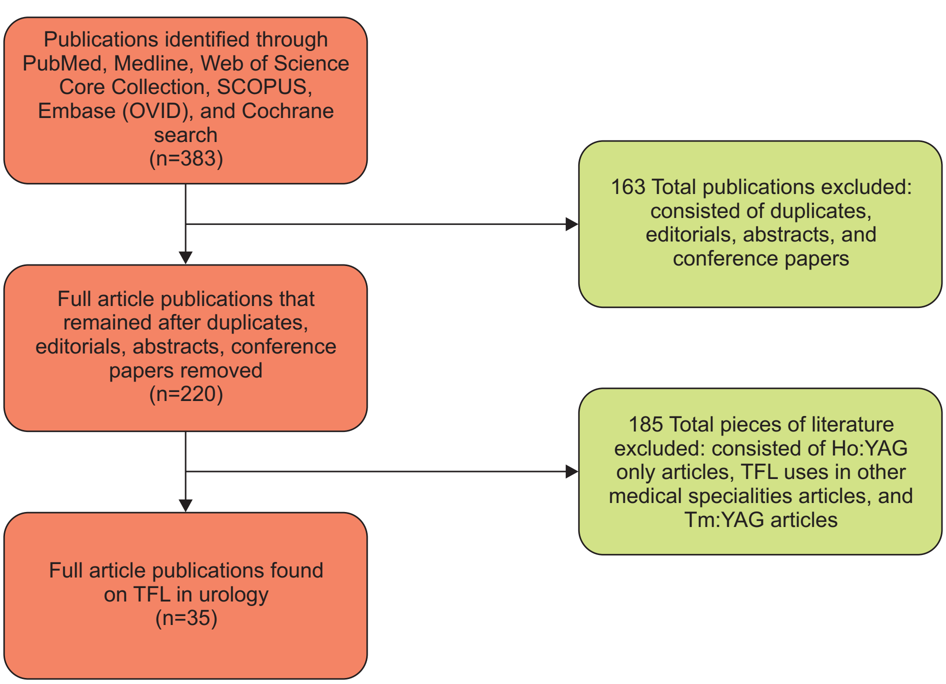

Fig. 1. Flowchart illustrating literature review. TFL, thulium fiber laser; Ho:YAG, holmium:yttrium-aluminum-garnet laser; Tm:YAG, thulium:yttrium-aluminum-garnet laser.

tested safety profile [13,14]. However, the Ho:YAG lasers have several shortcomings based on their underlying physics. Although not the sole determining factor, absorption of photons by water significantly affects ablation [9], and improved photon absorption, in theory, should improve ablation efficiency. In water, peak infrared photon absorption occurs with a wavelength of 1,940 nm while Ho:YAG generates photons at 2,120 nm [15]. Though water absorbs some photons at 2,120 nm, efficiency may be optimized at a wavelength of 1,940 nm [16]. Importantly this consideration is theoretical as other factors such as fiber tip-to-target distance may affect photon absorption.

A further limitation of Ho:YAG lasers is that, much of the energy from the flashlamp mechanism of this solid-state laser is wasted in the form of heat in the generator [6]. This excess heat limits the power generated by a single Ho:YAG laser cavity to 30 W. Multiple laser cavities can be placed in a single generator to overcome this power limit. However the use of multiple cavities requires a large water-cooling apparatus to prevent the laser generator from overheating, making the Ho:YAG laser generator physically bulky and difficult to transfer between operating rooms or reposition within an operating room during a procedure [17]. Another shortcoming of Ho:YAG is that the outputted laser beam is non-uniform which precludes the use of laser fibers smaller than 150 μm [4]. Of note, Tm:YAG lasers (also known at continuous wave Tm:YAG) are similar to Ho:YAG lasers in that a solid state YAG crystal is doped with thulium rather than holmium. The laser output wavelength for Tm:YAG is 2,010 nm which is closer to the peak infrared absorption for water. Though photon absorption is improved, the Tm:YAG laser has similar limitations as the Ho:YAG laser [18].

TFLs are a form of fiber laser rather than a solid-state laser. In a TFL, a thulium doped fiber is used as a gain medium rather than an ion doped YAG crystal. Diode lasers channel energy through this thulium doped fiber exciting the thulium electrons and generating photons which are then channeled to the surgical site via an outgoing laser fiber [19]. The emission spectrum of the diode laser can be matched to the absorption range of thulium, allowing the laser pumping mechanism to be more efficient, ultimately generating less heat than the flashlamp apparatus of the Ho:YAG or Tm:YAG laser. Accordingly, high powers can be achieved without the need for a bulky water-cooling apparatus [19]. For perspective, given the large cooling apparatus needed by the Ho:YAG laser generator, the entire laser unit weighs from 245 kg to 300 kg [20]. In contrast, the fan cooled TFL unit weighs only 36 kg [21]. Furthermore, since the gain medium in TFLs is extremely thin, the emitted laser's spatial profile is more uniform than that of a solid state laser (i.e. Ho:YAG or Tm:YAG) and hence a smaller surgical laser fiber can be employed [22]. The use of smaller laser fibers may allow for improved irrigation flow through existing endoscopic instruments, a decrease in retropulsion [23], and smaller future endoscopic instruments. *In vitro* studies using TFLs have evaluated the use of smaller laser fibers during laser lithotripsy [2,24-28]. Comparatively, these experimental fibers, ranging from 50–150 μm, are significantly smaller than the smallest currently available Ho:YAG laser fiber of 200 μm. Indeed, studies investigating stone ablation and retropulsion have found that these smaller fibers effectively ablated stones and led to less overall retropulsion [6,24,26,27,29-32]. Of note, the durability of these novel smaller laser fibers (≤150 μm) compared to existing larger fibers (≥200 μm) remains untested. Another advantage of TFLs is that the laser photons generated have a wavelength of 1,940 nm, a wavelength that is highly absorbed by water [15]. This, theoretically, should lead to more efficient laser ablation than the 2,120 nm or 2,010 nm wavelengths typically employed by the Ho:YAG and Tm:YAG lasers, respectively.

Bubble dynamics and temporal pulse profiles are key factors that affect stone retropulsion during laser lithotripsy as bubble formation during the delivery of a pulsed laser energy is an important mechanism for efficient stone and tissue ablation [33]. Additionally, the formation and collapse of the bubble may decrease stone retropulsion [34]. A study in 2016 observed that the TFL created smaller bubbles in comparison to the Ho:YAG, both in length and width, and also generated a stream of multiple bubbles during a single laser pulse at all power settings [35]. With previous study findings showing that the formation and collapse of a single bubble reduces stone retropulsion [34], multiple bubbles forming and collapsing may augment this decrease in retropulsion [36]. The same study also demonstrated that the TFL temporal pulse distribution is more uniform than the Ho:YAG laser distribution, leading to a more evenly dispersed energy across the duration of the laser pulse [36]. The utilization of smaller fibers, unique bubble dynamics, and temporal pulse profile of the TFL all contribute to the potential for more efficient laser lithotripsy and tissue ablation with the use of this technology.

IN VITRO AND *EX VIVO* STUDIES ON THULIUM FIBER LASER

The TFL has a broad range of theoretical applications in urology. Currently, the vast majority of data and published research comes from the experimental laboratory setting.

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Table 1. Summary of *in vitro* studies on TFL use in urologic surgery

Reference	Study purpose	Experiment apparatus	TFL setting	Result
Fried 2005 [37]	Tested TFL feasibility with performing laser lithotripsy	COM and UA stones were submerged in a saline bath	- 300 μm fiber - 1 J pulse energy - Average power 10 W - 2,000 μs pulse duration - 10 Hz	- TFL adequately fragmented COM and UA stones
Wilson et al. 2016 [27]	Tested miniature ball-tip laser fibers in TFL laser lithotripsy	COM stones fixed in a wire mesh and submerged in a saline bath	- 100 μm fiber with a 300 μm ball-tip - 35 mJ pulse energy - 500 μs pulse duration - 300 Hz	- No statistical difference in ablation rates were found with use of the ball-tip and bare tip fibers
Wilson et al. 2015 [28]	Tested use of a stone basket and miniaturized fibers in TFL lithotripsy	UA stones submerged in saline bath with laser and basket placed through ureteroscope	- 100 μm fiber - 32.5 mJ - 500 μs pulse duration - 500 Hz	- No damage to stone basket during stone ablation
Hutchens et al. 2017 [25]	Tested use of a "fiber muzzle brake" for reduction of fiber burnback and stone retropulsion	Stone phantoms and COM stones fixed and submerged in saline. Retropulsion measured based on distance stone traveled through a trough	- 100 μm fiber - 32.5 mJ - 500 μs pulse duration - Maximum 300 Hz	- Reduced stone retropulsion with use of the muzzle brake over bare tip - Minimal laser fiber tip degradation with muzzle brake
Scott et al. 2009 [22]	Tested TFL laser fibers less than 200 μm in laser lithotripsy	COM and UA stones submerged in saline baths	- 100, 150, and 200 μm fibers - 0.07–1 J - 1,000 μs pulse duration - 10–30 Hz	- Smaller fibers did not undergo damage at high power outputs during lithotripsy - Uniform laser beam with smaller fibers and decreased irrigation flow with smaller fibers
Blackmon et al. 2014 [30]	Tested a TFL 50 μm fiber core for lithotripsy	COM stones submerged in a trough in a saline bath	- 50 μm fiber - 35 mJ - 500 μs pulse duration - 50 Hz	- Ablation rates were similar to the 100 μm fiber - Minimal retropulsion but significant fiber burnback
Hall et al. 2019 [24]	Tested a vibrating laser fiber tip at 50, 100, and 150 core μm fibers in lithotripsy	UA stones were prepared using a wet saw on one face	- 50, 100, and 150 μm fiber - 33 mJ - 500 μs pulse duration - Maximum 300 Hz	- Vibrating fibers produced up to 2.8× greater ablated surface area versus fixed fibers
Hardy et al. 2016 [35]	Tested TFL bubble dynamics against Ho:YAG	TFL fired in a saline bath	- 105 and 270 μm fiber - 5–65 mJ - 200–1,000 μs pulse duration - Maximum 300 Hz	- TFL bubble dimensions 4× smaller than Ho:YAG

TFL, thulium fiber laser; COM, calcium oxalate monohydrate; UA, uric acid; Ho:YAG, holmium:yttrium-aluminum-garnet.

In particular, these *in vitro* and *ex vivo* studies explore the novel laser's application in lithotripsy, both in general (Table 1), and in comparison to Ho:YAG (Table 2).

1. Stone ablation

The first study evaluating the TFL for kidney stone lithotripsy was performed in 2005. Settings of 1 J pulse energy and 10 Hz frequency were used to target calcium oxalate monohydrate (COM) and uric acid (UA) stones in a saline bath. Investigators found that both UA and COM stones were adequately fragmented (<2 mm) by the new technology [37]. Over the past decade, numerous subsequent studies have investigated and compared TFL and Ho:YAG lasers for stone ablation rates, ablation thresholds, and other laser parameters across an array of laser specifications. When the Ho:YAG laser and TFL were tested at similar pulse energy settings, the TFL consistently recorded significantly faster stone ablation rates than the Ho:YAG laser [26,29,32,38]. Two of the first studies comparing stone ablation rates and efficacy between these two laser modalities were by Blackmon et al. in 2010 [29,32]. In one study, when the TFL and Ho:YAG transmitted the overall same total number of pulses and pulse energies to stone targets (COM and UA stones in a saline bath), the TFL was found to produce significantly more stone mass loss than the Ho:YAG laser, creating stone ablation craters 4–10 times deeper [32]. The second study conducted by this lab investigated corresponding ablation rates, ablation thresholds (defined as the lowest incident radiant exposure at which stone material is removed), and retropulsion effects across a multitude of Ho:YAG laser and TFL settings. TFL settings in this study consisted of a lower pulse energy range than the Ho:YAG laser (5–35 mJ vs. 30–550 mJ, respectively) and much higher frequencies (10–400 Hz vs. 10 Hz, respectively). The TFL energy ablation thresh-

Table 2. Summary of *in vitro* and *ex vivo* studies that compare Ho:YAG and the TFL

Reference	Study goal	Experiment apparatus	Laser setting		Result
			Ho:YAG	TFL	
Hardy et al. 2014 [43]	Comparing operative times and irrigation temperatures between TFL and Ho:YAG laser	6 mm-inner-diameter tube with an integrated 1.5 mm mesh sieve and microthermocouple	- 272 μm fiber - 0.6 J pulse energy - 350 μs pulse duration - 6 Hz	- 100 μm fiber - 35 mJ pulse energy - 350 μs–700 μs pulse duration - 150, 300, 500 Hz	- TFL significantly faster stone clearance; 1.5–7× faster at increasing frequencies - Significantly higher TFL irrigation temperatures at all tested frequency; reaching 39±6°C at 500 Hz
Blackmon et al. 2011 [29]	Comparing ablation thresholds and retropulsion between TFL and Ho:YAG laser	COM and UA stones fixed and submerged in saline bath	- 200 μm fiber - 30–500 mJ pulse energy - 350 μs pulse duration - 10 Hz	- 200 μm fiber - 5–35 mJ pulse energy - 500 μs pulse duration - 10–400 Hz	- TFL significantly lower stone ablation threshold; 4× lower - TFL had nearly no retropulsion at frequencies lower than 100 Hz; Ho:YAG retropulsion increased with pulse energies
Blackmon et al. 2010 [32]	Comparing stone vaporization rates between TFL and Ho:YAG laser	COM and UA stones fixed and submerged and clamped in saline bath	- 100 μm fiber - 70 mJ pulse energy - 220 μs pulse duration - 3 Hz	- 100 μm fiber - 70 mJ pulse energy - 1,000 μs pulse duration - 10 Hz	- At same pulse energies and total pulses delivered, TFL significantly more efficient in vaporization, 5–10× more than Ho:YAG - TFL created 4–10× deeper ablation craters when compared to Ho:YAG
Panthier et al. 2020 [26]	Comparing ablation rates and stone fragment sizes (dusting and fragmentation) produced between TFL and Ho:YAG laser	Stone phantoms fixed and submerged in saline bath	- 272 μm fiber - 0.5–1 J pulse energy - 15–30 Hz	- 272 and 150 μm fibers - 0.15–0.5 J pulse energy - 30–100 Hz	- TFL significantly higher ablation rates for both dusting and fragmenting when compared to Ho:YAG at similar sized fibers and laser settings - TFL 150 μm fiber produced significantly smaller stone fragments than TFL 272 μm fiber
Andreeva et al. 2020 [38]	Comparing ablation, retropulsion, and dusting/ fragmentation performance between TFL and Ho:YAG laser	Ablation Setup: Stone samples placed in double walled curvette with orifice at bottom measuring 1 or 3 mm Retropulsion: 4 mm glass rods inside water filled curvette	- Ho:YAG short pulse: 275 μm fiber - 0.2–3.5 J pulse energy - 127–300 μs pulse duration - Maximum 50 Hz - Ho:YAG long pulse: 275 μm fiber - 0.2–6.0 J pulse energy - 140–1,100 μs pulse duration - Maximum 80 Hz	- 200 μm fiber - 0.05–6 J pulse energy - 200–12,000 μs pulse duration - Maximum 2,000 Hz	- TFL higher ablation rates in dusting and fragmentation modes when compared to Ho:YAG - Similar irrigation temperature recordings for both lasers - TFL threshold for retropulsion was 2 to 4× higher than Ho:YAG laser
Ventimiglia et al. 2020 [31]	Comparing laser temporal pulse shaping, ablation efficiency and retropulsion between super pulse TFL and Ho:YAG	Stone phantoms submerged in saline bath with stone position being recorded with image processing platforms	- 230 μm fiber - 0.2–6 J pulse energy - 350 μs pulse duration - Maximum 80 Hz	- 200 μm fiber - 0.025–6 J pulse energy - 500 μs pulse duration - Maximum 1,600 Hz	- TFL produced slower retropulsion than Ho:YAG at similar power and frequency settings - TFL had higher ablation efficiency than Ho:YAG - TFL produced longer and lower peak power pulses when compared to Ho:YAG

Ho:YAG, holmium:yttrium-aluminum-garnet; TFL, thulium fiber laser; COM, calcium oxalate monohydrate; UA, uric acid.

old for COM stones to be nearly a quarter of the threshold of Ho:YAG (20.8 J/cm^2 vs. 82.6 J/cm^2, respectively) [29]. The same study also observed higher stone ablation rates using the TFL compared to the Ho:YAG laser, reaching maximum rates of 140 μg/s and 100 μg/s, respectively.

A relatively recent technique development in laser lithotripsy known as “dusting” is the creation of extremely small stone particles. Though the clinical significance of dusting remains under investigation [39,40], *in vitro* research thus far has shown the TFL has been more effective than the Ho:YAG at dusting [26,38]. A 2019 *in vitro* study compared ablation rate between TFLs and Ho:YAG lasers when performing lithotripsy on COM and UA stones. Notably, this study was one of the first comparative TFL studies to utilize a high-power Ho:YAG model (P-100 and P-120; Lumenis, Yokneam, Israel), which is more efficient, is able to utilize

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Moses technology, and can emit higher maximum powers and frequencies compared to previous Ho:YAG lasers. The lasers were tested across a variety of "fragmentation" and "dusting" settings. Even with the use of the novel Ho:YAG laser's higher power and frequency ranges, the TFL still exhibited significantly higher ablation rates for the vast majority of the laser settings tested. For "dusting" laser settings (creation of stone particles less than 1 mm), the TFL was observed to produce significantly faster ablation rates for all laser parameters tested as compared to Ho:YAG for both UA and COM stones. For "fragmentation," the study observed the TFL having overall two-fold faster ablation rates of UA stones (COM stones were not tested in fragmentation experiment), but did not find statistical significance when both lasers were tested at lower average power settings (≤6.4 W) [38]. Another *in vitro* study demonstrated that the TFL was capable of efficient stone ablation with 150 μm laser fibers (which are smaller than the smallest available Ho:YAG fibers). The investigators used stone phantoms in saline solution to compare ablation rates between a 150 μm laser fiber equipped to the TFL, a 272 μm laser fiber equipped to a Ho:YAG laser (MH1Rocamed®, Monaco), and also 272 μm laser fiber equipped to the TFL. They tested various stone sizes and various laser settings with both the TFL and Ho:YAG laser. The smaller 150 μm laser fiber when equipped to the TFL had significantly faster ablation rates in comparison to the 272 μm Ho:YAG fiber in all study arms except for the "fragmentation" of soft stones. When the TFL was equipped 272 μm laser fiber and compared to the 272 μm Ho:YAG fiber study arm, the TFL had significantly faster ablation rates in both the "dusting" and "fragmenting" experiments [26].

The observed faster ablation rates with the TFL is attributable to multiple variables. Importantly, the TFL emitted wavelength is nearly identical to the peak water absorption coefficient [16]. This allows for increased absorption of energy in the bound water molecules within the stone itself. Recent research suggests that vaporization of these sequestered water molecules augments fragmentation and breaking of the stone [41,42]. The TFL also can achieve notably higher frequencies than the Ho:YAG laser. Thus, the TFL can produce higher ablation speeds despite lower overall power being emitted.

2. Treatment times

Though much of the existing TFL literature primarily evaluates ablation rates, one study assessed treatment times using both the TFL and Ho:YAG laser in an *in vitro* ureter model (1.5 mm mesh sieve and microthermocouple) [43]. Treatment time was defined as the total time for fragmenting 4–5 mm diameter COM stones into fragments sized at 1.5 mm or smaller. For both lasers, the investigators periodically turned off the laser to allow for stone debris clearance and laser repositioning to simulate an *in vivo* lithotripsy procedure. Compared to the TFL, the Ho:YAG laser caused increased retropulsion and recoil of the stone, leading to increased ablation times in the experimental mesh sieve ureter. Indeed, the TFL had shorter laser and treatment times at all tested TFL frequency settings (150 Hz, 300 Hz, 500 Hz). Additionally, TFL treatment times were reduced nearly 4-fold at 300 Hz and 500 Hz as compared to Ho:YAG laser treatment times. Notably, the Ho:YAG laser was operating at a higher pulse energy than the TFL, (600 mJ vs. 35 mJ), but also a much lower frequency (6 Hz). However, since the publication of this study, technological advancements have allowed for decreased Ho:YAG treatment times [44,45]. Newer Ho:YAG models are now able to operate at much higher frequencies (80–120 Hz), and use of the "Moses effect" with the Ho:YAG laser has significantly decreased retropulsion during *in vivo* lithotripsy [46].

3. Retropulsion

Several *in vitro* comparison studies investigated stone repulsion differences between TFL and Ho:YAG lithotripsy. All studies observed less retropulsion with use of the TFL at varying frequency and power settings [29,31,38,43]. One of these studies found that retropulsion occurred at a 2–4 times higher energy threshold when using the TFL in comparison to the Ho:YAG laser [38]. Another study, defining significant retropulsion as stone movement >2 mm after an energy pulse, observed minimal retropulsion at all TFL power settings but noted significant retropulsion at frequencies greater than 150 Hz [29]. A third study examined retropulsion based on the different pulses each laser was able to generate. Stone displacement was significantly lower with use of the short pulse TFL as compared to the Ho:YAG laser across all pulses tested [31]. Notably, none of these studies were performed in an environment designed to simulate the urinary tract, mostly being performed in saline baths or common laboratory glassware. Thus, it is difficult to assess the true clinical significance of these findings. Furthermore, while these results indicate that the TFL may lead to less retropulsion in clinical practice at routine frequency settings, the use of markedly higher frequencies in clinical lithotripsy may be limited due to increased retropulsion. However, it is important to note that retropulsion in some laser lithotripsy cases may lead to a better clinical outcome. Stones that are located in difficult to reach anatomical locations, such as a calyceal diverticula or a calyx requiring significant ureteroscope flexion to access, may be dislodged with retropulsion, allowing the surgeon better access for more efficient lithotripsy. Therefore, less retropulsion may not necessarily translate to improved clinical outcomes for all laser lithotripsy surgeries. This technology needs to be further explored *in vivo* to establish frequency parameters that can maximize stone ablation without significant retropulsion.

4. Safety profile

Laser lithotripsy conducted with the Ho:YAG laser has been established as a safe procedure [47]. The specific wavelength of the TFL at 1,940 nm theoretically would translate to an advantageous safety profile due to the laser being more efficiently absorbed by water. This absorptive capacity of the TFL translates to the laser's initial energy dissipating almost completely (0.00024%) at 1 mm from the laser fiber tip in a water medium [48].

With the majority of published TFL research being *in vitro*, the full safety profile of this technology remains to be determined. However, local temperature changes with use of the TFL have been investigated [49,50]. One such study investigated temperature changes of both the TFL and Ho:YAG laser in an experimental curvette environment. The experiment observed temperature changes during a 60 second uninterrupted laser emission as well as changes during a simulated lithotripsy using irrigation flow and a stone phantom. The investigators found that during uninterrupted laser emission as well as during the simulated lithotripsy, the temperature of the curvette environment was similar for both laser modalities [50]. Notably the study was limited only a single laser setting was used: 0.2 J and 40 Hz for both modalities.

Another recent study investigated temperature changes with the TFL *in vitro* via the use of a model renal collecting system constructed from test tubes filled with normal saline. A wide spectrum of TFL settings (0.05–0.8 J and 60–300 Hz) and varying amounts of irrigation were used. Their basis for determining the clinical relevance of a temperature change, known as the "safety threshold of temperature increase," was derived from previous literature findings that 43℃ is the highest tolerable temperature during safe laser lithotripsy [51,52]. The investigators found that water temperature increases did indeed surpass the defined safety threshold within 60 seconds of use with higher power settings (≥15 W) when there were lower rates of irrigation (0–15 mL/min). However, when irrigation was raised to 25 mL/min and higher, the water temperature never surpassed the defined safety threshold, regardless of power used [49]. Another study investigating the TFL temperature changes in an *in vitro* ureter model observed irrigation temperatures did surpass 40℃ when the TFL frequency was set to 500 Hz [43]. The authors note that these high temperature states were short in duration (4 seconds or less), and therefore, less likely to be clinically significant. However, these are notable temperature increases and without adequate irrigant outflow (i.e. flexible ureteroscopy without an access sheath), heat may accumulate and result in in local tissue damage.

Two *ex vivo* studies investigated possible tissue damage with the TFL. One study assessed tissue damage with the TFL using varying fiber tips and energy settings in a porcine kidney model. To assess tissue damage, a histological evaluation was performed to measure ablation depths, thermo-mechanical damage zones and carbonization grades. They found that the ablation depths were not concordant with the physical penetration of the TFL in water, 2 mm, but more related to TFL power settings [53]. Thus, though the physical penetration of TFL in water is 2 mm, at high power settings, the energy appears to penetrate farther.

Another *ex vivo* study using a porcine ureter model evaluated time to ureteral perforation with direct laser fiber contact when using the TFL under various frequencies. The investigators experimented with frequency settings ranging from 50–500 Hz while on a fixed 0.035 J energy. They found that mean perforation time was inversely related to laser frequency, with perforation occurring in approximately 7.9 seconds at 150 Hz and 1.8 seconds at 500 Hz [54]. These findings suggest longer perforation times compared to those observed in *ex vivo* studies using the Ho:YAG laser [14]. Additionally, one *ex vivo* study did reveal that the TFL did produce greater carbonization than Ho:YAG on non-frozen porcine kidney [55]. However, the clinical implications of these findings are yet to be determined as there are no *in vivo* studies investigating tissue carbonization. This represents an important avenue for future research.

While some of these *ex vivo* results are promising, data regarding the safety of TFL *in vivo* remains limited. Indeed, though early *in vivo* studies reported no severe complications after a TFL procedure, including lithotripsy, prostate enucleation, and bladder tumor resection [56-58], further study with randomized controlled trials is required. Notably, the majority of studies examining the safety profile of the TFL were not conducted in biological tissue, leaving the TFL's true safety profile unknown at this time.

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Table 3. Summary of *in vivo* studies on TFL use in urologic surgery

Reference	Pathology treated	Study type	Sample size	Study period	Result
Enikeev et al. 2019 [56]	BPH	Retrospective two-arm cohort study (TFLEP vs. OSRP)	130 (90=TFLEP, 40=OSRP)	2015–2017 (months unspecified)	- TFLEP patients had less blood loss - TFLEP patients had shorter duration of catheterization - TFLEP patients had shorter post-operative catheter durations - No difference in IPSS, QoL score, maximum flow, or PVR at 6 months
Enikeev et al. 2019 [59]	BPH	Prospective randomized cohort study (TFLEP vs. monopolar TURP)	103 (51=TFLEP, 52=TURP)	Unspecified	- TFLEP patients had shorter duration of catheterization and shorter hospital stay - TFLEP patients had less intraoperative blood loss - TFLEP had longer operative time - No differences in IPSS, QoL score, maximum flow, or PVR at 6 and 12 months
Enikeev et al. 2020 [60]	NMIBC	Prospective non-randomized cohort study (TFL-EBRBT vs. conventional TURBT)	129 (71=TFL-EBRBT, 58= conventional TURBT)	February 2015–December 2017	- TFL-EBRBT tissue samples were more likely to contain muscle - TFL-EBRBT was less likely to elicit an obturator reflex - TFL-EBRBT patients were less likely to have bladder perforation - TFL-EBRBT patients had higher recurrent free survival at 6 months
Enikeev et al. 2020 [57]	Urolithiasis (percutaneous nephrolithotomy)	Prospective single-arm cohort study	120	August 2017–January 2019	- Using TFL-PCNL surgeons reported absent or minimal retropulsion in >95% of cases - Using TFL-PCNL surgeons reported no or minor difficulty with visualization in >95% of cases - After TFL-PCNL, 5% of patients required stent placement for urinary leakage. Otherwise, there were no Clavien grade IIIa or higher complications. - 85% of patients were stone-free at 3 months post-op
Enikeev et al. 2020 [58]	Urolithiasis (RIRS)	Prospective single-arm cohort study	40	February 2018–July 2018	- TFL settings of 0.15 J/200 Hz allowed for faster stone ablation speed than settings of 0.5 J/30 Hz - No patients treated with TFL RIRS had Clavien IIIa or greater complications - 92.5% of patients were stone free at 3 months post-op

TFL, thulium fiber laser; BPH, benign prostatic hyperplasia; TFLEP, thulium fiber laser enucleation of the prostate; OSRP, open simple retropubic prostatectomy; IPSS, International Prostate Symptom Score; QoL, quality of life; PVR, post void residual; TURP, transurethral resection of prostate; NMIBC, non-muscle invasive bladder cancer; TFL-EBRBT, thulium fiber laser en-bloc resection of bladder tumor; TURBT, transurethral resection of bladder tumor; TFL-PCNL, thulium fiber laser during percutaneous nephrolithotomy; RIRS, retrograde intrarenal surgery.

IN VIVO STUDIES ON THULIUM FIBER LASER

Given the novelty of TFL, the existing *in vivo* literature is limited (Table 3). Indeed, the first peer-reviewed *in vivo* TFL study we identified was only just published in January 2019 [56]. In this retrospective cohort study, the authors compared thulium fiber laser enucleation of the prostate (TFLEP) to open simple retropubic prostatectomy (OSRP) for large volume benign prostatic hyperplasia. There were no differences in mass of resected tissue or operative time between the two groups. Additionally, compared to OSRP, patients undergoing TFLEP had less blood loss (-2.8 g/dL; 5% patients required transfusion vs. -1.0 g/dL; 0% patients required transfusion, respectively), shorter hospital length of stay (9.0 days vs. 3.3 days, respectively), and shorter indwelling catheter duration (6.4 days vs. 1.4 days, respectively). There were no differences in International Prostate Symptom Score, quality of life score, max flow rate, or post-operative residual volume between the groups. In summary, this study suggests that compared to OSRP, TFLEP has comparable outcomes with reduced peri-operative morbidity. Another *in vivo* study was a randomized prospective study that compared outcomes in patients who underwent TFLEP with monopolar transurethral resection of prostate (TURP) in patients with prostates sized less than 80 mL [59]. Compared to patients who underwent monopolar TURP, they found that patients who underwent TFLEP had longer operative times (39.9±8.6 minutes vs. 46.6±10.2 minutes, respectively), but also shorter indwelling catheter duration (2.4±1.1 days vs. 1.4±0.6 days, respectively), and shorter post-operative hospital stay (4.7±1.3 days vs. 3.4±0.6 days, respectively). They also reported less blood loss in the TFLEP group in comparison to the monopolar TURP patients (1.01±0.4 g/dL vs. 1.8±0.8 g/dL, respectively), as well as a smaller change in pre- and post-operative serum sodium (1.1±1.1 mmoL/L vs. 4.1±1.1 mmoL/L, respectively). Although the study noted that TFLEP resulted in lower post-operative prostate volumes compared to monopolar TURP (11.7±3.4 mL vs. 18.3±3.5 mL, respectively), they found no differences in International Prostate Symptom Score, quality of life score, max flow rate, or post-operative residual volume between the groups at both 6-month and 12-month follow-ups. In summary, these results suggest that TFLEP has comparable outcomes to monopolar TURP with reduced hospitalization time and blood loss. Further research is required to assess how TFLEP compares to other minimally invasive techniques therapies for bladder outlet obstruction such as a bipolar TURP or robotic assisted laparoscopic simple prostatectomy.

A subsequent study evaluated the use of TFL for resection of non-muscle invasive bladder cancer (NMIBC) [60]. In this prospective, non-randomized study, 129 patients underwent either TFL en-bloc resection of bladder tumor (TFL-EBRBT) or conventional transurethral resection of bladder tumor (TURBT) using a monopolar resectoscope. The investigators found that tissue samples from patients undergoing TFL-EBRBT were more likely to contain muscle (91.5% vs. 58.6%, respectively) and that these patients had a higher 6-month recurrence free survival rate compared to those undergoing conventional TURBT (91.5% and 67.2%, respectively). Additionally, patients undergoing TFL-EBRBT had no instances of elicitation of the obturator nerve reflex or bladder perforation whereas in the TURBT cohort 17.2% of patients had elicitation of the obturator nerve reflex and 10.3% of patients had evidence of bladder perforation. These results are promising as the lower perforation rate allows more patients to be eligible for post-operative chemotherapy. Furthermore, the high rate of muscle-containing tissue specimens and higher recurrence free survival suggest that TFL-EBRBT may reduce the number of endoscopic resections NMIBC patients undergo, both in diagnosis and in surveillance. Further investigations using randomized-controlled studies are warranted.

Regarding urolithiasis, two *in vivo* TFL studies have been published. In one study, the authors evaluated the use of TFL during percutaneous nephrolithotomy (TFL-PCNL) [57]. In this prospective proof-of-concept study, 120 patients with stone burden <30 mm underwent TFL lithotripsy via a 12 Fr nephroscope in a "mini-perc" set (16.5–17.5 Fr sheath). The mean stone diameter treated was 12.5 mm and the mean operative time (excluding puncture time) was 24.9 minutes. Retropulsion was absent (87.5%) or minimal (10.8%) based on subjective surgeon perception. The surgeons reported clear visibility (94.2%) or minor difficulty with visibility (3.3%) in the vast majority of cases. Regarding complications, 5% of patients required stent placement for urinary leakage. Otherwise, there were no Clavien grade IIIa or higher complications. At three-month follow-up, 85% of patients were stone free. This initial proof of concept study suggests that TFL-PCNL may be a viable and safe treatment option for antegrade lithotripsy.

The second published study on urolithiasis and TFL evaluated optimal TFL dusting settings during retrograde intrarenal surgery (TFL-RIRS) [58]. The investigators prospectively compared dusting efficiency of differing laser settings in a cohort of 40 adults with stones <20 mm. Ultimately, only two settings were used: 0.5 J/30 Hz (higher power) and 0.15 J/200 Hz (higher frequency). They found that stone ablation speed was faster in the high-frequency group compared to the high-power group (8.5 mm^3/s vs. 5.5 mm^3/s, respectively). Additionally, the authors noted that in the full 40 patient cohort, there were no Clavien grade IIIa or higher complications. Furthermore, 92.5% of patients were stone free at 3-months post-op. This study demonstrated that the high frequencies attainable using TFL may allow for more efficient stone dusting. Additionally, it appears the TFL is safe for retrograde lithotripsy and can render patients stone free. However, there are three key limitations in this study: there was no control group; all patients were pre-stented prior to lithotripsy; if the stone fragmented and a piece was extracted, the patient was excluded from the study. Nevertheless, the potential of TFL, particularly for dusting, is demonstrated and warrants further study.

In summary, the early *in vivo* literature suggests the TFL may have multiple endourologic applications for both urolithiasis and soft tissue. However, it is important to note that the existing literature *in vivo* applications of TFL is limited as we identified only four peer-reviewed clinical studies on the use of TFL, and all were published by the same lead investigator. Additionally, none of the studies are randomized controlled studies, and the two lithotripsy studies did not have a control arm. Though these early studies are promising, further research is required to understand the full applicability and generalizability of TFL for urologic surgery.

CONCLUSIONS

The TFL exhibits numerous potential advantages over the current widely used Ho:YAG laser in laser lithotripsy. The TFL operates at a wavelength that optimizes absorption in water, increasing stone vaporization, energy efficiency, and potentially enhancing the laser's safety profile. Notably though, the majority of the published literature assessing the technology in laser lithotripsy is in the *in vitro* setting. Previous *in vitro* lithotripsy studies have illustrated that

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the TFL can utilize smaller fibers than what the Ho:YAG is capable of, as well as ablate stones more efficiently, with less retropulsion. Early *in vivo* studies have shown promising results in the application of the TFL in soft tissue ablation as well, but the literature on the use of TFL for urological soft tissue surgeries remains limited. Further study using randomized controlled trials is warranted to determine full utility of TFLs both for lithotripsy and for soft tissue urologic surgery.

CONFLICTS OF INTEREST

Dr. Mantu Gupta is compensated for educational training for Cook Urological Inc., Boston Scientific Inc., Olympus Inc., Lumenis Inc., and Retrophin Inc. Additionally, Dr. Gupta is the Editor in Chief for Video Urology. No other authors have any relevant conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Johnathan A. Khusid, Raymond Khargi, Benjamin Seiden, Areeba S. Sadiq, William M. Atallah, and Mantu Gupta. Data acquisition: Johnathan A. Khusid, Raymond Khargi, and Benjamin Seiden. Data analysis and interpretation: Johnathan A. Khusid, Raymond Khargi, Benjamin Seiden, and Mantu Gupta. Drafting of the manuscript: Johnathan A. Khusid, Raymond Khargi, and Benjamin Seiden. Critical revision of the manuscript: Johnathan A. Khusid, Areeba S. Sadiq, William M. Atallah, and Mantu Gupta. Administrative, technical, or material support: Raymond Khargi and Benjamin Seiden. Supervision: Johnathan A. Khusid, Areeba S. Sadiq, William M. Atallah, and Mantu Gupta.

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